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2024 OSHK Guideline for Clinical Management of Postmenopausal Osteoporosis in Hong Kong

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Executive Summary

- The burden of osteoporotic fractures notably hip fractures keeps growing with the increasing life expectancy and ageing of the world's population.
- Development and approval of new bone-forming drugs have broadened the landscape of anti-osteoporosis treatment in postmenopausal women.
- Evolving concepts on imminent fracture risk and new treatment data consolidate an individualised approach in selection of anti-osteoporosis drugs based on the individual's risk level.
- For patients with imminent or very high fracture risk, bone-forming drugs should be prioritised as the initial treatment option.
- For younger patients in their early years of menopause at low fracture risk, mild antiresorptive drugs such as raloxifene or hormone replacement therapy are preferred.
- For patients with age ≥ 65 years at high fracture risk, potent antiresorptive drugs such as bisphosphonates or denosumab are reasonable first-line therapy.
- Drug holidays are only applicable to patients who are no longer at high fracture risk after 5 years of oral or 3 years of iv bisphosphonate treatment. Drug holidays are inappropriate for patients on all other antiresorptive treatment.
- Denosumab discontinuation is associated with rapid rebound bone loss and a potential increase in risk of multiple vertebral fractures. Patients who discontinue denosumab are advised to receive a potent bisphosphonate with regular monitoring for excessive bone loss.
- Fracture liaison service plays an important role in bridging the care and treatment gap for patients after a fragility fracture.

(A) Introduction

- 1.1 The first Osteoporosis Society of Hong Kong (OSHK) Guideline for Clinical Management of Postmenopausal Osteoporosis in Hong Kong was published in 2013.¹ In the last decade, new data on the disease have emerged notably in the areas of epidemiology, fracture risk prediction, new pharmacological agents, issues on long-term pharmacological management and the associated potential risks, and post-fracture care.
- 1.2 The 2013 OSHK Guideline was the first among the world to propose an individualised selection of anti-osteoporosis therapy based on the level of fracture risk of an individual.¹ A better understanding of the fracture risk after an incident osteoporotic fracture and the clinical development of newer bone-forming drugs with different mechanisms of action have led to revision of most international guidelines in the past 3 to 4 years to put forward and endorse an individualised consideration of anti-osteoporosis therapy according to the fracture risk level of an individual.²⁻⁴
- 1.3 The 2013 OSHK Guideline was also the first to recommend an optimal duration of oral or intravenous (iv) bisphosphonate (BP) therapy, based on the fracture risk reassessed at 5-year or 3-year of oral or iv BP therapy, respectively.¹ This recommendation will be revised in this Guideline according to new data on potential benefits and risks of long-term BP therapy in the Asian population.
- 1.4 The new 2024 OSHK Guideline will discuss the new data in the different areas of osteoporosis in detail and will recommend a new clinical management algorithm to guide local practitioners to optimise anti-osteoporosis treatment for their patients according to the level of fracture risk of the individual patient.
- 1.5 This Guideline should be read as an updated document and viewed as a companion article to the previous 2013 Guideline, much of the information of which is still very valid, clinically useful and practical.

(B) Epidemiology of Osteoporosis

1. Basic facts on osteoporosis

- 1.1 One in three women and one in five men over the age of 50 years will have suffer from an osteoporotic fracture.⁵
- 1.2 Hip fracture survivors experience loss of independence, with 40% unable to walk independently, 80% restricted in other activities of daily living, and 33% totally dependent or in a nursing home. Up to 20-24% of patients die in the first year after a hip fracture.⁵
- 1.3 Hip fractures are associated with more than twofold increase in mortality, and fourfold increase in likelihood of requiring long-term nursing facility care within 1 year following hip fracture compared with matched subjects without a hip fracture.⁶

2. Update on Asian epidemiology

- 2.1 Previous estimate in the 1990s had projected that more than half of all hip fractures in the world

would occur in Asia by the year 2050, amounting to 3.25 million cases.⁷ This estimate however was based on data collected more than 20 to 30 years ago.

- 2.2 The 2018 Asian Federation of Osteoporosis Societies (AFOS) Study projected that the number of hip fractures in nine Asian regions, which accounted for 70.3% of the Asian population, would reach 2.56 million by 2050.⁸ This figure will increase to about 3.66 million if extrapolated to the whole Asian population, which is much higher than the previous estimate.⁷
- 2.3 A recent international study on the global epidemiology of hip fractures, based on data collected from 2005 to 2018 in 19 countries/regions reported that the age- and sex-standardised incidence rates of hip fracture ranged from the lowest 95.1 in Brazil to the highest 315.9 in Denmark per 100000 population.⁹ That of Hong Kong stood at 190.4 per 100000 population. Although the incidence rates of hip fracture had shown a decline in recent years in most countries/regions including Hong Kong, it appears insufficient to offset the impact of the growing ageing population such that the number of hip fractures was projected to almost double by 2050.⁹
- 2.4 The AFOS had called for concerted effort in Asia to reduce the annual incidence of hip fracture by 2-3% each year in order to stabilise the total number of hip fractures over time.^{8,10}

3. Update on hip fracture epidemiology in Hong Kong

- 3.1 In a systematic review of hip fracture incidence worldwide in 2012, the annual age-standardised incidence of hip fracture in Hong Kong women was 324 per 100000, which placed Hong Kong to the high-incidence category (defined as >300 per 100000) ranking number 23 among all 63 countries/regions in the world.¹¹ The Hong Kong data in this review were mainly based on a local study published in 2009.¹²
- 3.2 The age-specific incidence of hip fracture in Hong Kong had reached a plateau before the turn of the last century¹³ and showed a downward trend from 2001 to 2009.¹⁴
- 3.3 The latest reported age-standardised incidence of hip fracture in Hong Kong was 190.4 per 100000 over a period from 2005 to 2018 with a female-to-male ratio of 1.9.⁹
- 3.4 Despite the declining trend in the age-specific incidence rate, the absolute number of patients admitted for hip fracture surgery steadily increased from 3678 in 2000 to 4579 in 2011.¹⁵ The burden of osteoporosis keeps growing with the increasing life expectancy and ageing of the Hong Kong population.
- 3.5 In a more recent report combining fragility fractures of the hip, distal radius and proximal humerus, there was an overall increasing incidence from a total of 5596 cases in 2004 to 8465 cases in 2018 (Fig 1). Hip fracture remained the highest incidence for fragility fractures with 4002 cases in 2004 to 5241 cases in 2018.¹⁶
- 3.6 The local orthopaedic community had advocated the setting up and maintenance of a Fragility

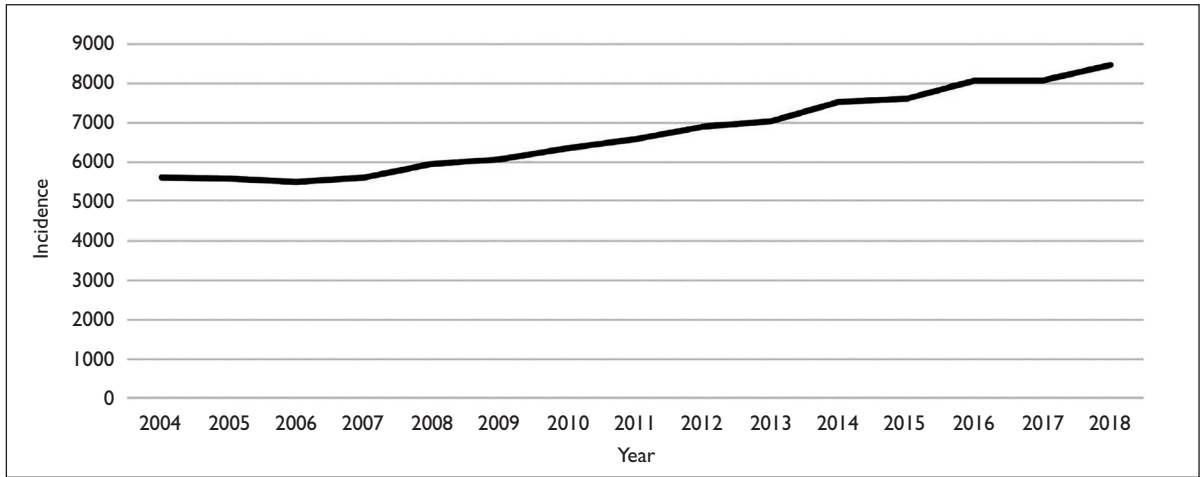


FIG 1. Incidence of major osteoporotic fractures (hip, distal radius, and proximal humerus) in Hong Kong public hospitals from 2004 to 2018⁶

- Fracture Registry in the Hospital Authority to help healthcare professionals to monitor and hence continuously improve the standards of care of patients with hip fractures.¹⁷
- 3.7 The instrumental roles of orthogeriatric co-management and fracture liaison service (FLS) are highlighted to improve patient outcomes and for secondary fracture prevention.¹⁸ Post-fracture care and management will be discussed in detail in Section V.
- 4. Update on vertebral fracture epidemiology in Hong Kong**
- 4.1 Accurate age-adjusted incidence for vertebral fracture is lacking because only about a third of all vertebral fractures noted on radiographs come to medical attention.
- 4.2 In the prospective Hong Kong Osteoporosis Study (HKOS) enrolling 2178 postmenopausal community-dwelling Southern Chinese women (mean age 61.2 years), 1372 had lateral spinal radiographs performed.¹⁹ 299 (22%) were noted to have prevalent vertebral fractures as defined by the quantitative procedures described by Black et al.²⁰ The prevalence increased with age, number of clinical risk factors and decreasing bone mineral density (BMD).¹⁹
- 4.3 In the Ms. OS (Hong Kong) Study involving 2000 community-dwelling older adult Chinese women (mean age 72.6 years), the prevalence of radiographic vertebral fractures as defined by the Genant semi-quantitative scoring system²¹ grade ≥ 1 was 12.1%.²² The prevalence progressively increased from 6.1% in the age-group 65-69 years to 13.6% in the age-group 70-79 years, and to 22.6% in the age-group ≥ 80 years. Older age, lower BMD, lower physical activity, lower grip strength, fracture history, and low back pain were significantly associated with higher vertebral fracture rate.²²
- 4.4 The difference in prevalence of vertebral fracture in the two studies might mostly be accounted for by the differences in definitions of vertebral fractures and more likely sampling bias.

- 5. Mortality of patients with hip fracture in Hong Kong**
- 5.1 Hip fracture is associated with reduced mobility, impaired self-care, deteriorated quality of life, increased health care cost, and most importantly, increased mortality. 20 to 40% of patients with hip fracture die within 1 year of the event.^{5,6,23}
- 5.2 In a local 12-year audit report from 2000 to 2011 of 48992 Chinese patients (mean age 82.1 years) who were admitted to public hospitals and underwent a hip fracture surgery, the overall 30-day and 1-year mortalities were 3.0% and 18.6%, respectively. Advanced age and male sex were associated with an increase in mortality.¹⁵
- 5.3 In another retrospective 2-year report from 2009 to 2010 involving 759 operated hip fracture patients (mean age 84 years) in a tertiary referral hospital, the in-patient, 30-day and 1-year mortality rates were 0.8%, 2.5%, and 16.3%, respectively.²⁴
- 5.4 The latest reported 1-year mortality after hip fracture ranged from 12.1% to 25.4% in females, and from 19.2% to 35.8% in males over a period from 2005 to 2018 in Hong Kong.⁹
- 5.5 In an interesting report specifically on the operative outcome of 114 centenarians with hip fracture (age range 100-109 years), the 1-month, 6-month, and 1-year mortalities were 8%, 25% and 37%, respectively. The median survival time was 2 years suggesting that surgery even at an extreme age may be worthwhile to maintain quality of life. Extreme age should not be a barrier to operative treatment in patients with satisfactory pre-morbid state.²⁵

(C) Definitions of Osteoporosis

1. Medical definition: The 2001 National Institute of Health Consensus Development Panel defined osteoporosis as a skeletal disorder characterised by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality. Bone quality refers to other skeletal properties that include

- bone geometry, mineralisation, microdamage, remodelling, and microarchitecture.²⁶
2. World Health Organization (WHO) Diagnostic Criteria: Based on the T-scores derived from BMD measurements at the lumbar spine or proximal femur, patients are classified as having normal BMD (T-score ≥ -1.0), osteopenia or low bone mass ($-2.5 < \text{T-score} < -1.0$) or osteoporosis (T-score ≤ -2.5).²⁷
 3. For practical purpose, if a postmenopausal woman or elderly man has sustained a low-trauma or low-energy fracture, defined by a fracture that occurs from a fall from standing height or less, a clinical diagnosis of osteoporosis can be established.

(D) Diagnosis of Osteoporosis

1. Dual-energy X-ray absorptiometry

- 1.1 Discussions on the role of dual-energy X-ray absorptiometry (DXA) in the management of osteoporosis have been provided in detail in the 2013 Guideline Section C2.¹ Important points and updates are highlighted below.
- 1.2 DXA remains the gold standard for diagnosis of osteoporosis; it is the only means to measure BMD to obtain T-scores for diagnostic classification according to the WHO diagnostic criteria.²⁷
- 1.3 Central DXA at the femoral neck, total hip and the lumbar spine are the recommended sites for measurement. The 1/3 radius may be considered as an alternative site when the lumbar spine/hip are not interpretable.²⁸
- 1.4 The International Society of Clinical Densitometry (ISCD) recommends using a uniform Caucasian female normative database [the third United States National Health and Nutrition Examination Survey (NHANES III) reference database derived from Caucasian women aged 20-29 years] for women and men of all ethnic groups to determine the T-score. To cater for the ethnic difference and local needs according to individual country/region, ISCD also stated that the “application of this recommendation may vary according to local requirements”.²⁸
- 1.5 Regional studies in Asia consistently demonstrated that the prevalence of osteoporosis would be considerably overestimated if the NHANES III database was employed as the reference to determine the T-score. A Vietnamese study showed that the prevalence of postmenopausal osteoporosis was 29% with a Vietnamese-derived T-score compared to 44% with the NHANES III database.²⁹ Similarly, a Thai study reported that the prevalence of osteoporosis in elderly women aged over 75 years was 59.2% with a Thai-derived T-score at the femoral neck compared to 80.3% using the NHANES III database, which would imply having to treat the majority of the older adult elderly population if the latter was adopted.³⁰
- 1.6 Caucasians have larger bone size than Asians and hence tend to have a higher measured areal BMD (aBMD). The use of the NHANES III as reference might produce a distorted T-score in Asian subjects. The ISCD Asia-Pacific Region Consensus in 2010 had recommended the use of Asian normative databases for diagnosing osteoporosis in Asian subjects.³¹

1.7 Vertebral fracture assessment (VFA) is the correct term to denote densitometric spine imaging performed for the purpose of detecting vertebral fractures. It can be incorporated during DXA imaging by including a high-resolution lateral image of the thoracolumbar spine. VFA is an established low-radiation method for detection of prevalent vertebral fractures.³²

1.8 *Recommendations:* OSHK continues to recommend that the determination of BMD T-score from a DXA scan should be based on a local or Asian database. The utilities of DXA in the management of osteoporosis include:

- (i) diagnosis of osteoporosis;
- (ii) assessment of fracture risk; and
- (iii) monitoring of BMD changes upon initiation, switching or cessation of anti-osteoporosis therapies.

2. High-resolution peripheral quantitative computed tomography

- 2.1 High-resolution peripheral quantitative computed tomography (HR-pQCT) is a non-invasive, low-radiation approach for imaging bone microarchitecture in vivo at peripheral skeletal sites, most commonly the distal radius and tibia.³³
- 2.2 HR-pQCT is increasingly used for the assessment of bone microarchitecture and bone strength especially in secondary osteoporosis and metabolic bone disorders under a research setting.³³ The use of HR-pQCT in clinical practice requires further studies.
- 2.3 Standardisation on the imaging techniques, terminology, analysis methodologies, and guidance on interpretation and reporting of results are being laid down to facilitate comparison of results across studies.³⁴

3. Trabecular bone score

- 3.1 Trabecular bone score (TBS) of the lumbar spine is a textural index that evaluates pixel grey-level variations in the lumbar spine image acquired by DXA. It has been validated to be an index of trabecular microarchitecture.^{35,36}
- 3.2 TBS measurement can be obtained through an advanced imaging software integrated into the DXA scanner to complement the BMD analysis. BMD measures bone quantity and TBS measures bone quality. These tests can be considered complementary in assessing fracture risk.^{35,36}
- 3.3 TBS is an independent predictor of fracture risk; it predicts hip and major osteoporotic fractures (MOFs) in men and women independent of BMD, clinical risk factors and fracture risk assessment tool (FRAX®).^{28,35-37} The adjustment of FRAX® for TBS resulted in a small but significant increase in fracture risk prediction, independent of gender and ethnicity.³⁷
- 3.4 ISCD in the latest 2023 Adult Official Positions stated that TBS should be performed only within BMI range recommended by the manufacturer and can be used regardless of sex, race/ethnicity, and prior or current osteoporosis treatment.²⁸
- 3.5 Limited data suggest that TBS is less influenced by degenerative and inflammatory spinal disease than

- BMD measured by DXA.³⁶ ISCD recommended L1-L4 vertebral levels, without exclusions, should be used for TBS measurement and to calculate TBS-adjusted FRAX[®] probabilities even in the presence of moderate degenerative changes and chronic lumbar compression fractures. It is recommended not to report TBS if there is severe structural or pathological artifact, eg, vertebra plana, laminectomy, hardware or metastatic lesions.²⁸
- 3.6 The recommended clinical applications of TBS include the following:
- (i) Addition of TBS assessment to FRAX[®] and/or BMD enhances fracture risk prediction, which may constitute a therapeutic decision tool in treatment initiation in individuals who are close to a specific pharmacologic intervention threshold.^{28,36}
 - (ii) TBS is especially useful in many metabolic disorders that involve distortion of bone microarchitecture notably type 2 diabetes (T2D), glucocorticoid-induced osteoporosis, chronic kidney disease (CKD), and rheumatoid arthritis.³⁶
 - (iii) The role of TBS in monitoring therapy is unclear such that monitoring and reporting TBS change are not recommended in routine clinical practice.²⁸ Studies have shown that TBS is not useful to monitor treatment with BPs, hormone replacement therapy (HRT) and selective estrogen receptor modulators (SERMs), whereas preliminary data suggest that TBS may provide useful adjunctive information in monitoring treatment with long-term denosumab and bone-forming agents.^{36,38}
- 4. Bone turnover markers**
- 4.1 Bone turnover markers (BTMs) are released during the bone remodelling cycle and their blood or urine levels would reflect the bone remodelling rate.
 - 4.2 Discussions on the role of biochemical BTMs in the management of osteoporosis have been provided in detail in the 2013 Guideline Section C6.¹ Salient points and updates are highlighted below.
 - 4.3 The International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine Joint Working Group on Bone Marker Standards recommended the use of serum procollagen type 1 N-propeptide (P1NP) and C-terminal telopeptide of type 1 collagen (β -CTX) in blood as standard reference markers for bone formation and bone resorption, respectively, in clinical osteoporosis studies.³⁹
 - 4.4 Measurement of BTMs is subject to considerable biological and analytical variabilities. Appropriate patient preparation, sample handling, standardisation of assays are important factors to obtain accurate measurement of BTMs.^{39,40}
 - 4.5 Currently there is no role for BTMs in the diagnosis of osteoporosis. BTMs are also not included in FRAX[®] as most patients with uncomplicated osteoporosis have BTMs in the normal reference ranges.⁴⁰
- 4.6 BTM measurements, if available, may be useful in the following scenarios:⁴⁰
- (i) A very high BTM value (3 standard deviations (SD) above mean or 1 SD above the upper reference limit) at initial assessment may indicate the presence of a secondary cause for osteoporosis.
 - (ii) Serial BTM monitoring is a useful tool to confirm adherence and effectiveness of anti-osteoporosis therapies.
 - (iii) BTM monitoring following cessation of antiresorptive therapies provide a useful guide for indication of offset of drug action and consideration of resumption of therapy.
- 4.7 The Asian-Pacific experts in a recent Consensus Statement endorsed the use of BTMs as short-term monitoring tools to help clinicians assess the responses to osteoporosis therapies and appropriately adjust treatment regimens earlier than BMD. Incorporation of BTMs in osteoporosis care programmes improves patient adherence and treatment outcomes.⁴¹
- (E) Screening for Osteoporosis**
1. Not until recently, there was no convincing evidence for the benefit of a population-based screening strategy. A case-finding approach was recommended in the 2013 Guideline Section D.¹
 2. Several large randomised population screening studies for fracture prevention have been recently published.⁴²⁻⁴⁴ Although none of the individual studies observed a statistically significant reduction in osteoporotic fractures or MOFs, a meta-analysis of the three studies involving a total of 42009 subjects did show a statistically significant and clinically relevant 5% reduction for all osteoporotic fractures, 9% reduction for MOFs, and 20% reduction for hip fractures. The numbers needed to screen to prevent one fracture were 247 and 272 for all osteoporotic fractures and hip fractures, respectively.⁴⁵
 3. A recent report from the IOF concluded that population screening for high fracture risk in primary care should strongly be considered for incorporation into the health care systems to reduce the burden of fractures, particularly hip fractures.⁴⁶
 4. Based on cost-effectiveness analysis, local experts proposed to have universal DXA screening for all men aged ≥ 70 years and women aged ≥ 65 years. Anti-osteoporosis treatment would then be offered to those with a BMD-adjusted FRAX[®] score $\geq 3\%$ for hip fracture. With such a protocol, an estimate of 5234 hip fractures would be prevented in 10 years with an annual incidence reduction of around 7%. The number needed to screen is 111 for both men and women to prevent one hip fracture. There would be an expected saving of HK\$425 million in direct medical costs, not including substantial indirect savings.⁴⁷
 5. *Recommendations:* OSHK recommends universal DXA screening for all men aged ≥ 70 years and women aged ≥ 65 years. Screening at a younger age

should be considered if additional risk factors for osteoporosis are present.

(F) Assessment of Fracture Risk

1. The clinical use of BMD measurement with DXA at the central skeletal sites and the ethnic-specific FRAX[®] in the assessment of fracture risk have been discussed in detail in the 2013 Guideline Section E.¹
2. The FRAX[®] tool was developed in 2008 to compute the ethnic-specific fracture risk of a patient in terms of a 10-year probability of hip fracture and MOF (ie, clinical spine, forearm, hip or shoulder fracture). The FRAX[®] models have been developed from population-based cohorts from Europe, North America, Asia and Australia and have now embraced 81 countries/regions.^{48,49} It is a simple and useful tool for fracture risk prediction especially for primary care physicians.
3. The clinical factors which have been incorporated into the FRAX[®] algorithm include age, body weight, prior fragility fracture, parental history of hip fracture, smoking, use of systemic glucocorticoids, alcohol consumption, secondary osteoporosis, and rheumatoid arthritis.^{48,49}
4. However, the FRAX[®] algorithm has not incorporated other well-known important clinical risk factors such as the propensity to falls, the diagnosis of T2D as an important secondary cause, and the information on the lumbar spine BMD, TBS and the hip axis length (HAL). The dose-response relationship regarding glucocorticoid, smoking, the number of prior fractures, and most importantly, the recency of fracture, have not been taken into consideration.
5. A more refined web-based algorithm, the FRAXplus[®], became recently available as a web-based tool to provide adjustments to conventional FRAX[®]-based fracture probabilities on the following aspects⁵⁰:
 - (i) recency of osteoporotic fracture;
 - (ii) the dose of oral glucocorticoids;
 - (iii) the duration of T2D;
 - (iv) the number of recent falls;
 - (v) concurrent data of lumbar spine BMD;
 - (vi) information on TBS; and
 - (vii) information on HAL.
6. The performance of the FRAX[®] in predicting fractures in Asian populations may not be as good as that in Caucasian populations. It has been shown that simple ethnic-specific clinical risk factors outperformed the ethnic-specific FRAX[®] in predicting hip fracture in a cohort of Hong Kong Chinese women.⁵¹
7. Chinese-specific fracture prediction tools have recently been developed. The Chinese Osteoporosis Screening Algorithm (COSA) for hip fracture prediction includes age, sex, weight, and history of fragility fracture.⁵² The HKOS score is a five-factor risk score which had been validated to specifically predict 10-year risk of hip fracture in Chinese patients aged 80 years or older.⁵³ Both fracture prediction tools are however not in wide

clinical use.

8. It must be stressed that all these prediction tools predict long-term fracture risk over a 10-year period but do not adequately reflect fracture risk prediction in the short term, which may be much more important in patients with recent incident fractures.
9. The concept of imminent fracture risk helps to identify certain patient populations at very high risk of fracture in the coming 1-2 years and will be discussed in the next section (Section G).

(G) Concept of Imminent Fracture Risk

1. **Recency of fracture**
 - 1.1 A previous osteoporotic fracture predicts future fracture independent of BMD.⁵⁴ However, the increase in fracture risk is not uniform after an incident fracture.
 - 1.2 In a large population-based cohort study involving 18872 men and women over 510265 person-years of follow-up, MOF occurred in 5039 individuals, of whom 1919 experienced a second MOF. The risk of the second MOF was noted to rise sharply to a very high level immediately after the first MOF, and remained at a very high level for 2 years, after which the risk was stabilised at a level still higher than that of the general population.⁵⁵ This 2-year period with exceptionally high fracture risk has been termed the period of “imminent fracture risk”. Majority of the second MOF occurred within this 2-year period.
 - 1.3 A systematic review and meta-analysis of 19 studies covering worldwide data reported that the overall incidence of imminent fracture in the first year after an osteoporotic fracture was 7.6% and the cumulative incidence in the first 2 years was 11.6%. The cumulative incidence in the first 2 years in Asia was noted to be lower than that of Europe/North America (7.3% vs 13.2%). Women had an overall slight increase in the risk of imminent fracture compared to men [hazard ratio (HR)=1.18].⁵⁶
 - 1.4 A retrospective study involving 7039 patients with fragility fractures of the hip, proximal humerus and distal radius from Hong Kong in the public sector from 2013 to 2018 concurred with these findings, showing 3.87% imminent fracture risk at 1 year, and 6.50% at 2 years with 49.5% of the second fractures occurred within 2 years of the primary fragility fracture.¹⁶
 - 1.5 The mechanisms contributing to imminent fracture risk have not been well defined. This may possibly be related to both bone-related factors (underlying osteoporosis) and fall-related factors (including those related to post-fracture care). Concomitant central nervous system diseases or use of central-acting drugs are important contributing factors.⁵⁷
2. **Independent clinical predictors of short-term fracture risk**
 - 2.1 In the epidemiologic Study of Osteoporotic Fractures involving 2499 women aged ≥65 years with osteoporosis, the incidence of fracture in the 1-year period after enrolment was 2.2% for hip fracture and 6.6% for any non-vertebral fracture.

Multivariate analyses showed that the independent predictors of hip fracture included a low total hip T-score, prior fracture after age 50 years, and risk factors for falls, whereas the independent predictors of any non-vertebral fracture included age, total hip T-score, prior falls, prior fracture after age 50 years, walking speed, Parkinson's disease or stroke, and smoking.⁵⁸

- 2.2 In the Study of Osteoporotic Fractures, women with total hip T-score < -3.5 had 2.3 times the risk of hip fracture, and women with total hip T-score in the range -3.0 to -3.5 had 1.6 times the risk of hip fracture when compared to reference group of women with total hip T-score in the range -2.5 to -3.0. The corresponding HRs for non-vertebral fractures were 1.9, and 1.6 respectively, signifying lower BMD T-scores have significant influences on the imminent risk of hip and non-vertebral fractures over 1 year.⁵⁸
- 2.3 Identification of fractured patients with a near-term fracture risk offers a very important opportunity for intervention. The preferred use of bone-forming drugs and the role of FLS will be discussed in detail in Sections M and V6, respectively.

(H) Clinical Assessment of Osteoporosis

- 1.1 A comprehensive approach to all subjects with osteoporosis is recommended (see 2013 Guideline Section F).¹
- 1.2 One of the main objectives of a detailed clinical assessment is to exclude underlying secondary causes of osteoporosis. On top of those secondary causes listed in Table 4 of the 2013 Guideline,¹ there have been additional novel secondary causes identified in recent literature, including:
 - (i) bariatric surgery notably bypass surgery⁵⁹⁻⁶¹;
 - (ii) pheochromocytoma and paraganglioma⁶²;
 - (iii) human immunodeficiency virus (HIV) infection^{63,64};
 - (iv) psychological stress^{65,66}; and
 - (v) exposure to air pollutants.^{67,68}
- 1.3 In the area of medication-related osteoporosis, local studies had extended our understanding of the effect of conventional anticoagulants (warfarin and heparin) to the newer-generation non-vitamin K dependent oral anticoagulants (NOACs) on fracture risk.
 - (i) In a propensity score-matched cohort of 8152 adults with non-valvular atrial fibrillation (NVAf) receiving anticoagulation, the use of dabigatran, a NOAC, was associated with a much lower risk of osteoporotic fractures compared with warfarin [incidence rate ratio=0.38; 95% confidence interval (95% CI): 0.22-0.66].⁶⁹
 - (ii) In a territory-wide analysis involving 23515 patients newly prescribed oral anticoagulants for atrial fibrillation, use of NOACs was associated with a lower risk for fractures than warfarin irrespective of the choice of the NOACs (apixaban, dabigatran, or rivaroxaban) over a period of 24 months.⁷⁰

(iii) In an analysis involving 15770 T2D patients with NVAf, NOAC use was associated with a lower risk of MOFs than warfarin use (HR=0.80; 95% CI: 0.64-0.99). The authors concluded that NOAC may be the preferred anticoagulant in T2D patients comorbid with atrial fibrillation from the perspective of bone health.⁷¹

- 1.4 The prevalence of secondary causes of osteoporosis have been reported in up to 30% of postmenopausal women, more than 50% of premenopausal women, and between 50% and 80% of men.⁷² Common secondary causes of osteoporosis are updated and summarised in Table 1.
- 1.5 General screening is recommended for all patients with osteoporosis, with advanced investigations reserved for premenopausal women and men aged younger than 50 years, for older patients in whom classical risk factors for osteoporosis are absent, and for all patients with the lowest bone mass (Z-score ≤ -2.0).⁷²
- 1.6 Specialty clinics should perform basic laboratory investigations including full blood counts, erythrocyte sedimentation rate (ESR), renal and liver function tests, bone profile (including alkaline phosphatase, serum calcium and phosphate), 25-hydroxyvitamin D (25OHD), thyroid function, parathyroid hormone (PTH), haemoglobin A1c (HbA1c), and a 24-hour urine test for calcium excretion. Measurement of BTMs such as serum CTX is strongly advisable if available.
- 1.7 General practitioners are advised to perform full blood counts, ESR, renal and liver functions, bone profile, 25OHD and HbA1c as the basic investigations.
- 1.8 Additional special tests such as serum protein electrophoresis, serum or urinary cortisol level, serum magnesium, coeliac serology, HIV testing may be considered if the history and initial workup are suggestive of a related disorder.

(I) Diabetes Mellitus and Bone Fragility

1. General considerations

- 1.1 Both diabetes and osteoporosis are major global health problems. The global prevalence of diabetes was estimated to be 10.5% in 2021 and is expected to rise to 12.2% by 2045.⁷³ On the other hand, 1 in 3 postmenopausal women and 1 in 5 men aged 50 years or older will have osteoporotic fractures.⁵ With an ageing global population, both diabetes and osteoporosis are becoming more prevalent especially in the older adult population.
- 1.2 Patients with diabetes who develop osteoporotic fractures will have significant additional impairment in morbidities and mortality on top of those from diabetes *per se*.
- 1.3 Osteoporosis and fractures in patients with diabetes constitute a special patient population with a much more complex pathophysiology than that of the typical postmenopausal osteoporosis.
- 1.4 Diabetic bone disease (DBD) is the term which broadly describes osteoporosis and bone fragility secondary to diabetes. DBD is emerging as a serious but previously neglected chronic complication of

Table 1. Updated summary of secondary causes of osteoporosis

Endocrine disorders	
<ul style="list-style-type: none"> • hyperthyroidism • hyperparathyroidism • Cushing syndrome • pheochromocytoma / paraganglioma 	<ul style="list-style-type: none"> • hypogonadism • hyperprolactinaemia • anorexia nervosa
Disorders of calcium metabolism	
<ul style="list-style-type: none"> • vitamin D deficiency 	<ul style="list-style-type: none"> • hypercalciuria
Gastrointestinal disorders	
<ul style="list-style-type: none"> • primary biliary cholangitis • pancreatic diseases • low acidity states, eg, gastrectomy, gastric bypass, pernicious anaemia 	<ul style="list-style-type: none"> • haemochromatosis • malabsorption syndrome, eg, inflammatory bowel disease, coeliac disease
Medications	
<ul style="list-style-type: none"> • glucocorticoids • anticonvulsants • proton pump inhibitors • aromatase inhibitors • thiazolidinediones 	<ul style="list-style-type: none"> • anticoagulants (warfarin/heparin) • depo-medroxyprogesterone • chemotherapy • immunosuppressants • excessive thyroxine replacement
Miscellaneous medical conditions	
<ul style="list-style-type: none"> • bariatric surgery • multiple myeloma • thalassemia • rheumatoid arthritis 	<ul style="list-style-type: none"> • HIV infection • exposure to air pollutants • psychological stress • stroke (hemi-osteoporosis)

diabetes.

1.5 The American Diabetes Association (ADA) devoted a new section on bone health in the latest yearly update on the Standards of Care in Diabetes—2024, specifically giving a grade A recommendation that fracture risk should be assessed in older adults with diabetes as a part of routine care in diabetes clinical practice, according to risk factors and comorbidities.⁷⁴

2. Epidemiology of fractures in diabetes

2.1 The risks of vertebral and hip fractures are all elevated in people with type 1 diabetes (T1D) and T2D compared with the general population. The risk is more pronounced in T1D than T2D.^{72,75,76}

2.2 A meta-analysis including 138645 subjects with fractures reported a significant increase in the pooled relative risk (RR) of any fracture of 3.16, hip fractures of 3.78, and vertebral fractures of 2.88 in T1D subjects compared to subjects without diabetes. Women and men with T1D had 4 times and 2 times higher risk of any fractures, respectively, compared with people without diabetes.⁷⁷

2.3 A United Kingdom cohort study showed that the increase in risk of fractures in T1D began in childhood and persisted across the lifespan.⁷⁸

2.4 An updated meta-analysis reporting hip fracture data from 17571738 participants and non-vertebral fracture data from 2978487 participants showed that there was a significant increase in the risks of hip fracture and non-vertebral fracture in both T1D and T2D [hip fracture (RR=4.93 in T1D; RR=1.33 in T2D); non-vertebral fractures (RR=1.92 in T1D; RR 1.19 in T2D)]. Overall, the risk of hip fracture was significantly higher in T1D compared to T2D whereas there was no significant difference between T1D and T2D in the risk of non-vertebral

fractures.⁷⁹

2.5 A local cohort of 5469 Chinese T2D subjects with a median follow-up of 7.5 years concurred that T2D subjects had a significantly higher incidence of hip fracture (3.01 per 1000 person-years) than non-diabetic subjects (1.36 per 1000 person-years).⁸⁰ A territory-wide cohort study from the Hong Kong Diabetes Database of 83282 Chinese T2D subjects aged 60 years or older showed that hip fracture was common in T2D, with an incidence of 5.44 per 1000 person-years upon a median follow-up of 6.8 years.⁸⁰

2.6 BMD was found to be discordant in T1D and T2D. When compared to people without diabetes, BMD was lower in T1D subjects⁸¹ but BMD was comparable to or even higher in T2D subjects^{81,82}; the phenomenon also known as the ‘diabetic paradox of bone fragility’ suggests that bone fragility in diabetes especially T2D cannot be explained by BMD alone.

3. Diabetes-specific risk factors for fracture

3.1 Bone fragility in patients with T1D is multifactorial. Insulin deficiency and lower level of insulin-like growth factor-1 during childhood and adolescence will hinder the attainment of peak bone mass.⁷² Longstanding disease will lead to complications that will affect the skeleton in a similar way as T2D.

3.2 Certain diabetes-specific parameters have been identified to be related to an increase in fracture risk in people with diabetes especially T2D, ie, the duration of the disease, the level of glycaemic control, and the presence of microvascular complications.^{72,74-76}

3.3 Fracture risk in T2D appears to be related to the duration of diabetes. Fracture risk was not significantly elevated in T2D until after a duration

of more than 5 years.⁸³ In FRAX[®]-adjusted analyses, only duration longer than 10 years was associated with a higher risk for MOFs.⁸⁴ The current FRAX[®] tool underestimates fracture risk in T2D subjects especially in those with long duration of the disease (>10 years).⁸⁴

- 3.4 Glycaemic control is highly relevant to fracture risk in diabetes. For T1D, a 3.5-fold increase in risk for two or more fractures was noted in subjects in the highest tertile of HbA1c (≥7.9%) compared with the lowest tertile (≤7.17%).⁸⁵ For T2D, there was a 25% increase in risk of hip fracture observed in subjects with HbA1c ≥8.0%, as compared to reference group with HbA1c <7.0% both in the Taiwan Diabetes Cohort Study⁸⁶ and the Hong Kong Diabetes Database cohort.⁸⁰ Significant linear trend of increasing HbA1c levels with increasing risk of hip fracture was also observed in the Taiwan Cohort such that when HbA1c exceeded 9%, the risk of hip fractures increased to >50% compared to subjects with good glycaemic control.⁸⁶
- 3.5 Besides the overall glycaemic control, glycaemic stability has also been implicated in the fracture risk. Hypoglycaemia has been reported to be associated with increased fracture risk in both T1D and T2D.⁸⁷⁻⁸⁹ The occurrence of falls probably explains most of the association. In the Hong Kong Diabetes Database cohort, HbA1c variability, an index to reflect the stability of blood glucose levels, positively predicted the occurrence of hip fractures in T2D across varying degrees of glycaemic control,⁸⁰ highlighting the importance of minimising glucose variability in addition to bringing HbA1c to target.
- 3.6 The presence of diabetic microvascular complications is associated with increased fracture risk in both T1D and T2D.^{90,91} Whereas neuropathy and retinopathy may contribute to increased fracture risk via gait disturbance and propensity to falls,⁷⁵ chronic hyperglycaemia favours non-enzymatic reactions between proteins and glucose producing advanced glycation end products (AGEs) which might lead to bone microstructural alterations.^{72,75,92}

4. Anti-diabetic medications and fracture

- 4.1 There are essentially no prospective clinical trials evaluating the effect of anti-diabetic drugs on fracture risk in diabetic subjects. Observational studies and reports of adverse effects in clinical trials of anti-diabetic drugs provide some insights on this aspect.
- 4.2 The effects of different classes of anti-diabetic drugs on BMD and fracture risk^{76,93,94} are summarised in Table 2.
- 4.3 Within the class of sodium-glucose cotransporter-2 (SGLT-2) inhibitors, canagliflozin was associated with an increase in fracture incidence compared with placebo (15.4 vs 11.9 per 1000 patient-years; HR=1.26; 95% CI: 1.04-1.52) in the randomised controlled CANVAS Program.⁹⁵ Recent meta-analyses pooling data for all SGLT-2 inhibitors however did not show an increase in fracture risk.^{96,97} Further studies are required to clarify if the increase in risk is specific to canagliflozin.

Table 2. Summary on the effects of common anti-diabetic medications on bone mineral density (BMD) and risk of fracture in people with diabetes^{76,93,94}

Anti-diabetic medications	BMD	Fracture risk
Insulin	→	↑
Sulfonylureas	NA	↑ / → / ↓
Metformin	→ / ↑	↓ / →
Pioglitazone	↓ / →	↑ / →
SGLT-2 inhibitors	→	→ / ↑
DPP-4 inhibitors	NA	↓ / →
GLP-1 receptor agonists	↑ / →	→

Abbreviations: ↑ = increase; ↓ = decrease; → = unchanged; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NA = not available; SGLT-2 = sodium-glucose cotransporter-2

- 4.4 Insulin, sulfonylurea, pioglitazone and canagliflozin may be associated with increased fracture risk and they should be used with caution in diabetic patients at high risk of fracture. Nevertheless, the selection of an anti-diabetic drug for a diabetic subject should primarily be based on its glucose-lowering effect or its prognostic benefits in certain subgroups of diabetic patients according to the latest clinical practice guidelines on diabetes management.^{98,99}
- 4.5 For diabetic patients at elevated fracture risk, the ADA recommended glycaemic goals be individualised, prioritising glucose-lowering medications with a proven safety profile for bones, and prioritising use of medications that are associated with low risk for hypoglycaemia to reduce the risk of falls and fractures.⁷⁴
- 4.6 Diabetic patients should always be ensured to have sufficient calcium and vitamin D intake, either from diet or from supplements if necessary.⁷⁴

5. Pathophysiological mechanisms for bone fragility in diabetic bone disease

- 5.1 The pathophysiological mechanisms leading to DBD are yet to be fully elucidated. They are very complex and multifactorial. A detailed discussion on each potential mechanism is beyond the scope of the current clinical Guideline.
- 5.2 Low bone turnover is characteristic of diabetes with low levels of bone formation and bone resorption in biochemical assays and histomorphometric studies.¹⁰⁰ Decrease in insulin signalling, increase in oxidative stress, decrease in Wnt signalling, accumulation of AGEs, chronic inflammation, and microvascular impairment may all contribute to increased fracture risk in diabetes.^{72,75,76,91,92,100}

6. Fracture risk assessment in diabetes

- 6.1 Comprehensive clinical assessment including the specific diabetes-related risk factors is mandatory for fracture risk assessment in diabetes, ie, disease duration >5 years, unsatisfactory glycaemic control (HbA1c >7%), the presence of microvascular complications, and the use of anti-diabetic drugs associated with increased fracture risk (insulin, sulfonylurea, pioglitazone and canagliflozin).⁷⁶
- 6.2 T1D is a risk factor that has already been

incorporated into the FRAX® algorithm as a cause of secondary osteoporosis for patients older than 40 years. Clinical use of FRAX® without BMD was reported to be a useful tool in identifying adults with T1D at risk for MOFs.¹⁰¹

- 6.3 The FRAX® algorithm however does not currently include T2D as a risk factor for fracture, and the FRAX® score underestimates the fracture risk in subjects with T2D.^{102,103} It has been estimated that the fracture risk in T2D computed with FRAX® is equivalent to adding 10 years of age.¹⁰³
- 6.4 T2D is associated with higher BMD but paradoxically with increased fracture risk. Data have clearly confirmed that BMD systematically underestimates fracture risk in T2D.¹⁰³ At the same risk of hip fracture, the BMD T-score of a T2D woman was reported to be approximately 0.5 units higher than the BMD T-score of a woman without diabetes, such that a correction factor of '-0.5' to the BMD T-score has been proposed to more accurately predict the fracture risk in T2D.¹⁰³
- 6.5 TBS is an index of microarchitecture (see Section D3). TBS has been shown to be lower among individuals with T2D than those without diabetes in the Asian population.¹⁰⁴ TBS adjustment to FRAX® (TBS-adjusted FRAX®) will capture some of the excess fracture risk associated with T2D¹⁰⁵ and is currently available as an optional input variable in FRAX®.⁴⁹
- 6.6 In the absence of T2D as an independent input variable in FRAX®, four methods for the adjustment of the FRAX® score for T2D are proposed.^{74,76,106} Each approach represented a significant improvement in the performance of FRAX® by reducing, or in some cases, eliminating the effect of diabetes on incident MOF and hip fracture.¹⁰⁶ These methods include:
 - (i) TBS-adjusted FRAX®;
 - (ii) using "rheumatoid arthritis" as a proxy for diabetes;
 - (iii) reducing the femoral neck BMD T-score by 0.5; and
 - (iv) increasing the age input by 10 years.
- 6.7 The refined algorithm, FRAXplus®, also provide adjustment to conventional FRAX®-based fracture probabilities for the duration of diabetes (see Section F5).⁵⁰
- 7. Pharmacological management for bone fragility in diabetes**
- 7.1 The indications for osteoporosis treatment should generally follow those of non-diabetic subjects (see Section K) but the BMD T-score or the FRAX® score may need to be adjusted in T2D as suggested in Section I6.6 although such proposed adjustments require further validation in the Asian populations. ADA recommended anti-osteoporosis drugs to be considered for people with diabetes who have low BMD (T-score \leq -2.0) or have experienced fragility fractures.⁷⁴
- 7.2 No randomised controlled trials (RCTs) have specifically evaluated the anti-fracture efficacy of the different anti-osteoporosis therapies in diabetes.
- 7.3 Post-hoc analyses of RCTs suggested that diabetes

did not impact treatment efficacy with regard to increase in BMD, fracture risk reductions, and reduction in levels of BTMs with antiresorptive drugs (oral BPs, raloxifene and denosumab).^{107,108}

- 7.4 With regard to bone-forming therapies, subgroup analysis from a large observational study of 291 subjects with T2D and 3751 non-diabetic subjects showed comparable benefits in BMD and non-vertebral fractures with teriparatide therapy.¹⁰⁹ There have been no studies examining effect of romosozumab in patients with diabetes.

(J) Non-Pharmacological Management of Osteoporosis

1. Lifestyle measures (diet and physical activities) play critical roles in building and maintaining good bone health for people at every life stage and should always be recommended to the general population in the prevention of osteoporosis. Lifestyle measures also constitute the basic non-pharmacological management for patients with osteoporosis.
2. Detailed discussions on the role of lifestyle measures on osteoporosis management were provided in the 2013 Guideline Sections G1 and G6.¹ Areas of special interests are highlighted below.
- 3. Physical activities and exercise**
- 3.1 Updated meta-analyses demonstrated that both weight-bearing and resistance exercises had favourable effects on BMD at all skeletal sites.^{110,111}
- 3.2 Tai-chi, a traditional Chinese martial art, is strongly recommended for our local older adults for its beneficial effects on balance and muscle strength, fall prevention, cognitive functions, and general health and fitness. Importantly no published studies have found Tai-chi worsening a condition.¹¹²
- 4. Calcium and vitamin D**
- 4.1 The importance of calcium and vitamin D in the management of osteoporosis have been described in detail in the 2013 Guideline Sections G2 and G3.¹ Important points and recent updated information are provided below.
- 4.2 According to the 2014 First Hong Kong Total Diet Study conducted by the Centre for Food Safety, the average dietary calcium intake of local people remained low at around 410-440 mg per day. The main dietary sources of calcium intake were vegetables and their products contributing to 28% of the dietary intake. Dairy products only contributed to 18% of the intake.¹¹³
- 4.3 There have been worries on the potential cardiovascular adverse effects with calcium supplementation¹¹⁴ but the causative role of high level of calcium intake in the development of cardiovascular disease has never been established. An updated meta-analysis concluded that calcium intake within tolerable upper intake levels (2000-2500 mg/day) was not associated with cardiovascular risk in generally healthy adults.¹¹⁵
- 4.4 Vitamin D is essential for skeletal health and bone mineralisation by increasing intestinal calcium absorption, reducing secondary hyperparathyroidism, and decreasing bone

- turnover. It also plays an important role in neuromuscular function and fall prevention.¹¹⁶
- 4.5 Optimal serum 25OHD concentration should be ≥ 75 nmol/L (30 ng/mL) to prevent secondary hyperparathyroidism and bone loss.¹¹⁷ This level is also recommended by the US Endocrine Society as the level that denotes vitamin D adequacy.¹¹⁸
 - 4.6 Earlier study in the 2000s had shown a high prevalence (62.8%) of vitamin D inadequacy (25OHD level < 75 nmol/L) in local community-dwelling adults older than 50 years of age.¹¹⁹ A more recent local study reported that the prevalence of vitamin D deficiency (25OHD level ≤ 50 nmol/L) and inadequacy (50 nmol/L $<$ 25OHD level ≤ 75 nmol/L) remained high at 43.8% and 46.3%, respectively, among 5276 participants aged 20 years or older in the HKOS.¹²⁰
 - 4.7 Previous meta-analyses showed conflicting results on whether calcium and/or vitamin D supplementation would reduce the risk of fractures. A recent systematic umbrella review of 31 meta-analyses of controlled trials concluded that calcium/vitamin D reduced the risk of hip and any fractures, possibly driven by findings from institutionalised individuals.¹²¹
 - 4.8 For community-dwelling populations, several recently published mega-randomised controlled trials on vitamin D supplementation failed to demonstrate a reduction in fracture incidence in subjects not selected for vitamin D deficiency, low bone mass, or osteoporosis.¹²²⁻¹²⁴
 - 4.9 *Recommendations on vitamin D and calcium intake*
 - (i) A daily elemental calcium intake of 1000-1200 mg should be recommended for osteoporosis subjects if there are no contraindications. The total amount of calcium intake should not exceed 2000 mg daily to avoid harmful effects notably renal stones.
 - (ii) Individuals should meet their daily calcium requirement preferably from dietary source. Calcium supplementation is indicated for those with low dietary calcium intake such as patients with lactose intolerance.
 - (iii) Vitamin D supplementation should always be considered unless patients have documented serum 25OHD level ≥ 75 nmol/L without supplement. Repeated testing in the winter months is recommended to ensure vitamin D adequacy throughout the whole year.
 - (iv) A vitamin D intake of at least 800 IU daily is recommended; a higher dose being required for certain subgroups who are at risk of vitamin D inadequacy such as those with limited sun exposure (institutionalised, homebound) and malabsorption, and for certain ethnic populations known to be at high risk for vitamin D deficiency (Middle East and South Asia).
 - (v) Active vitamin D analogues are not recommended for ordinary postmenopausal women because these analogues have a relatively low margin of safety with potential risks of hypercalcaemia and hypercalciuria.¹²⁵
 5. **Other dietary nutrients related to bone health**
 - 5.1 In addition to calcium and vitamin D, the roles of other nutrients such as magnesium, potassium, vitamin K and vitamin C have been implicated in bone health.¹²⁶ Nevertheless, these nutrients are required in small amounts and should be readily sufficient from a well-balanced diet. Supplementation with these nutrients is not usually necessary unless frank deficiency has been documented.
 - 5.2 Adequate dietary protein intake is necessary for optimal growth and maintenance of structure and function of the musculoskeletal system.¹²⁷ The controversies on whether high dietary protein intake with associated acid loading would exert deleterious effects on bone and increase in fracture risk have essentially been resolved.¹²⁸
 - 5.3 A recent expert consensus paper endorsed by the ESCEO (European Society for Clinical and Economical Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases) and IOF concluded that there were no adverse effects from higher protein intake on bone, with even benefits in attenuating age-related bone loss and reducing hip fracture risk, provided calcium intake is adequate. Insufficient dietary protein intake may be a much more severe problem than protein excess.¹²⁸
 - 5.4 The ESCEO recommends optimal dietary protein intake of 1.0-1.2 g/kg body weight per day with at least 20-25 g of high-quality protein at each main meal.¹¹⁶
 - 5.5 Some forms of dietary restriction for weight loss have gained popularity recently, such as intermittent fasting, ketogenic diet, vegetarian diet, vegan diet, and the very low-energy diets, especially in the younger generations. Clinicians should be aware of the potential adverse effects of these diets on bone health.^{129,130}
 - 5.6 Data on the association between coffee consumption and the risk of fractures are inconclusive. In one meta-analysis involving 253514 participants with 12939 fracture cases, coffee consumption was associated with an increased risk of fractures in women in a dose-dependent fashion. Consumption of 2 and 8 cups per day was associated with a 2% and 54% higher risk of fractures, respectively, than those who did not drink coffee. Interestingly, the risk of fractures was 24% lower in men with the highest level of coffee consumption.¹³¹
 - 5.7 The effect of coffee consumption on bone health could be ethnic-specific. Coffee consumption was associated with higher BMD in Asian populations, including Hong Kong¹³², Korea¹³³ and Taiwan¹³⁴.

(K) Pharmacological Treatment of Osteoporosis

1. General considerations

- 1.1 There were only few changes in the available options of anti-osteoporosis drugs in Hong Kong in the past 10 years. The updated medication list is shown in Table 3.

Table 3. Available pharmacological treatment options for postmenopausal osteoporosis in Hong Kong: Indications and anti-fracture efficacy of individual anti-osteoporosis drug (evidence from randomised placebo-controlled treatment trials)

	Approved indications		Documented fracture reduction		
	Prevention	Treatment	Vertebral	Non-vertebral	Hip
Antiresorptive drugs					
HRT	+	-	+	+	+
Raloxifene	+	+	+	-	-
Calcitonin	-	+	+	-	-
Alendronate	+	+	+	+	+
Risedronate	+	+	+	+	+
Ibandronate	+	+	+	+ ^a	-
Zoledronic acid	+	+	+	+	+
Denosumab	+	+	+	+	+
Bone-forming drugs					
Teriparatide	-	+	+	+	-
Romosozumab	-	+	+	+ ^b	+ ^b

Abbreviation: HRT = hormone replacement therapy

^a post-hoc analysis in high-risk subgroups

^b randomised controlled trial vs alendronate

- 1.2 Strontium ranelate was no longer available since August 2017 as the manufacturer ceased marketing and supply of this drug following its safety concerns about its association with an increased incidence of cardiovascular events and venous thromboembolism.¹³⁵
- 1.3 Detailed discussions on the antiresorptive drugs, ie, HRT, raloxifene, calcitonin, oral or iv BPs, and denosumab have been provided in the 2013 Guideline Section H.¹ Important points and updated information are provided below.
- 1.3.1 The benefits and safety of HRT in young postmenopausal women or women in their early years of post-menopause had been consolidated¹³⁶ such that many updated international guidelines supported the use of HRT in young postmenopausal women in the management of osteoporosis.^{2-4,137}
- 1.3.2 Raloxifene is the only SERM available in Hong Kong for treatment of postmenopausal osteoporosis. It is a non-hormonal antiresorptive drug that suppresses bone turnover to premenopausal level. Safety data were available up to 8 years in a report published in 2005,¹³⁸ after which no additional long-term safety signals are evident.
- 1.3.3 Calcitonin was currently approved by the US Food & Drug Administration (FDA) for treatment of osteoporosis only in postmenopausal women who are at least 5 years post-menopause. Safety analysis by the European Medicines Agency showed that long-term use of calcitonin was associated with a small increase in risk of various types of cancers notably for the nasal formulation (2.4% absolute incidence) such that the nasal spray formulation was withdrawn from the European market whereas the parenteral formulations are limited to be used with the smallest effective dose for the shortest possible duration under three clinical conditions: prevention of acute bone loss due to sudden immobilisation, Paget’s disease, and hypercalcaemia of malignancy.¹³⁹
- 1.3.4 Oral BPs are currently the most common class of anti-osteoporosis medication prescribed from the public sector with alendronate being the first-line medication for use in patients with prior osteoporotic fractures as endorsed by the Hospital Authority Drug Formulary.¹⁴⁰
- 1.3.5 Ibandronate remains a less favourable BP option in view of its lack of data on risk reduction for hip fracture.¹
- 1.3.6 Zoledronic acid remains the only anti-osteoporosis drug which has demonstrated survival benefit in RCT in patients with recent hip fractures.¹⁴¹ Long-term published data of zoledronic acid are available for up to 9 years. In this randomised second extension study to the HORIZON-Pivotal Fracture Trial, there were no adjudicated cases of osteonecrosis of the jaw (ONJ) nor atypical femur fracture (AFF) in the 95 women who were randomised to continue zoledronic acid for a total of 9 years of therapy.¹⁴²
- 1.3.7 Denosumab, which was a new drug at the time of publication of the 2013 Guideline, has now been in the market for more than 10 years. The FREEDOM Extension study had documented its anti-fracture efficacy and safety for long-term use up to 10 years.¹⁴³ However, there have been reports that discontinuation of denosumab was associated with rebound bone loss and a potential increase in the incidence of vertebral fractures.¹⁴⁴ A detailed discussion on the issue of discontinuation of denosumab will be provided in a separate section (see Section R4).
- 1.3.8 Clinicians should always observe the contraindications for the individual antiresorptive drug before contemplating treatment.¹ Severe and potentially fatal hypocalcaemia may develop in patients with pre-existing vitamin D deficiency if potent

- parenteral antiresorptive drugs (zoledronic acid or denosumab) are administered. Vitamin D deficiency must be corrected before the administration of potent antiresorptive drugs.
- 1.3.9 In a recent published retrospective cohort study involving 1523 dialysis-dependent women (mean age 74.5 years) being initiated denosumab treatment, compared with 1281 dialysis-dependent women (mean age 73.8 years) being initiated oral BP treatment, the 12-week weighted cumulative incidence of severe hypocalcaemia (serum calcium level <1.88 mmol/L) was 41.1% with denosumab and 2.0% with oral BPs (RR=20.7; 95% CI: 13.2-41.2). The 12-week weighted cumulative incidence of very severe hypocalcaemia (serum calcium level <1.63 mmol/L) was also increased with denosumab (10.9%) compared to oral BPs (0.4%) (RR=26.4; 95% CI: 9.7-449.5).¹⁴⁵
- 1.3.10 The FDA issued a boxed warning in January 2024, stating denosumab increases the risk of severe hypocalcaemia for adults with advanced CKD, particularly for those on dialysis.¹⁴⁶
- 1.3.11 Given the complexity of diagnosing the underlying bone pathophysiology in patients with advanced CKD, OSHK strongly recommends against starting denosumab treatment in patients with CKD stage 5 or below. Oral BPs are also contraindicated in patients with estimated glomerular filtration rate (eGFR) <30 mL/min.
- 1.4 Regarding bone-forming therapy, the available options have been extended following the registration of romosozumab in Hong Kong in July 2020 (Table 3). This new bone-forming drug will be discussed in detail in Section K2. Other updates on bone-forming therapy are highlighted below.
- 1.4.1 Teriparatide previously carried a boxed warning regarding the potential risk of osteosarcoma at its initial approval by FDA in 2002 such that the duration of treatment should be limited to 24 months in a patient's lifetime. This boxed warning was removed by FDA in November 2020 following a 15-year post-marketing surveillance study in which the observed incidence of osteosarcoma was not different from the background incidence.¹⁴⁷ The restriction to the 24-month lifetime use was hence lifted but the revised teriparatide label stated that use for more than 2 years should only be considered if a patient remains at or has returned to having a high risk for fracture.¹⁴⁸
- 1.4.2 Clinicians can be reassured on the increase in cortical porosity and early decrease in hip BMD associated with teriparatide treatment especially in patients previously treated with BPs. Literature review consistently showed that teriparatide increased cortical thickness and bone formation throughout the whole skeleton, including the hip, as demonstrated by bone scan and positron emission tomographic studies. The majority of the porosity was located at the endocortex such that finite element analyses demonstrated there was either no decrease or an increase in hip strength during teriparatide treatment.^{149,150}
- 1.4.3 Another novel bone-forming drug, abaloparatide, a parathyroid hormone related-peptide analogue,¹⁵¹ was approved by the FDA in April 2017 for the treatment of postmenopausal women with osteoporosis at high risk of fracture. However, this drug has not been registered in Hong Kong.
- 2. Romosozumab**
- 2.1 Romosozumab is a novel bone-forming drug approved by the FDA in April 2019 for treatment of postmenopausal women with osteoporosis at high risk of fracture.
- 2.2 It is a humanised immunoglobulin G2 monoclonal antibody against the glycoprotein, sclerostin, which is secreted by osteocytes to inhibit the Wnt signalling pathway involved in the process of bone formation.¹⁵²
- 2.3 In phase 1 and 2 clinical studies, romosozumab demonstrated prompt, transitory increases in markers of bone formation and moderate, sustained decreases in markers of bone resorption, implying that it has intrinsic antiresorptive property on top of its bone-forming property.^{153,154}
- 2.4 In a phase 2 study, romosozumab administered at a dose of 210 mg subcutaneous (sc) monthly resulted in mean increases in BMD of 11.3% at the lumbar spine, 4.1% at the total hip, and 3.7% at the femoral neck at 12 months. These magnitudes of increase in BMDs were significantly greater than those observed in the two open-label active comparator groups of alendronate and teriparatide.¹⁵⁴ The divergent effects on bone formation and bone resorption with romosozumab are believed to produce a strongly positive balance in bone turnover, accounting for the rapid and large increases in BMD.¹⁵⁴
- 2.5 Elimination of romosozumab occurs via proteolysis by the liver or reticuloendothelial system.¹⁵² Renal elimination of romosozumab is minimal and no dose adjustment is required in patients with renal impairment.¹⁵⁵
- 2.6 Clinical efficacy
- 2.6.1 In the phase 3 FRAME study, 7180 postmenopausal women (mean age 71 years) with high fracture risk were randomised to receive sc romosozumab 210 mg or placebo injection monthly for 12 months followed by an open-label phase in which both groups received sc denosumab injection 60 mg every 6 months for 12 months. The romosozumab-to-denosumab group achieved a significant improvement in BMD at the spine (13.1% vs 0.4% at 12 months and 16.6% vs 5.0% at 24 months; P<0.001), femoral neck (5.5% vs 0.3% at 12 months and 7.3% vs 2.3% at 24 months; P<0.001), and total hip (6.0% vs 0.3% at 12 months and 8.5% vs 3.2% at 24 months; P<0.001) when compared to the placebo-to-denosumab group. Significant 73% and 75% RR reductions in new vertebral fractures

- were observed in the romosozumab-to-denosumab group at 12 and 24 months, respectively. Romosozumab also significantly reduced the risk of all clinical fractures by 36% at 12 months. The 25% risk reduction in non-vertebral fracture at 12 months however did not reach statistical significance ($P=0.096$).¹⁵⁶
- 2.6.2 A pre-specified subgroup analysis of the FRAME study revealed that the risk reduction in non-vertebral fractures differed according to the location of the study sites. Latin Americans, which accounted for 43% of the entire study population, were noted to have a much lower background risk of non-vertebral fracture such that there was no effect of romosozumab therapy on the risk of non-vertebral fracture. In a post-hoc analysis after excluding the Latin American study sites, there was a significant 42% risk reduction of non-vertebral fractures at 12 months.¹⁵⁶
- 2.6.3 When the magnitude of BMD gain associated with romosozumab in the FRAME study was compared to that of denosumab in the FREEDOM and FREEDOM Extension study, 1 year of romosozumab treatment produced BMD gains at the spine and total hip comparable to those achieved with 4.5 and 3 years of continuous denosumab treatment, respectively. The 2-year gain in BMD (1 year of romosozumab followed by 1 year of denosumab therapy) approximated the effect of 7 years of continuous denosumab treatment at both the spine and total hip.¹⁵⁷ This sequence of romosozumab followed by denosumab provides an excellent opportunity for rapid bone mass accrual in high-risk patients.
- 2.6.4 Histomorphometry and microtomography (μ CT) analysis of transiliac bone biopsies from a subset of 107 patients from the FRAME study showed that 12 months of romosozumab treatment resulted in an increase in trabecular thickness and improved trabecular connectivity.¹⁵⁸
- 2.6.5 Head-to-head comparison study of romosozumab and alendronate was performed in 4093 very high-risk women (mean age 74.3 years) in the ARCH Study in which romosozumab 210 mg sc monthly was compared to oral alendronate 70 mg weekly for 12 months, followed by open-label alendronate therapy in both treatment groups for up to an additional 2 years. Concomitant with significant increases in BMD at both the lumbar spine (13.7% vs 5.0%) and the total hip (6.2% vs 2.8%) after 12 months of romosozumab compared to alendronate treatment, there was a significant 37% RR reduction in vertebral fracture compared to alendronate at 12 months (4.0% vs 6.1%; $P=0.003$). Clinical fracture risk was also reduced by 28% (HR=0.72; 95% CI: 0.54-0.96). The 26% reduction in non-vertebral fracture risk at 12 months however did not reach statistical significance ($P=0.06$). In the final primary analysis, clinical fracture risk was reduced by 27% ($P<0.001$), non-vertebral fracture risk by 19% ($P=0.04$), and hip fracture risk by 38% ($P=0.02$) in the romosozumab-to-alendronate group compared to alendronate alone.¹⁵⁹
- 2.6.6 A sub-analysis of the ARCH study involving 275 patients from Hong Kong, Korea, and Taiwan demonstrated significant increase of BMD at all sites in the romosozumab group as compared to the alendronate group in the first 12 months of treatment. The significant gain in BMD was maintained at 24 months after switching to alendronate in the second year for the romosozumab-to-alendronate group. Although the study was not adequately powered to determine the antifracture efficacy between the two groups, there were numerical reductions in the incidences of vertebral, clinical, non-vertebral and hip fractures in the romosozumab-to-alendronate group.¹⁶⁰
- 2.6.7 Head-to-head comparison of romosozumab and teriparatide was performed in the open-label STRUCTURE study in which 436 older adult postmenopausal osteoporotic women (mean age 71.5 years) previously treated with oral BP for at least 3 years were randomised to receive monthly romosozumab injection or daily teriparatide injection for 12 months. The mean percentage changes from baseline in aBMD at the total hip, femoral neck, and lumbar spine were all significantly greater in the romosozumab than the teriparatide group at both 6 and 12 months. Specifically at the total hip, there was a significant treatment difference of +3.2% change in aBMD in favour of the romosozumab group (2.6% vs -0.6%; $P<0.001$) at 12 months.¹⁶¹ QCT at the hip showed that romosozumab treatment resulted in significant gains in volumetric BMD and bone mineral content (BMC) of both cortical and trabecular compartments of the hip as compared to teriparatide. Teriparatide treatment resulted in an early drop in volumetric BMC of the cortical component of the hip at both 6 and 12 months. The romosozumab group also had a greater gain in hip strength as estimated by finite element analysis than the teriparatide group at 6 months (2.1% vs -1.0%; $P<0.001$) and 12 months (2.5% vs -0.7%; $P<0.0001$), respectively.¹⁶¹
- 2.7 Preparation: Romosozumab is administered as a dose of 210 mg monthly sc injection for a recommended duration of 12 months. Each dose is delivered by two separate prefilled syringes each containing 105 mg of romosozumab.
- 2.8 Adverse effects: Mild local injection site reaction was reported in 4.4-8.0% of romosozumab-treated patients.^{156,159,161} For the serious adverse events, two cases of ONJ and one case of AFF were reported in romosozumab-treated patients in the FRAME study.¹⁵⁶ In the ARCH study, there were more adjudicated serious cardiovascular events (2.5%) in the romosozumab group than the alendronate group (1.9%) at 12 months.¹⁵⁹ In contrast, there

was no difference in the rate of cardiovascular events between the romosozumab and placebo groups (1.2% vs 1.1%) in the FRAME study.¹⁵⁶ The underlying mechanism for the possible adverse cardiovascular effect of romosozumab is yet to be determined.

- 2.9 Contraindications: Romosozumab is contraindicated in patients with history of myocardial infarction or stroke, hypocalcaemia, or hypersensitivity to romosozumab.¹⁵⁵
- 2.10 In a review article on the cardiovascular safety of romosozumab, preclinical and genetic studies did not identify any potential mechanisms for an increase in cardiovascular risk with sclerostin inhibition. The authors concluded that romosozumab should be considered for the treatment of patients at high risk of fracture after careful evaluation of a balance between benefits and risks.¹⁶²
- 2.11 Use of romosozumab in CKD
 - (i) A post-hoc analysis of the FRAME and ARCH studies showed that the anti-fracture efficacy in patients with mild to moderate CKD was maintained and there were no particular safety issues in this group of 2353 patients with eGFR between 30-60 mL/min.¹⁶³
 - (ii) Safety data for patients with severe renal impairment (eGFR <30 mL/min) or receiving dialysis are limited. 29 patients with severe CKD (eGFR <30 mL/min) in the FRAME and ARCH studies were not included in the above post-hoc analysis due to the small sample size. It was reassuring that no episode of hypocalcaemia was reported in this subgroup of high-risk patients. There were also no positively adjudicated cardiovascular events in the 11 patients with eGFR <30 mL/min in the ARCH study.¹⁶³ Nonetheless, these patients are at greater risk of developing hypocalcaemia and calcium levels must be carefully monitored.¹⁵⁵
- 2.12 Completion of the course of romosozumab therapy needs to be followed by sequential antiresorptive treatment preferably denosumab or oral/iv BPs.
- 2.13 *Recommendations:* Romosozumab is recommended as one of the first-line drugs for treatment of postmenopausal women at very high risk of fracture (see Section M).

(L) Indications of Osteoporosis Treatment

1. In principle, all postmenopausal women at high risk of fracture should be considered for definitive anti-osteoporosis drug treatment.
2. Studies have not provided unequivocal evidences on the treatment threshold based on the FRAX[®] score and the cost-effectiveness of different treatment strategies applicable to our local population.¹⁶⁴⁻¹⁶⁶ Hence, the 2013 OSHK Guideline recommendations on the indications of treatment remain unchanged,¹ which include:
 - (i) prior low-energy hip or vertebral fractures;
 - (ii) BMD T-score \leq -2.5 at the lumbar spine or proximal femur in a DXA scan; and

- (iii) low bone mass (T-score between -1 and -2.5) and one of following:
 - (a) 10-year probability of any MOF of \geq 20% as computed by the ethnic-specific FRAX[®] algorithm; or
 - (b) 10-year probability of hip fracture of \geq 3% as computed by the ethnic-specific FRAX[®] algorithm.
3. All treatment decisions should require individualised clinical judgement, taking into consideration of individual patient factors including patient preference, affordability, comorbidities, quality of life, and life expectancy.

(M) The 2024 OSHK Osteoporosis Management Algorithm

The 2013 OSHK Management Guideline had already adopted a treatment approach based on the level of risk of the individual patient.¹ Ample evidence has accumulated in the past decade to support this management approach. Coupled with the advent of new and effective bone-forming drug, a new OSHK Osteoporosis Management Algorithm has been developed.

1. **Superiority of bone-forming over antiresorptive drugs**
 - 1.1 Head-to-head comparison study of sc teriparatide and oral risedronate treatment in 1360 postmenopausal women at very high fracture risk (at least 2 moderate or 1 severe vertebral fracture and a BMD T-score \leq -1.5) in the VERO Study showed that treatment with teriparatide was associated with a significant 56% reduction in the incidence of radiographic vertebral fractures and 52% reduction in all clinical fractures compared with risedronate at 24 months. A significant 48% reduction of radiographic vertebral fractures was already obvious at 12 months. The numbers needed to treat with teriparatide for 24 months to prevent one radiographic vertebral fracture and one clinical fracture were 15 and 20, respectively.¹⁶⁷ The superior anti-fracture efficacy of teriparatide, and its early fracture risk reduction especially on vertebral fracture are fully demonstrated.
 - 1.2 Results of the ARCH study, which is a RCT of romosozumab versus alendronate treatment, have been discussed in Section K2.6.5. The 37% reduction of vertebral fractures and 28% reduction of clinical fractures at 12 months with the romosozumab as compared to the alendronate group again demonstrated the superior anti-fracture efficacy and rapid fracture risk reduction achieved with bone-forming drug.¹⁵⁹
 - 1.3 Only bone-forming drugs (teriparatide and romosozumab) have demonstrated evidence of new bone formation in histomorphometric analyses, as well as significant improvement in bone microarchitecture in μ CT analyses of iliac crest biopsies.^{158,168}
 - 1.4 The FRAME study had demonstrated the rapidity of gain in BMD with bone-forming drug such that 96% and 76% of romosozumab-treated patients experienced \geq 3% gains in BMD at the lumbar spine and total hip, respectively. This was believed to

provide a stronger skeletal foundation leading to fewer fractures upon transition to antiresorptive treatment.¹⁵⁷

2. Impact of treatment sequence on clinical efficacy of anti-osteoporosis drugs

- 2.1 A recent meta-regression analysis showed that therapies that produce the largest increases in BMD are associated with the greatest reductions in fracture risk.¹⁶⁹
- 2.2 The largest gain in BMD in postmenopausal osteoporotic women has consistently been shown to be achieved with initial treatment with a bone-forming drug followed by sequential therapy with a potent antiresorptive drug.^{156,159,170}
- 2.3 The reverse treatment sequence, ie, antiresorptive before bone-forming therapy has been shown to reduce the magnitude of BMD gain with initial bone-forming therapy. In the STRUCTURE study in which all subjects had prior oral BP therapy for at least 3 years, the total gains in BMD at the spine (+9.8%), total hip (+2.9%) and femoral neck (+3.2%) at 12 months of romosozumab treatment¹⁶¹ were numerically much smaller than those achieved with romosozumab in treatment-naïve postmenopausal women at 12 months in the FRAME study (spine +13.3%, total hip +6.8%, femoral neck +5.2%).¹⁵⁶ Similarly, in a small post-hoc exploratory analysis of the romosozumab phase 2 dose-finding study,¹⁷¹ women who were randomised to romosozumab after denosumab treatment had gains in BMD at the spine (+5.3%), total hip (+0.9%) and femoral neck (+1.0%) at 12 months numerically much lower than those achieved with treatment-naïve women in the FRAME study.¹⁵⁶

2.4 In order to maximise the BMD gain and hence fracture risk reduction, these clinical observations strongly support the treatment sequence of bone-forming drug before antiresorptive treatment being the most optimal sequence, and not the reverse, particularly in patients with a very high risk of fracture.^{157,172-174}

3. Treatment stratification by risk categories

- 3.1 Identification of patients who would benefit most from the optimal treatment sequence of bone-forming followed by antiresorptive drugs are yet to be established. Based on the best existing evidence, the new 2024 OSHK Osteoporosis Management Algorithm is outlined in Figure 2.
- 3.2 Logically, patients at imminent or very high risk of fracture should be offered bone-forming drugs as the initial treatment option followed by sequential potent antiresorptive drugs, if cost is not a concern. These include patients with a recent MOF in the past 2 years, presence of two or more osteoporotic fractures, a BMD T-score ≤ -3.0 , or fracture while on antiresorptive treatment. The local orthopaedic community has also put forward similar recommendation on the preferential use of bone-forming drugs in patients who had sustained a recent fragility fracture.¹⁷⁵
- 3.3 For women with relatively low risk of fracture such as younger women in their early postmenopausal years, it is reasonable to start with a mild antiresorptive drug such as HRT or raloxifene unless there are additional high-risk clinical features.
- 3.4 Postmenopausal women with osteoporosis falling out of the above two categories are regarded as high risk and they should be considered for

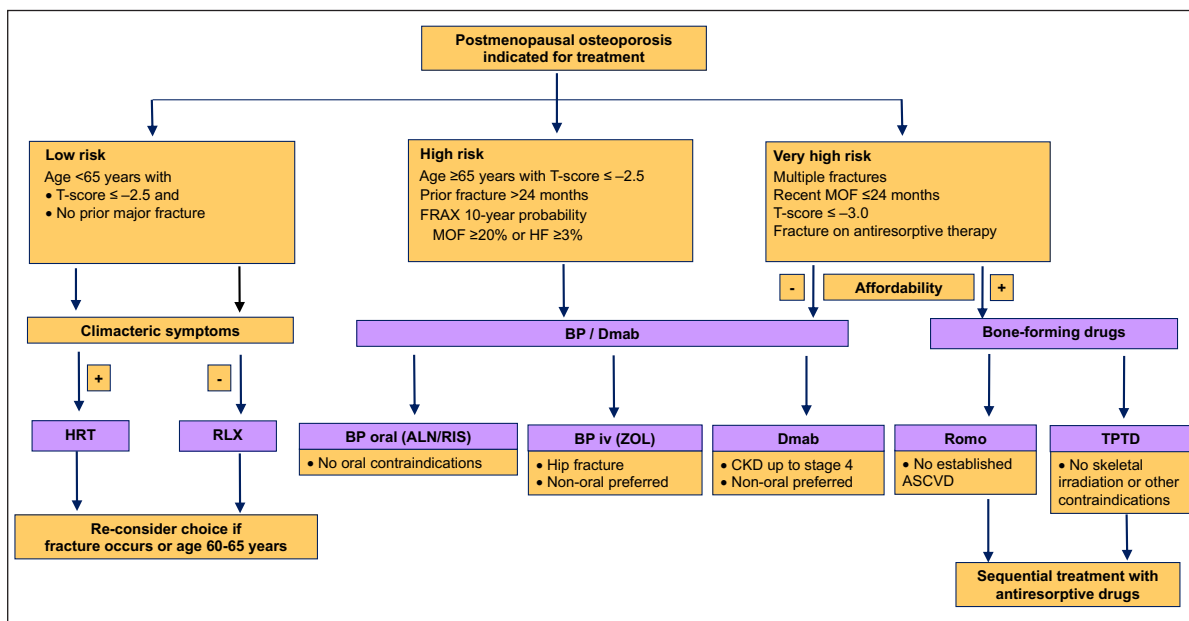


FIG 2. The 2024 Osteoporosis Society of Hong Kong (OSHK) Osteoporosis Management Algorithm

Abbreviations: ALN = alendronate; ASCVD = atherosclerotic cardiovascular diseases; CKD = chronic kidney disease; BP = bisphosphonates; Dmab = denosumab; HF = hip fracture; HRT = hormone replacement therapy; MOF = major osteoporotic fractures; RIS = risedronate; RLX = raloxifene; Romo = romosozumab; TPTD = teriparatide; ZOL = zoledronic acid

potent antiresorptive drugs such as oral or iv BPs, or sc denosumab. Other clinical factors that may modify the treatment choices include the renal function status, the presence of contraindications to individual drugs, and most importantly, patient preference and affordability of individual drug.

(N) Monitoring of Osteoporosis Treatment

1. The roles of surrogate markers, BMD and BTMs, in the monitoring of osteoporosis treatment have been discussed in detail in the 2013 Guideline Section J.¹
2. Updated recommendations of the 2023 ISCD Adult Official Positions on the use of DXA in monitoring are listed below.²⁸
 - (i) Repeat BMD testing should be used to monitor individuals prior to a temporary cessation of BP therapy and during the period of planned interruption of treatment.
 - (ii) Repeat BMD testing intervals must be individualised considering an individual's age, baseline BMD, the type of pharmacological treatment, and the presence of clinical factors which are associated with bone loss.
 - (iii) Shorter intervals between BMD testing may be indicated in the presence of factors associated with rapid change in BMD. Examples include the use of certain medications such as glucocorticoids, aromatase inhibitors, androgen deprivation therapy, and bone-forming therapies, medical disorders such as malabsorption and severe systemic inflammatory diseases, and other conditions such as prolonged immobilisation, bariatric surgery, and surgical menopause.
3. *Recommendations on monitoring of osteoporosis treatment*
 - (i) The same DXA model and preferably the same equipment should be employed for monitoring of treatment response.
 - (ii) In the absence of other clinical factors that may accelerate bone loss, a repeated BMD measurement should be performed 1-2 years after initiation of antiresorptive treatment and preferably 1 year after treatment with bone-forming drugs.
 - (iii) Subsequent BMD monitoring can be performed at 2-to-3-year intervals after therapeutic effect is established.
 - (iv) In the presence of other clinical factors that may accelerate bone loss, shorter intervals between BMD testing may be indicated.
 - (v) Patients who have a significant decrease in BMD despite treatment should be evaluated for treatment adherence, inadequate calcium and/or vitamin D intake, poor drug absorption, or the presence of previously unrecognised secondary causes of osteoporosis.
 - (vi) Changes in BTMs are much more rapid than the changes in BMD such that BTMs may be employed in monitoring treatment response especially within the first 3-6 months of initiation of antiresorptive therapy at a time

when BMD changes are too small to be detected clinically.

- (vii) Changes in BTMs are also useful in monitoring bone loss upon discontinuation of therapy.⁴⁰

(O) Medication-Related Osteonecrosis of the Jaw

1. General considerations

- 1.1 BP-related ONJ (BRONJ) was discussed in the 2013 Guideline Section K.¹
- 1.2 Denosumab and other non-antiresorptive drugs (such as anti-angiogenic medications and tyrosine kinase inhibitors) have also been linked to the development of ONJ such that this adverse effect of medical treatment is collectively termed medication-related osteonecrosis of the jaw (MRONJ).¹⁷⁶ Most of these drugs are employed for cancer treatment and the full spectrum of drugs linked to development of ONJ can be found in the three reference articles.¹⁷⁷⁻¹⁷⁹
- 1.3 Osteonecrosis of the jaw (ONJ) can occur in patients not exposed to antiresorptive drugs or other medications.¹⁸⁰
- 1.4 MRONJ is a rare entity. Patients should always be reminded that the benefits of fracture prevention offered by antiresorptive therapy far exceed the risk of MRONJ.^{176,181}

2. Definition and staging of MRONJ

- 2.1 MRONJ is defined as an exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region, that has persisted for more than 8 weeks, in patients with current or previous treatment with antiresorptive therapy alone or in combination with immune modulators or anti-angiogenic medications, but without a history of radiation therapy or metastatic disease to the jaws.¹⁷⁶
- 2.2 The mandible is more frequently affected than the maxilla (75% vs 25%) possibly due to its thick cortical bone structure with relatively low blood supply^{176,181}; however, ONJ can develop at both jaws at the same time.
- 2.3 The American Association of Oral and Maxillofacial Surgeons (AAOMS) staging system is the most commonly used clinical tool for assessing the severity of MRONJ.¹⁷⁶
 - (i) Stage 0 disease (a precursor to MRONJ) refers to patients without clinical evidence of necrotic bone, but who present with either non-specific symptoms or compatible clinical and radiological findings. Up to 50% of stage 0 disease may progress to stage 1 disease.
 - (ii) Stage 1-3 diseases refer to patients with exposed necrotic bone of increasing severity, stratified according to the presence of symptoms and/or infection/inflammation, as well as extent of involvement and complications, eg, pathologic jaw fracture or extraoral fistula.

3. Pathophysiology and risk factors of MRONJ

- 3.1 The pathogenesis of MRONJ is likely multifactorial.
- 3.2 Oversuppression of bone remodelling by

antiresorptive drugs is believed to be the principal mechanism leading to ONJ. Other important pathophysiological mechanisms include infection/inflammation, angiogenesis inhibition, soft tissue toxicity, immune dysfunction, vitamin D deficiency and osteomalacia, as well as genetic predisposition.^{176,181}

- 3.3 Risk factors for development of MRONJ are diverse: both local and systemic factors are involved. Dental extraction is the most frequently cited predisposing factor.^{176,181} Other invasive dental procedures involving alveolar bone exposure and damage such as dental implant installation and removal also confer an increased risk.¹⁸² In contrast, restorative dental treatment, endodontic treatment, and conservative periodontal therapies are associated with minimal risk.¹⁸³
- 3.4 Other reported local risk factors include (1) dental infection; (2) periodontal or periapical disease; (3) conditions predisposing to mucosal trauma, eg, ill-fitting dentures; and (4) anatomical variations such as torus mandibularis or palatinus, exostosis, and the mylohyoid ridge.¹⁸³
- 3.5 Reported systemic risk factors include (1) advanced age >65 years; (2) diabetes; (3) inflammatory joint diseases; (4) anaemia; (5) smoking and alcohol; and (6) concomitant use of certain drugs, eg, glucocorticoids, chemotherapy, immunosuppressants and angiogenesis inhibitors.^{176,181}
- 4. MRONJ in patients receiving antiresorptive drugs for osteoporosis treatment**
- 4.1 The incidence of MRONJ is consistently reported to be much lower in patients treated for osteoporosis compared to patients treated for cancer (Table 4).^{176,181-185} This is most likely due to the more intense and prolonged suppression of bone turnover by the higher doses and more frequent dosing of antiresorptive drug regimens in cancer patients. Concurrent therapies with glucocorticoids or angiogenesis inhibitors, as well as an overall decrease in oral and general health in cancer patients, may also contribute.¹⁸¹
- 4.2 The reported incidence of MRONJ in osteoporosis patients treated with BPs in Asians was similar to that of the Caucasians. The incidence rates were 0.21 and 0.23 per 1000 patients-years as reported from recent population-based studies from Korea and Japan, respectively.^{184,185}
- 4.3 No case of ONJ has been reported with HRT whereas only three cases of ONJ were reported in the literature to be associated with raloxifene

treatment, one of which had prior BP use.^{186,187} Raloxifene, being a milder antiresorptive drug, may offer as an alternative treatment for patients with osteoporosis at high risk of ONJ or recovered from ONJ.

- 4.4 In a recent multicentre retrospective cohort study in Taiwan comparing the incidence of MRONJ in 8962 patients with osteoporosis treated with BPs and denosumab, the cumulative incidence rate of ONJ was significantly higher in patients treated with long-term BP than denosumab (2.49 vs 1.47 per 1000 person-years). The risk of ONJ increased with the duration of exposure to BPs, whereas the risk stabilised and plateaued in patients treated with denosumab after 4 years.¹⁸⁸
- 4.5 In the FREEDOM Extension study, 3591 subjects were enrolled to have regular survey of invasive oral procedures and events (OPEs) for up to 10 years. 1621 subjects (45.1%) reported at least one invasive OPEs and there were 13 positively adjudicated cases of ONJ; 12 cases occurred among women who participated in the survey and 1 occurred in a woman who did not complete the survey. The exposure-adjusted ONJ rate was 5.2 per 10000 person-years. ONJ incidence was much higher in those reporting invasive OPEs (0.68%) than those not reporting any OPEs (0.05%). There was no clear relationship between the duration of denosumab exposure and the occurrence of ONJ.¹⁸⁹
- 4.6 It has been proposed that BPs accumulate in the jawbone at concentrations toxic to the oral epithelium, impairing healing of soft tissue injuries caused by invasive dental procedures.¹⁹⁰ High doses of potent BPs have also been consistently associated with decreased angiogenesis *in vitro* and *in vivo*.¹⁹¹ On the contrary, there is no evidence that denosumab exerts soft tissue toxicity or antiangiogenic effects.¹⁹¹
- 5. Prevention of MRONJ in patients treated for osteoporosis**
- 5.1 Maintenance and restoration of good oral health is always essential in the primary prevention of MRONJ. A comprehensive dental evaluation and management is recommended preferably before (or shortly after) the initiation of antiresorptive drugs, which should include^{176,181,183}:
 - (i) oral health examination;
 - (ii) education on importance of practising oral hygiene (eg, toothbrushing, dental flossing, antimicrobial mouth rinses, etc);
 - (iii) adjustment of ill-fitting dentures;
 - (iv) management of predisposing dental conditions (eg, dental infection, periodontal disease); and
 - (v) elective invasive dental procedures should ideally be performed before or shortly after commencement of antiresorptive drugs.
- 5.2 Potentially reversible systemic risk factors associated with MRONJ (eg, diabetes, smoking, concomitant glucocorticoid use) should be corrected or controlled.
- 5.3 Serum biochemical markers of bone resorption demonstrated low performance in predicting

Table 4. Reported incidence of MRONJ associated with the use of antiresorptive drugs for treatment of osteoporosis and malignant conditions^{176,181-185}

Antiresorptive drugs	Incidence (per 1000 patient-years)	
	Malignant conditions	Osteoporosis
Bisphosphonate (oral)	No data	0.2-0.5
Zoledronic acid (iv)	0-180 (mostly <50)	≤0.2
Denosumab (sc)	0-69 (mostly <50)	0.4-3.0

- MRONJ after invasive dental procedures in patients on antiresorptive drugs^{192,193} such that no biomarkers have been validated for clinical recommendations.¹⁷⁶
- 5.4 Patients are advised to report and seek dental advice promptly when clinical features suggestive of MRONJ arise. Early signs of MRONJ include odontalgia, non-specific sinus pain, dull aching jawbone pain which may radiate to the temporomandibular joint region, and altered neurosensory function.¹⁷⁶
- 5.5 Dental management in osteoporosis patients receiving antiresorptive drugs is listed as below.
- (i) Preventive or conservative dental treatment to maintain functionally healthy teeth should be considered as far as possible to minimise the need for invasive dental procedures.
 - (ii) Specific preventive measures, including primary wound closure, antimicrobial mouth rinsing, and peri-procedural antibiotics can help reduce the risk of MRONJ after invasive dental procedures.^{181,194,195}
 - (iii) A retrospective Belgian study in 126 patients with osteoporosis on antiresorptive therapy showed that antibiotic prophylaxis or post-dental extraction therapeutic antibiotic use significantly reduced the risk of MRONJ by 93% and 89%, respectively.¹⁹⁵
 - (iv) Antibiotic prophylaxis should be started 2-3 days before dental extraction and continued until complete wound healing. The most frequently used antibiotics were amoxicillin, amoxicillin/clavulanic acid, metronidazole, and a combination of the above. Erythromycin and clindamycin could be used in patients with penicillin allergy.¹⁹⁶
 - (v) Early but limited data suggested that the use of leucocyte and platelet-rich fibrin membrane placement might reduce the risk of, and enhance early recovery from MRONJ.¹⁹⁷
- 5.6 The need for temporary interruption of antiresorptive therapy before invasive dental procedures remains controversial in the absence of high-quality scientific evidence.
- (i) A recent meta-analysis of eight observational studies involving 6808 patients showed that temporary discontinuation of BPs or denosumab did not reduce the risk of development of MRONJ after dental procedures.¹⁹⁸
 - (ii) Major updated osteoporosis management guidelines did not offer specific recommendations on this issue.²⁻⁴
 - (iii) BP do have increased skeletal uptake at the sites of local bone injury, and withholding BP therapy following oral surgery may be of value in reducing the local deposition in the mandible and maxilla after oral surgery.
 - (iv) The working group of the 2022 AAOMS Position Paper on MRONJ could not come to a consensus recommendation on BP drug holidays before invasive dental procedures.¹⁷⁶
 - (v) Other professional associations including the European Calcified Tissue Society (ECTS),¹⁸¹ the International Task Force on ONJ,¹⁹⁴ the Korean Task Force,¹⁸³ and the Japanese Allied Committee on ONJ¹⁹⁹ recommend discontinuing oral BP in patients at high risk of MRONJ. High-risk features include expected extensive invasive dental surgery, long duration of BP exposure (more than 3-4 years), and presence of multiple local or systemic risk factors.
 - (vi) However, the recommendation on the duration of oral BP drug holidays in high-risk patients varies. The ECTS recommended stopping oral BPs at least 1 week before invasive dental procedures and until 4 weeks after surgical site healing,¹⁸¹ whereas the Korean Task Force recommended 2-4 months of oral BP discontinuation before dental procedures and until 2 months after surgical site healing.¹⁸³
 - (vii) Patients on denosumab should be advised against discontinuation while awaiting dental treatment. The issue of discontinuation of denosumab will be discussed in detail in Section R4.
 - (viii) AAOMS recommended elective invasive dental procedures can be planned at around 3-4 months following the last denosumab injection when the level of osteoclast inhibition is waning,¹⁷⁶ whereas the ECTS and Korean Task Force recommended 4-6 months after the last injection.^{181,183}
 - (ix) Regarding resumption of denosumab, ECTS recommended the next injection should be given no later than 4 weeks,¹⁸¹ whereas the Korean Task Force recommended no later than 3 months¹⁸³ after the next due date. The practical principle is to avoid excessive delay in resuming denosumab, which may otherwise result in rebound bone loss and potential multiple vertebral fractures (see Section R4).
 - (x) No relevant data and recommendations are available on this aspect with reference to iv BP.
- 6. Osteoporosis management after MRONJ**
- 6.1 There are no reported RCTs on the optimal medical treatment of patients remaining at high fracture risk after MRONJ.
 - 6.2 Major updated osteoporosis management guidelines have not offered specific recommendations on this issue.²⁻⁴
 - 6.3 A balanced evaluation of the risk-to-benefit ratio of continuing or stopping the antiresorptive drugs should always be carried out in patients who have developed MRONJ.¹⁸¹
 - 6.4 Since the uptake of BP is comparatively increased at sites of local bone injury with high bone turnover, withholding BP treatment may reduce their local deposition in the area of ONJ-affected jawbone.
 - 6.5 A clinical case series involving 84 patients with established BRONJ confirmed that continuing BPs might delay resolution of maxillofacial symptoms by approximately 6 months compared to stopping BPs at diagnosis of MRONJ.²⁰⁰

- 6.6 The ECTS and the Korean Task Force suggested discontinuation of antiresorptive drugs until complete soft tissue closure after carefully weighing the risk of ongoing MRONJ with the risk of osteoporotic fractures.^{181,183}
- 6.7 In the aforementioned FREEDOM Extension study with regular survey of invasive OPEs, 8 out of the 13 patients with established MRONJ continued denosumab treatment after development of ONJ. 7 patients healed with appropriate dental management despite continuing denosumab therapy whereas the remaining patient had ONJ ongoing at the closure of the study period.¹⁸⁹
- 6.8 Teriparatide promotes alveolar bone regeneration in both human and animal MRONJ studies.²⁰¹ A recent meta-analysis showed that teriparatide is an effective therapeutic modality, especially when used in combination with antibiotic therapy in the management of MRONJ.²⁰² The ECTS recommended to consider teriparatide until complete soft tissue closure in patients with MRONJ.¹⁸¹
- 6.9 There is at present no literature report describing the use of romosozumab in the management of MRONJ. In fact, two cases of ONJ were reported in the FRAME study, both having specific risk factors.¹⁵⁶ Further research is needed to delineate the association between romosozumab and MRONJ.
- 6.10 Subsequent use of anti-osteoporosis medications after resolution of MRONJ poses another clinical challenge. The decision should be individualised, depending on the updated fracture risk, the incriminated antiresorptive drugs, the comorbid conditions and patient affordability.
- 7. Recommendations on prevention and management of MRONJ in osteoporosis patients**
- 7.1 Maintenance and restoration of good oral health is the key strategy for primary prevention of MRONJ.
- 7.2 A comprehensive dental examination is recommended preferably before (or shortly after) the initiation of antiresorptive drugs, and at regular intervals thereafter.
- 7.3 For patients who need invasive dental procedures, good communications with the dental surgeons should be ensured, regarding the appropriate timing of surgery, adoption of a relative less traumatic surgical approach and primary wound closure if feasible.
- 7.4 For osteoporosis patients who are on antiresorptive treatment and planning to have elective invasive dental procedures:
- (i) stop oral BP at least 1 week before the procedure, and until surgical site healing;
 - (ii) plan the procedure at 2-3 months before the next due dose of iv BP, and administer the next dose only after surgical site healing is confirmed;
 - (iii) plan the procedure at 2-3 months before the next due dose of denosumab, and administer the next dose of denosumab as scheduled unless the surgical wound shows signs of non-healing; delay of denosumab injection awaiting dental procedure must be discouraged;
- (iv) administer antimicrobial mouth rinses perioperatively; and
 - (v) consider prophylactic antibiotic before or on the day of dental procedure, and continue until surgical wound closure in patients with additional high-risk features.
- 7.5 Subsequent anti-osteoporosis management after MRONJ:
- (i) Patients should always be reminded that the benefits of fracture prevention offered by antiresorptive therapy far exceeds the risk of MRONJ. The AAOMS advocates prioritisation and support of continued bone health and the prevention of fragility fractures.¹⁷⁶
 - (ii) In theory, a history of MRONJ is not an absolute contraindication for resumption of antiresorptive drug in patients with high fracture risk after complete healing of MRONJ. In clinical practice, both patients and clinicians are usually hesitant or reluctant to do so.
 - (iii) Teriparatide or raloxifene may serve as alternative options after MRONJ.
 - (iv) Switching from BPs to teriparatide may have additional merits in promotion of healing of MRONJ; sequential raloxifene treatment should ensue following completion of the course of teriparatide.²⁰³
 - (v) Switching from denosumab to teriparatide should be avoided because teriparatide may not be able to suppress the rebound bone loss associated with denosumab discontinuation (see Section R4).
 - (vi) Direct switching from denosumab to raloxifene is an option as raloxifene may partially prevent the rebound bone loss following denosumab discontinuation (see Section R4).
- (P) Atypical Femur Fracture**
- 1. General considerations**
- 1.1 Fractures located in the subtrochanteric/diaphyseal regions account for 7-10% of all fractures of the femur.²⁰⁴
- 1.2 Atypical femur fracture (AFF) refers to a special type of fracture occurring in the subtrochanteric or diaphyseal region of the femur with characteristics of 'atypia'.²⁰⁵
- 1.3 The American Society of Bone & Mineral Research (ASBMR) Task Force published the first report on AFF in 2010 to formulate five major and seven minor features for the diagnosis of AFF.²⁰⁵
- 1.4 The diagnostic criteria were revised in the second report in 2014 (Table 5), which stated that at least four out of five major features need to be present in order to designate a fracture as 'atypical' whereas the minor features are no longer required for diagnosis although they have been found to be associated with AFF.²⁰⁶
- 1.5 Patients on BPs should be counselled to report thigh pain and, if present, imaging should be

Table 5. American Society of Bone & Mineral Research (ASBMR) Task Force 2014 Revised case definition of atypical femur fractures (AFFs)²⁰⁶

<ul style="list-style-type: none"> To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. In addition, at least four of five major features must be present. None of the minor features is required but these minor features have sometimes been associated with these fractures.
Major features
<ol style="list-style-type: none"> The fracture is associated with minimal or no trauma, as in a fall from a standing height or less. The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur. Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex. The fracture is non-comminuted or minimally comminuted. Localised periosteal or endosteal thickening of the lateral cortex is present at the fracture site (“beaking” or “flaring”).
Minor features
<ol style="list-style-type: none"> Generalised increase in cortical thickness of the femoral diaphyses Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh Bilateral incomplete or complete femoral diaphysis fractures Delayed fracture healing

- conducted to assess potential occurrence of AFF.
- 2. Incidence of AFF**
 - AFFs have been reported in patients taking antiresorptive medications including BPs^{205,206} and denosumab^{207,208}; but they can also occur in patients with no exposure to these drugs.²⁰⁹
 - A recent adverse event report from the FDA also reported AFF on raloxifene (1 case) and teriparatide (10 cases) without prior BP or denosumab treatment.²¹⁰
 - The FRAME study reported one patient developing AFF 3.5 months after receiving the first dose of romosozumab though this patient had prodromal symptoms at the site of fracture before enrolment.¹⁵⁶
 - The incidence of AFF is very low, ranging from approximately 1 in 100000 to 5 in 10000 among BP users. When compared to the more common osteoporotic vertebral and hip fractures, about one AFF occurred for every 265 hip fractures in BP-treated patients (3-5 per 1000 hip fractures).^{211,212}
 - The incidence of AFF in denosumab-treated patient is even lower. A review article documented only four patients to have developed AFF after the use of denosumab for the purpose of osteoporosis management.²⁰⁸ The incidence reported in the FREEDOM Extension study was 0.8 per 10000 patient-years.¹⁴³
 - Bilateral involvement occurs in about 30% of patients.^{205,206,211}
 - 3. Pathophysiology of AFF**
 - The exact pathogenesis of AFF remained unclear.
 - AFFs are believed to be lower limb stress or insufficiency fractures. Stress fractures occur when a bone is unable to repair the damage associated with repetitive loading.²⁰⁶
 - BP molecules after absorption tend to localise at sites of stress fracture where bone turnover is relatively high such that bone remodelling as a repair mechanism is being suppressed, allowing the microcracks to progress to create a clinical stress fracture.²⁰⁶
 - 4. Clinical risk factors of AFF**
 - There is consistent epidemiological evidence, including one local study, that the incidence of AFF correlated with the duration of BP treatment, particularly after 5 years of use.^{206,211,212,217-219}
 - Evidence also showed that there was a rapid 70% reduction in risk of AFF within 1 year of BP discontinuation irrespective of prior duration of treatment.^{211,212,218}
 - Glucocorticoid users and the Asian ethnicity are the two clinical risk factors that have shown a strong relationship to AFF, whereas evidence for diabetes, use of proton pump inhibitors, or rheumatoid arthritis are inconsistent.^{206,211,212}
 - Asians are particularly at high risk with a HR of 4.8 when compared to Caucasians.²¹² Some studies suggested that Asians had an unfavourable geometry at the femur with a larger femorotibial angle, leading to a higher stress especially at the more diaphyseal location.^{206,211,213,214}
 - 5. Clinical management of AFF**
 - The clinical management of AFF has been discussed in detail in the 2013 Guideline Section L.¹ It must be

emphasised that bilaterality is present in around 30% of cases such that the contralateral femur must always be evaluated with prophylactic procedures performed if indicated.^{1,205,206}

- 5.2 For medical treatment, potent antiresorptive agents should be discontinued. Adequate calcium and vitamin D status should be ensured.
 - 5.3 Operative management might confer a better clinical and functional outcome than non-operative treatment for incomplete AFF.^{220,221} A local study confirmed the superiority of dynamic locking of intramedullary nails over static locking in the treatment of AFFs with faster time to union, lower rate of non-union, and fewer treatment failure.²²²
 - 5.4 There is no evidence-based indication for teriparatide to enhance healing of AFF. Recent reviews observed potential benefits on lowering the rate of delayed union and non-union and shortening the fracture healing time with teriparatide for surgically managed AFFs.^{208,223}
- 6. Osteoporosis management after AFF**
- 6.1 There are no reported RCTs on the optimal medical treatment of patients remaining at high fracture risk after sustaining an AFF.
 - 6.2 The risk of causing new atypical fractures should be weighed against the risk of fragility fractures when not treating the underlying osteoporosis.
 - 6.3 A local retrospective cohort study of patients with osteoporosis who sustained BP-related AFF reported that teriparatide, followed by raloxifene, represented a feasible strategy to maintain BMD following AFF.²¹⁹

6.4 Recommendations on osteoporosis management after AFF

- (i) Patients at low risk of fracture may consider stopping BP treatment after sustaining an AFF.
- (ii) Patients remaining at high risk of fracture should be considered a course of teriparatide, not for the purpose of AFF healing, but for its bone-forming effect for treatment of the underlying osteoporosis.
- (iii) Patients contraindicated for teriparatide, not affordable for teriparatide, or after completion of the course of teriparatide treatment should be maintained with antiresorptive therapy for fracture protection. Raloxifene with its less potent suppression on bone turnover might be the preferred drug of choice especially after teriparatide treatment.
- (iv) Patients who already have bilateral surgically nailed femurs may continue to be treated with potent antiresorptive drugs such as denosumab or even BP after documented healing of the AFFs.
- (v) Patients who have denosumab-related AFF should have the additional consideration of preventing the rebound bone loss and multiple vertebral fractures associated with denosumab discontinuation especially if the prior duration of denosumab treatment has exceeded 2 years. These patients should preferably receive raloxifene early (see Section R4).

7. Atypical fractures at other skeletal sites

- 7.1 Fractures with characteristics similar to those of AFF have also been reported at other skeletal sites such as the ulna, humerus, and tibia.^{224,225}
- 7.2 These fractures are likely to be exceedingly uncommon, but clinicians should be fully aware of such possibilities.
- 7.3 The implication of the occurrence of atypical fracture at other skeletal sites with the use of antiresorptive drugs is unknown. It is advisable to continue potent antiresorptive medications if the patient remains at high risk of fracture.

(Q) Duration of Bisphosphonate Treatment

1. General considerations

- 1.1 Osteoporosis is a chronic disease. It is logical that osteoporosis requires long-term medical therapy, just like other chronic diseases such as hypertension and diabetes.
- 1.2 To minimise the occurrence of potential serious but rare adverse effects such as AFF with long-term anti-osteoporosis treatment, the concept of drug holiday has been advocated.
- 1.3 The prerequisite for a drug holiday relies on the persistence of the effect of the drug on the bone after discontinuation of the drug.²²⁶ Only BPs have been documented to be retained in the bone for varying periods of time after discontinuation, and hence, only patients treated with BPs are eligible for consideration of drug holidays. Patients on other antiresorptive drugs such as HRT, raloxifene and denosumab are not appropriate candidates for drug holidays.

2. Drug holidays on long-term bisphosphonate treatment

- 2.1 As discussed in Section P4, the incidence of AFF correlated with the duration of BP treatment, particularly after 5 years of use^{206,211,212,217-219} and there was a rapid 70% reduction in risk of AFF within 1 year of discontinuation of BP irrespective of prior duration of treatment.^{211,212,218}
- 2.2 Previous analyses had shown that the benefit-risk ratio is overwhelmingly positive for BP treatment in the initial years of therapy. For each AFF caused by oral BP treatment for 3 years, round 1200 fractures, including 135 hip and 850 vertebral fractures, would be prevented.^{211,212}
- 2.3 OSHK has recommended in the 2013 Guideline on the optimal treatment duration of oral and iv BP being 5 years and 3 years, respectively, after which the decision whether to stop or continue treatment should depend on the fracture risk at the completion of the initial period of therapy. Patients who do not have incident MOFs or whose BMD T-score at the hip having achieved a value > -2.5 can be considered for drug holidays.¹
- 2.4 These recommendations were later supported by similar recommendations from Report of a Task Force of the ASBMR in 2016²²⁷ and the United Kingdom National Osteoporosis Guideline Group in 2017.²²⁸
- 2.5 On the other hand, patients who have incident MOF or whose achieved hip BMD T-score

remaining ≤ -2.5 after 5 years of oral or 3 years of iv BP therapy should continue anti-osteoporosis treatment.^{1,227,228}

- 2.6 A recent analysis showed that Asians had a much higher risk for development of AFF upon long-term BP treatment when compared to other ethnic groups (HR for Asians vs Caucasians, 4.8). By 10 years of therapy, the number of BP-associated AFF was 236 per 10000 women, which was only slightly less than the number of hip fractures prevented (360 per 10000 women).²¹² The benefit-risk ratio for continuing long-term oral BP therapy beyond 5 years becomes much less favourable.
- 2.7 On the other hand, the incidence of AFF with up to 10 years of denosumab treatment reported in the FREEDOM Extension study was very low at 0.8 per 10000 patient-years.¹⁴³ There is no evidence in the literature linking duration of denosumab treatment to an increased risk of AFF, such that denosumab appears to be a more preferred antiresorptive medication if long-term therapy beyond 5 years is warranted.
3. **Recommendations on long-term bisphosphonate treatment**
 - (i) It is reasonable to reassess the need for continuing treatment after an initial treatment duration of 5 years of oral BP or 3 years of iv BP therapy.
 - (ii) Patients without incident major fracture or with an achieved hip T-score > -2.5 can be considered drug holidays; patients on drug holidays should be monitored for recurrence of bone loss with DXA and/or serial BTMs for decision of resumption of anti-osteoporosis therapy.
 - (iii) Patients with incident major fractures or with an achieved hip T-score ≤ -2.5 should continue anti-osteoporosis therapy preferably switching to denosumab.

(R) Discontinuation of Antiresorptive Medications

1. General considerations

- 1.1 Osteoporosis is a lifelong disease requiring continuous monitoring and medical therapy if indicated.
- 1.2 This section provides information on the issues that should be carefully considered before an antiresorptive drug is discontinued due to various reasons.

2. Discontinuation of oral or intravenous bisphosphonates

- 2.1 As discussed in Section Q, BPs will be retained in the bone, such that the antiresorptive effect will persist for a certain period of time after discontinuation of treatment, albeit at varying durations for different BPs.²²⁶
- 2.2 Alendronate and zoledronic acid have higher affinity and longer binding durations whereas risedronate has lower affinity and shorter binding durations.²²⁶
- 2.3 Patients on drug holidays should always be monitored for recurrence of bone loss with BMDs

and/or serial BTMs for decision of resumption of anti-osteoporosis therapy.

3. Discontinuation of hormone replacement therapy or raloxifene

- 3.1 Prospective observational studies showed that women who discontinued HRT experienced an accelerated rate of bone loss at both the spine²²⁹ and the hip²³⁰ compared with age-related bone loss in non-HRT users.
- 3.2 It was disappointing that engagement in usual physical activities did not mitigate bone loss after stopping HRT in a recently published prospective cohort study involving 961 postmenopausal women (mean age 65.9 years).²³⁰
- 3.3 Large observational studies on discontinuation of postmenopausal oestrogen therapy however have not demonstrated an increase in fracture risk.^{231,232}
- 3.4 Significant reductions in spinal and femoral neck BMD were observed 1 year after discontinuation of raloxifene in young healthy postmenopausal women who had received 5 years of prior therapy. After raloxifene discontinuation, the rate of bone loss returned to that of untreated women.²³³
- 3.5 *Recommendations:* Drug holidays are inappropriate for women on HRT or raloxifene. When these women get older (eg, aged 60-65 years) with increasing risk of hip fracture, switching to more potent antiresorptive drugs needs to be considered.

4. Discontinuation of denosumab

- 4.1 Denosumab is a potent antiresorptive drug but it does not incorporate into the bone matrix. Denosumab discontinuation will result in rebound activity of the previously suppressed osteoclasts, leading to rapid increase in bone turnover and bone loss after discontinuation.²³⁴
- 4.2 An off-treatment extension of a phase 3 study showed that after short-term treatment for 2 years, denosumab discontinuation resulted in a rapid increase of BTMs to values above baseline within 3-6 months and only returned to baseline by 24 months. There was an associated rapid loss in BMD at the spine and hip dropping back to baseline values at 12 months, and even significantly dropping below baseline BMD at the distal radius 24 months after treatment discontinuation (Fig 3).²³⁵
- 4.3 In women who had received long-term denosumab treatment for 10 years in the FREEDOM-Extension study, lumbar spine BMD decreased by 9.1%, total hip BMD decreased by 8.3% and femoral neck BMD decreased by 8.1% 1 year after discontinuation. Similar albeit less pronounced BMD losses were observed in those treated with denosumab for 7 years, suggesting that prior treatment duration may predict the rate and amount of bone loss after discontinuation.²³⁶
- 4.4 Quantitative histomorphometric studies of 15 patients who had denosumab discontinuation for a mean period of 25 months demonstrated evidence of bone remodelling indistinguishable from those of untreated postmenopausal women.²³⁷
- 4.5 Denosumab discontinuation-related rebound increase in bone turnover and rapid decrease in

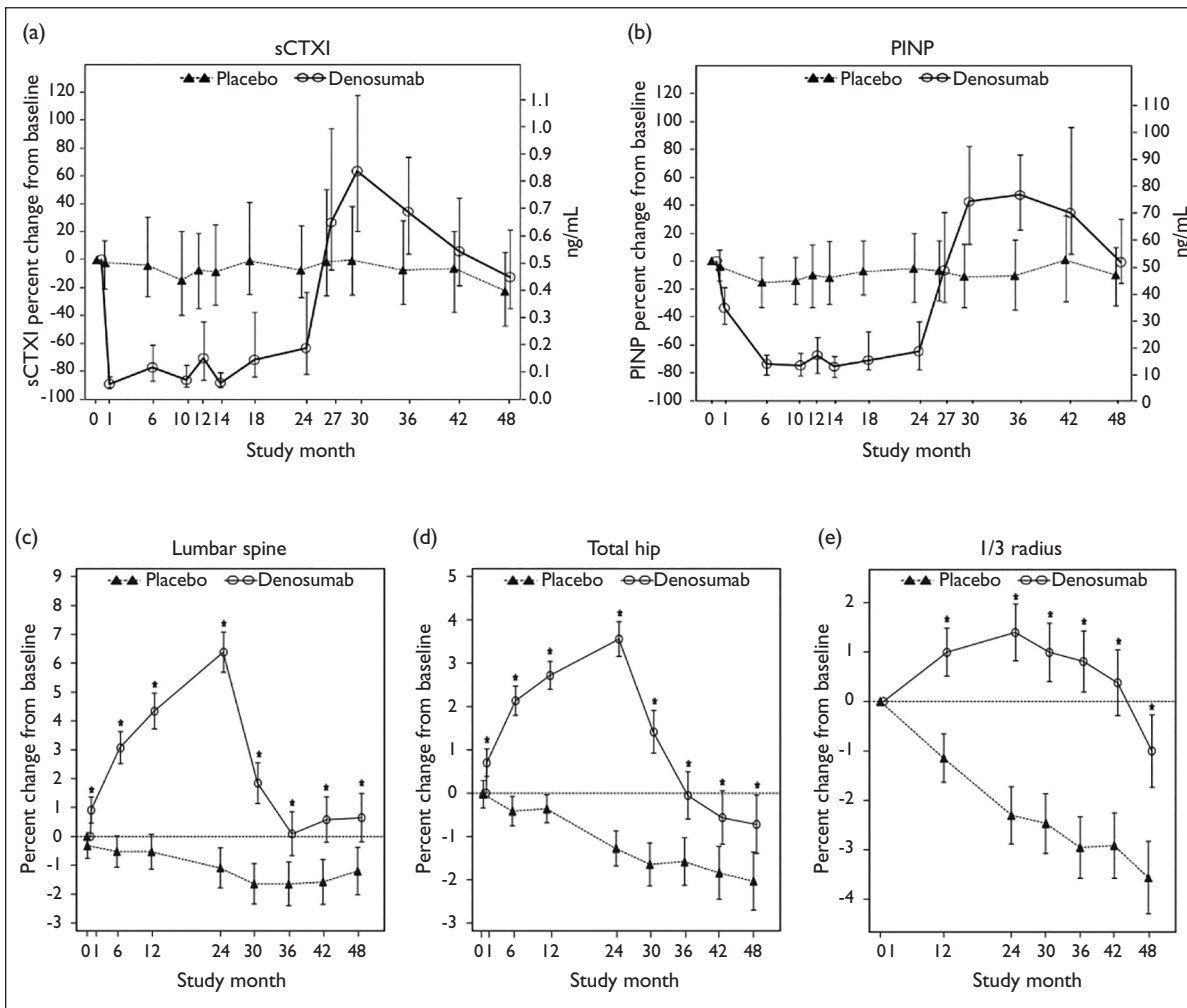


FIG 3. Changes in biochemical bone turnover markers (a, b) and bone mineral densities (c to e) upon denosumab discontinuation after 2 years of denosumab treatment²³⁵ (Reproduced with permission from The Endocrine Society)

BMD were subsequently reported to be associated clinically with an increase in risk of vertebral fractures in observational studies^{238,239} and multiple vertebral fractures in case series.^{144,240-242}

- 4.6 A recent post-hoc exploratory analysis of the FREEDOM and FREEDOM Extension studies showed that the risk of multiple vertebral fractures after denosumab discontinuation was significantly associated with the previous denosumab treatment duration (odds ratio=3.0; 95% CI: 1.4-6.5) especially after 3 years of treatment.²⁴³
- 4.7 Evidence whether previous BP treatment may confer protective effects after denosumab discontinuation is conflicting. Prevention of excessive rebound of bone resorption markers after denosumab discontinuation was suggested in patients with prior BP treatment in a small study²⁴⁴ but clinical series reported the development of multiple vertebral fractures despite prior prolonged BP treatment.²⁴⁵ Prior BP treatment did not appear to adequately prevent the vertebral fractures associated with denosumab discontinuation.
- 4.8 Prevention of rebound bone loss had been attempted

with BP administration. A small retrospective study involving 121 patients comparing the change in BMD following denosumab discontinuation showed that there was no difference in bone loss between patients receiving risedronate and no treatment, whereas there were some mitigations in bone loss in patients treated with alendronate or zoledronic acid.²⁴⁶

- 4.9 The efficacy of zoledronic acid was studied in small case series, which suggested that a single dose of zoledronic acid infusion might not be effective in the suppression of bone turnover and preventing bone loss following denosumab discontinuation.^{247,248} Nevertheless, the overall bone loss after 24 months was reported as 4.2% at the spine and 3.8% at the total hip in a 2-year randomised study,²⁴⁹ the magnitude of which were definitely less than what had been observed in untreated patients.^{236,238}
- 4.10 The duration of denosumab treatment may affect the efficacy of zoledronic acid in preventing bone loss after denosumab discontinuation. In a multicentre prospective cohort study involving

47 postmenopausal women who received a single zoledronic acid infusion 6 months after the last denosumab injection, follow-up BMD at 1 year showed that the lumbar spine BMD were maintained in the 27 women who had received six or less denosumab injections (0.98 ± 0.10 to 0.99 ± 0.9 g/cm²; $P=0.409$) whereas significant bone loss was observed in the 20 women who had received more than six denosumab injections (1.0 ± 0.11 to 0.93 ± 0.12 g/cm²; $P<0.001$). The percentage change in spinal BMD between the two groups were significant ($P<0.001$). The duration of denosumab treatment negatively correlated with the percentage change of lumbar spine BMD ($r_s = -0.669$, $P<0.001$).²⁵⁰

- 4.11 A position statement released by the ECTS stated that patients and physicians should be advised against discontinuing denosumab without evaluation and consideration of an alternative therapy, especially in those patients considered at high fracture risk. The optimal preventive regimen is however unknown.²⁵¹
- 4.12 The ECTS recommended the use of iv zoledronic acid 6 months after denosumab discontinuation in patients who had been treated for a long duration (≥ 2.5 years) and monitored with BTMs at 3 and 6 months to decide whether repeated dose of zoledronic acid is required. In case BTMs were not available, the ECTS experts suggested a pragmatic approach to administer a second infusion 6 months after the first infusion.²⁵² This recommendation is reasonable but whether more frequent administration of a potent BP would increase the risk of serious complications, such as MRONJ, is not known.
- 4.13 *Recommendations on denosumab discontinuation*
- (i) Clinicians should be advised against stopping denosumab treatment in patients who have received long-term treatment ≥ 24 months (4 doses).
 - (ii) Patients who have received short-term treatment < 24 months should be considered alternative anti-osteoporosis treatment after denosumab discontinuation if they remain at high fracture risk.
 - (iii) Patients who opt to stop denosumab treatment for whatever reasons after long-term therapy must be fully informed of the risk of rapid bone loss and potential risk of multiple vertebral fractures. They should receive alternative antiresorptive therapies, preferably a potent iv BP and definitely not oral risedronate.
 - (iv) Neither alendronate nor zoledronic acid completely prevents rebound bone loss after denosumab discontinuation and the optimal BP regimen remains to be defined by prospective studies.
 - (v) Patients who have stopped denosumab treatment and switched to BP should be monitored for changes in BMD by DXA at intervals not longer than 1 year or changes in BTMs at even shorter intervals (3 and 6 months) if laboratory tests are available.
 - (vi) Resumption of denosumab should be

considered if bone loss is considerable or incident fracture occurs.

- (vii) Published data on safety and fracture risk reduction for denosumab treatment beyond 10 years are not available. OSHK recommends continuation of denosumab if deemed necessary, unless data against its long-term use become evident.

(S) Switching of Anti-Osteoporosis Medications

1. General considerations

1.1 During the course of anti-osteoporosis treatment, patients may encounter many clinical events that may lead to a switch of anti-osteoporosis medications. Such events may be a new incident fracture, an occurrence of a serious adverse effect such as AFF, or simply getting older or other personal reasons.

1.2 Practical guides of how to switch among different anti-osteoporosis medications have not been systematically outlined in published international osteoporosis management guidelines.

2. Switching between antiresorptive therapies

2.1 In principle, switching from a mild antiresorptive drug such as raloxifene or HRT, to a more potent antiresorptive drug, such as BP or denosumab, needs no special precautions, provided that contraindications of the new drug are being observed. Switching to the new drug can proceed directly without any time gap.

2.2 The same principle applies to switching from oral/iv BP to denosumab. Switching from oral BP to denosumab can proceed directly without any time gap. Switching from iv zoledronic acid to denosumab can be made at the next due day of the injection therapy. There are no medical contraindications for an earlier switching from zoledronic acid to denosumab if deemed desirable.

2.3 A better improvement in BMDs at all skeletal sites would be expected with switching from oral BP to denosumab.^{253,254} Denosumab was also associated with greater BMD increases at all skeletal sites and greater inhibition of BTMs compared with zoledronic acid in postmenopausal women with prior oral BP treatment.²⁵⁵ However, there are no RCTs employing fracture as the clinical end-points.

2.4 Upon switching from denosumab to oral/iv BP, the patient must be fully informed of the potential risk of rapid bone loss and multiple vertebral fractures. BPs have not been demonstrated to be able to fully suppress the rebound increase in bone turnover associated with denosumab discontinuation especially after long-term denosumab treatment. If switching from denosumab to BP is deemed necessary, an iv BP, zoledronic acid, is preferred and can be started 6 months after the last dose of denosumab and patient should be monitored with DXA for bone loss at interval not more than 1 year or monitored for an increase in BTMs at shorter intervals (see Section R4).

3. Switching from antiresorptive to bone-forming drugs

3.1 Switching from antiresorptive to bone-forming

drugs may be considered under the following conditions:

- (i) occurrence of incident MOF, which immediately put the patient into the imminent fracture risk category^{55,57}; and
- (ii) ongoing bone loss especially with BMD T-score falling <−3.0, after exclusion of potential underlying undiagnosed secondary causes and non-adherence to antiresorptive drugs.

3.2 Switching from bisphosphonates to bone-forming drugs

3.2.1 Prior BP treatment would modestly attenuate the BMD response to teriparatide. The magnitude of BMD gain at the spine would be smaller and there would be a transient decrease in the hip BMD during the first 6-12 months of switching from BP to teriparatide treatment. Nevertheless, teriparatide can still achieve a significant improvement in hip BMD at 18-24 months despite previous BP therapies.^{256,257}

3.2.2 Prior BP treatment would also attenuate the BMD response to romosozumab. The magnitude of the BMD gains at the lumbar spine and hip regions (spine +9.8%, total hip +2.9%, femoral neck +3.2%) at 1 year in the STRUCTURE Study, in which all subjects had received prior oral BP treatment for at least 3 years,¹⁶¹ were numerically much less than that reported with romosozumab in treatment-naïve postmenopausal women in the FRAME study (spine +16.6%, total hip +8.5%, femoral neck +7.3%).¹⁵⁶

3.2.3 The STRUCTURE study also demonstrated the superiority in BMD gains at the lumbar spine and hip region in the romosozumab group when compared to the teriparatide group at 1 year of switching from oral BP¹⁶¹ (see Section K2).

3.2.4 A QCT scan sub-study of the STRUCTURE study demonstrated that teriparatide treatment resulted in an early drop in volumetric BMC of the cortical component of the hip at both 6 and 12 months.¹⁶¹ Vertebral and femoral strength as estimated by finite element analysis showed a decrease in the teriparatide group as compared to a gain in the romosozumab group at 12 months.²⁵⁸

3.2.5 The decision of switching from BP to teriparatide should be made with caution, especially for patients at high risk of hip fracture. Romosozumab appears to be a preferred option when switching from BP to bone-forming drug is being considered, unless there are contraindications.

3.3 Switching from denosumab to teriparatide

3.3.1 No RCTs have been performed to address this clinical issue but important clinical insights on the effects of teriparatide following denosumab treatment can be obtained from the DATA and DATA-Switch studies. In the DATA study, 94 postmenopausal osteoporotic women were randomly assigned to receive

teriparatide (20 µg sc daily), denosumab (60 mg sc every 6 months) or both drugs for 24 months.²⁵⁹ The DATA-Switch study was a pre-planned extension of the DATA study; women originally assigned to teriparatide received denosumab, those originally assigned to denosumab received teriparatide, and those originally assigned to both drugs received denosumab alone for additional 24 months.²⁶⁰

3.3.2 The DATA study showed that combined teriparatide and denosumab treatment resulted in greater increases in BMD at all measured skeletal sites (spine, total hip, femoral neck and distal radius) compared to either drug used alone.²⁵⁹

3.3.3 The DATA-Switch study showed that after switching therapy, there were consistent BMD drops at all the four skeletal sites at 6 months in the denosumab-to-teriparatide group. The spine BMD only started to increase at 12 months whereas the total hip and femoral neck BMD started to increase later at 18 months. The distal radius BMD however continued to drop throughout the 24 months after switching therapy (Fig 4).²⁶⁰

3.3.4 Teriparatide apparently does not offer adequate protection against the rebound increase in bone turnover and bone loss in the early switching period associated with denosumab discontinuation such that switching from denosumab to teriparatide is not recommended if alternative bone-forming therapy is available.

3.3.5 In patients who plan to receive teriparatide therapy while on denosumab treatment, it is highly recommended not to stop denosumab such that teriparatide should be administered concomitantly with denosumab throughout the course of teriparatide treatment.

3.4 Switching from denosumab to romosozumab

3.4.1 Useful clinical information was obtained from an exploratory analysis of a small subset of women who had completed the romosozumab phase 2 dose-finding study,¹⁵⁴ and who were re-randomised to receive either denosumab or placebo for 12 months, and then received romosozumab for another 12 months. In those who were randomised to denosumab, romosozumab treatment for 12 months maintained the BMD that was gained during denosumab treatment at the hip (mean change +0.9% and +1.0% at the total hip and femoral neck respectively) and there was further BMD gain at the lumbar spine (mean change +5.3%). The levels of BTMs gradually returned to baseline from their suppressed reduced values during denosumab treatment.¹⁷¹

3.4.2 The exploratory analysis provided evidence that romosozumab might offer better protection against rapid increase in bone turnover and bone loss associated with denosumab discontinuation possibly by virtue of its intrinsic antiresorptive property.

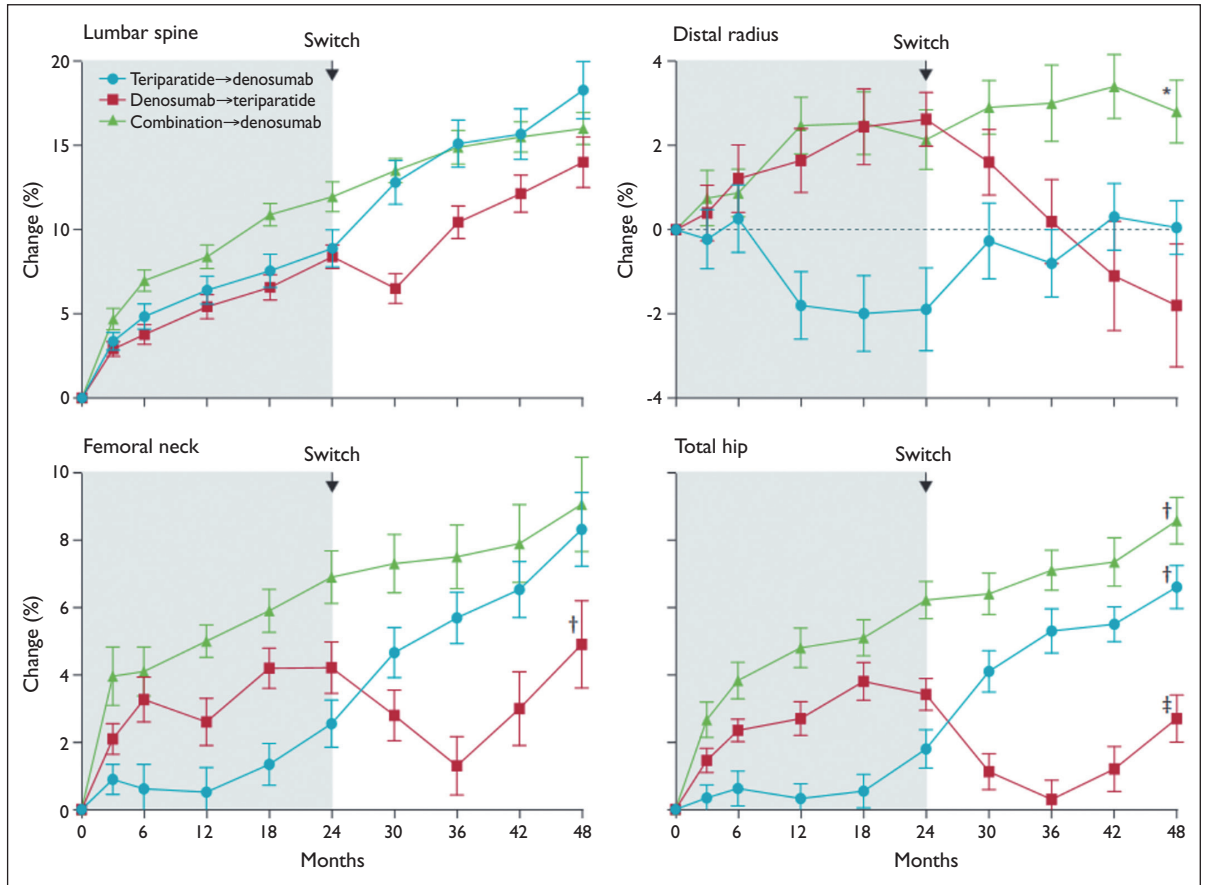


FIG 4. Changes in bone mineral density from baseline to 48 months in the lumbar spine, distal radius, femoral neck and total hip in the DATA-Switch study²⁶⁰ (Reproduced with permission from Elsevier Ltd.)

- 3.4.3 Prior denosumab treatment would also attenuate the BMD gain from romosozumab. The exploratory analysis also showed that the magnitude of total BMD gains at the spine and hip regions 1 year after switching to romosozumab (spine +5.3%, total hip +0.9%, femoral neck +1.0%)²⁶¹ were numerically much smaller than those reported with romosozumab in treatment-naïve postmenopausal women in the FRAME study (spine +16.6%, total hip +8.5%, femoral neck +7.3%).¹⁵⁶
- 3.4.4 An observational study in Japan also reported that prior denosumab treatment attenuated the BMD gain at the lumbar spine (6.4% vs 18.2%; $P < 0.001$), femoral neck (1.5% vs 4.2%; $P < 0.05$) and the total hip (0.6% vs 5.6%; $P < 0.01$) at 12 months when compared to treatment-naïve patients started on romosozumab treatment.²⁶¹
- 3.4.5 Romosozumab appears to be a preferred option when patients are considered to switch from denosumab to bone-forming therapy, unless there are contraindications. An immediate switch can be initiated without the need to wait for 6 months after the last denosumab dose.

(T) Effect of Osteoporosis Treatment on Mortality

1. Excess mortality had been reported to be associated with all types of osteoporotic fractures, notably hip fractures.^{5,15,262-264}
2. In a Swedish cohort study comparing 1013 hip-fractured patients with 2026 matched community controls, excess mortality was evident within the first year after hip fracture. All-cause and excess mortality in hip-fractured patients remained higher than the community controls even over two decades of follow-up, with men having a higher excess mortality throughout.²⁶⁵
3. Survival benefit with osteoporosis treatment was first demonstrated in the HORIZON-RFT in which zoledronic acid infusion administered within 90 days after hip fracture surgery was associated with a 28% reduction in all-cause mortality in a group of 1065 men and women followed up for a median of 1.9 years.¹⁴¹
4. A 25% reduction in all-cause mortality was reported with the use of osteoporosis medications after hip or vertebral fracture in a population-based study in Taiwan involving 87935 older adult subjects aged ≥ 65 years with follow-up for a mean of 4.13 years.²⁶⁶
5. An early meta-analysis of 10 RCTs involving 39549

subjects treated with five anti-osteoporosis drugs (alendronate, risedronate, zoledronic acid, strontium ranelate, and denosumab) showed that osteoporosis treatment was associated with a significant 10% reduction in mortality (RR=0.90; 95% CI: 0.81-1.00; P=0.044). The mortality reduction was mainly observed in studies of older, frailer individuals at high risk of fracture.²⁶⁷

6. A more recent meta-analysis of 38 RCTs involving 101642 subjects treated with 14 anti-osteoporosis drugs (alendronate, risedronate, ibandronate, clodronate, zoledronic acid, denosumab, bazedoxifene, lasofoxifene, raloxifene, arzoxifene, odanacatib, teriparatide, PTH 1-84, and romosozumab) however showed no significant association between osteoporosis treatment and overall mortality rate (RR=0.98; 95% CI: 0.91-1.05; P=0.56).²⁶⁸ A sub-analysis involving 21 RCTs of BP treatment in 42867 subjects also did not show significant association between treatment with overall mortality (RR=0.95; 95% CI: 0.86-1.04; P=0.17).²⁶⁸
7. Although evidence on whether anti-osteoporosis treatments would improve survival and decrease mortality is conflicting, anti-osteoporosis treatments do reduce fracture risk. The possibility that decreasing the risk of fracture may be associated with reducing the early excess mortality associated with fractures cannot be excluded.
8. A number of studies had shown that the excess mortality after fracture was attributed to cardiovascular diseases and infections notably pneumonia.^{265,269}
9. An exploratory analysis of the reduction in mortality in the HORIZON-RFT trial showed that subjects treated with zoledronic acid were less likely to die from pneumonia and arrhythmias than placebo-treated subjects.²⁷⁰
10. In a propensity score-matched cohort study involving 4594 hip-fractured patients treated with alendronate matched with 13568 untreated patients, alendronate was associated with a significantly lower risk of 1-year cardiovascular mortality (HR=0.33; 95% CI: 0.17- 0.65; P=0.001) and incident myocardial infarction (HR=0.55; 95% CI: 0.34-0.89; P=0.014).²⁷¹
11. In another propensity score-matched cohort study involving 4041 hip-fractured patients who received nitrogen-containing BPs and 11802 without anti-osteoporosis medication, treatment with nitrogen-containing BPs were associated with a significantly lower risk of pneumonia compared with no treatment (HR=0.76; 95% CI: 0.70-0.83; P<0.001). A similar association was observed with pneumonia mortality (HR=0.65; 95% CI: 0.56-0.75; P<0.001).²⁷²
12. The reduction in risks of myocardial infarction and pneumonia associated with zoledronic acid treatment were also observed in post-hoc analyses of the 6-year zoledronic acid fracture prevention study in osteopenic women.^{273,274}
13. These potential benefits with nitrogen-containing BPs in patients with osteoporosis need to be confirmed in well-designed RCTs.

(U) Management of Osteoporotic Fractures

1. An overview on the practical management of different types of osteoporotic fractures have been outlined in the 2013 Guideline Section Q.¹ Detailed description of the orthopaedic approach such as the choice of implants and the specific surgical techniques is beyond the scope of the current Guideline.
2. The care of patients with hip fracture in Hong Kong follows the principles laid down in the Blue Book published by the British Orthopaedic Association and the British Geriatrics Society.²⁷⁵ The key elements of good care include:
 - prompt admission to orthopaedic care;
 - rapid comprehensive assessment—medical, surgical and anaesthetic;
 - minimal delay to surgery;
 - accurate and well-performed surgery;
 - prompt mobilisation;
 - early multidisciplinary rehabilitation;
 - early supported discharge and ongoing community rehabilitation; and
 - secondary prevention, combining bone protection and falls assessment.
3. Regarding management of osteoporotic vertebral compression fractures, an international consensus on the non-pharmacological and non-surgical management of osteoporotic vertebral fractures has been published recently to provide multidisciplinary biopsychosocial recommendations to guide the management of osteoporotic vertebral fractures.²⁷⁶
4. **Update on vertebral augmentation procedures**
- 4.1 Early RCTs with sham procedure controls^{277,278} had casted some controversies on the efficacy and safety of vertebral body augmentation procedures for rapid pain relief, as discussed in detail in the 2013 Guideline Section Q2.¹ The recruitment of patients with relative long duration of the painful vertebral collapse, the under-recruitment of subjects with severe pain, and the injection of local anaesthetic into the posterior vertebral cortex in the sham procedure controls had been criticised to have negated the efficacy of the vertebral augmentation procedures.²⁷⁹
- 4.2 In a more recent RCT, the VAPOUR trial, which was a multicentre, randomised, double-blind, placebo-controlled trial of vertebroplasty with sham control procedure, in which local anaesthetic was confined to sc injection, in 120 hospitalised older adult patients (mean age 81 years) with 1-2 osteoporotic vertebral fractures of less than 6 weeks' duration and a high pain score, a significant between-group difference in improvement of pain score was noted at 14 days in favour of vertebroplasty (between-group difference 23%, 95% CI: 6-39; P=0.011). A subgroup analysis suggested that most benefit from vertebroplasty was in the thoracolumbar spinal segment.²⁸⁰
- 4.3 After comprehensive systematic literature review and meta-analyses, the second ASBMR Task Force Report on the efficacy and safety of vertebral

augmentation, summarised the evidence with the following statements²⁸¹:

- (a) For patients with acutely painful vertebral fracture, percutaneous vertebroplasty provides no demonstrable clinically significant benefit over placebo. Results did not differ according to duration of pain.
 - (b) There is also insufficient evidence to support kyphoplasty over non-surgical management, percutaneous vertebroplasty, or vertebral body stenting.
 - (c) There is limited evidence to determine the risk of incident vertebral fracture or serious adverse effects related to either percutaneous vertebroplasty or kyphoplasty. No recommendation can be made about harms, but they cannot be excluded.
 - (d) Routine use of vertebral augmentation is not supported by current evidence. When it is offered, patients should be fully informed about the evidence.
- 4.4 A recent editorial pointed out that vertebroplasty should still deserve to be used in carefully selected patients. Based on the benefits demonstrated in the VAPOUR study, early vertebroplasty is an appropriate treatment option in older adult patients admitted for a recent vertebral fracture responsible for severe pain, particularly if it is located at the thoracolumbar junction and/or if the patient has comorbidities.²⁸²

5. Update on hip fracture surgery timing and outcomes

- 5.1 Controversies exist whether early surgical stabilisation and fixation of hip fracture will reduce mortality because of the presence of confounding comorbidities in observational studies. In the past years, there has been growing body of evidence to support the benefits of early surgery.
- 5.2 In a local territory-wide retrospective review, 43 830 geriatric patients (aged ≥65 years) who had surgery for hip fracture in the public sector from 2000 to 2011 were categorised into three groups according to the timing of surgery: early (0-2 days), delayed (3-4 days), and late (≥5 days). The overall 1-year mortality rate was 16.8%. Both the delayed and the late groups had a significant increase in RR of 30-day mortality (RRs 1.20 and 1.66 for the delayed and late groups, respectively), as well as 1-year mortality (RRs 1.21 and 1.52 for the delayed and late groups, respectively) than the early group.²⁸³
- 5.3 A more systematic analysis was reported by a Canadian group, which was a population-based, retrospective cohort study of 42 230 adults (mean age 80.1 years) undergoing hip fracture surgery in Ontario. The 13 731 subjects who received surgery within 24 hours were matched with the same number of subjects who received surgery after 24 hours using propensity score matching. The late surgery group was found to have a significantly higher risk of 30-day mortality (6.5% vs 5.8%; 95% CI: 0.23-1.35; P<0.006) compared with the early surgery group. The early surgery group also had a more favourable secondary composite outcome of mortality or other medical complications (myocardial infarction, deep vein thrombosis,

pulmonary embolism and pneumonia) (10.1% vs 12.2%; 95% CI: 1.43-2.89; P<0.001). The authors concluded that 24 hours appeared to be the inflection time after which complications begin to increase.²⁸⁴

- 5.4 Many factors will influence the timing of hip fracture surgery, which embraces patient factors, structural/organisational factors and resources factors. A comprehensive analysis of all the potential factors and their interplay relationship were provided in a well-written review article.²⁸⁵
- 5.5 A recent editorial called for the development of an orthopaedic and medical/geriatric co-management team with more efficient preoperative patient evaluation and stabilisation, more flexibility of scheduling and surgical workforce capacity, and effective approaches to ensure surgical repair as early as possible, ideally within 24 hours as the standard of care.²⁸⁶
- 5.6 Early surgery may occasionally be impeded by the presence of holidays. A local study tried to explore the effect of small delays in surgery due to holidays. In a cohort of 31 592 patients with 0, 1, 2 or 3 days of holidays following admission, they had significantly increase in the mean time to operation of 2.25, 2.47, 2.67 and 2.84 days, respectively (Kruskal-Wallis test P<0.0001). Nonetheless, there was no difference in mortality at 6 months (P=0.431) and 2 years (P=0.785).²⁸⁷
- 5.7 While striving for surgery as early as safely possible may be an ideal target, early surgery within 24-48 hours may be a more practical and more easily achievable performance indicator as recommended by recent international guidelines.²⁸⁸⁻²⁹⁰

(V) Post-Fracture Care and Management

1. A detailed account on the rehabilitation of patients after a fragility fracture has been provided in the 2013 Guideline Section R.¹ A recent IOF review article updated the latest global approach to rehabilitation after an osteoporotic fragility fracture.²⁹¹
2. One of the most important areas of deficits remains on the post-fracture treatment gap that most patients (up to 80%) with fragility fractures are not actively identified, appropriately assessed and treated for secondary fracture prevention.^{17,292-294}
3. The recent recognition of the concept of imminent fracture risk in the initial 2 years of a fragility fracture (see Section G) and the adoption of a risk-based treatment approach in most osteoporosis management guidelines (see Section M) have specifically called for the need of timely assessment and early interventions for secondary fracture prevention in patients presented with fragility fractures.
4. In response to this widely documented gap in care and treatment, models of care have been developed to ensure that fragility fracture patients would receive secondary preventive care including both osteoporosis management and intervention to prevent falls, in a consistent and reliable fashion. The most common models are referred to as orthogeriatric services and FLS.²⁹⁵

5. Orthogeriatric care model

- 5.1 Orthogeriatric services typically deliver secondary preventive care for geriatric hip fracture patients.
- 5.2 Several orthogeriatric care models have been employed in clinical practice, namely geriatric medicine consultant service, geriatric medical ward with orthopaedic surgeon consultant service, and integrated care model.²⁹⁶
- 5.3 A recent systematic review and meta-analysis involving 37294 patients in 37 studies showed that orthogeriatric care significantly reduced length of stay by 1.55 days, with a 28% reduction in in-hospital mortality, 14% reduction in 1-year mortality, but there was no significant effect on time-to-surgery and 30-day readmission rate. The report noted a substantial heterogeneity across the studies and there was complete lack of direct comparison among the three models of orthogeriatric care. No consistent effect was found on functional outcome. Limited data suggested orthogeriatric care was cost-effective.²⁹⁶
- 5.4 An early local experience had shown a shorter length of stay, shorter time to surgery, lower in-hospital mortality, and lower hospital cost with implementation of an orthogeriatric programme for hip fracture patients.²⁹⁷
- 5.5 A more recent local study reported that implementation of a multidisciplinary geriatric hip fracture clinical pathway significantly reduced the time to surgery (from 5.8 days to 1.3 days), the total length of stay in both acute and rehabilitation hospitals (shortened by 6.1 days and 14.2 days, respectively), and the rate of postoperative pneumonia (from 1.25% to 0.25%). Both 30-day mortality (decreased from 5.4% to 1.7%) and the 1-year mortality (decreased from 23.9% to 13.8%) showed a significant reduction. The shortened length of stay resulted in a significant 29.8% reduction in cost in manpower per hip fracture case treated in the rehabilitation hospital.²⁹⁸

6. Fracture liaison service

- 6.1 Fracture liaison service is a coordinator-based, secondary fracture prevention service with a multidisciplinary approach to care of patients aged 50 years or older after fragility fractures. Key elements of a FLS include case finding, patient assessment, osteoporosis assessment, initiation of osteoporosis treatment, falls prevention, education, and exercise. The role of the coordinator is typically performed by a specially trained advanced practice provider such as a nurse practitioner. FLS is currently accepted as the best secondary fracture prevention model of care for managing osteoporosis following fragility fractures.²⁹⁹
- 6.2 The IOF Capture the Fracture Best Practice Framework has laid down 5 domains and 13 standards as a guidance and benchmarking for FLS.^{300,301} Based on the IOF framework, a consensus on best practice standards for FLS in the Asia-Pacific Region was published in 2018.³⁰² Currently, more than 900 FLSs from 56 countries have joined the IOF Map of Best Practice by January 2024, including five public hospitals from Hong Kong.³⁰³
- 6.3 Systematic reviews and meta-analyses consistently

showed that patients in FLS had higher rates of BMD testing, treatment initiation and greater adherence, and a much lower rate of re-fracture and mortality,^{304,305} and had been proven to be cost-effective or even cost-saving.^{306,307}

- 6.4 A FLS dedicated for patients with vertebral fracture had also been reported with anecdotal favourable outcomes.³⁰⁸ In this local study involving 226 patients with a recent vertebral fracture recruited into the FLS followed up for 2 years, 97.8% underwent DXA assessment with 100% treatment initiation. The treatment compliant rate was 89.8% at 2 years with significant improvement in pain, quality of life, and disability scores.³⁰⁸
 - 6.5 Apart from treating bone health, management of other important risk factors that contribute to fracture are also important in a comprehensive FLS, namely fall prevention and attention to sarcopenia.
 - 6.6 A local study reported a very high prevalence of sarcopenia (73.6% in males and 67.7% in females) in a cohort of 239 geriatric hip fracture patients, with a mean age 82 years.³⁰⁹ These findings are consistent with a recent systematic review, which reported that up to 95% of male and 64% of female fragility fracture patients had sarcopenia.³¹⁰
- ## 7. Fall prevention
- 7.1 As discussed in detail in the 2013 Guideline Section R3, it must be emphasised again that fall prevention should receive at least as much attention as drug therapy for osteoporosis.¹
 - 7.2 Updated evidence on the key strategies for prevention and management of elderly falls is outlined below.³¹¹⁻³¹⁶
 - (i) Exercise is consistently reported to be the principal component of single, multiple or multifactorial intervention programmes that are effective for fall prevention.
 - (ii) The benefit of Tai-chi in balance training was further demonstrated in a RCT in a group of community-dwelling older adults at high risk of falls to be more effective than conventional multimodal exercise programme in reducing the incidence of falls.³¹⁷
 - (iii) Besides exercise, components of multiple interventions that are significantly associated with reduction in falls are assistive technology (including vision or hearing impairment assessment and treatment), environmental assessment and modifications, quality improvement strategies, and basic fall risk assessment (including medication review).
 - (iv) Effective fall prevention quality improvement strategies are multi-faceted, and include components targeting patients (such as education and reminders), as well as components targeting clinicians (such as team changes, case management and staff education).
 - (v) Recent large-scale population RCTs showed that vitamin D supplementation did not reduce the risk of falls or fall-related fractures in the general population.¹²²⁻¹²⁴
 - (vi) Whole-body vibration was associated with

a lower risk of falls, but only investigated in a few studies with small sample size.³¹⁸⁻³²⁰ Whole-body vibration had no demonstrable effects on BMD.³²¹

8. Role of nutritional support in post-fracture care

- 8.1 Nutritional care has been a neglected part in the rehabilitation of patients after a fragility fracture.
- 8.2 Malnutrition, in particular protein and caloric under-nutrition, impairs muscle strength and function, which will increase the risks of falling and fracture. Malnutrition will also negatively influence fracture healing, slow down the process of rehabilitation, and increase risk of complications and disabilities, and hence, increase the risk of subsequent fracture.
- 8.3 Mortality is increased by more than twofold (odds ratio 2.4) with malnutrition in patients with hip fracture.³²²
- 8.4 Nutritional intervention studies have shown a decrease in medical complications such as infection and pressure ulcers, shorter wound healing times, reduced length of stay, lower mortality, a preservation of BMD, improvements in activities of daily living, and better muscle function, albeit most studies involved small number of patients.^{323,324}
- 8.5 Systematic review and meta-analysis showed that perioperative oral nutritional supplementation had a positive effect on the serum total protein, and a significant reduction in the number of postoperative infections including wound, respiratory and urinary tract infections but there was no significant reduction in mortality.^{322,323}
- 8.6 In a local study involving 126 older adult patients after hip fracture surgery being randomised to receive oral liquid nutritional supplementation (18-24 g protein and 500 kcal per day) in addition

to hospital diet or hospital diet only, there was a significant benefit in terms of body weight maintenance, reduction in the number of infection episodes, and reduction in the length of rehabilitation stay in the supplementation group. However, there was no significant change in functional outcome assessed at discharge as well as follow-up at 4 weeks.³²⁵

- 8.7 A critical pathway targeting at detection of malnutrition and implementation of nutrition supplement should be a full part of fracture rehabilitation.

(W) Conclusions

1. In the past decade, there has been a vast quantity of new information from the published literature in the field of osteoporosis.
2. The current Guideline aims to summarise the evolving concepts in medical treatment of postmenopausal osteoporosis with an emphasis on the benefits of bone-forming agent-first strategy for patients with very high risk or imminent risk of fracture.
3. The current Guideline provides a comprehensive discussion on the management of the two most serious but rare complications of antiresorptive drug treatment, namely MRONJ and AFF. Osteoporosis and bone fragility in diabetes as an emerging serious chronic complication of diabetes is also highlighted.
4. The Guideline also provides the most comprehensive guidance for the local specialists and primary care practitioners on when to stop or switch anti-osteoporosis drug therapies, and the precautions to note upon switching among different classes of anti-osteoporosis medications.

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