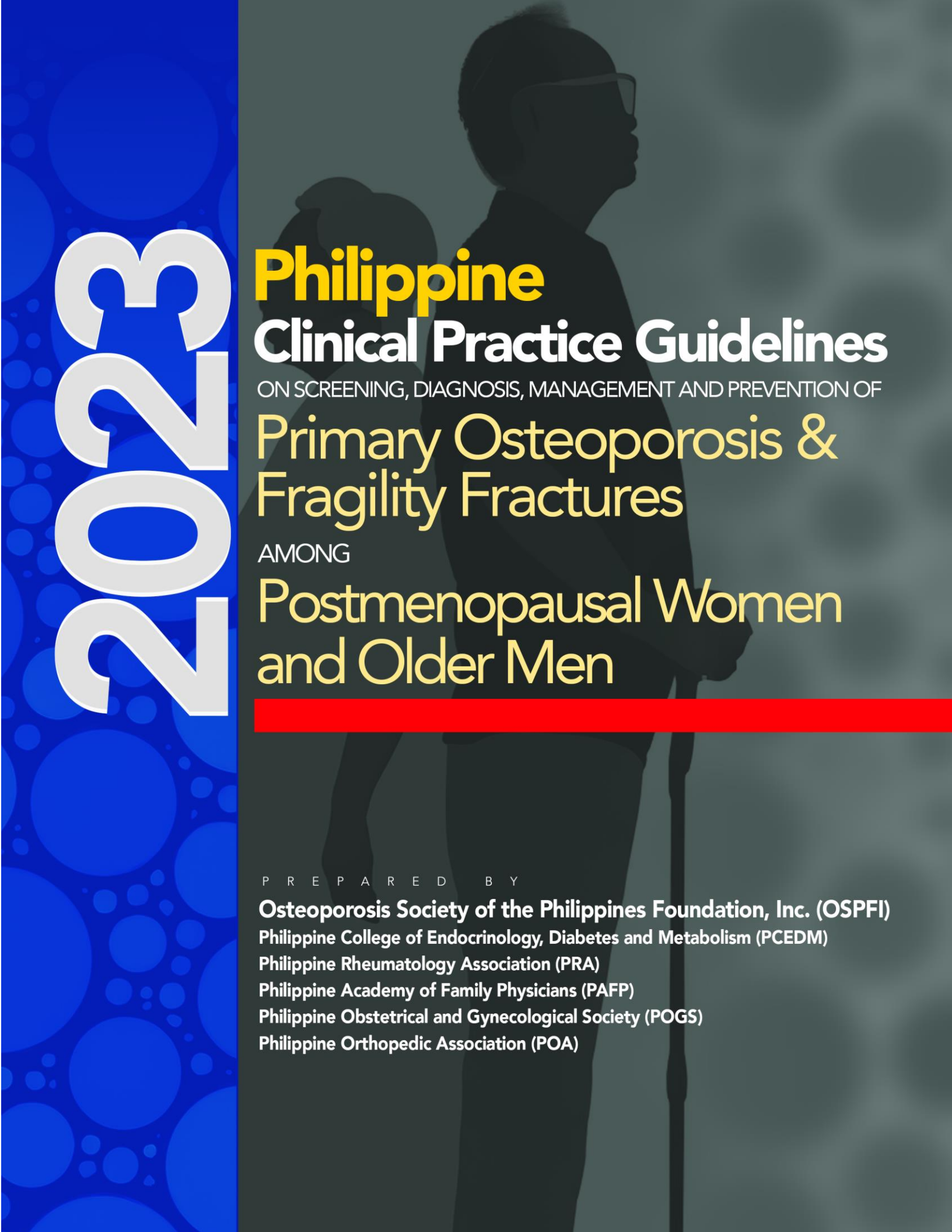

2023

Philippine Clinical Practice Guidelines

ON SCREENING, DIAGNOSIS, MANAGEMENT AND PREVENTION OF

Primary Osteoporosis & Fragility Fractures

AMONG

Postmenopausal Women and Older Men

PREPARED BY

Osteoporosis Society of the Philippines Foundation, Inc. (OSPFI)
Philippine College of Endocrinology, Diabetes and Metabolism (PCEDM)
Philippine Rheumatology Association (PRA)
Philippine Academy of Family Physicians (PAFP)
Philippine Obstetrical and Gynecological Society (POGS)
Philippine Orthopedic Association (POA)

2023 Philippine Clinical Practice Guidelines on Screening, Diagnosis, Management, and Prevention of Primary Osteoporosis and Fragility Fractures Among Postmenopausal Women and Older Men

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ABBREVIATIONS AND ACRONYMS

AGREE	Appraisal of Guidelines for Research and Evaluation
ARD	Absolute risk difference
BMD	Bone mineral density
COI	Conflict of interest
CPG	Clinical Practice Guideline
DALY	Disability-adjusted life years
DXA	Dual-energy X-ray Absorptiometry
DOH	Department of Health
ERE	Evidence Review Expert
EtD	Evidence to Decision
FLS	Fracture Liaison Service
FRAX	Fracture Risk Assessment Tool
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HR	Hazard ratio
HMO	Health maintenance organization
MHT	Menopausal Hormone Therapy
NCD	Non-communicable disease
OSPFI	Osteoporosis Society of the Philippines Foundation, Inc
PICO	Population, Intervention, Comparator, Outcome
PAFP	Philippine Academy of Family Physicians
PCEDM	Philippine College of Endocrinology Diabetes and Metabolism
PMW	Postmenopausal women
POGS	Philippine Obstetrical and Gynecological Society
POA	Philippine Orthopaedic Association
PRA	Philippine Rheumatology Association
RR	Relative risk
RCT	Randomized controlled trial
SC	Steering Committee
SD	Standard deviation
TVS	Trans-Vaginal Ultrasound
TWG	Technical Working Group

EXECUTIVE SUMMARY

Osteoporosis is a chronic bone disease that affects millions of individuals and constitutes a major public health problem. As the global population continues to age, the burden of osteoporosis is projected to increase in the coming years due to increasing life expectancy, population aging and the growing prevalence of noncommunicable diseases that impact negatively on osteoporosis risk factors.

This first clinical practice guideline on osteoporosis prevention and management in the Philippines is the output of a shared undertaking by a multidisciplinary CPG development team spearheaded by the Osteoporosis Society of the Philippines Foundation, Inc. and joined by the Philippine Academy of Family Physicians, Philippine College of Endocrinology, Diabetes and Metabolism, Philippine Orthopedic Association, Philippine Obstetrics and Gynecological Society and Philippine Rheumatology Association. This guideline seeks to augment and update the “Consensus statements on osteoporosis diagnosis, prevention and management in the Philippines” initially published in 2011, by incorporating evidence-based practices that had been developed in the last decade.

Clinical practice guidelines are important tools that seek to improve patient outcomes by improving clinical decision-making. This CPG is a systematic synthesis of scientific evidence related to primary, secondary, and tertiary prevention strategies for osteoporosis in postmenopausal women. Guideline development followed the ADAPTE process, a validated and systematic approach of adapting existing guidelines for use in a specific organizational context or setting with limited time and resource commitments. Developers also planned for de novo systematic review and meta-analysis using the widely accepted GRADE approach for clinical questions that were unsuitable for adaptation. Finally, the Evidence to Decision (EtD) Framework was used to guide panel discussions and inform decision-making when the final recommendations were formulated.

Thirty-four recommendations were formulated to address 27 clinical questions related to screening, prevention, diagnosis, pharmacologic and nonpharmacologic treatment, surgical management, follow-up, and continuity of care. With these recommendations, the developers aim to establish a standard of care in the prevention, diagnosis, and management of osteoporosis and fragility fracture in both in-patient and out-patient cases that is appropriate to the Philippine context. Specifically, the CPG development group aims that these recommendations will be used to define osteoporosis standard of care as part of Universal Health Care services once the program is implemented on a national level. The recommendations may also be used by relevant stakeholders to inform public and private payor policies for patients with fragility fractures as well as by local government units or private companies looking to establish orthogeriatric centers with fracture liaison services.

The 2023 Philippine Osteoporosis Guidelines were created to benefit primary care physicians and allied health professionals involved in the care of patients with or at risk for osteoporosis.

The recommendations in this CPG shall hold and will be updated after 3 years or when any member of the CPG Steering Committee encounters new evidence that could potentially impact the recommendations.

SUMMARY OF RECOMMENDATIONS

SCREENING AND ASSESSMENT

Clinical Question	Recommendations	QOE	SOR
1. Among the adult population, who should be screened for osteoporosis?	It is recommended that the following individuals be screened for osteoporosis: • All postmenopausal women • Men aged >/= 50 years • Adults with clinical risk factors	Mod to High	Strong
2. Among the adult population, what factors increase the risk of osteoporosis?	**Screening for the following risk factors is recommended**: advanced age (>70 years), previous fragility fracture, menopause or untreated early menopause, parental history of osteoporosis and/or fractures, excessive alcohol consumption (>3.5 units per day), smoking, frailty or low level of physical activity, coexisting illnesses, and certain medications. **Comorbidities**: diabetes, hyperparathyroidism or other endocrine diseases, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, malabsorption, institutionalized patients with epilepsy, chronic liver disease, neurological disease (Alzheimer's, Parkinson's, multiple sclerosis, stroke), moderate to severe chronic kidney disease, bronchial asthma, HIV **Medications**: glucocorticoids, antidepressants, anti-epileptic agents (i.e. enzyme-inducing drugs), aromatase inhibitors, GnRH agonists for prostate cancer, PPIs, thiazolidinediones, anticoagulants, methotrexate, thyroid hormones	High	Strong
3. What tool should be used for osteoporosis screening in the adult population?	Osteoporosis screening should be performed using the FRAX tool.	High	Strong
	The OSTA tool maybe used as an alternative to FRAX for osteoporosis screening.	High	Strong
4. What is the clinical presentation of osteoporosis in the adult population?	Patients who present with the following history, signs and symptoms should be suspected to have osteoporosis: acute onset back pain, height loss, previous fragility fracture, menopause or untreated early menopause, parental history of osteoporosis and/or fractures. Physical examination findings include any of the following: low weight or BMI (<18.5 kg/m^2), ≥ 4 cm height loss, or thoracic kyphosis	High	Strong

DIAGNOSIS

Clinical Question	Recommendations	QOE	SOR
5. Among at-risk PMW, should bone mineral density measurement by dual energy x-ray absorptiometry be used to diagnose osteoporosis?	Among at-risk PMW, it is recommended that bone mineral densitometry (BMD) test using dual energy x-ray absorptiometry (DXA) be used for the diagnosis of osteoporosis.	High	Strong
	Among at-risk PMW, it is recommended that the following criteria be used to diagnose osteoporosis: history of fragility fracture/s, BMD T-score ≤-2.5, or low bone mass (BMD T-score between < -1.0 and > -2.5) with fragility fractures, or high fracture risk according to country-specific FRAX.	High	Strong
	Among at-risk PMW of vertebral fracture, it is recommended that vertebral fracture assessment (VFA) using DXA or lateral spine radiograph be done.	High	Strong
	Among at-risk PMW without fracture, it is suggested that FRAX w/o BMD be used for the diagnosis of osteoporosis in settings where BMD measurement via DXA is unavailable or not feasible. A fracture intervention threshold of 3.75% for major osteoporotic fractures and/or 1.25% for hip fractures is suggested.	High	Strong

MANAGEMENT

PHARMACOLOGIC

Clinical Question	Recommendations	QOE	SOR
6. Among PMW with osteoporosis, is alendronate, ibandronate, zoledronate, denosumab, raloxifene effective in reducing vertebral, non-vertebral, hip fractures compared to placebo?	Among PMW with osteoporosis, it is recommended that alendronate, denosumab, risedronate and zoledronate be used as initial therapy to reduce vertebral, non-vertebral, and hip fractures.	High	Strong
	Ibandronate or raloxifene can be an alternative treatment in reducing vertebral fractures in certain cases.	Mod	Strong

7. Among PMW with severe osteoporosis, is teriparatide, abaloparatide, and romosozumab effective in reducing vertebral, non-vertebral, hip fractures compared to placebo? How long should treatment duration be?	Among PMW with severe osteoporosis, it is recommended that teriparatide, abaloparatide and romosozumab be used. Abaloparatide and romosozumab prevent vertebral, non-vertebral and hip fractures while teriparatide reduces the risk of further vertebral and non-vertebral fractures. Treatment duration of bone forming agents for maximum treatment benefits is recommended to be referred to specialists.	High	Strong

NONPHARMACOLOGIC (Vitamin D and Calcium)

Clinical Question	Recommendations	QOE	SOR
8. Among PMW women with osteoporosis, should Calcium and Vitamin D be given as supplement to reduce fragility fracture risk?	Among PMW with osteoporosis, calcium and vitamin D supplementation is recommended along with anti-osteoporosis medications to reduce the risk of fragility fractures. The recommended dose for elemental calcium is 700-1200 mg/day and vitamin D at least 800 IU per day.	High	Strong
9. Among PMW with osteoporosis, should levels of calcium and vitamin D be normal before initiation of anti-resorptive therapy?	Among PMW with osteoporosis, it is recommended that calcium insufficiency/ deficiency be treated prior to initiation of anti-osteoporosis drugs. It is also recommended that vitamin D insufficiency/ deficiency should be addressed alongside the initiation of anti-osteoporosis drugs.	Mod High	Strong Strong

SURGICAL MANAGEMENT

Clinical Question	Recommendations	QOE	SOR
10. Among patients with previous fragility fractures, what is the effect of pharmacologic intervention on the risk of having a subsequent or second fracture?	Among patients with previous or prevalent fragility fractures, it is recommended to give pharmacologic therapies specifically bisphosphonates and teriparatide to reduce the risk of subsequent fractures.	Mod	Strong

11. Among patients with acute displaced fragility fractures of the distal radius, is early surgical intervention superior to conservative management for improving functionality?	Among patients 65 years old and above with acute displaced fragility fractures of the distal radius, it is **not recommended** to proceed with surgery to improve long-term patient functional outcomes.	High	Strong
12. Among patients who have painful osteoporotic compression fractures of the spine, is kyphoplasty superior to nonsurgical management for controlling pain and improvement of quality of life (QOL)?	Among patients with painful osteoporotic compression fractures of the spine, it is suggested that kyphoplasty be done over non-surgical treatment for acute pain control (6 to 8 weeks) and improvement of QoL.	Mod	Weak
13. Among patients who sustained fragility fractures of the hip, is early surgical intervention superior to delayed surgical intervention in improving overall survival, morbidity, mortality, and functionality of patients?	Among patients who sustained fragility fractures of the hip, it is suggested that early surgical management (24 to 48 hours) be done to reduce morbidity and improve survival.	Mod	Strong
14. Among patients with a previous osteoporotic fragility fracture, will enrollment in a secondary fracture prevention program or fracture liaison service (FLS) improve treatment adherence and prevent re-fractures?	Among patients who have experienced a fragility fracture, it is recommended that they be managed within a formal integrated system of care that incorporates a fracture liaison service (FLS) to prevent re-fractures and improve adherence to osteoporosis treatment.	High	Strong
	Among patients who have fragility fracture/s, it is recommended that appropriate interventions including both pharmacological and non-pharmacological be started.	High	Strong

FOLLOW-UP CARE

Clinical Question	Recommendations	QOE	SOR
15. Among adults receiving osteoporosis treatment, what is the appropriate interval between central DXA scans in monitoring treatment response?	Among adults receiving osteoporosis treatment, it is recommended that central DXA test should be done every 1-2 years especially in patients at high risk for fracture, then at longer intervals thereafter once definite satisfactory treatment response is achieved	Mod	Strong
16. Among adults with recent fragility fracture, what factors should be considered when recommending referral to an osteoporosis specialist?	It is recommended that patients with the following risk factors/conditions be referred to an osteoporosis specialist: a. patients with fragility fracture and/or subsequent fragility fractures b. BMD T-score ≤ − 3.5 c. treatment with high dose glucocorticoids (≥7.5 mg/day of prednisolone or equivalent over 3 months) d. patients with co-morbidities such as CKD, endocrine and rheumatic diseases	High	Strong

PREVENTION (Lifestyle, Nutrition and Hormone Replacement Therapy)

Clinical Question	Recommendations	QOE	SOR
17. Should at-risk PMW receive calcium supplementation and/or Vitamin D supplementation for prevention of osteoporosis and fragility fractures?	Among at-risk adults with normal FRAX and BMD scores, calcium and vitamin D supplementation is recommended for those who do not meet country-specific reference standards. Potential hazards and adverse effects of calcium and vitamin D supplementation include: increased risk for renal insufficiency, myocardial infarction, coronary artery disease and stroke.	Mod	Strong
18. Among PMW, what doses of calcium and Vitamin D are associated with reduced fragility fracture risk?	Among at-risk adults with normal FRAX and BMD scores who do not meet country-specific reference standards, supplementation with Vitamin D at 400 to 600 IU/day and Calcium at 700 to 800 mg/day is recommended.	Mod	Mod
19. Among PMW, what is the benefit of physical activity in the prevention of osteoporosis and fragility fractures?	Among PMW, regular physical activities using a combination of exercise types *(such as weight bearing, balance training, flexibility or stretching exercises, endurance and progressive strengthening exercises)* are recommended to increase BMD and reduce the risk of fragility fractures.	High	Strong

20. Among PMW and older men, does smoking cessation prevent osteoporosis and fragility fractures?	Among PMW and older men, smoking cessation is recommended to reduce risk of osteoporotic fractures. Specific guidelines on smoking cessation are outlined in the Philippine Guidelines on Periodic Health examination - Lifestyle advice CPG.	Mod	Strong
21. Among PMW and older men, what diet is effective in the prevention of osteoporosis?	Among PMW and older men, a balanced diet or nutrient-dense diet (fruits, vegetables, and whole grains) is recommended to prevent osteoporosis and fragility fractures.	Mod	Strong

ROLE OF MHT IN PREVENTION OF OSTEOPOROSIS

Clinical Question	Recommendations	QOE	SOR
22. Should at-risk postmenopausal women receive menopausal hormone therapy (MHT) for the prevention of fragility fractures? For how long will the duration of use be?	Among at-risk peri and postmenopausal women with climacteric symptoms but without contraindications to MHT, it is recommended that MHT be given for a minimum duration of 2 years but not longer than 3 years to reduce fracture risk.	High	Strong
	Among at-risk peri and post-menopausal women with climacteric symptoms but with contraindications to MHT, MHT is not recommended.	High	Strong
23. When should menopausal hormone therapy be initiated to reduce fracture risk?	Among at-risk peri and postmenopausal women with climacteric symptoms but without contraindications to MHT younger than 60 years of age, Initiation of MHT may be of greater benefit in fracture risk reduction.	High	Strong
24. Which hormone preparation should be used for fracture risk reduction?	Among hysterectomized PMW, it is recommended to give estrogen only replacement therapy for fracture risk reduction. Addition of progestins is recommended for women with intact uterus to prevent endometrial pathology.	High	Strong
25. What are the safety issues of MHT?	The safety issues of MHT include an increased risk for coronary events, stroke, venous thromboembolism, breast cancer and gallbladder disease. Among at-risk peri and postmenopausal women with climacteric symptoms but without contraindications to MHT, transdermal estrogen (gel/patch) is recommended over oral estrogen to decrease the	High	Strong

	risk of VTE.		
26. Should SERMS be an alternative to MHT for the prevention of osteoporosis?	Among women at risk of breast cancer, raloxifene is recommended as an alternative to MHT to reduce the risk of vertebral fractures.	High	Strong
27. How are adverse events monitored in women receiving MHT for osteoporosis prevention?	1. Among women on MHT who are at risk of breast cancer, it is recommended for them to undergo annual mammograms. 2. Among women with postmenopausal bleeding on MHT, it is recommended for them to undergo transvaginal ultrasound every 6 months for the first year and annually thereafter. 3. Among women on MHT, it is recommended that they be monitored for signs and symptoms of venous thromboembolism, cardiovascular and cerebrovascular diseases.	High	Strong

COE = Quality of Evidence; SOR = Strength of Recommendations

INTRODUCTION

POPULATION AGEING, NON-COMMUNICABLE DISEASES AND OSTEOPOROSIS

The global health landscape has rapidly evolved in the past century. Health priorities and agendas which have been mostly focused on communicable diseases and maternal and child mortality have now shifted to modern and complex challenges such as population aging, the growing burden of non-communicable diseases (NCDs), and the persistent threat of global pandemics.[1]

Global demographics are shifting. In every country in the world, both the size and proportion of older people in the population are expanding dramatically. In 2018, for the first time in history, persons aged 65 and older outnumbered children under five years of age globally.[2] The number of persons aged 60 and above is expected reach 2.1 billion in 2050 and more than half of this demographic growth will occur in Asia.[2] Populations are aging at unprecedented rates, primarily driven by increasing life expectancy, decreasing mortality rates, falling fertility rates and better health care.[3]

Aging is inevitable. Due to socioeconomic progress, most of the world's populations are living longer.[4] By 2050, one in four persons living in Europe and Northern America could be aged 65 or over.[2] In the Philippines, the average life expectancy is estimated to increase from 72 years in 2013 to 80 years by the year 2050.[4,5] The proportion of the Filipino population aged over 70 years is predicted to grow from 2.8 million in 2013 to 13.4 million in 2050.[5]

Aging creates a public health problem as the old adult population is faced with an increased susceptibility to age-related conditions and non-communicable diseases that significantly affect functional health and demand for healthcare services.[3]

NCDs are on the rise and contribute to 74% of deaths globally.[6] With age comes a gradual decrease in physiologic reserves, cognitive capacity and functioning. Aging also leads to bone loss, especially after menopause, therefore the prevalence of age-related musculoskeletal conditions like osteoporosis and fragility fractures will likely track the trajectory of the aging population.[7,8] Some NCDs can exert negative effect on bone health. For instance, obesity and diabetes have been associated with higher risk of fractures independent from bone mineral density (BMD).[9] The burden of osteoporosis and fragility fractures is projected to increase dramatically in the next decade primarily due to the effect of population aging, but the growing prevalence of NCDs is expected to add to this burden.[9]

OSTEOPOROSIS

Osteoporosis is a chronic disease characterized by bone microarchitecture deterioration and reduced bone mineral density, leading to decreased bone strength, bone fragility and increased risk of fractures.[7,10] Osteoporosis has many etiologies, the most common causes are estrogen deficiency occurring after menopause and bone loss due to aging (primary osteoporosis). Secondary osteoporosis is caused by diseases (e.g., endocrine disorders, malabsorption), treatments (e.g., chronic glucocorticoid use) or idiopathic.[11]

Osteoporotic or fragility fracture is the most serious complication of osteoporosis. These are fractures that result from low-level trauma or mechanical forces that do not typically result in fracture, such falls from a standing height or less.[12,13]

The diagnosis of osteoporosis is based on bone mineral density (BMD) values in relation to a reference standard. The World Health Organization (WHO) defines osteoporosis as a BMD T-score less than or equal to -2.5 SD (see Table 1).[14] Osteoporosis is also diagnosed based on the presence of fragility fractures, even with a normal bone mineral density (T-score).[10]

Table 1. WHO Criteria for Classification of Osteopenia and Osteoporosis[14]

Category	T-score
Normal	≥ -1.0 or above
Low bone mass (Osteopenia)	Between -1.0 and -2.5
Osteoporosis	≤-2.5 or below
Severe or established osteoporosis	≤-2.5 or below with fragility fracture
Fracture rates vary widely. The category "low bone mass" when applied to real-world patients must be combined with clinical information to make a well-informed medical decision.	

EPIDEMIOLOGY OF OSTEOPOROSIS

Global

Reports estimate that approximately 200 million people suffer from osteoporosis and approximately 8.9 million fractures are caused by osteoporotic fractures worldwide, but these figures are 2 decades old and likely underestimate the current prevalence of the disease.[15,16] In 2021, the estimated global prevalence of osteoporosis was 18.3% based on a large meta-analysis of 86 studies across Asia, Europe, USA, Africa and Australia (N=103 million people aged 15-105 years).[17] If calculated against the current world population, this suggests that there are almost 1.4 billion people now living with osteoporosis globally.

Women, especially postmenopausal women, are disproportionately affected. In the 2017-2018 CDC National Health and Nutrition Examination Survey, the age-adjusted prevalence of osteoporosis at the femur neck, lumbar spine or both among adults aged ≥50 years was 12.6% higher among women than men (19.6% vs 4.4%).[18] Similarly, the prevalence of low bone mass at the same skeletal sites was 43.1% higher among women than men (51.5% vs 33.5%). Globally, 1 in 3 women and 1 in 5 men aged 50 years or older will sustain an osteoporotic fracture in their remaining lifetime.[19]

Philippines

Osteoporosis is greatly underdiagnosed and undertreated in Asia, particularly in the rural areas. Poor access to diagnostics and treatment, lack of awareness about the disease and insufficient epidemiological data are key barriers to osteoporosis care in this region.[5] Still, it is estimated that about 50% of all osteoporotic hip fractures will occur in Asia by the year 2050, scoring the need for greater efforts in primary and secondary prevention among Asian countries.[20]

Dual energy x-ray absorptiometry (DXA), the gold standard diagnostic tool for osteoporosis, is not readily available in a resource limited setting like the Philippines. Estimates on the local prevalence of osteoporosis are based on institutional data where central BMD machines are available and accessible. Hence the true incidence and prevalence of osteoporosis in the Philippines is not available.

In 2003, the National Nutrition and Health Survey (NNHeS) in adult Filipinos reported that the overall prevalence of osteoporosis by peripheral bone densitometry was 0.8% in adults aged 60-69 years and 2.5% in those aged >70 years old. The overall prevalence of low bone mass was 65.2% in females and 70.0% in males, while the prevalence of fragility fractures was 11.2% in females and 9.0% in males.[5] In the same study, more than half of the participants were classified as intermediate (44.8% of females vs 41.9% of males) to high risk (17.6% of females vs 12.9% of males) for osteoporosis based on the Osteoporosis Screening Tools for Asians (OSTA).[5] . Based on this data, the number of Filipinos at risk of osteoporosis is projected to reach 4 million by 2020 and 10.2 million by 2050.[21]

Admissions data from the Philippine Orthopedic Center from 1995-1997 (N=19,920 patients aged ≥50 years) showed that femoral fractures accounted for 41% of fractures seen, followed by forearm fractures (31%) and vertebral fractures (22%).[22] Of the 11,354 female patients seen, 58% of them suffered from hip fractures. Meanwhile, data from the trauma registry of Philippine Orthopedic Association from 2002-2003 report that in patients admitted in the 18 orthopedic training centers in the country, 70% of the mixed fractures were due to falls.[23]

BURDEN OF OSTEOPOROSIS

Global

In 2019, a total of 178 million new fractures were recorded globally, equivalent to 25.8 million years lived with disability.[24] Majority of these fractures occurred in the older adult population (>50 years). Age-standardized incidence accelerated at around 50-54 years in females and 65-69 years in males, coinciding with the age at which low-trauma osteoporosis becomes prevalent in both populations. Of these, 437,000 deaths and 16.6 million disability-adjusted life years (DALY) in 2019 were attributed to osteoporosis and low bone mass while 301,482 annual deaths and 9.8 million DALYs were attributed to osteoporosis-related hip fractures.[25] Females had a higher burden of disease compared with males and the gap widened with age.

Fracture-related burden is projected to increase in the coming years because of population aging, potentially causing significant socioeconomic strain on individuals, families, societies and healthcare systems. Fractures can lead to work absence, decreased productivity, disability, impaired quality of life, health loss, and high health-care costs.[24] The EU6 recorded 2.7 million fragility fractures in 2017 which is expected to increase to 3.3 million in 2030, a 23% increase. The annual fracture-related costs amounting to €37.5 billion in 2017, is also projected to increase by 27% in 2030.[26]

In 2017, the estimated cost of hospitalization for a hip fracture was estimated to be US$10,075, and total health and social care costs for one hip fracture after 12 months amounted to a global mean of $43,669.[27] Fragility fractures are not only costly, but deadly. The mortality rate after a hip fracture is 79%, with almost half of patients succumbing within 1-year post-fracture.[28]
Despite this huge burden, only a few are properly treated after an index osteoporotic fracture. Less than 30% of postmenopausal and women and 10% of men receive treatment after a fracture creating a significant treatment gap.[28]

Philippines

According to the latest data from the Global Burden of Disease Study, an estimated 1.6 million new fractures were recorded in the Philippines in 2019, equivalent to more than 200,000 years lived with disability.24 Majority of these fractures occurred in the older population (≥50 years). In the same study, 1,317 deaths and 45,000 disability-adjusted life years (DALY) were attributed to osteoporotic fractures in 2019.[25]

Local data on the epidemiology and burden of osteoporosis and fragility fractures is scarce and mostly concentrated on direct costs of hip fractures. Analysis of Philippine Health Insurance Corporation claims from 2007-2012 recorded a total of 17,875 hip fractures, 4,610 cases of vertebral fractures, and 27,340 fractures (non-hip, non-spine) from 2007–2012 in individuals aged 50 years and older.[5] The study found direct hospital costs of hip fracture to be approximately PhP 94,611 (US$ 2,200); less than half of hip fractures were treated surgically.[5]

An unpublished data generated from the Philippine Orthopedic Association in 2003 shared the estimated directs costs of treatment of hip fractures among the Filipino old adults varied between US$ 2000 per case (government hospital) to US$ 6500 per case (private hospital).[22] Authors project a total cost burden of US$ 10.5-43 million by 2020 and US$ 27-117 million by 2050. A more recent study investigated the economic impact of acute fragility fracture based on 118 patients admitted in a tertiary government hospital in the Philippines.[29] The annual treatment costs of acute fragility hip fractures in a single tertiary government hospital is PhP 1,094,048,363.00 (US$ 22,595,007.79) per year.

Burden from indirect costs, such as loss of productivity for the patient and family members during hospitalization, loss of salary, reduced productivity for the employer and other tangible costs, is largely unknown.

CURRENT OSTEOPOROSIS MANAGEMENT

Initial evaluation for osteoporosis consists of a detailed history to assess for clinical risk factors for fracture and secondary causes of bone loss, a thorough physical exam, and laboratory tests to assess the general health and well-being of an individual.[30]

Diagnostic evaluation is usually determined by an individual's fracture risk profile. DXA measurement of the hip (femoral neck and total hip) and spine is the preferred method of evaluating bone mass and diagnosing osteoporosis, as well as predicting future fracture risk, and monitoring patients.[30,31] In the absence of a central DXA scan, any fractures sustained after fall from standing height among adult patients above 45 years of age are suspected to be osteoporosis related unless proven otherwise.

After diagnosis, the primary goal of initiating pharmacologic therapy is to reduce the risk of fractures and improve quality of life.[31] Approved therapies for osteoporosis are classified according to their mechanism of action on bone metabolism. Antiresorptive drugs like bisphosphonates, raloxifene (a selective estrogen receptor modulator) and denosumab (a monoclonal antibody that inhibits RANKL) inhibit bone resorption. Meanwhile, anabolic drugs like teriparatide, abaloparatide and romosozumab (a monoclonal antibody that inhibits sclerostin) stimulate new bone formation.[30,31] Other non-pharmacologic components of osteoporosis management include optimizing nutrition, lifestyle modification and fall prevention interventions.

In cases of osteoporotic fractures, current surgical options include conservative treatment, conventional surgery, and minimally invasive techniques (cementoplasty, percutaneous instrumentation).[32] More recently, Fracture Liaison Services (FLS) are becoming an important model of care for secondary fracture prevention worldwide. The FLS model is a multidisciplinary, coordinator-based, secondary fracture prevention service which is implemented by a healthcare system or institution to address the so-called treatment gap and provide clearly defined pathways of communication and coordination between healthcare providers (clinicians, nurses, allied health professionals and administrators) involved in osteoporosis care.[33]

SCOPE AND PURPOSE OF THE GUIDELINE

This first publication of the 2023 Philippine Osteoporosis guidelines is the output of a shared undertaking by a multidisciplinary CPG development team composed of leading experts on osteoporosis care in the country. Currently, there are no existing national practice guidelines on osteoporosis care. This guideline is an enhancement and update of the "Consensus statements on osteoporosis diagnosis, prevention, and management in the Philippines" initially published in 2011, by incorporating evidence-based tools, treatments and care models that were advanced in the last decade.[34] This current guideline included reviews and synthesis of the best available evidence and provide updated evidence-based recommendations on the screening, prevention, diagnosis, treatment, and surgical and follow-up care of primary osteoporosis in postmenopausal women. Secondary osteoporosis and osteoporosis in older men were not included in the scope of the present CPG but were slated for inclusion in future iterations of this guideline.

This guideline is primarily intended to be used by primary care physicians and allied health professionals involved in the care of patients with or at risk for osteoporosis. This CPG maybe used by internists, specialists, family physicians, geriatricians, obstetricians and gynecologists, orthopedic surgeons, physiatrists, nutritionists, policy makers (e.g., Department of Health), and health insurance representatives (e.g., PhilHealth and other HMOs) as a guide for delivering quality, evidence-based osteoporosis care. Relevant stakeholders may use the recommendations to inform public health programs and define PhilHealth benefit packages under the Universal Health Care services as well as private payor health policies. This CPG can also serve as a guide to local government units or private companies looking to establish orthogeriatric centers with fracture liaison services.

Because osteoporosis is more prevalent in postmenopausal women (PMW), clinical questions, evidence review, and recommendations drafted were therefore focused mainly on these PMW only. Osteoporosis may affect men as well as women before menopause. There are limited studies and directness of evidence on recommendations amongst male osteoporosis, though most guidelines extrapolate data from the PMW and make sound clinical judgment to include recommendations for males.

With this CPG, the developers aim to elevate the quality of osteoporosis management in the country, help bridge the treatment gap among osteoporosis patients and establish a standard of care that is appropriate to the Philippine context and improve clinical outcomes for patients.

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GUIDELINE DEVELOPMENT METHODOLOGY

CREATING THE GUIDELINE DEVELOPMENT GROUPS

In June 2021, the Osteoporosis CPG Steering Committee (SC) was convened under the leadership of the Osteoporosis Society of the Philippines Foundation, Inc. (OSPFI) chaired by J. Li-Yu. Members included a multidisciplinary team of osteoporosis specialists, each representing the Philippine Academy of Family Physicians (PAFP), Philippine College of Endocrinology, Diabetes and Metabolism (PCEDM), Philippine Obstetrics and Gynecological Society (POGS), Philippine Orthopaedic Association (POA), and Philippine Rheumatology Association (PRA).

In a series of meetings from June 2021 to February 2022, the Steering Committee established the CPG objectives, scope, target audience, and key topics in accordance with international and local standards as outlined in the AGREE II (Appraisal of Guidelines for Research and Evaluation II) and the DOH Manual for Clinical Practice Guideline Development, respectively.[1,2] To obtain stakeholder perspectives on clinical topics and questions for prioritization in the CPG, the Steering Committee members also conducted independent consultations with their respective societies and patients in the form of informal and formal interviews, surveys or questionnaires (see Supplementary Appendix 1). The clinical questions in this CPG were derived from the themes and key topics identified from these consultations, namely: screening, prevention, diagnosis, pharmacologic and nonpharmacologic management, surgical management, and follow-up care.

The Steering Committee (SC) also organized the Technical Working Group and Consensus Panel. Each of the 6 Steering Committee members were assigned to assemble and supervise a Task Force composed of 3 to 4 Evidence Review Experts (ERE) belonging to their respective medical society. A total of 31 Clinical questions were distributed among the 6 Task Forces based on relevance to their clinical area of expertise. The TWG was tasked to appraise, summarize, interpret, and draft recommendations based on the current body of available evidence on osteoporosis.

Content experts, members of the target population and other stakeholders were invited to join a multisectoral Consensus Panel (CP) whose main tasks were to 1) assist in prioritizing clinical questions; 2) develop final recommendations through consensus building, and 3) vote on the adoption of specific recommendations into the guideline. The 15-member consensus panel was comprised of representatives from the 6 lead societies (OSPFI, PAFP, POGS, POA, PRA, PCEDM) as well as experts in rehab medicine, internal medicine, nutritionist/dietitian, radiology, nuclear medicine, and geriatric medicine, patient advocate, and representatives from the Department of Health and Philippine Health Insurance Corporation.

MANAGING CONFLICTS OF INTEREST

To ensure integrity of the CPG process, all members of the CPG development groups disclosed all potential conflicts of interest (COI) according to Department of Health criteria.[2] Members of the SC, CP and TWG submitted their curriculum vitae (CV) and a declaration of COI prior to participation, which included a 4-year period of potential personal intellectual and/or financial conflicts of interest.

Compliance to the COI policy was monitored and managed by the Steering Committee. Conflicted TWG members were re-assigned to handle issues where they are not conflicted while panel members were asked to abstain from discussions and voting on recommendations with potential conflict during the *en banc* meeting. All eligible members of the consensus panel, including the patient representative, were active voting participants of the panel. The funding body of this CPG did not influence the development of this practice guideline.

FORMULATING THE RECOMMENDATIONS

Generating the Research Questions

Thirty one clinical questions were formulated and prioritized by the SC based on meetings and stakeholder consultations. A PICO (Population, Intervention, Comparator, Outcome) format was used to formulate the clinical questions and guide the systematic search for evidence.

Search, Retrieval and Selection of Guidelines

From January to April 2022, a systematic review of literature was performed by 3 independent reviewers. A focused search strategy was used to identify relevant CPGs on osteoporosis from international databases (MEDLINE/Pubmed, National Guidelines Clearinghouse, Guideline International Network, National Institute for Clinical Evidence). Supplementary search of other databases and medical specialty websites were also performed by the TWG to look for articles not covered by the main search (see Appendix A and B). The POA Taskforce carried out an independent literature search due to the highly specialized nature of their clinical questions on surgical management, the details of which are documented in the Evidence Base (see supplementary Appendix 1).

The combined output of all searches yielded a total of 315 articles, whose abstracts were retrieved for assessment. After removing duplicates, checking for relevance to the PICO questions and applying pre-specified inclusion and exclusion criteria (see Appendix C), 67 original full-text articles were identified and retrieved for review.

Guideline Adaptation

Guideline adaptation followed the ADAPTE process, a validated and systematic approach of adapting or customizing existing guidelines for use in a specific cultural or organizational context.[3] The ADAPTE methodology has been used by many organizations wanting to develop high-quality practice guidelines but lacking the expertise, time and resources needed for the undertaking. The major filtering step for guideline selection in ADAPTE is the AGREE II instrument, a 23-item checklist that evaluates guideline quality based on scope and purpose, stakeholder involvement, rigor of guideline development, clarity of presentation, applicability, and editorial independence.[1,4] AGREE is an effective method of identifying and prioritizing source guidelines with high methodological quality for use in an adapted guideline.

At least 2 reviewers from each task force appraised all 69 CPGs using the AGREE II instrument (see Supplementary Appendix 2). The guidelines were also evaluated for quality, currency, content, consistency and applicability by the TWG, using tools outlined specified in the ADAPTE manual. After appraisal, an overall judgment was made by the reviewers on the utility and eligibility of the guideline for use in the current CPG (i.e., yes/recommend, recommend with modifications, and no/would not recommend). The overall adaptation process concluded with one of two main decisions: 1) ‘adoption’ of the best available CPG and acceptance of some or all of its recommendations as they were written, or 2) ‘adaptation’ or tailoring, which involved selecting relevant recommendations from different source CPGs.[4]

CPGs were then ranked from highest to lowest based on overall AGREE score. Of the 69 CPGs, only 12 CPGs were selected for adaptation based on high-quality assessment on AGREE (overall

score >75%, rigor score >75%) and confirmation that the recommendations of the source guideline directly answered the PICO question (see Appendix D). All evidence summaries and supporting references were retrieved for review and the reference lists were updated if needed. Recommendations and corresponding evidence were summarized in the evidence base and recommendation matrix (see Supplementary Appendix Evidence Base).

Recommendations in this CPG were adapted from 12 source guidelines, namely: American Association of Clinical Endocrinologists (AACE/ACE, 2020); American Academy of Orthopedic Surgeons (AAOS) Distal Radial Fracture 2021; AAOS Hip Fracture 2021; African Society of Bone Health and Metabolic Bone Diseases (2020), the American Society for Bone and Mineral Research (ASBMR, 2019); the Belgian Bone Club (2020); Latin American Federation of Endocrinology 2022; North American Menopause Society (NAMS 2022); Royal Australian College of General Practitioners (RACGP) 2017; Scottish Intercollegiate Guideline Network (SIGN 2021); UK National Osteoporosis Guideline Group (NOGG, 2021); and US Preventive Services Task Force (USPSTF) 2018.

De Novo Guideline Development

If a clinical question was not answerable by any of the guidelines that passed the AGREE II appraisal, the CPG development group planned to conduct systematic search, review, and meta-analysis (see Supplementary Appendix 3) of published evidence and developed de novo recommendations. However, of the 27 clinical questions, none required *de novo* formulation of evidence-based recommendations.

Evidence to Recommendations

Each ERE drafted the initial recommendation statement/s to include level of evidence based on the source guidelines' supporting references. Source CPGs used different recommendation standards to rate and indicate quality of evidence and strength of recommendations (see Appendix D and Supplementary Appendix 4).

One guideline used the American Association of Clinical Endocrinologists protocol for grading evidence and qualifying recommendations while 2 guidelines used the Oxford Centre for Evidence-Based Medicine.[6] Two guidelines used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for grading the certainty or quality of evidence and strength of recommendations.[7]

For ease of interpretation and comparison across source CPGs, all recommendation statements and evidence ratings of the source CPGs were appraised and re-classified by the ERE using the GRADE approach (Table 1 and 2, see Supplementary Appendix Evidence Base), which was the rating system used for the present CPG.

Table 1. Rating Quality of the Evidence Using the GRADE Approach[7]

Quality of Evidence	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Any estimate of effect is very uncertain.

Table 2. Rating Strength of Recommendation Using the GRADE Approach[7]

Strength of Recommendation	Interpretation
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects (strong recommendation of an intervention) The undesirable effects of an intervention clearly outweigh the desirable effects (strong recommendation against an intervention)
Weak/Conditional	The trade-offs between desirable and undesirable effects are less certain, either because of low quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced.

Consensus Building and Drafting the Final Guideline Report

Draft recommendations, along with evidence summaries and Evidence to Decision (EtD) Framework tables (see Supplementary Appendix 1 Evidence Base), were presented during a series of *en banc* meetings to the consensus panel for finalization.

The EtD Framework was developed to help healthcare decision-makers use evidence in a systematic and transparent way.[8] Specifically, the framework informs panels about the relative benefits and harms of interventions being considered, ensures that panel members consider all the important factors in their decisions (e.g., patient preferences, cost and feasibility, equitability, and acceptability), provides panel members with a concise summary of the best available evidence to inform their judgments, and helps panels structure and document discussion and identify reasons

for disagreements.[9] For the purpose of this CPG, it also helped panel members consider whether clinical recommendations can and should be implemented in the Philippine setting, thereby facilitating adaptation of recommendations to the local context.

The Panel formulated final recommendations by approving or amending the draft recommendations presented by the TWG. The Panel also followed the GRADE approach in rating the quality of evidence and the strength of recommendations. Following the GRADE approach, the language used for strong recommendations included “we recommend” or “should”, while weak or conditional recommendations included “we suggest” or “may”.

The final recommendation statements comprising 27 clinical questions with 34 recommendations and corresponding quality of evidence and strength of recommendation were determined through voting. A consensus decision was reached if 75% of all panel members agree on a decision.[2] Up to 3 rounds of voting were planned to reach consensus. A consensus was not reached in one question on the duration of menopausal hormone therapy, hence a Delphi technique was done to come up with the final recommendation. Evidence-based draft recommendations were revised based on consensus decisions. Panel discussions and specific considerations on the applicability, equity and economic issues pertinent to each statement as well as the justifications of their decision-making were documented in the final guideline manuscript.

PREPARING FOR EXTERNAL REVIEW AND FUTURE UPDATE

The final manuscript was reviewed by 3 independent stakeholders who were not members of the CPG development group. Comments and suggestions by the reviewers were incorporated into the document with the approval of the Steering Committee.

The SC agreed that the recommendations of this CPG will be updated after 3 years or when any member of the Steering Committee encounters new evidence that could potentially impact the recommendations.

PLANNING FOR DISSEMINATION AND IMPLEMENTATION

Once the CPG is approved, the SC plans to discuss with relevant stakeholders and policymakers (i.e., DOH and PhilHealth) a dissemination plan that will promote the adoption of this guideline with strategies for copyrights. These include publication and presentation of full and abridged versions on medical specialty websites, press conferences, social media sites, medical and specialty conventions, and journal publications.

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RECOMMENDATIONS FOR POSTMENOPAUSAL OSTEOPOROSIS

SCREENING AND CLINICAL ASSESSMENT

Question 1: Among the adult population, who should be screened for osteoporosis?

Recommendation:

It is recommended that the following individuals be screened for osteoporosis:
- All postmenopausal women
- Men aged >/= 50 years
- Adults with clinical risk factors

(Strong Recommendation, High quality of evidence)

Panel Considerations on the Recommendation

After initial panel discussion, it was suggested that changes be made in the recommendations. It was suggested that all post-menopausal women be included and mentioned first. This is because osteoporosis is more common in women. The line "All postmenopausal women" captures both natural and surgical menopause. Data from a study in Taiwan, which is nearest to the Philippines, shows that men >50 years old are included in osteoporosis screening. Hence, men >/= 50 years old should be also included. The line "adults with clinical risk factors" capture the following: women and men with personal history of fractures, parental history of hip fractures, low body mass index, inflammatory arthritis, medications that affect bone health, alcoholism, current smokers, etc.

Summary of Evidence

The following recommendations were based from the UK clinical guideline for the prevention and treatment of osteoporosis (UK NOGG 2022) and the development of the Asia Pacific Consortium on Osteoporosis (APCO) Framework: clinical standards of care for the screening, diagnosis, and management of osteoporosis in the Asia-Pacific region.[1,2]

Both guidelines recommended screening men age ≥ 50 and postmenopausal women with fragility fracture. The guidelines suggest health evaluation for those with clinical risk factors, specifically FRAX assessment and BMD measurement with timely referral and drug treatment if indicated.

UK NOGG 2022 recommends, as part of screening, vertebral fracture assessment for postmenopausal women or men age ≥ 50 years old with the following characteristics: history of ≥ 4 cm height loss, kyphosis, recent or current long-term oral glucocorticoid therapy, a BMD T-score ≤ − 2.5 at either the spine or hip, or in cases of acute onset back pain with risk factors for osteoporosis.[1]

APCO recommends bone health assessment to individuals with hip fractures, clinical or morphometric vertebral fractures and non-hip, non-vertebral major fractures. Two guidelines proposed bone health assessment and Identification of fall risks to patients taking drugs associated with bone loss and/or with increase fracture risk and/or with conditions associated with bone loss.[2]

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Question 2: Among the adult population, what factors increase the risk of osteoporosis?

Recommendation:

Factors that increase the risk of osteoporosis include: *advanced age (>70 years), previous fragility fracture, menopause or untreated early menopause, parental history of osteoporosis and/or fractures, excessive alcohol consumption (>3.5 units per day), smoking, frailty or low level of physical activity, coexisting illnesses, and certain medications.*

Comorbidities: *diabetes, hyperparathyroidism or other endocrine diseases, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, malabsorption, institutionalized patients with epilepsy, chronic liver disease, neurological disease (Alzheimer's, Parkinson's, multiple sclerosis, stroke), moderate to severe chronic kidney disease, bronchial asthma, HIV*

Medications: *glucocorticoids, antidepressants, anti-epileptic agents (i.e. enzyme-inducing drugs), aromatase inhibitors, GnRH agonists for prostate cancer, PPIs, thiazolidinediones, anticoagulants, methotrexate, thyroid hormones*
(Strong Recommendation, High quality of evidence)

Panel Considerations on the Recommendation

After initial panel discussion, the following points were raised. First, is the list in the recommendation comprehensive enough? Is low BMI lumped together with frailty? If yes, can it be included? Where can it be placed? It was also suggested that >70 y.o be removed and only "advanced age" be placed. This is done to have consistency with the 1st recommendation. It was also clarified if a specific cut-off BMI be placed for "Low BMI".

Summary of Evidence

The following recommendations were based from the UK clinical guideline for the prevention and treatment of osteoporosis (UK NOGG 2022) and the development of the Asia Pacific Consortium on Osteoporosis (APCO) Framework: clinical standards of care for the screening, diagnosis, and management of osteoporosis in the Asia-Pacific region.

Non-Modifiable risk factors

The development of peak bone mass throughout adolescence and the subsequent bone loss after maturity account for two processes that define adult bone mass. The bone remodeling cycle results in changes in bone mass that might eventually result in skeletal fragility. In women, the most vulnerable times are during fast linear development in adolescence (ages 10–16 years) and later in life, typically just after menopause (ages 45–60 years). Male bone loss is much more sluggish but is also influenced by age-related loss and the peak acquisition period.[1]

Similar to hip fractures, the rate of vertebral fractures rises exponentially with age, and the number of fractures is correlated with a higher risk of death. This suggests that preventing additional

vertebral fractures could reduce the mortality rate. A vertebral fracture cascade is when a second vertebral fracture occurs within a year of the first incident vertebral fracture in women, and it is associated with decreased vertebral BMD and vertex height. Women with vertebral osteoporotic fractures have lower vertebral BMD and vertex height. Similar results were found for men.

Intervertebral distribution of bone mass, bone quality parameters, vertebral macroarchitecture, amount of intervertebral disc degeneration, and balance control are factors that differ significantly between people with and without vertebral fractures. A study has shown that at ages 55 to 85 years, there is a fourfold increased risk of hip fractures in women. This is largely due to the decrease in bone mass associated with age.[2]

Race and ethnicity are significant determinants of the commonality of osteoporosis. Asian older males are reported to have a 50% lower chance of getting a hip fracture compared to men of Caucasian race. Similar to men, Asian women also have lower fracture risk than Caucasian women.[3]

Osteoporosis and metabolic problems linked to lifestyle are becoming more common in Asia. In Asian men, metabolic syndrome may be related to bone loss, and atherosclerosis is related to an increase in fractures.[4] The mortality rate following a hip fracture is significantly higher in men than in women, but the hip fracture rate in men was roughly half that reported in women. This low prevalence in men has been attributed to 12%-13% greater bone mass in men. These findings demonstrated that the variation in hip fracture incidence between countries was much greater than the differences between genders within a country.

Family and medical history play a role in risk evaluation, as parental history of hip fracture is a significant risk factor that is largely independent of bone mineral density. During more than 2.9 million person-years of follow-up, 7,323 adults experienced a major osteoporotic fracture, including 331 incident hip fractures. Of those, 4.4% had a parent who experienced an incident hip fracture. Researchers found that parental hip fracture was independently associated with increased risk for major osteoporotic fracture in offspring after multivariable adjustment (HR = 1.3; 95% CI, 1.2-1.41). Results were similar for men (adjusted HR = 1.26; 95% CI, 1.12-1.43) and women (adjusted HR = 1.32; 95% CI, 1.19-1.46). Researchers found that the association between major osteoporotic fracture in offspring and parental hip fracture was strongest when parental hip fracture occurred before age 70 years (adjusted HR = 1.5; 95% CI, 1.3-1.73), with the association decreasing with age and becoming nonsignificant for parental hip fracture at age 80 years or older.[5]

A history of a prior fracture, particularly if sustained from low trauma and at a site characteristic of osteoporosis, is an important risk factor for further fracture. The risks are, in part, independent of BMD. Fracture risk is approximately doubled in the presence of a prior fracture, including asymptomatic moderate or severe (grade 2 or 3) morphometric vertebral fractures.[6] A history of previous fracture increases osteoporosis risk based on a registry based cohort study (n=64,428 women and men). An increased risk of osteoporotic fracture was seen in patients with a history of high(Adjusted HR 1.31, 95% CI 1.08-1.59) and low(Adjusted HR 1.55, 95% CI 1.47-1.63) trauma fracture.[5] A meta-analysis of seven prospectively studied cohorts (n=59,232) showed that parental history of hip fracture increases the risk of osteoporotic (RR 1.54; 95CI=1.25-1.88) and hip(RR 2.27; 95% CI=1.47-3.49) fracture.[7]

Modifiable Risk factors

Studies have shown that sedentary lifestyles, excessive alcohol intake, and smoking have deleterious effects on bone health and increase the risk of fracture. A low level of physical activity contributes to bone loss.[3]

Low BMI (<20kg/m^2) increases osteoporosis risk based on a meta-analysis of prospective population-based cohorts (n=60,000). It is seen that a per unit increase in BMI was associated with a lower risk of any fracture(RR 0.98 95% CI, 0.97-0.99 p <0.001), osteoporotic fracture (RR 0.97 95% CI, 0.96-0.98 p <0.001) and hip fracture(RR 0.93 95%CI, 0.91-0.94 p <0.001).[8] In a nationwide cross sectional survey conducted in Korea in 1998 to 2012, 4,982 postmenopausal women were included in the Korean National Health and Nutrition Survey examining the optimal BMI that minimizes the risk of both diabetes and osteoporosis in an Asian population. There was an inverse relationship with osteoporosis: from 38.3% (BMI < 18.5 kg/m^2) to 8.1% (BMI ≥ 30 kg/m^2) in men and from 76.5% (BMI < 18.5 kg/m^2) to 21.2% (BMI ≥ 30 kg/m^2) in women. Women with a BMI < 18.5 kg/m^2 showed the highest risk for osteoporosis (OR, 3.67; 95% CI, 2.23 to 6.05), but those with a BMI of < 18.5 kg/m^2 carried the lowest risk for type 2 diabetes (OR, 0.44; 95% CI, 0.22 to 0.87). Similar to men, a BMI of 23.0 to 24.9 kg/m^2 was the highest BMI category for lowering osteoporosis risk without increasing type 2 diabetes risk among BMI categories.[9]

Smoking is a risk factor that is dependent on part of bone mineral density. Smoking cessation has been shown to reduce the risk of vertebral and hip fractures in women. Pre-operative smoking cessation is associated with fewer postoperative complications.[12] A meta-analysis of 10 prospective cohorts (n=42,000) showed that smoking increases osteoporosis risk (RR 1.25,95%CI 1.15-1.36).[6]

Alcohol consumption, whether low, moderate, or high, may have a damaging impact on bone health in both the cortical and trabecular compartments at the distal radius in men and in the trabecular and distal tibia compartments of women.[1] Alcohol intake of 3 or more units daily is associated with a dose-dependent increase in fracture risk.[10] A unit of alcohol varies slightly in different countries from 8-10g of alcohol. This is equivalent to a standard glass of beer (285ml), a single measure of spirits (30ml), a medium-sized glass of wine (120ml), or 1 measure of an aperitif (Chris Health). Excessive alcohol intake is associated with increased risk of any(RR 1.23 95% CI, 1.06-1.43), osteoporotic(RR = 1.38; 95% CI, 1.16-1.65) and hip(RR = 1.68; 95% CI, 1.19-2.36) fracture based on three prospectively studied cohorts (n=16,971).[11]

A meta-analysis of 19 studies showed inconsistent evidence linking exposure to air pollution and outcomes associated with osteoporosis. The research does, however, point to a higher incidence of osteoporotic fracture and osteoporosis when outdoor air pollution is present. Evidence was suggestive of the negative role of pollutants PM10, PM2.5, and nitrogen dioxide (e.g. bone mineral density pooled estimate: -0.02, 95%CI: -0.03: -0.01).The results should be interpreted with care due to the small number of studies in each group, as well as the heterogeneity that was identified and publication bias.[12]

Via a variety of methods, long-term psychological stress has an impact on numerous bodily functions, including the skeleton. Endocrinological changes such as elevated glucocorticoids, prolactin, leptin, and parathyroid hormone levels and decreased gonadal hormones are among the physiological alterations that are harmful to bone health, in addition to low-grade inflammation and sympathetic nervous system hyperactivity. This hypothesis, however, needs more concrete proof to be proven. As a result, it is important to acknowledge chronic psychological stress as a risk factor for osteoporosis and include stress-relieving techniques in a comprehensive osteoporosis prevention plan.[13]

Comorbidities should be taken into account during fracture evaluation, as these raise the risk of bone loss and fracture. Diabetes, hyperparathyroidism or other endocrine diseases, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, malabsorption, institutionalized patients with epilepsy, chronic liver disease, neurological disease (Alzheimer's, Parkinson's, multiple sclerosis, stroke), moderate to severe chronic kidney disease, bronchial asthma, HIV increases the risk of osteoporosis.[1] Diabetes mellitus increases the risk of any(RR 1.5 95% CI 1.3-1.8; P < 0.05) and hip fracture(RR 2.0 95% CI 1.8-2.3; P < 0.05) based on a meta-analysis of 37 studies.[14]

It is well established that a food plan with high consumption of dairy products, fruits, and whole grains may improve bone health.[15] Moreover, absence of vitamin K, particularly as vitamin K2, in junk food results in impairment of the calcium removal process and increases the risk of calcification of the blood vessels. An increased intake of vitamin K2 could be a means of lowering calcium-associated health risks.[16] A meta analysis of observational studies showed that Bariatric procedures are associated with an increased risk of fractures, especially the malabsorptive techniques (RR 0.49; 95% CI 0.40-0.61; P < .00001).[17] Thus, conditions that result in nutritional calcium deficiencies may be associated with osteoporosis.

The risk of osteoporosis or osteoporotic fractures was higher in male NAFLD groups than that in the non-NAFLD group [OR = 2.10, 95%CI(1.36,3.25)], while no significant difference was found among women [OR = 1.13, 95%CI (0.86,1.48)] in a 2022 meta analysis of 7 studies.[18] A meta-analysis of 17 studies comprising 10,289 individuals revealed patients with Parkinson's Disease (PD) had a lower BMD, BMD T score, and BMD Z score compared with non-PD controls.[19] Chronic kidney disease (CKD) is an independent risk factor for osteoporosis. Meta-analysis showed increased incidence of end stage renal disease (ESRD) among patients having osteopenia (HR 1.14 95% CI 0.92-1.41) and osteoporosis (HR 1.43 95% CI 1.01-2.04).[20]

Chronic inflammation induces proinflammatory cytokine cascades. In addition to systemic inflammation, hypoxemia, hypercapnia, a catabolic metabolism, gonadal or thyroid dysfunction, musculoskeletal dysfunction and inactivity as well as vitamin D deficiency contribute to an increased risk of fragility fractures. Iatrogenic causes of osteoporosis are long-term use of inhaled or systemic glucocorticoids (GC). Inhalative GC application in asthma is often indicated in childhood and adolescence, but interstitial lung diseases such as chronic organizing pneumonia, COPD, sarcoid or rheumatic diseases with lung involvement are also treated with inhalational or oral GC.[21]

Drug induced osteoporosis poses a significant health issue. Awareness of physicians to commonly prescribed medications allow bone health monitoring and therapeutic interventions to prevent or treat drug-induced osteoporosis. Glucocorticoids, antidepressants, anti-epileptic agents (i.e. enzyme-inducing drugs, Carbamazepine), aromatase inhibitors, GnRH agonists for prostate cancer, PPIs, thiazolidinediones, anticoagulants had been linked to osteoporosis.[1] A meta-analysis of seven prospectively studied cohorts (n=42,000) showed that oral glucocorticoid intake increases the risk for any(RR 1.98 95% CI 1.35–2.92), osteoporotic(RR 2.63 95% CI 1.68–4.13) and hip (RR 4.42 95% CI 1.26–15.49) fracture.[22]

Resource Implications

The International Osteoporosis Foundation's flagship Capture the Fracture® Program and examples of national clinical standards for FLS from other nations are among the initiatives aimed at making it possible to compare the caliber of care offered by FLS. Furthermore, taken into consideration is the development of national clinical registries to permit benchmarking against

clinical standards. A FLS Toolbox for Asia-Pacific was developed, which included: the burden of fragility fractures, a summary of evidence for FLS; a generic, fully referenced FLS business plan template; potential cost savings based on a country-specific FLS Benefits Calculator; how to start and expand FLS programs; a step-by-step guide to setting up FLS; and other practical tools to support FLS establishment, including FLS online resources and publications.[23] Funding and capacity building in learning and development are needed to deploy an effective and efficient prevention scheme.

A total of 159 papers were found by the SLR, reporting 37 studies in the Asia-Pacific, and 5663 distinct citations were found overall. These investigations showed the unmet need for departments and doctors to work together more closely, as well as for public health education, proper funding, and staff resourcing.[24]

Acceptability and Applicability Issues

The pathogenesis of osteoporosis is multifactorial, and fracture risk depends upon several independent risk factors. A low BMD, a medical history of fragility fracture, age, and a family history of osteoporosis are risk factors for osteoporotic fracture.[25] The idea that a history of fracture can lead to a subsequent fracture requires risk stratification. The concept of stratification of osteoporotic fracture risk may guide clinicians in the choice of assessment tool and initiation of therapy. Higher fracture risk patients may require initiation of potent therapy while low risk patients will need to be evaluated as to the need or when to initiate therapy.[26]

Fracture rates among the elderly will dramatically rise by the middle of the century if systematic approaches to managing chronic diseases, and in particular to the prevention and treatment of osteoporosis and fragility fractures, are not widely adopted. Characterizing the present and future costs associated with fragility fractures, assessing the current inadequacies in the application of best clinical practice in the area of risk factor screening will enhance Fracture Liaison Service models of care. Similarly, the Asia Pacific Fragility Fracture Alliance has developed educational resources including a Hip Fracture Registry Toolbox and a Primary Care Physician Education Toolkit, which are ready for cascading.[27]

Research Gaps

The prevalence of fragility fractures is now high and is expected to rise, according to epidemiological studies carried out in nations and areas around Asia Pacific. With more country and regional specific data coming in, quality improvement initiatives intended to advance the care and prevention of fragility fractures across the Asia Pacific region need to be heightened. In order to address the epidemiological emergency posed by fragility fractures during the United Nations' "Decade of Healthy Aging," national Road Maps must be developed and implemented as soon as possible. These Road Maps must be influenced by the findings of this review.[27] Furthermore, regional and local cost effectiveness and cost-benefit analysis studies are wanting to push actualization of road maps.[27]

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Question 3: What tool should be used for osteoporosis screening?

Recommendation 1:

Osteoporosis screening should be performed using the FRAX tool.
(Strong Recommendation, High Quality of Evidence)

Recommendation 2:

The OSTA tool maybe used as an alternative to FRAX for osteoporosis screening.
(Strong Recommendation, High Quality of Evidence)

Panel Considerations on the Recommendations

The panel suggested that the question should be re-stated based on the following: 1. FRAX is used for "general adult population" But previous evidence focused on a specific population (post-menopausal women, men and adults with risk factors). The ERE/TWG explained that FRAX can be used on all PMW. The panel also raised whether the previous issue should be directed to the clinical question or the recommendation. The first 2 clinical questions already stated "WHO" should be screened for osteoporosis. The target population of this third recommendation should be based on the population of the first 2 recommendations. Hence the panel agreed that the clinical question be rephrased to "What tool should be used for osteoporosis screening?".

Summary of Evidence

The main goal of osteoporosis screening is to identify individuals at risk of fracture and provide necessary treatment to improve their bone mass, prevent further bone losses and prevent the occurrence of fracture-related morbidity and mortality. Measuring bone density is the standard method of screening for osteoporosis. However, due to limited access to central bone densitometry machines, fracture risk assessment in the community has been utilized as alternative strategies to identify individuals who may benefit from pharmacologic therapies.

Several risk assessment instruments have been developed over the years to identify individuals with low bone density or to predict future fracture risk. The Fracture Risk Assessment Tool (FRAX), a well-studied risk assessment instrument developed by WHO and the University of Sheffield UK in 2008, employs an algorithm that predicts the 10-year probability of hip fracture or major osteoporotic fractures (hip, spine, forearm, shoulder) based on 12 clinical risk factors (with or without femoral neck BMD).[1] More than 70 country-specific FRAX instruments are available to aid in diagnostic and/or treatment decisions worldwide, including the Philippines.[2] A recent study of the Philippine FRAX model identified 3 intervention thresholds – age-dependent, fixed and hybrid – that can be used to identify Filipino adults at high risk of fracture who need anti-osteoporosis medication.[3]

These recommendations were adapted from the United States Preventive Services Task Force (USPSTF) 2018 guideline. The USPSTF conducted a comprehensive systematic review and meta-analysis (168 fair to good quality studies) to formulate updated recommendations on screening and treatment for prevention of osteoporotic fractures in community-dwelling American adults. For women 65 years and older, it is recommended that osteoporosis screening with bone mineral density test be done to prevent osteoporotic fractures. For post-menopausal women <65 years it is

recommended that a clinical risk assessment tool be used to determine osteoporosis risk. Once increased risk for osteoporosis is determined, screening with bone mineral density tests is done to prevent osteoporotic fractures. This is based on the USPSTF assessment that the net benefit of screening in this subgroup is at least moderate. At present, current evidence is insufficient to determine the balance of benefits and harms of screening for osteoporosis to prevent osteoporotic fractures in men.[4]

Benefits and Harms of Screening

The SCOOP (Screening for Osteoporosis in Older Women for the Prevention of Fracture) trial enrolled 12,483 older women (aged 70 to 85 years) and randomized them to screening either with FRAX or usual care.[5] Patients in the FRAX group who were identified as high risk underwent DXA and were treated as appropriate by their primary care physicians. After 5 years of follow-up, no difference was reported between the FRAX group and those who received usual care in terms of any osteoporotic fractures (12.9% vs 13.6%; hazard ratio [HR] 0.94, 95% CI 0.85-1.03), clinical fractures (15.3% vs 16.0%; HR 0.94, 95% CI 0.86-1.03), or mortality (8.8% vs 8.4%; HR, 1.05, 95% CI 0.93- 1.19). However, investigators observed a significantly lower incidence of hip fracture incidence in the screening group (2.6% vs 3.5%; HR 0.72, 95% CI 0.59-0.89). Investigators also reported no increase in anxiety (State-Trait Anxiety Inventory) and no decrease in quality of life (EuroQol 5-Dimension tool and Short-Form Health Survey 12) in patients who were screened compared with the usual care group (P>0.10 for all outcomes).[6]

Accuracy of Screening for Osteoporosis

Risk Assessment Tools

The diagnostic accuracy of 16 different clinical risk assessments tools, calculated as area under the curve (AUC), were reviewed by USPSTF based on data from 38 studies.[4] The AUC estimates the probability that a random person with the disease will have a higher test score than a random healthy person; AUCs nearer to 1 or 100 are interpreted as high quality overall diagnostic performance while AUCs nearer to 0.5 or 50 are interpreted as poor quality.[7]

There is adequate evidence that risk assessment tools are moderately accurate in identifying risk of osteoporosis. In women, pooled AUCs for Osteoporosis Self-Assessment Tool for Asians (OSTA) was 0.76 (4 studies, 2962 participants)[8-11] Pooled AUCs in women for FRAX ranged from 0.67 for predicting major osteoporotic fractures with inclusion of BMD to 0.79 for predicting hip fractures with BMD. [12,13] Instruments with more clinical risk factors had similar AUCs with those measuring fewer risk factors. Other measures of diagnostic accuracy (sensitivity and specificity) also varied widely across all studies.[8-11]

Bone Measurement Tests

Meta-analysis of 10 studies comparing calcaneal quantitative ultrasound to central DXA for identification of osteoporosis reported moderate diagnostic accuracy among women and men (pooled AUC 0.77, 95% CI 0.72 to 0.81 and 0.80, 95%CI 0.67-0.94, respectively). Digital x-ray radiogrammetry, peripheral DXA, and radiographic absorptiometry showed similar results.[4]

Accuracy of Screening for Predicting Osteoporotic Fractures

Risk Assessment Tools

Meta-analysis of one systematic review of 45 studies and 13 additional studies provided evidence on the diagnostic accuracy of 12 different clinical risk assessment tools for predicting incident

fracture (see Table).[4] AUCs ranged from 0.53 to 0.89 in women 0.63 to 0.88 in men, and varied by instrument, type of fracture, and use of BMD. Prediction of hip fractures and tools that use BMD tend to report higher AUCs than tools that do not use BMD.

FRAX's accuracy for predicting future fracture was evaluated in many studies and varied by sex, type of fracture and use of BMD for risk prediction. Pooled AUCs in women ranged between 0.66 and 0.79 and were higher than in men (0.62 to 0.76). Pooled AUC estimates were higher for predicting hip fracture than for major osteoporotic fracture and improved further when BMD was included in the prediction model. In cohorts of men and women, pooled AUCs showed similar estimates at 0.67 and 0.69, respectively. Other risk assessment instruments also demonstrated poor to moderate accuracy for predicting fractures. Pooled AUC for OSTA and other instruments demonstrated higher scores for hip fracture (0.80 to 0.89) than major osteoporotic fracture (0.53 to 0.82).[8-19]

Bone Measurement Tests

Twenty-three studies evaluated the accuracy of various bone measurement tests for predicting fracture . Based on data from 23 studies, the USPSTF found no significant differences in accuracy for fracture prediction among the bone measurement tests, regardless of type of test or gender population tested.[4] Higher AUC estimates were reported for prediction of hip fracture than for prediction of other fracture at other sites.

The current evidence shows that initial screening for osteoporosis should be done using the FRAX Tool. The OSTA tool can be used as an alternative screening tool.

Resource Implications

All screening tools mentioned are available at no cost on the internet. Clinicians just need to log onto each website and plot in the clinical risk factors taken from the medical history of the patient. Results are then interpreted based on the frequently used threshold for increased fracture risk.[4]

Central bone densitometry machines are situated in most tertiary health centers (both public and private). Most of these are located in the National Capital Region where access is an issue to the general population. Cost of doing bone densitometry also varies from one Center to another. The cost of central DXA ranged from Php 2000 to Php 8000 in government and Php 1865 to Php 5600 in private institutions. The cost of DXA with VFA ranged from Php 4800 to Php 5125.

In a study evaluating the cost-effectiveness of FRAX-based intervention thresholds among postmenopausal Singaporean women aged >50 years, treatment with alendronate is cost-effective at age-dependent FRAX® intervention thresholds at 65 years and older.20 Moreover, identifying all at-risk women ≥50 years with a 10-year risk of 14% for major osteoporotic fractures or 3.5% for hip fractures would result in more economical use of resources. Authors conclude that cost-effective access to therapy for patients at high fracture probability based on FRAX® could help reduce the growing burden of osteoporotic fractures in Singapore.

Of the various fracture preventive strategies, namely: watchful waiting, bone density based strategy (DXA screening followed by pharmacotherapy based on BMD results), clinical risk factor based strategy (pharmacotherapy given to women at high risk of fractures by FRAX tool), studied in a simulated cohort of rural women aged 65 years who live in rural setting with limited access to DXA facility, DXA screening followed by pharmacotherapy based on BMD results is the ideal strategy. However, in areas where availability of DXA machine is a challenge, initiating anti-osteoporosis

medication to women at high fracture risk based on FRAX was shown to improve health and save money based on the ICER computed. [21]

In a cost-effectiveness analysis of screening and treatment strategies for Thai postmenopausal women, OSTA and sequential DXA was shown to provide better value for money for screening among younger age individuals age 45-55 years. There was a very slight difference in ICERs bet OSTA and sequential DXA vs DXA alone in the older age groups (60 – 80 years).[22]

Acceptability and Applicability Issues

A survey on real-world practice of 403 Filipino general practitioners on management of osteoporosis done in 2016 showed that OSTA is used by 74.9% as screening tool to identify risk of osteoporosis while 86.8% of them considered doing a bone mineral densitometry in women at least 65 years of age and 28% considered it in men at least 70 years old.[23] A cross sectional study done in Malaysia among 350 primary care physicians in 2021, only 27.7% practice osteoporosis screening due to inaccessibility of BMD machines and pharmacotherapy, and inadequate knowledge. Of the screening tool asked, 8.6% used FRAX, 3.4% BMD, 3.4% OSTA, 5.4% combined FRAX and BMD. [24]

Spine surgeons who participated in a survey on attitudes regarding osteoporosis screening in British Columbia, Canada, do not routinely do DXA scans or clinical lab tests to evaluate for osteoporosis. Some of those who did perform workups commented this will change their surgical plan or preoperative treatment.[25]

Research Gaps

Further prospective studies are suggested to validate the FRAX intervention threshold among Filipino postmenopausal women who have recent fragility fractures. A country-wide large-scale efficacy analysis on secondary prevention of osteoporosis related fracture using fracture liaison service is also suggested. This will further strengthen its use, consider its use in the community setting. Studies on the Utility of clinical practice guidelines in the community setting – both urban and rural settings – in reducing the burden of osteoporosis and its related consequences.

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Question 4: Among the adult population, what is the clinical presentation of osteoporosis?

Recommendation:

The clinical presentation of osteoporosis in the adult population may include any of the ff: acute onset back pain, height loss, or thoracic kyphosis, previous fragility fracture, menopause or untreated early menopause, parental history of osteoporosis and/or fractures, alcohol consumption >3.5 units per day or smoking and/or physical examination findings of low weight or BMI (<18.5 kg/m^2)[3], ≥ 4 cm height loss, or thoracic kyphosis

(Strong recommendation, HIgh quality of evidence)

Panel Considerations on the Recommendation

The panel suggested that the recommendation be stated as a complete sentence. The clause "may include" should be added in order to make it clear that all findings will not be present in one individual. The panel also pondered if specific cut-off values should be placed for weight and BMI. It was also argued as to which among "low weight" or "low BMI" should be used. A panel member stated that weight is already factored in with BMI, hence BMI should be used. It was also pointed out that if the evidence data is based on BMI, hence it should be used. Specific cut offs should be stated. In the Asia-Pacific, the cut off value for low BMI is <18.5.

Summary of Evidence

The following recommendations were based on the UK clinical guideline for the prevention and treatment of osteoporosis (UK NOGG 2022) and the development of the Asia Pacific Consortium on Osteoporosis (APCO) Framework: clinical standards of care for the screening, diagnosis, and management of osteoporosis in the Asia-Pacific region.[1,2]

Both guidelines recommended that a detailed history and physical examination be performed on individuals at risk for osteoporosis. The following history should alert the clinician to suspect osteoporosis: acute onset back pain aggravated by standing, height loss, previous fragility fracture, menopause, parental history of osteoporosis and/or fractures, alcohol consumption >3.5 units per day and smoking. The following are the physical examination findings for osteoporosis: low weight or BMI (<18.5 kg/m^2), ≥ 4 cm height loss and thoracic kyphosis.

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DIAGNOSIS

Question 5: Among at-risk PMW, should bone mineral density measurement using dual energy x-ray absorptiometry be used to diagnose osteoporosis?

Recommendation 1:

> Among at-risk PMW, tit is recommended that bone mineral densitometry (BMD) test using dual energy x-ray absorptiometry (DXA) be used for the diagnosis of osteoporosis.
> ***(Strong recommendation, High Quality of evidence)***

Recommendation 2:

> Among at-risk PMW, it is recommended that the following criteria be used to diagnose osteoporosis: history of fragility fracture/s, BMD T-score ≤-2.5, or low bone mass (BMD <-1.0 and <-2.5) with fragility fracture, or high fracture risk according to country-specific FRAX.
> **(*Strong recommendation, High Quality of evidence)***

Recommendation 3:

> Among at-risk PMW of vertebral fracture, it is recommended that vertebral fracture assessment (VFA) using DXA or lateral spine radiograph be done.
> ***(Strong recommendation, High Quality of evidence)***

Recommendation 4:

> Among at-risk PMW without fracture, it is suggested that FRAX w/o BMD be used for the diagnosis of osteoporosis in settings where BMD measurement via DXA is unavailable or not feasible. A fracture intervention threshold of 3.75% for major osteoporotic fractures and/or 1.25% for hip fractures is suggested.
> ***(Strong recommendation, High Quality of evidence)***

Panel Considerations on the Recommendations

Recommendation 1:

Should we include the population of men at risk for osteoporosis in the recommendation? This was mentioned in SIGN and USPTF. In order to limit the recommendation, we focused on PMW. There's paucity of data in men, hence focused on PMW.
For clarification: Next recommendation will be on the criteria
Suggest to include the same population mentioned in the SCREENING Section.

Suggestion: In previous sessions, it was agreed inclusion of men will be done if data available. If there is no data, just place that there is paucity of data. A: We are not totally excluding men, but hopefully we will include men (this will be more expensive since de novo synthesis will be done).

Re: Inclusion of men: there are some international studies that included men > 50y.o (BMD and DXA), ie. Scottish, USPSTF, and Belgian recommendations included men>50y.o. Some only focused on women, others both on men and women. This will be discussed in the task force. If we screen men, what happens with their diagnosis (does screening classify them as high risk)? A panel member questioned if we should include men at-risk for osteoporosis in the recommendation. Another suggested that the same population used in the screening section should be used. The SIGN and USPSTF guidelines included men and women. The ERE answered that we limited the population to PMW because of paucity of data among men. The available data present would require de novo analysis which will be beyond the time and budget allotted. The panel suggested to indicate paucity of data in men. Future revisions of the guideline can include recommendations for men. But a panel member raised the issue of diagnosis of men found to be high-risk in screening.

Recommendation 2:
No issues identified.

Recommendation 3:
Can someone give an idea regarding cost? These tests can be a standard of care, hence cost might be a factor. A: Depends on packaging of institutions. VFA=1500, if with BMD 4500 to 5500. There are some stand alone labs offering combination @ 1800 to 2k. Lateral spine xray cost: varies on institution. but in Phil Ortho Center, spine APL is used and the cost is P750. For private institutions its P2-P3k.

VFA is already a part of the DXA exam. However, some institutions don't have the software for VFA, hence lateral spine radiograph is used as an alternative to VFA. Bone densitometry can be chopped down. BMD is focused on spine and hip. VFA is included to assess the spine. Packages vary from institutions- package can be BMD or BMD+VFA.

A panel member raised the issue of the cost of additional test besides BMD-DXA. Vertebral fracture assessment (VFA) costs about Php 1500.00; if it is done with DXA, the total cost of is Php 4500.00 to 5500.00, but some stand-alone centers offer Php 1800.00 to 2000.00. The cost of a lateral spine x-ray varies per institution; in one government referral center for orthopedic cases in Metro Manila it costs Php 750.00 and in private hospitals it costs Php 2000.00 to 3000.00.

Recommendation 4:
Concern about why not include men in the diagnosis/starting them on treatment. Frax cannot be used in the Phil setting for men. Only for PMW women.
Indicate the threshold values in the recommendation. Indicate this table in the discussion. We used intervention thresholds as high/low risk of fractures. In the US, FRAX fracture risk cutoffs are 20% and 3% for major osteoporotic and hip fracture respectively. In the Phils, 3.75% and 1.25% are the equivalent. Population: Post Menopausal Women.

The issue of inclusion of men was again raised. FRAX is only used for PMW in the Philippine setting. We used intervention thresholds as treatment decision in starting anti-osteoporosis medication. The fracture risk cutoff using FRAX are 20% for major osteoporotic fracture and 3% for hip fracture in other countries. In the Philippines, they are 3.75% and 1.25%, respectively. The panel suggested to include performance of fixed major osteoporosis and hip fracture intervention thresholds from the study of J Li-Yu and S Lekamwasam (2021) in the discussion of FRAX.

Summary of Evidence

The most important clinical outcome of osteoporosis is the occurrence of fracture/s, such as vertebral fractures, fracture of the distal forearm, and hip fracture.[1,2] Before devices that measure bone strength were developed, fracture occurrence was the lone indicator of osteoporosis. Bone mineral density (BMD) comprises 70% of bone strength and its measurement is representative of the bone mass.[3] Fracture risk increases with decline in BMD.[1,2] BMD measurement of the hip or spine to fracture risk assessment is similar or even better to the performance of blood pressure and serum cholesterol in predicting cardiovascular disease.[4] Devices measure areal mineral density (grams per centimeters squared, g/cm2) rather than volumetric density. The difference from mean BMD, called standard deviation (SD), is preferred over mean BMD to standardized different devices and sites of measurements. When a patient's BMD is compared to age-matched controls, it is a Z-score; when it is compared to a young normal population, it is a T-score. T-score is the recommended statistic in postmenopausal women (PMW) because BMD is expected to decline with age. Young normal population consisted of men and women aged 20-29 years old of the National Health and Nutrition Examination Survey (NHANES) III.[5]

Dual-energy x-ray absorptiometry (DXA) is the standard BMD measurement device [ISCD]. A DXA scan machine consists of a patient table from which an x-ray is emitted and a detector system that hovers over the patient's body. BMD is measured through comparison of attenuation values with standard values (the higher the attenuation, the higher the density). An algorithm or edge detector system removes the soft tissues from the analysis. Other BMD devices are portable DXA, quantitative CT (QCT), vertebra morphometry, and quantitative ultrasound (QUS). Portable DXA scanners measure peripheral bone (distal radius, calcaneus) BMD. Quantitative CT gives separate estimates of trabecular and cortical bone BMD as g/cm3, the volumetric BMD. Quantitative vertebral morphometry is the measurement of vertebral body heights for the determination of vertebral osteoporotic fractures. Quantitative US do not display images of bone structure and do not emit radiation unlike the others.[3]

These recommendations were adapted from the guideline statements of the American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis – 2020 Update and the UK Clinical Guideline for the Prevention and Treatment of Osteoporosis.[6,7]

Osteoporosis is diagnosed in four ways: 1) history of fragility fracture, 2) T-score ≤-2.5 in the lumbar spine (LS), femoral neck (FN), total femur (TF), or distal third of radius, 3) T-score between -1.0 and -2.5 and a fragility fracture of the spine, hip, proximal humerus, pelvis, or distal forearm, or 4) T-score between -1.0 and -2.5 and high fracture risk according to a fracture risk assessment tool such as FRAX.[6]

Fragility fracture is any fracture that was sustained at low levels of trauma; other terms used are low-trauma fracture and low-energy fracture. In the absence of fragility fracture, BMD is used for diagnosis and for assessment of fracture risk. The T-score value of -2.5 at the spine, hip, and forearm was the WHO criteria of diagnosis. When this cut-off is used, 30% of PMW have osteoporosis which approximates the lifetime fracture risk (16-30%) in those sites.[1,2,8] The value also excludes osteoporosis in healthy premenopausal women.[8]

The reference technology of BMD testing is DXA. DXA of LS has a sensitivity of 71% and a specificity of 89%, while hip DXA has sensitivities of 34% (femoral neck, FN) and 25% (trochanter) and specificity of 97% (FN) and 98% (trochanter).[8] Hip BMD values derived from hip DXA (composed of FN, TH) were used as the reference database of the WHO t-score cut-off value. Hip

BMD-DXA had the highest relative risk (RR) for the same site measured, ie, hip fracture, and performed as well as the other measured sites in predicting fracture at any site.[8] The RR is 2.6 (95% CI 2.0 to 3.5) for hip fracture and 1.6 (95% CI 1.4 to 1.8) for all fractures for every SD decrease in BMD by DXA below the age-adjusted mean.[4,8,9] Reference values for LS and distal forearm are based on DXA machine manufacturer's standard and have not been validated.[6,7] However, a BMD-DXA T-score ≤-2.5 at the LS or distal forearm is still diagnostic of osteoporosis in PMW regardless of the T-score of the hip.[6,7,10,11] Distal forearm BMD-DXA had the lowest RR in predicting all fractures.[8,9] Patient disability, weight over the DXA scan table limit, spine or hip structural abnormality or presence of hardware preclude reliable BMD measurement in the spine and hip; distal radius can be used in these circumstances.[6,7,11]

Clinical fracture risk (CFR) profile improves detection of osteoporosis and treatment decisions. The AACE guideline recommends FRAX to aid treatment decisions when the BMD-DXA is in osteopenic range/low bone mass.[6] The FRAX tool integrates hip BMD and other clinical risk factors to give a 10-year probability of major osteoporotic fracture (MOF) and hip fracture.[6,12] High fracture risk (MOF, hip) by FRAX was concordant with T-score <-1.0 in majority of patients.[13] Many fragility fractures occur in patients with low bone mass/osteopenia; diagnosis by T-score alone can delay intervention. FRAX with BMD performed better in predicting hip fracture than MOF.[14]

Vertebral fractures (VF) are common and often remain asymptomatic and undiagnosed.[6] There are two imaging techniques for detection of VF – lateral spine radiography and vertebral fracture assessment (VFA) by DXA). VFA is as well as radiograph in detecting moderate (grade 2) and severe (grade 3) VF, but not mild (grade 1) VF, or in the presence of scoliosis or disk space osteoarthritis. It emits less radiation and can be conveniently performed with DXA.[15]

Assessment for VF should be done when the T-score is <-1.0 plus one or more of the following: PMW aged ≥70 years or men aged ≥80 years, historical height loss >4 cm (>1.5 in), self-reported but undocumented previous VF, glucocorticoid therapy equivalent to ≥5mg of prednisone or equivalent per day for ≥3 months[6], or when the T-score is ≤-2.5 regardless of existence of the other factors.[7]

The current evidence shows that bone mineral densitometry (BMD) test using dual x-ray absorptiometry (DXA) scan should be used in the diagnosis of osteoporosis in PMW.The following criteria constitutes the diagnosis of osteoporosis in PMW: history of fragility fracture/s, BMD T-score ≤-2.5, or low bone mass (BMD T-score bet <-1.0 and <-2.5) and high fracture risk according to FRAX.

Among PMW at risk of vertebral fracture, vertebral fracture assessment (VFA) can be made using DXA or lateral spine radiograph. If BMD is unavailable, FRAX, without BMD, can be used for diagnosis of osteoporosis among PMW without fractures.

Resource Implications

The availability and price of central DXA was surveyed online among members of the Osteoporosis Society of the Philippines Foundation, Inc. (OSPFI) and Philippine Rheumatology Association (PRA). Fourteen respondents represented 5 government hospitals (NCR, Region I, CAR) and 10 private hospitals (NCR, Region I, III, IV, VI, and CAR. Two government hospitals (NCR, Region VIII) and one private diagnostic clinic (NCR) also responded after personal inquiry. The cost of central DXA ranged from Php 2000 to Php 8000 in government and Php 1865 to Php 5600 in private institutions. The cost of DXA with VFA ranged from Php 4800 to Php 5125.

Acceptability and Applicability Issues

In the Philippines, it was estimated that there were only 0.1 DXA machines per million general population, a much lower number compared to the recommended 10 machines per million general population.[15] Compounding the dilemma is the disregard of osteoporosis as a national health priority. The costs of diagnostic tests and treatment are usually paid by individual patients. In addition, lack of knowledge of DXA interpretation and inadequate doctor-patient interaction are factors that deter wide use of DXA.[16]

Hip BMD-DXA is the gold standard of osteoporosis diagnosis. The t-score of -2.5 was the value that excluded osteoporosis in young healthy premenopausal women. BMD measurement is both a diagnostic and prognostic tool. Several issues arise on the use of BMD, DXA, hip BMD-DXA, and the reference range as the standard diagnostic tool recommended by WHO. First is whether spine BMD could be used for diagnosis of osteoporosis in PMW. The problem with spine BMD lies with the DXA machines' algorithm and detection of the irregularly shaped vertebrae and different bone composition (trabecular vs cortical) compared to the hip.[8] However, fragility fracture (compression fracture) and low BMD of the spine or any site are still considered osteoporosis. Secondly, mean BMD, SD, and t-score cut-off values may be different among countries and ethnicities. Mean BMD of LS and hip of adult Filipino women (age >20 years old) approximated Asian values than those of Caucasians.[17] ISCD maintains that the reference data from NHANES III should be applied internationally for simplicity and convenience until a new compelling reason arises.[5] Thirdly, other devices of BMD measurement are widely available (peripheral densitometry, ultrasound, CT scan) but clinical utility of those devices are uncertain. In the latest ISCD position statement, heel/calcaneal quantitative ultrasound (QUS) and peripheral DXA (pDXA) devices can be used in settings where hip DXA is not available or practical.[18] Fourth is the value of hip BMD-DXA in CFR profile using FRAX. Fracture risk assessment using risk factors and/or other BMD devices help clinicians determine which patients would need further testing by DXA or which ones should receive treatment in the absence of information by DXA.

The UK NICE and AACE endorse FRAX to guide clinical decisions.[6,7] According to the UK NICE, BMD-DXA can be reserved for patients with intermediate risk. Fracture risk by FRAX without BMD is sufficient criterion for treatment consideration.[7] Addition of BMD to CFR (or FRAX) delivers optimal fracture risk prediction for hip fracture in younger (<70 years old) PMW but the same improvement was not as substantial in other types of fractures across all age groups.[19] Hip fractures become less common for individuals aged ≥65 years.[20]; and the risk factors do not differ substantially between hip and other fractures.[21] When the 10-year fracture probability cut-off of 20% (MOF) and 3% (hip fracture), the values set by National Osteoporosis Foundation (NOF), were used with or without DXA, FRAX reliably predicted risk of any osteoporotic fracture among PMW aged >75 years.[22] The NOF threshold was adopted by the 2011 national consensus statement.[23] Local intervention thresholds were suggested by recent cross-sectional research on Filipino women from a single center in Metro Manila.[24] Translation into Filipino and cultural appropriation of FRAX was also recently published.[25]

Research Gaps

Other BMD devices and clinical risk factors are used as screening tools and should not replace DXA for diagnosis.[8] Like DXA, they are prognostic tools for fracture risk assessment. If fracture is an outcome of osteoporosis, then BMD devices could potentially become diagnostic tools when combined with clinical risk factors or CFR profile such as FRAX.

Theoretically, an increase in the number of DXA machines and more affordable BMD-DXA test would boost osteoporosis diagnosis and fracture risk assessment in the general population, however, it is uncertain if fracture incidence would improve through such measures especially for the populations at-risk. Although a 2017 survey of general physicians from a single center in Metro Manila found that 91% of general physicians use BMD of hip and LS by DXA for diagnosis, it is unknown if acceptability of the test is the same in all regions.[26] Knowledge gaps on screening, diagnosis, and management should be investigated and addressed to obtain the most from the limited number of DXA scan machines.

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PHARMACOLOGIC MANAGEMENT

Question 6: Among PMW with osteoporosis, are the anti-resorptive agents, ie. alendronate, ibandronate, zoledronate, denosumab, raloxifene, effective in reducing vertebral, non-vertebral, hip fractures compared to placebo?

Recommendation 1:

> Among PMW with osteoporosis, it is recommended that alendronate, denosumab, risedronate and zoledronate be used as initial therapy to reduce vertebral, non-vertebral, and hip fractures.
>
> ***(Strong recommendation, High quality of evidence)***

Recommendation 2:

> Ibandronate or raloxifene can be an alternative treatment in reducing vertebral fractures in certain cases.
>
> ***(Strong recommendation, Moderate quality of evidence)***

Panel Considerations on the Recommendations

Recommendation 1:
Definition of very high fracture risk individuals (AACE 2020)
Issues on male osteoporosis - not included in the search of evidence (only PMW)
not enough evidence on male osteoporosis - need to do de novo synthesis on male
Straight forward, no further issues

A panel member suggested to include the AACE 2020 guideline definition of very high fracture risk individuals. Another one suggested to include male osteoporosis, but as with the question on diagnosis, a de novo synthesis is needed.

Recommendation 2:
Due to limited data that the benefit is only seen in reducing vert fractures identify the cases where IBN or RLX can be used - only in vertebral fracture reduction, but not hip fracture.
Allergy to bisphosphonates - may use raloxifene issues on how to position ibandronate and raloxifene in the management
Some cases to be expounded in the manuscript
Can suggestion in the recommendation be strongly recommended? meaning the panel strongly recommends the recommendation suggestion
Suggest leave room to discuss with patient

Summary of Evidence

These recommendations were adapted from the 2020 American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) clinical practice guidelines. The AACE guidelines recommend alendronate, risedronate, zoledronate and denosumab as appropriate initial therapy for most osteoporotic patients with very high fracture risk defined as patients with a recent fracture (within 12 months), fractures while on approved osteoporosis therapy, multiple fractures, fractures while on long-term glucocorticoids, very low T-score (eg. < −3.0), high risk for falls or history of injurious falls, and very high fracture probability by FRAX® (fracture risk assessment tool, ie. major osteoporotic fracture >30%, hip fracture >4.5%) or other validated fracture risk algorithm. High fracture risk are those patients who have been diagnosed with osteoporosis but are not at very high fracture risk as defined above. For patient requiring drugs with efficacy in reducing vertebral fracture, Ibandronate or raloxifene are the initial options for treatment.[1]

Bisphosphonates

Alendronic acid, raloxifene, zoledronic acid and denosumab have evidence to effectively reduce vertebral, nonvertebral and hip fractures (“broad-spectrum” anti-fracture efficacy) and should be considered as initial options for postmenopausal women with osteoporosis lest with contraindications.[1]

Alendronic and Zoledronic acid have evidence for broad spectrum antifracture efficacy.[2-6] Alendronic acid treatment reduced the risk for vertebral (RR 0.55 95% CI 0.38 to 0.80), non-vertebral (RR 0.77 95% CI 0.64-0.92) and hip fractures (RR 0.47 95% CI 0.26-0.85) compared to placebo. [5,15-17] Zoledronic acid treatment also reduced the risk of vertebral (RR 0.0.30 95% CI 0.24 to 0.38) and hip fractures (RR 0.59 95% CI 0.42-0.83) compared to placebo.[4,18-21]

Oral Bisphosphonates should be used with caution with active esophageal disease and with reduced kidney function (GFR <35 mL/min).[7] Bisphosphonates particularly the IV form may cause transient or permanent decreases in kidney function on rapid infusion. In HORIZON study, hypocalcemia was noted 9-11 days post infusion of zoledronic acid.[8] Drug hypersensitivity and hypocalcemia are contraindications to both oral and IV bisphosphonates.[1]

Denosumab

In the FREEDOM trial which enrolled 7808 postmenopausal women, denosumab showed broad spectrum anti-fracture efficacy as early as 12 months. Denosumab treatment reduced the risk of new radiographic vertebral fracture (RR 0.32, 95% CI 0.26 to 0.41 P<0.001) compared to placebo.[9] Denosumab is generally well tolerated without evidence of symptomatic hypocalcemia, osteonecrosis of the jaw and/or atrial fibrillation. The most common side effects include musculoskeletal pain, hypercholesterolemia and cystitis.[9] Denosumab is contraindicated in patients with hypocalcemia. One advantage of denosumab is no dose adjustment needed in patients with renal insufficiency, however, with limited evidence on its use among patients on hemodialysis.

Drug holiday from denosumab is not recommended because the protection from vertebral fractures is lost upon discontinuation. Individuals should be shifted to another anti-resorptive agent if denosumab administration would be discontinued.[10-12]

Ibandronate

In the BONE study where 2946 postmenopausal women with BMD T score ≤ -2.0 at the lumbar spine in at least one vertebra (L1-L4) and one to four prevalent vertebral fractures (T4-L4) given daily or intermittent ibandronate vs PBO[6], the rate of new vertebral fractures was significantly reduced in patients receiving oral daily (4.7%) and intermittent ibandronate (4.9%), compared to placebo (9.6%). Daily and intermittent oral ibandronate significantly reduced the risk of new morphometric vertebral fractures by 62% (p = 0.0001) and 50% (p = 0.0006), respectively, vs placebo. Both treatment groups also produced a statistically significant relative risk reduction in clinical vertebral fractures (49% and 48% for daily and intermittent ibandronate, respectively). Significant and progressive increases in lumbar spine (6.5%, 5.7%, and 1.3% for daily ibandronate, intermittent ibandronate, and placebo, respectively, at 3 years) and hip BMD, normalization of bone turnover, and significantly less height loss than in the placebo group were also observed for both ibandronate regimens. The overall population in the study though was at low risk for osteoporotic fractures.

Raloxifene

In the MORE trial, evaluable spine radiographs from 6828 postmenopausal women kept on either 60 or 120 mg raloxifene showed that risk of vertebral fracture was reduced in both treatment arms (for 60-mg/d group: relative risk [RR], 0.7; 95% confidence interval [CI], 0.5-0.8; for 120-mg/d group: RR, 0.5; 95% CI, 0.4-0.7). Frequency of vertebral fracture was reduced both in women who did and did not have prevalent fracture. Risk of nonvertebral fracture for raloxifene vs placebo did not differ significantly (RR, 0.9; 95% CI, 0.8-1.1 for both raloxifene groups combined).[22] For patients at high-risk of spine fracture but not at risk for hip and vertebral fracture, raloxifene may be appropriate and has the side benefit of reducing the risk of breast cancer.[22-23]

The most common adverse effects of Raloxifene include hot flashes, leg cramps and peripheral edema. In a meta-analysis of nine trials with 24,523 postmenopausal women, raloxifene was associated with an increase in the risk of deep venous thrombosis (DVT) and pulmonary embolism (ORs 1.5, 95% CI 1.1-2.1 and 1.9, 95% CI 1.0-3.5, respectively).[13] Raloxifene is contraindicated in patients with venous thromboembolism and drug hypersensitivity.[14]

Resource Implications

Drug	Dosage	Price/dose	Price for 1 year dose
Alendronic acid	70 mg Once a week	₱ 210- 650	₱10,920 -33,800
Zoledronic acid	5 mg once a year	₱ 18,500-25,894	₱ 18,500-25,894
Denosumab	60 mg every 6 months	₱ 18,490	₱ 37,980
Ibandronic acid	150 mg once a month	₱ 1,807	₱ 21,684
Raloxifene	60 mg tab daily	P70.00	P25,550

The Prices of the above medications were estimated from a leading drugstore in the Philippines (Mercury drug store). To date, there is no local study on the cost-effectiveness of antiresorptive drugs in reducing osteoporotic fractures.

Internationally, studies searched were mainly in European settings in the years 2003-2007. According to Osteoporosis international in 2006, the incremental cost per quality-adjusted life years (QALY) gained from a 5-year intervention with risedronate compared to "no intervention" in 70-year-old women at the threshold of osteoporosis was estimated to be €860, €19,532, €11,782, and €32,515 in Sweden, Finland, Belgium, and Spain, respectively. Also in the same study, Among 70-year-old women at the threshold of osteoporosis without previous fracture the estimated cost per QALY gained ranged from €21,148 (Sweden) to €80,100 (Spain) [24] For the alendronic acid, treatment 71-year-old osteoporotic women with a prior spine fracture with alendronate resulted in a cost per quality-adjusted life-year (QALY) gained of SEK76000, which is well below the threshold for cost effectiveness of SEK300000. For women aged 65 years, the cost-effectiveness ratio increased to SEK173000 and for women aged 77 years, the cost-effectiveness ratio decreased to SEK52000 .[25] The cost per QALY gained of treating postmenopausal women with prior vertebral fractures ranged in the base case from "cost saving" in the Scandinavian countries to €15,000 in Italy. Corresponding estimates for women without prior vertebral fractures ranged from "cost saving" to €40,000 [26]

Acceptability and Applicability Issues

These medications, though with proven efficacy and safety, have limited acceptability to Filipino patients especially among those with financial constraints.

Research Gaps

Additional research is still needed particularly in the cost-effectiveness of the antiresorptive drugs in the Philippine setting.

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Question 7: Among postmenopausal women with severe osteoporosis, is teriparatide, abaloparatide and romosozumab effective in reducing vertebral, non-vertebral, and hip fractures compared to placebo? How long should treatment duration be?

Recommendation:

Among PMW with severe osteoporosis, it is recommended that teriparatide, abaloparatide and romosozumab be used. Abaloparatide and romosozumab prevent vertebral, non-vertebral and hip fractures while teriparatide reduces the risk of further vertebral and nonvertebral fractures. Treatment duration of bone forming agents for maximum treatment benefits is recommended to be referred to specialists.

(Strong recommendation, High quality of evidence)

Panel Considerations on the Recommendation

Straight forward, no issues
Consider severe osteoporosis as defined by WHO and those at very high fracture risk
Criteria to say when the medications can be stopped, how treatment is effective. Effect is seen in 12 months, but need to follow through with anti-resorptive if one will discontinue meds.
Maximal benefit seen after 2 years of teriparatide or 1 year of romosozumab.
When should one stop the bone forming agents/indications when should one stop the medication
How to evaluate if drug works - 1. improvement or stability of BMD after one year or 2 years of treatment, 2. no occurrence of further fractures. Needs to be captured in manuscript.

If a patient does not have a budget, best not to start the bone forming drug. Should patients with severe osteoporosis be handled by and referred to specialists? Criteria when to refer to specialists should be included. In caring for osteoporosis patient, it's a case-to-case analysis on how long should one keep them on treatment. Laboratory exams that will help in deciding how long should one continue with treatment - include bone turnover markers and bone densitometry
Role of bone turnover markers. Refer to specialists for further management - under specialists
Should be in therapeutics under specialists level can be listed under PNDF. PNDF inclusion
DOH - med should be in the CPG, also in Omnibus guidelines, also recommended by HTAC

Summary of Evidence

These recommendations were adapted from the American Association of Clinical Endocrinologists (AACE)/ American College of Endocrinology (ACE) Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis – 2020 update and Scottish Intercollegiate Guidelines Network (SIGN 142) Management of Osteoporosis and the Prevention of Fragility Fractures.[1,2]

SIGN 142 recommends teriparatide for the prevention of vertebral and non-vertebral fractures in PMW women with severe osteoporosis based on analysis of one placebo-controlled RCT and one observational study in which teriparatide was compared with standard of care. Meanwhile, AACE recommends abaloparatide, teriparatide and romosozumab as initial therapy for patients at very high fracture risk or have failed or intolerant to previous anti-osteoporosis medications. Recommendations

were based on the same studies and an additional RCT of abaloparatide on PMW with severe osteoporosis.[1,2]

Teriparatide vs. Placebo

Teriparatide efficacy and safety for fracture prevention was evaluated in an RCT involving 1,637 postmenopausal women with severe osteoporosis (mean T-score -2.6 and mean number of previous vertebral fractures of 2.3).[3] Two doses of teriparatide were used (20 mcg daily and 40 mcg daily given by subcutaneous injection for up to 18 months). Both had similar effects, but only the 20 mcg dose is currently licensed for clinical use. Teriparatide at 20 mcg dose was associated with a reduced risk of vertebral fractures (RR 0.35, 95% CI 0.22 to 0.55), and non-vertebral fracture (RR 0.47, 95% CI 0.25 to 0.88) compared with placebo. With the 20-µg dose, a vertebral fracture was prevented for every 12 patient-years of treatment, and with the 40-µg dose, a vertebral fracture was prevented for every 10 patient-years of treatment. There was no significant reduction in hip fractures due to low frequency of observable events.[3]

A post hoc analysis of the RCT investigated whether teriparatide treatment would be more effective when given to postmenopausal women at greater risk of fracture based on FRAX-estimated fracture risk. Pooled analysis of teriparatide treatment groups (20 mcg and 40 mcg) vs placebo showed a significant reduction in morphometric vertebral fractures and non-vertebral fractures irrespective of baseline fracture probability, 37% decrease in all non-vertebral fractures (95% CI 10 to 56%), 56% decrease in low-energy non-vertebral fractures (95% CI 24 to 75 %) and 66% decrease in morphometric vertebral fractures (95% CI 50 to 77%). Hazard ratios for efficacy of teriparatide on fracture outcomes did not change significantly with increasing fracture probability (p>0.30).[4]

In terms of safety, adverse effects that were more common in teriparatide-treated patients compared with placebo-treated patients included nausea (18% v 8%), headache (13% v 8%), dizziness (9% v 6%), leg cramps (3% v 1%) and mild hypercalcaemia (11% v 2%).3 Teriparatide and abaloparatide. have boxed warnings because of the occurrence of osteosarcomas in animal studies using very. high doses. The annual incidence of osteosarcoma in women aged ≥50 years old in the general population is approximately 1 in 250,000. While the actual incidence of osteosarcoma in teriparatide. users is unknown, there are rare reports consistent with the background incidence.5,6 Teriparatide. and abaloparatide should not be administered to patients with primary or any form of secondary. untreated or unresolved hyperparathyroidism. Treatment should be limited to no longer than 2 years in total duration.[7,8]

Abaloparatide vs. Placebo

The Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE) was a phase 3, double-blind, RCT whereby 2463 postmenopausal women with bone mineral density (BMD) T score ≤−2.5 and >−5.0 at the lumbar spine or femoral neck and radiological evidence ≥2 mild or ≥1 moderate lumbar or thoracic vertebral fracture or history of low-trauma nonvertebral fracture within the past 5 years were included as well as postmenopausal women (>65 y) with fracture criteria and a T score ≤−2.0 and >−5.0 or without fracture criteria and a T score ≤−3.0 and >−5.0. New morphometric vertebral fractures occurred in 0.58% (n = 4) of the abaloparatide group, 4.22% (n = 30) of the placebo group), and 0.84% (n = 6) of the teriparatide group. The Kaplan-Meier estimated event rate for nonvertebral fracture was 2.7% for abaloparatide, 4.7% for placebo (hazard ratio [HR], 0.57 [95% CI, 0.32-1.00]; *P* = .049), and 3.3% for teriparatide. The study showed that BMD increases were greater with abaloparatide than placebo (all P < .001). Incidence of hypercalcemia was lower with abaloparatide (3.4%) vs teriparatide (6.4%) (P = .006). It was concluded that among postmenopausal women with osteoporosis, the use of subcutaneous abaloparatide, compared with placebo, reduced the risk of new vertebral and nonvertebral fractures over 18 months.[9]

ACTIVExtend, an extension of ACTIVE, enrolled patients who completed 18 months of Abaloparatide (ABL) or placebo (PBO) in ACTIVE to receive up to 24 additional months of open-label Alendronate (ALN). Of 1243 eligible ACTIVE patients, 1139 (92%) were enrolled in ACTIVExtend. Findings indicated percentages of patients with new morphometric vertebral fractures: PBO/ALN, 4.4% vs ABL/ALN, 0.55%; (relative risk RR, 0.13; 95% CI, 0.04-0.41; P<.001). Kaplan-Meier estimated rates of nonvertebral fractures were PBO/ALN, 5.6% vs ABL/ALN, 2.7%; (hazard ratio [HR], 0.48; 95% CI, 0.26-0.89). There was also a 58% risk reduction of major osteoporotic fractures (HR, 0.42; 95% CI, 0.21-0.85) and a 45% risk reduction of clinical fractures (HR, 0.55; 95% CI, 0.33-0.92) in the ABL/ALN group vs the PBO/ALN group. At 25 months, bone mineral density percentage change from ACTIVE baseline for ABL/ALN vs PBO/ALN was as follows: lumbar spine, 12.8% vs 3.5%; total hip, 5.5% vs 1.4%; femoral neck, 4.5% vs 0.5% (group differences at all sites P<.001). It was concluded that use of ABL for 18 months followed by ALN for 6 months improved bone mineral density and reduced fracture risk throughout the skeleton and may be an effective treatment option for postmenopausal women at-risk of osteoporosis-related fractures.[10]

Romosozumab vs. Placebo/Control

The Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) involved 7,180 postmenopausal women with total hip or femoral neck T-scores of -2.5 to -3.5. For the first 12 months participants were randomly assigned to monthly subcutaneous injections of 210 mg romosozumab or placebo followed by 60 mg denosumab by subcutaneous injection every six months in both groups for 12 months. All patients were given calcium and vitamin D supplements. Proportion of participants who received romosozumab vs PBO throughout 1 year who developed new vertebral fractures [0.5% vs 1.8% (OR 0.27, 95%CI 0.15-0.47)], clinical fractures [1.6% vs 2.5% (HR0.64, 95%CI 0.46-0.89)], major non-vertebral fractures [1% vs 1.5% (HR 0.67, 95%CI 0.44-1.02)], new or worsening vertebral fractures [0.5% vs 1.8% (OR 0.28, 95%CI 0.17-0.49)], hip fractures [0.2% vs 0.4% (HR 0.54, 95%CI 0.22-1.35)] , major osteoporotic fractures [1.1% vs 1.8% (HR0.6, 95%CI 0.4-0.9], multiple new or worsening vertebral fractures [0.03% vs 0.3% (OR0.11, 95%CI 0.01-0.87)].

Within the second year, for patients who had received romosozumab first, RRRs of fracture were 81% for vertebral fractures (p < 0.001), 32% for clinical fractures (p=0.052), 25% for nonvertebral fractures (p=0.16), 55% for hip fractures (p= 0.18), 39% for major osteoporotic fractures (p=0.034), and 32% for major nonvertebral fractures (p= 0.092). The study found a significant reduction in the risk of vertebral fractures but no significant difference in non-vertebral fracture risk between groups at either 12 or 24 months.[11]

The Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) study randomized 4,093 postmenopausal women aged 55–90 years to 210 mg romosozumab monthly or alendronate 70 mg weekly for 12 months followed by an open-label period of 12 to 24 months of alendronate 70 mg weekly in both groups. Calcium and vitamin D supplements were prescribed in both groups throughout the study. At entry, participants have a T-score of -2.5 or lower at the femoral neck or total hip and one or more moderate or severe grade vertebral fractures or two or more mild vertebral fractures. Participants with a T-score at the femoral neck or total hip of less than -2.0 and two or more moderate or severe grade vertebral fracture or proximal femur fracture in the previous 3–24 months were included. There was a significant reduction in vertebral fractures at 24 months in the romosozumab-alendronate group compared with those treated with alendronate alone with a RR of 0.52 (95% CI 0.40 to 0.66, p<0.001), 27% lower risk of clinical fracture (hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001), 19% lower risk of non-vertebral fractures (HR 0.81, 95% CI 0.66 to 0.99), as was the 38% lower risk of hip fractures (HR 0.62, 95% CI, 0.42 to 0.92). Therefore, in the target population 12 months romosozumab followed by 12 months alendronate was superior to 24 months of alendronate in preventing vertebral, non-vertebral and hip fractures.[12]

No cases of osteonecrosis of the jaw or atypical femoral fracture were identified during the period of romosozumab-alone treatment. Events were observed in the alendronate open-label period, with four events of atypical femoral fracture in the alendronate-to-alendronate group and two in the romosozumab-to-alendronate group. Serious cardiovascular adverse events, both cardiac with cardiac ischemic and cerebrovascular events were more frequent in the romosozumab group than in the alendronate group.[12] Corrected serum calcium levels were lower at one month in the romosozumab group than in the placebo group. Binding anti-romosozumab antibodies developed in 18% in the romosozumab group, and neutralizing antibodies developed in 0.7% in the romosozumab group with no detectable effect on efficacy or safety [13]

The current evidence shows that teriparatide, abaloparatide and romosozumab can be used in postmenopausal women with severe osteoporosis with minimal adverse effects.

Treatment Duration

Treatment duration of bone forming agents should be 24 months for teriparatide and 12 months for romosozumab. Use of teriparatide for more than 2 years during a lifetime should be considered only if a patient remains at high risk for fracture. Use of romosozumab beyond 12 months requires more safety and efficacy data. These recommendations were adapted from the Latin American Federation of Endocrinology position statement and the UK Clinical Guideline 2022.[14, 15] The Latin American Federation of Endocrinology position statement recommends administration of teriparatide for 2 years and romosozumab for 1 year. The aforementioned durations showed the greatest benefit in terms of increased BMD and reduction of fracture risk.[14]
The UK NICE 2022 guidelines made similar recommendations of limiting treatment duration to 24 months and 12 months for teriparatide and romosozumab, respectively.[15] There is some uncertainty about how long patients should be treated with teriparatide due to the association of osteosarcoma with its administration. In 2020, the FDA approved changes to the label for teriparatide by removing the 2-year lifetime treatment limitation since no apparent association between longer treatment with teriparatide and osteosarcoma has been observed in humans to date. This is supported by findings in a 15-year post-marketing surveillance study which showed that treatment with teriparatide did not increase the incidence of adult osteosarcoma.[16, 17] Despite its potency and efficacy, the FDA issued a warning of potential risk of myocardial infarction, stroke and cardiovascular death with the use of romosozumab.[18]

Resource Implications

Teriparatide (Forteo)[8] costs approximately P34,470 a month in the Philippines. Both abaloparatide (Tymlos)[7] and Romosozumab are not available locally however treatment costs are estimated at $2,189 US average monthly price for abaloparatide and $2,046.71 per month for romosozumab (Evenity) in the USA.[19, 20]

A US-healthcare perspective economic study compared the incremental cost-effectiveness ratios (ICER, incremental costs per QALY gained) of denosumab, teriparatide, abaloparatide, and romosozumab against zoledronate for the treatment of postmenopausal osteoporosis patients with a very high fracture risk. Base-case analysis indicated that zoledronate had the lowest cost and utility in all age groups (65-, 70-, 75-, and 80-year-old patients). Compared with zoledronate, the cost-effectiveness of the other drugs was dependent on the willingness-to-pay (WTP) threshold. The probability sensitivity analysis results showed that denosumab was the most cost-effective option under WTP thresholds of $50,000/QALY, $100,000/QALY and US$ 150,000/QALY. Authors conclude that zoledronate is the cheapest strategy and denosumab is the most cost-effective choice among the 5 treatment strategies.[8]

In another cost analysis study done in China on the use of sequential teriparatide/zoledronic acid versus zoledronic acid monotherapy for women with postmenopausal osteoporosis showed that the sequential teriparatide/zoledronic acid was not cost-effective. The latter was associated with higher health care cost of $5,196.69 and QALY of 0.03 compared with zoledronic acid monotherapy. [21]

Acceptability and Applicability Issues

In terms of acceptability of these anabolic drugs like teriparatide in the Philippines, being a 3rd world country, cost is an important factor. Majority of the Filipinos' healthcare disease investigation and management will be coming from the patient's own account. For those who cannot afford these drugs, they would settle for the lesser expensive alternatives. On the other hand, in terms of applicability, those patients with osteoporosis who need teriparatide and can afford to purchase this drug another concern would be its administration. They need go to a healthcare provider, a caregiver or these patients should be taught how to administer the medicine via subcutaneous route daily for 1 to 2 years.

There is a need to educate Filipinos about osteoporosis, its complications and the available treatment options in our country. Information dissemination and availability of this drug at the far flung areas of the country should be looked into.

Research Gaps

We have to bridge the gap between the application of these guidelines based on research to actual clinical practice in terms of improving the care and management of our patients with osteoporosis. A lot of Filipinos are still not treated at all or would stop osteoporosis treatment because of lack of information about the condition and its complications. Some are afraid of the side effects of these anabolic drugs since it is maintained for a long period of time. Other patients would opt to prioritize and buy other medications like antihypertensives, antidiabetics, antithyroid drugs, etc over anti osteoporosis drugs due to limited funds. There are also those patients who do not prefer injections and would rather take their medicine through the oral route.

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NONPHARMACOLOGIC MANAGEMENT

Question 8: Among postmenopausal women with osteoporosis, should calcium and vitamin D supplementation be given to reduce fragility fracture risk?

Recommendation:

Among PMW with osteoporosis, calcium and vitamin D supplementation is recommended along with anti-osteoporosis medication to reduce risk of fragility fracture. The recommended dose for calcium is 700-1200 mg/day and vitamin D at least 800 IU per day. (***Strong recommendation, High quality of evidence***)

Panel Considerations on the Recommendation

A panel suggested to put in the write up calcium and vitamin D (table) in terms of recommended doses. Also, to include sources of calcium and vitamin D just like in the 2010 consensus statement. It was mentioned that most clinical trials give calcium and vitamin D together with anti-osteoporosis medication.

Summary of Evidence

These recommendations were adapted from the guideline statements of the UK National Osteoporosis Guidelines Group (NOGG), Belgian Bone Club, American Society for Bone and Mineral Research (ASBMR) and African Society of Bone Health and Metabolic Bone Diseases. All recommend that in patients with osteoporosis, a daily intake of 700-1200 mg/day of calcium should be primarily achieved through dietary sources, or supplementation if necessary.[1-4] Higher doses are needed among old patients who are homebound, institutionalized, or those with conditions that could affect intestinal absorption of calcium such as Crohn's, achlorhydria, post bariatric surgery, use of proton pump inhibitors.[1] The recommended dose of vitamin D is at least 800 IU but higher levels are necessary among those who are vitamin D insufficient.[1-4]

In a 2019 network meta-analysis of 193,987 postmenopausal women with osteoporosis, combined calcium with vitamin D supplementation was associated with reduced hip fractures compared with placebo (RR 0.81, 95% CI 0.71 to 0.93) but did not demonstrate any benefit for reducing vertebral (RR 0.88, 95% CI 0.61 to 1.27) or nonvertebral fractures (RR 0.93, 95% CI 0.85 to 1.01).[5] Vitamin D supplementation alone showed significant reduction in nonvertebral fractures (RR 0.44, 95% CI 0.23 to 0.85) but calcium supplementation alone did not reduce the incidence of any fragility fracture. This finding for lack of benefit for calcium is consistent with the findings of a systematic review of dietary calcium supplementation for prevention of fragility fractures in adults aged >50.[6] On the other hand, benefits for combined calcium and vitamin D supplementation were similarly reported in 3 large meta-analyses that examined supplementation with vitamin D and calcium for fracture prevention in the general old adult population. [7-9] Vitamin D in combination with calcium was associated with reduced hip fractures but inconsistent effects on fractures in other sites.

The UK NOGG states that it is of clinical importance that patients taking antiresorptive and anabolic medications to be vitamin D replete.[1] One RCT and 2 observational studies observed that the response to antiresorptive agents were enhanced in terms of BMD changes and anti-fracture efficacy in patients who were vitamin D and calcium replete.[10-12] Moreover, majority of the trials on

the pharmacologic therapies of osteoporosis included the use of calcium and vitamin D supplementation as part of their study design hence replicating this setting provides a strong basis for recommending supplementation.[1,2,13] There is little evidence that vitamin D supplementation alone reduces fracture incidence, although it may reduce falls risk.[14] The use of supplemental calcium and vitamin D has been associated with a risk of developing urinary calculi due to the passage of absorbed calcium in the urine. In the Women's Health Initiative trial (N= 36,282), postmenopausal women who received 1000 mg of elemental calcium as calcium carbonate and 400 IU of Vitamin D had an increased risk of urinary calculi (HR, 1.17; 95% CI, 1.02 to 1.34).[15] Furthermore, there have been controversies in the past linking calcium supplements with increase in cardiovascular and cerebrovascular disease but there was insufficient evidence to support this as long as the daily calcium intake falls within the tolerable upper intake levels of 2000-2500 mg per day.[16] Based on a large meta-analysis of calcium and vitamin D supplementation (11 RCTs, N=51,419), the UK NOGG states that calcium and vitamin D supplements may increase the risk of kidney stones (RR 1.18, 95% CI 1.04 to 1.35), but no association has been found with respect to incidence of cardiovascular disease or cancer.[1,17]

Current evidence shows that vitamin D with and without calcium supplementation has been associated with significant reductions in hip and nonvertebral fractures among postmenopausal women with osteoporosis, with no associated increase in adverse events if given at appropriate doses.

Food and Nutrition Research Institute: Recommended Nutrients Intake per Day (Vitamins)[18]

Adults	Weight		Calcium (mg)		Vit D (ug)[a]		Magnesium (mg)		Phosphorus (mg)		Zinc (mg)	
	M	F	M	F	M	F	M	F	M	F	M	F
19-29	60.5	52.5	750	750	5	5	240	210	700	700	6.5	4.6
30-49	60.5	52.5	750	750	5	5	240	210	700	700	6.5	4.6
50-59	60.5	52.5	750	800	10	10	240	210	700	700	6.5	4.6
60-69	60.5	52.5	800	800	15	15	240	210	700	700	6.5	4.6
≥70	60.5	52.5	800	800	15	15	240	210	700	700	6.5	4.6

[a]In the absence of adequate exposure to sunlight, as calciferol;1 µg calciferol = 40 IU vitamin D

Tolerable Upper Intake Levels or Upper Limits per day[18]

Adults	Vitamin D (ug)	Calcium (mg)	Magnesium (mg)	Phosphorus (mg)	Zinc (mg)
19-29	50	3000	350	4000	45
30-49	50	3000	350	4000	45
50-59	50	3000	350	4000	45
60-69	50	3000	350	4000	45
≥70	50	2000	350	3000	45

Adapted from WHO/FAO Guidelines on Food Fortification with Micronutrients (WHO/FAO, 2006); however, WHO/FAO have only recommended ULs for vitamins D, calcium, and zinc for adults. The remaining values are those recommended by Institute of Medicine Food and Nutrition Board (IOM-FNB).

Resource Implications

Adequate intake of calcium and vitamin D should come primarily from dietary sources. However, when proper diet and nutrition are lacking, supplementation becomes necessary. The 2022 Department of Health recommended drug price reference index of combined calcium and vitamin D (600 mg/400 IU) is PHP 6.20.[19] To date, there is no local study examining the cost-effectiveness of calcium and vitamin D supplementation for the prevention of fractures. An international study conducted in the European Union and US in 2019 showed a net cost benefit of €5,710,277,330 and $3,312,236,252, respectively assuming supplementation was able to reduce overall fracture rate by 14%.[20]

Acceptability and Applicability Issues

There is no local study on acceptability and applicability issues of calcium and vitamin D supplementation among patients diagnosed with osteoporosis. However, a qualitative study done in nursing homes in Denmark revealed the following reasons for low implementation of supplementation included: lack of prescription by the general practitioner in the central electronic database (60%), resident-refusal to eat tablets (43%), chewing-swallowing difficulties (40%), and a high number of tablets given to the residents daily (34%).[21]

Research Gaps

More research is required to ascertain the role of calcium and vitamin D in the prevention of fractures among patients with osteoporosis since most therapeutic trials of anti-resorptive and anabolic drugs prescribed supplementation as part of standard of care. The recommended doses of calcium and vitamin D also vary per guideline and further studies on supplementation could provide a definitive dosing recommendation in the future. Local studies on baseline calcium intake and vitamin D status of postmenopausal women, cost-effectiveness of supplementation and acceptability are still lacking.

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Question 9: Among postmenopausal women diagnosed with osteoporosis, should serum calcium and vitamin D levels be normal prior to initiating anti-resorptive therapy?

Recommendation:

Among PMW with osteoporosis, it is recommended that calcium insufficiency/deficiency be treated prior to initiation of anti-osteoporosis drugs.
(Strong Recommendation, Moderate quality of evidence)

It is also recommended that vitamin D insufficiency/ deficiency should be addressed alongside the initiation of anti-osteoporosis drugs.
(Strong Recommendation, High quality of evidence)

Panel Considerations on the Recommendation

For patients who have normal calcium levels, should supplementation be given?
No trials looked into the calcium levels before anti-osteoporosis treatment. However, if someone is not meeting the dietary requirement of 700-1200 mg calcium per day supplementation should be given. Similarly, vitamin D levels (NOGG) need to be measured before starting any treatment.
Question 20 before 19. In someone who sustained fragility fracture, should clinicians therefore wait for 2-3 months before initiating anti-osteoporosis medication if there's evidence of calcium and/or vitamin D insufficiency? Calcium levels must be measured and ensured to be normal before initiation of anti-osteoporosis medication to prevent further hypocalcemia while on medication esp parenteral bisphosphonate. Equally important is to address vitamin D insufficiency. One way is to give loading dose of Vitamin D followed by daily supplementation for optimal efficacy of anti-osteoporosis medication esp parenteral preparation. (UK NOGG)

Summary of Evidence

These recommendations are adapted from the UK National Osteoporosis Guideline Group (NOGG) statements which recommend initiating calcium and/or vitamin D supplementation as an adjunct to anti-osteoporosis drug treatment if dietary calcium is low and/or vitamin D insufficiency is a risk, respectively. It is likewise recommended to treat vitamin D deficiency and insufficiency prior to initiation of parenteral anti-osteoporosis drug treatment (e.g., zoledronate and denosumab) and alongside or concurrently with oral anti-osteoporosis drug treatment.[1]

According to UK NOGG and other guidelines, serum determination of calcium and 25-hydroxyvitamin D is mostly reserved for the initial work-up of osteoporosis patients who are suspected of deficiency or secondary causes osteoporosis.[1-3] There were no clinical trials that looked into the calcium levels before anti-osteoporosis treatment. However, patients who do not meet the dietary requirement of 700-1200 mg calcium per day should be given appropriate calcium supplementation. Similarly, vitamin D levels (NOGG) need to be measured before starting any treatment.

Routine or widespread calcium and vitamin D supplementation for fracture prevention is also not advised based on potential long-term harms caused by hypercalcemia and raised vitamin D levels.[1-3] UK NOGG states that dietary sources of calcium are still the preferred option and combined

supplementation with vitamin D is only targeted to those with insufficient dietary intakes or proven deficiency, as well as high fracture risk individuals such as those living in care facilities or have malabsorption syndromes.[1]

These recommendations are based on randomized controlled trials for antiresorptive drugs which have all included daily co-administration of calcium and vitamin D supplements as adjuncts to therapy. In pivotal trials of ibandronate and zoledronic acid for fracture prevention in PMW, all patients received daily calcium (500-1500 mg) and vitamin D (400-1200 IU).[4,5] In the FIT trial for alendronate, patients with low calcium intakes (<1000 mg/day) were given calcium 500 mg and vitamin D 250 IU daily at randomization.[6] Mean daily calcium intake in the study population was generally low (619 and 652 mg/day in the placebo and alendronate groups, respectively). In the risedronate VERT trials, all patients received daily calcium 1000 mg/day alongside treatment and vitamin D up to 500 IU/day if baseline levels were low.[7,8] Of these, only the VERT studies reported baseline incidence of Vitamin D deficiency in the study population (34-37% across treatment groups in the EU/Australian trial and 9% overall in the North American trial).[7,8] Based on these studies, there is robust evidence on the efficacy of bisphosphonates for fracture prevention when given with calcium and vitamin D. Co-administration of calcium and vitamin D with bisphosphonates resulted in 40-60% reduced risk for vertebral fractures (RR 0.40-0.60, NNT 60-89) and 20-40% reduced risk for nonvertebral fractures (RR 0.60-0.80, NNT 50-60) after 1 to 3 years of treatment.[9-10]

UK NOGG recommends investigating preexisting hypocalcaemia in osteoporosis patients, and if caused by vitamin D deficiency, be treated with vitamin D (e.g., 100,000 to 300,000 IU orally as a loading dose in divided doses) before zoledronate treatment is initiated.[1] The zoledronic acid prescribing information advises that serum calcium must be measured and corrected prior to initiating zoledronic acid injection. This is based on safety data derived from clinical trials which reported hypocalcemia in patients treated with zoledronic acid injection, with some patients developing cardiac arrhythmias and neurologic adverse events (seizures, tetany and numbness) in cases of severe hypocalcemia.[11]

Evidence on the utility of treating calcium and vitamin D deficiency before starting bisphosphonate therapy was not discussed in the NOGG guidelines but can be found elsewhere. A post-hoc analysis of the Fracture Intervention Trial of alendronate investigated the impact of vitamin D status on alendronate efficacy on a subpopulation of 1,000 PMW with at least 1 vertebral fracture.12 At baseline, 14% of participants were vitamin D sufficient (>30 ng/ml), 83% were insufficient (>10 to 30 ng/ml), and 2% were deficient ≤10 ng/ml). Linear regression analysis found no association between vitamin D status at initiation of therapy and BMD response to alendronate as long as the medication is co-administered with vitamin D and calcium.

Adequate intake of calcium and vitamin D is essential in all osteoporosis patients.[1] As stand-alone treatment, meta-analyses have reported reduction in hip and nonvertebral fractures with combined calcium and Vitamin D supplements compared with placebo.[13-15] Observational studies have also shown increased response to bisphosphonates with optimal vitamin D status; vitamin D replete patients generally had greater improvement in T-scores or BMD and lower incidence of fractures than vitamin D deficient patients while on bisphosphonate therapy.[16-18]

In terms of safety, calcium and vitamin D supplementation in the adult population has been shown to increase the risk of kidney stones but not the incidence of cardiovascular disease or cancer. In a large meta-analysis (11 RCTs, N=5149) conducted for the US Preventive Services Task Force report on primary prevention of osteoporosis, supplementation with a combined preparation of vitamin D and calcium was associated with increased risk of kidney stones (RR 1.18, 95% CI 1.04 to 1.35) but no significant association with cancer or cardiovascular disease (i.e., myocardial infarction, stroke, heart failure) was detected.[19] UK NOGG advises against routine administration of

large doses of vitamin D (≥60,000 units) among PMW as this has been shown to be associated with an increased risk of fracture (RR 1.26, 95% CI 1.00 to 1.59, P=0.047) and falls (RR 1.15, 95% CI 1.02 to 1.30; P=0.03).[20]

Resource Implications

Based on the 2022 Department of Health Drug Price Reference Index, the current price of combined calcium and vitamin D (600 mg/400 IU) is PHP 6.20.[21]

This review did not find any local or international studies evaluating the economic benefits of early initiation vs co-administration of calcium and vitamin D with bisphosphonate therapy in postmenopausal osteoporosis. Nevertheless, the cost-effectiveness of combined preparations has been demonstrated in some studies. A study using a Markov microsimulation model in a Belgian population of men and women aged > 60 years with osteoporosis demonstrated that the cost per QALY gained of vitamin D/calcium supplementation was €40,578 in women and €23,477 in men.[22] Estimates decreased to €7,912 and €10,250 at the age of 70 years and vitamin D and calcium supplementation became cost-saving at the age of 80 years, leading the authors to conclude that supplementation cost was less than the costs of treating osteoporotic fractures in those receiving no supplementation.

In a French cost-effectiveness analysis of supplementation strategies among osteoporosis patients aged ≥65 years without previous fracture, “treat then check” Vitamin D serum after 3 months and “screen (i.e. vitamin D insufficiency) then treat” supplementation strategies were found to be highly cost-effective compared with “treat without check”.[23] Compared with no treatment, the incremental cost-effectiveness ratio (ICER) of “treat and check” was €5,219/QALY gained, and the ICER of “screen then treat” versus “treat then check” was €9,104/QALY gained.

Acceptability and Applicability Issues

A 2006 study evaluated the attitudes and beliefs of 237 Asian physicians and 1463 patients with respect to the use of vitamin D and calcium in osteoporosis treatment; 50 physicians and 194 patients were recruited from the Philippines.[24] Results showed that 72-80% of Filipino physicians 73-90% of Filipino patients believe that supplementation was extremely important. Among Filipino patients, 55% of patients reported taking both calcium and vitamin D either separately (45%) or as a combination pill (10%), majority of whom (98%) take their supplements on a regular basis. Patients also reported no (16%) or infrequent (25%) discussions with their physicians regarding vitamin D, while 3% reported no and 16% reported infrequent discussions about calcium.

In an open-label, randomized, cross-over trial done in Netherlands, preference between two preparations of calcium and Vitamin D were investigated among adult osteoporotic patients requiring supplementation. Majority of patients preferred the chewable tablet taken twice a day (67%), 19% preferred the sachet with dissolvable powder while 15% had no preference. The chewable form also had significantly higher acceptability scores compared to the sachet form.[25] The cost of serum calcium and vitamin D assay as well as the availability of these tests in the Philippine setting are potential barriers to the implementation of the recommendation. In practice, most physicians would start calcium and vitamin D supplementation upon initiation of bisphosphonates without the benefit of laboratory results.

Research Gaps

There are no high-quality randomized controlled trials investigating the effect of bisphosphonates among postmenopausal women with calcium and/or vitamin D insufficiency or deficiency with prevention of fragility fracture as primary outcome. Existing guidelines also do not provide clear evidence on whether underlying deficiency should be treated or not prior to initiating bisphosphonate therapy.

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SURGICAL MANAGEMENT

Question 10: Among patients with previous fragility fractures, what is the effect of pharmacologic intervention on the risk of having a subsequent or second fracture?

Recommendation:

> Among patients with previous or prevalent fragility fractures, pharmacologic therapies, such as bisphosphonates, and teriparatide, are recommended to reduce the risk of subsequent fractures.
>
> (***Moderate quality of evidence, Strong recommendation***)

Panel Considerations on the Recommendation

Since these patients already have fragility fractures and severe osteoporosis, romosozumab is not included in the pharma option because of unavailability. Definition of Fragility fracture - need not have BMD T-score ≤ -2.5. Limitation of SIGN - did not include denosumab as an option. Data of denosumab on fragility fracture will be reviewed. Another perspective from an ortho surgeon was that no BMD evidence at the time of fragility fractures. For these patients, regardless of bone density will these be the only drugs used? PMW w severe osteoporosis vs patients with fragility fractures, it is suggested to reconcile question 19 and 21 on the recommendation. It was mentioned to use "such as" - so other drugs may still be included later on.

Summary of Evidence

This recommendation was adapted from guideline statements from the Scottish Intercollegiate Guideline Network. SIGN142 recommends initiating pharmacotherapy, specifically bisphosphonates, and teriparatide in patients with prevalent or previous vertebral and hip fractures to reduce the risk of subsequent fractures based on moderate- to high-quality evidence of efficacy and safety in this population.[1]

Bisphosphonates

SIGN 142 recommends both alendronate and risedronate in postmenopausal women with pre-existing vertebral fractures for secondary fracture prevention. A 2008 Cochrane systematic review (11 trials, N=12,068 women) showed that compared to placebo, alendronate significantly reduced secondary vertebral fractures by 45% (RR 0.55, 95% CI 0.43 to 0.69), non-vertebral fractures by 23% (RR 0.77, 95% CI 0.64 to 0.92), hip fractures by 53% (RR 0.47, 95% CI 0.26 to 0.85) and wrist fractures by 50% (RR 0.50, 95% CI 0.34 to 0.73).[2] A later post-hoc analysis of the pivotal Fracture Intervention Trial (FIT) of alendronate reported similar findings with 60% reduction in secondary vertebral fractures.[3] Meanwhile, a separate 2008 Cochrane systematic review of risedronate (7 trials, N=14,049 women) showed that compared with placebo, risedronate significantly reduced secondary vertebral fractures by 39% (RR 0.61, 95% CI 0.50 to 0.76), non-vertebral fractures by 20% (RR 0.80, 95% CI 0.72 to 0.90) and hip fractures by 26% (RR 0.74, 95% CI 0.59 to 0.94).[4] These findings were consistent with a NICE meta-analysis (5 studies, N=2,620 women) demonstrating a reduced risk of repeat vertebral fracture after 3 years of risedronate treatment (RR 0.64, 95% CI 0.52 to 0.78).[1,5]

SIGN142 also recommends the use of zoledronic acid for secondary prevention based on 2 large RCTs in postmenopausal women with previous fractures. The HORIZON Trial (N=3,889) which included women with baseline vertebral fractures, demonstrated that compared with placebo, treatment with zoledronic acid reduced the risk of morphometric vertebral fracture by 70% (10.9% vs 3.3%, respectively; RR 0.30, 95% CI 0.24 to 0.38), and reduced the risk of hip fracture by 41% (2.5% vs 1.4%; RR 0.59, 95% CI 0.42 to 0.83) and nonvertebral fractures by 25% (10.7% vs 8.0%; RR 0.75, 95% CI 0.64 to 0.87) after 3 years of follow-up.[6] In the HORIZON Recurrent Fracture trial (N=2,127) of postmenopausal women with previous hip fracture, zoledronic acid reduced the risk of new clinical fractures by 35% compared to placebo (8.6% vs 13.9%, respectively; RR 0.65, 95% CI 0.50 to 0.84).[7]

The efficacy of bisphosphonates significantly overwhelms the risk of fracture impairment and other adverse events associated with its use. While there are concerns that bisphosphonates may intervene with bone healing after fracture surgery, no association was found with bisphosphonates and delayed bone fusion if the medication was given within 2 weeks from surgery.[8-11] Although rare, adverse events that were associated with bisphosphonate exposure included atrial fibrillation[12-14] and esophageal reactions (esophagitis, ulcerations, erosions, strictures),[13,15,16] but the risk of esophageal cancer,[17,18] osteonecrosis of the jaw,[19] atypical femoral fractures,[20-24] or uveitis[25-27] was not significantly increased in the treatment populations.

Parathyroid hormone

The Scottish guidelines also recommend parathyroid hormone or teriparatide for the treatment of postmenopausal women who have previously experienced a fragility fracture.[1] This recommendation was based on a multi-country trial of 1,637 postmenopausal women with previous vertebral fracture. Treatment with teriparatide at the licensed dose of 20 µg significantly reduced the risk for vertebral and nonvertebral fractures as well as improvement in vertebral, femoral, and total-body BMD.[28] The incidence of secondary vertebral fractures (14% vs 5%, respectively; RR 0.35, 95% CI 0.22 to 0.55) and new nonvertebral fractures (6% vs 3%, respectively; RR 0.47, 95% CI 0.25 to 0.88) were higher in the placebo group than the teriparatide group. Adverse events that were more frequently reported with teriparatide include nausea (18% vs 8%), headache (13% vs 8%), dizziness (9% vs 6%), leg cramps (3% vs 1%) and mild hypercalcemia (11% vs 2%). No cases of atypical femur fracture or osteonecrosis of the jaw were reported.[29]

As BMD decreases with abrupt discontinuation of teriparatide, SIGN142 recommends that after completing a course of teriparatide treatment, patients should be given antiresorptive agents to maintain gains in bone mineral density.[1,30] The guideline did not indicate data on reduction in fracture risk of denosumab amongst individuals with fragility fractures.

Across all bisphosphonate and teriparatide studies, the incidence of secondary fractures was lower in patients who received bisphosphonate therapy (Absolute Risk Reduction, ARR 2-5%), or teriparatide (ARR 3-9%) than placebo therapy. [2-4,6,7,30]

Resource Implications

There are no local studies on the cost-effectiveness of secondary prevention using pharmacologic therapy. In a recent meta-analysis, 8 out of 12 studies comparing the cost-effectiveness of oral bisphosphonates to other interventions (denosumab, zoledronic acid, risedronate and teriparatide) reported that newer active agents are in general more cost-effective or dominant compared to oral bisphosphonates.[31] Sequential therapy was likely to generate extra benefits and was more cost-effective than monotherapy. However, the studies included populations of postmenopausal women

without prior fracture and the reported data were suboptimal in terms of side effects, treatment effect after discontinuation and adherence to treatment.

In an older cost-effectiveness study from Thailand, alendronate provided the lowest incremental cost-effectiveness ratio (ICER) for secondary prevention followed by risedronate, raloxifene, and nasal calcitonin when compared with the base scenario of no intervention.[32] Secondary prevention of osteoporotic fractures was also more cost-effective for older than younger women. Alendronate offered 1,753,378 THB/QALY and 1,702,343 THB/QALY for secondary prevention of fractures in a patient aged 50 and 80 years respectively. Assuming Thai decision makers would employ a willingness to pay threshold of THB 1,700,000/QALY, alendronate would be a cost-effective option.

Bisphosphonates (alendronate, zoledronic acid) and teriparatide are available all over the Philippines. The cost of treatment per year from PHP 20,000 – 30,000 for bisphosphonates and around PHP 300,000 for teriparatide.

Acceptability and Applicability Issues

No local studies related to acceptability and applicability of pharmacotherapy for secondary prevention was found in this review.

A discrete choice experiment enrolling patients from 7 European countries investigated patient preferences related to osteoporosis medications.[33] Patients were questioned on 5 attributes, namely: efficacy of medication, common side effects, mode and frequency of administration and out-of-pocket cost. Patient preferences tended to favor treatments with higher effectiveness; monthly subcutaneous injections (Denosumab) were preferred over weekly oral bisphosphonates (Alendronate, Risedronate). In 5 countries, monthly oral tablets and yearly IV injections (Zoledronic acid) were preferred over weekly oral tablets (oral bisphosphonates). In countries where out-of-pocket cost was included as an attribute, lower costs were preferred (oral bisphosphonates). The authors concluded that there were statistically significant differences in patients' preferences for pharmacologic interventions between countries, especially for the mode of administration.

Research Gaps

The absence of an established registry for fragility fractures in the Philippines and the lack of local studies on the clinical efficacy and cost-effectiveness of pharmacologic therapy for secondary fracture prevention precludes extrapolation of data on the risk of secondary fractures among the older Filipino population. Local qualitative studies on patient knowledge, attitudes and perceptions are also lacking, which could also help inform decisions regarding guideline implementation and the use of bisphosphonates and other therapies for secondary fracture prevention.

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Question 11: Among patients with acute displaced fragility fractures of the distal radius, is early surgical intervention superior to conservative management for improving functionality?

Among patients 65 years old and above with acute displaced fragility fractures of the distal radius, it is not recommended to proceed with surgery to improve long-term patient functional outcomes. ***(Strong recommendation, High quality of evidence)***

Recommendation:

Panel Considerations on the Recommendation

Discussion was started when the ERE disclosed he is a hand surgeon. On the indirect evidence - there was no mention on timing of surgery. Statistically significant difference but not clinically relevant. Functional outcome following fracture is best measured in 12 months.

Age of patients included in the study - not defined in the study - because of concern on functional demands of much younger patients. Functional demands will matter as to operative timing. If functional demands are not needed, then surgical intervention is not recommended.

Fragility fracture in 65 years old equates to senior group as an assumption. Are geriatric fractures same as fragility fractures? Any fracture in an older person, though not all geriatric fracture is fragility fracture. Even if question pertains to any age group, only recommendations found in the geriatric patients are included in the evidence. Hence, partially answering the question. It was agreed to include 65 years and above instead of geriatric patients. It was raised that age above 65 might not be given benefits to undergo surgery if this will be endorsed as national policy.
If recommendation is strong against, then the patient will not be able to have the surgery under universal health care. Long term functional outcome is hard to support. Surgery may shorten the morbidity period, better function. Early intervention to shorten disability. Evidence - no strong evidence to support early intervention in shorter period. How about the short term functional outcome? Dominant hand and active, might be disadvantageous and have hard time coping with daily activities. Early intervention considered to reduce morbidity? Some studies show advantage
Reason why age is not included in the recommendation. For undisplaced fracture - no surgery needed, only splint is needed. Will this be covered in UHC?

Some panel members voted this as weak recommendation considering the disability and difficulty in daily activities in someone who might be 65 years of age, but with good functional dominant hand affected by the fracture.

Summary of Evidence

These recommendations were adapted from the American Academy of Orthopedic Surgeons (AAOS) CPG on distal radius fracture. This CPG included 1 question on managing fractures of geriatrics/older adults including those with, but not limited to, fragility fractures.[1]

The 2020 AAOS states that there is strong evidence suggesting that operative treatment of distal radius fractures for geriatric patients does not lead to improved long-term patient reported outcomes compared to non-operative treatment. The treatment modalities in the included studies covered the commonly used surgical options like open reduction and internal fixation with plate, closed reduction

with pain and fixation with external fixators.[2] The outcomes included both radiographic and functional outcomes and complications. The recommendation is supported by 2 high[3-4] and 11 moderate[5-15] quality studies with consistent results. There's limited evidence that short-term benefit of return to function in an old patient will significantly affect the long term patient reported outcomes. For undisplaced fractures, putting these patients on splint is recommended, but not surgery.

The 2020 AAOS, however, emphasized that age was used as a proxy for functional demand which varies in the individual level. The 2020 AAOS question supersedes the timing of surgery as outcomes are not necessarily improved with surgery.[2]

Resource Implications

The AAOS CPG had no discussion on resource implications and may be a concern in adapting the recommendations in a different setting. No local publication on the estimated cost of treatment was found. Based on average costing in a private hospital, the facility fee, professional fees and implant using pins or a volar locking plate, operative treatment a distal radius fracture (excluding medical optimization) may range from Php 80,000 – 200,000. Non-operative management of distal radius fractures costing in clinics including professional fees and materials for immobilization range from Php 3,000 – 15,000. In public settings, the costs not covered by Philhealth are the implants (pins to volar locking plates) which may range from Php 1,000 – Php30,000.

Acceptability and Applicability Issues

While there is very little published in literature about distal radius fractures in the Philippines[16], operative and non-operative options have been around in the local setting and most options are offered by general orthopedic surgeons. With the preference for non-surgical management still prevalent and with limited access to operating rooms in some areas, non-operative management has been the default mode of care in many distal radius fractures, especially in the elderly. This serves as a facilitator for recommending non-operative management of distal radius fractures.

Research Gaps

There are several ongoing studies attempting to compare the result of different operative versus non-operative treatments in randomized controlled and observational designs.[17-18] This comes from the variety of options available and the nuances in the population that may have not been considered in previous studies. While the current trend seems to favor non-operative treatment, the question may need to be revisited in a few years for updates.

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Question 12: Among patients who have painful osteoporotic compression fractures of the spine, is kyphoplasty superior to nonsurgical management for controlling pain and improving quality of life (QOL)?

Recommendation:

Among patients with painful osteoporotic compression fractures of the spine, it is suggested that kyphoplasty be done over non-surgical treatment for acute pain-control (6 to 8 weeks) and improvement of quality of life. .
(Strong recommendation, Moderate quality of evidence)

Panel Considerations on the Recommendation

Due to performance and attrition bias of studies reviewed, hence QOE was moderate. The usual practice is kyphoplasty comes after conservative management, more useful to have kyphoplasty. Meaning, there should still be a trial of conservative management before considering kyphoplasty. Even if kyphoplasty is superior to other approaches, one needs to consider other issues - cost, applicability. A question was raised - to define "failure of conservative management". Acute pain control is defined as pain control within 6 to 8 weeks. In terms of long term pain control or is chronic pain a consideration, there is no difference on pain control for those resorting to kyphoplasty after using conservative treatment. Even though best early pain control, it's costly, and requires specialist. There's a probable benefit of pain control in the first week. This is a suggestion given the cost-effectiveness and accessibility. Kyphoplasty can be an option after a trial of conservative management does not achieve adequate pain control considering the cost effectiveness and accessibility.

1. Evidence available assessed to have performance and attrition bias – hence moderate QoE

2. Some significant improvement in pain evident after 1st week, but not significant pain improvement seen in 12 months.

3. In real world practice, kyphoplasty is offered after conservative management. There's no difference in pain control for those after using conservative treatment.

4. However, one needs to consider cost and applicability of kyphoplasty too.

Summary of Evidence

This recommendation was derived from moderate quality evidence presented by the Scottish Intercollegiate Guideline Network guideline.[1] Kyphoplasty was associated with significant short-term improvement in pain and quality of life compared with conservative treatment (CT) or standard of care (e.g. analgesics, bed rest, back braces, physiotherapy, rehabilitation programs, walking aids and pharmacotherapy with calcium and vitamin D supplements, antiresorptive or anabolic agents) in patients with painful vertebral fractures, but the benefits were shown to attenuate over time.[2,3]

A multi-country RCT (FREE study) comparing balloon kyphoplasty vs CT in 300 patients with acute painful vertebral compression fracture found significant improvements in quality of life until 9 months and pain relief until 6 months in patients who received kyphoplasty. However, benefits attenuated over time and no significant difference between the treatment groups were observed at 12 months

post-procedure.[2] In terms of other pain-related outcomes, kyphoplasty significantly reduced the need for opioid medication at 1 and 6 months and was associated with significant improvement in the kyphotic angle of the fracture at 24 months follow-up. The extension study reported similar results after a longer follow-up of 24 months.[3] Quality of life, function and disability outcomes improved from baseline measures in the first 6 to 12 months, but benefits diminished over time. Only reduction in back pain scores from baseline remained statistically significant 24 months after the procedure. Although changes in patient-reported quality of life and pain scores were significant, some experts remain uncertain whether these improvements will result in clinically meaningful differences in practice.[4]

Kyphoplasty can be an option after a trial of conservative management does not achieve adequate pain control considering its cost effectiveness and accessibility. Kyphoplasty was not associated with an increased risk of adverse events, serious adverse events, new fractures, adjacent fractures or mortality.[2,3] The most frequent adverse events associated with the procedure include new osteoporotic VCFs (20%), cement leakages (18.9%), and adjacent fractures (15.5%).[5] In a recent meta-analysis of over 2 million patients with osteoporotic VCFs, those who underwent vertebral augmentation were 22% less likely to die up to 10 years after treatment compared to patients who received conservative treatment.[6,7]

Resource Implications

When compared to nonsurgical management, balloon kyphoplasty has been found to be more cost effective in terms of cost per life year gained. BKP may be more expensive than CT in the short term, but studies have implied that surgical treatment is cost-effective for patients amenable to surgery.[8,9]

There is no local cost-benefit analysis of BKP among patients with VCF. Percutaneous kyphoplasty is available only in highly specialized centers in the Philippines. Based on an informal survey in 5 private hospitals, the cost of BKP can range from PHP 300,000 - 400,000. The PhilHealth case rates for BKP are as follows: vertebral augmentation and cavity creation, PHP 30,300; fluoroscopic/CT-guidance, additional PHP 8,020.[10] At present, kyphoplasty is only available in tertiary hospitals in urban settings, requiring highly trained specialists. And costs are not fully covered under PhilHealth.

Acceptability and Applicability Issues

BKP was developed to reduce the complications (radicular pain, paralysis, cement leaks) from vertebroplasty.[11-13] While pain relief for both procedures may be similar, BKP provides better kyphosis correction and vertebral height restoration, improving quality of life and earlier mobilization.[2,3,14-16] There are no local studies on the acceptability and applicability of kyphoplasty for the management of VCFs in the local setting. However, in a recent Turkish qualitative study, 75% of patients who underwent BKP for VCF would accept if the same surgery was recommended again.[17]

Many osteoporosis guidelines recommend vertebral augmentation but not specifically kyphoplasty in the management of VCFs in patients with select indications such as: inadequate pain relief following a trial of conservative treatment; persistent pain despite optimal pain management or pain that substantially affects quality of life; contraindication to medication; and need for parenteral narcotics and admission.[4,18-21] There is no use at present for vertebral augmentation as prophylaxis against future fractures.[4]

Research Gaps

The absence of an established registry for osteoporotic vertebral fractures in the Philippines and the lack of local studies on the efficacy, safety and cost-effectiveness of kyphoplasty and other vertebral augmentation procedures significantly impact the delivery of optimal osteoporosis care in the local setting. Qualitative studies on patient knowledge, attitudes and perceptions are also lacking, which could also help inform decisions regarding the use of kyphoplasty as an option in the management of VCFs.

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Question 13: Among patients who sustained fragility fractures of the hip, is early surgical intervention superior to delayed surgical intervention in improving overall survival, morbidity, mortality, and functionality of patients?

Recommendation:

> Among patients who sustained fragility fractures of the hip, it is suggested that early surgical management (24 to 48 hours) be done to reduce morbidity and improve survival. ***(Strong recommendation, Moderate quality of evidence)***

Panel Considerations on the Recommendation

The discussion started on defining early (24 to 48 hours) vs late surgery, though in practice, timeline varies. There's limited evidence that hip fracture is actually done in 24 to 48 hours. A component of humanitarian reasons should be taken into consideration. Though for this question, reviewers utilized evidence on registry data, using well designed observational data are still of good quality, hence upgraded this guideline due to the importance of this condition and outcome. Strong recommendation - even if the level of evidence is moderate. No other issues raised. Recommendation is straight forward.

Summary of Evidence

These recommendations were adapted from the American Academy of Orthopedic Surgeons (AAOS) CPG. The AAOS states that there is limited evidence suggesting hip fracture surgery within 24-48 hours of admission may be associated with better outcomes. This is supported by 8 low level studies (pre-2009) with significant confounders that may have affected the results. Most of the studies included decreased mortality for patients who underwent earlier surgery. A similar pattern is observed in preventing complications but is not clearly demonstrated in improving functional outcomes. The definition of early varied depending on comparisons ranging from 1-5 days after the injury. Improved outcomes are seen closer to the 1–2-day interval.[1]

The AAOS CPG did not discuss resource implications and may be a concern in adapting the recommendations in a different setting. In the Philippines, the cost of hospitalization and procedure including hip implants may range from Php300,000-750,000 in the private setting. The implementation of the Philhealth Z package for hip fractures in old adults is dependent on the cooperation of implant providers. Public medical centers are able to optimize Philhealth packages for hospital fees but procurement of implants may still be challenging since the time needed to process goes beyond the ideal timing of performing the surgery. The patients may need to come up with out-of-pocket funds ranging from Php30,000 – Php 100,000 to ensure timely delivery of care.

In terms of acceptability and applicability, availability of multispecialty care and cost of care may be a concern in many patients who will need early surgical management. A comprehensive care for Orthogeriatric patients is usually available in tertiary centers which are not geographically accessible for many Filipinos, considering the recommended timing of surgery. Access to implants required to perform the procedure is still limited despite local and national policies providing subsidies for such

needs. The process of facilitating procurement of funds requires time usually beyond the ideal time for surgery.

There are recent publications, not considered in the AAOS CPG, that compared standard versus accelerated surgery for hip fractures in the old adult population. While the conclusion showed that accelerated surgery did not significantly lower mortality and morbidity, the definition of accelerated is less than 24 or less than 6 hours which falls as a subset already of what is locally considered as early (less than 72 hours). Essentially the “standard” in the study is still considered early in the local context. There is still a need to regularly update the evidence as new information comes out.[3-4]

Resource Implications

The AAOS CPG did not discuss resource implications and may be a concern in adapting the recommendations in a different setting. The cost of hospitalization and procedure including hip implants may range from Php300,000-750,000 in the private setting. The implementation of the PhilHealth Z package for hip fractures in the elderly is dependent on the cooperation of implant providers. Public medical centers are able to optimize Philhealth packages for hospital fees but procurement of implants may still be challenging since the time needed to process goes beyond the ideal timing of performing the surgery. The patients may need to come up with out-of-pocket funds ranging from Php30,000 – Php 100,000 to ensure timely delivery of care.

Acceptability and Applicability Issues

Availability of multispecialty care and cost of care may be a concern in many patients who will need early surgical management. A comprehensive care for Orthogeriatric patients is usually available in tertiary centers which are not geographically accessible for many Filipinos, considering the recommended timing of surgery.

Access to implants required to perform the procedure is still limited despite local and national policies providing subsidies for such needs. The process of facilitating procurement of funds requires time usually beyond the ideal time for surgery.

Research Gaps

There are recent publications, not considered in the AAOS CPG, that compared standard versus accelerated surgery for hip fractures in the elderly. While the conclusion showed that accelerated surgery did not significantly lower mortality and morbidity, the definition of accelerated is less than 24 or less than 6 hours which falls as a subset already of what is locally considered as early (less than 72 hours). Essentially the “standard” in the study is still considered early in the local context. There is still a need to regularly update the evidence as new information comes out.[3,4]

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Question 14: In patients with a previous osteoporotic fragility fracture, will enrollment in a secondary fracture prevention program or fracture liaison service (FLS) improve treatment adherence and prevent re-fractures?

Recommendation 1:

> Among patients who have experienced fragility fracture, it is recommended that they be managed within a formal integrated system of care that incorporates a fracture liaison service (FLS) to prevent re-fractures and improve adherence to osteoporosis treatment.
> ***(Strong recommendation, High quality of evidence)***

Recommendation 2:

> Among patients who have fragility fracture/s, it is recommended that appropriate interventions including both pharmacologic and non-pharmacological approaches be started.
>
> ***(High quality of evidence, Strong recommendation)***

Panel Considerations on the Recommendations

Recommendation 1:
A discussion on the cost effectiveness of establishing FLS was given. There is no cost to the institution but rather improved services for patients who sustained fractures and not kept on medication. Expense to set-up is very small. One major staff member needed to follow-up patients who had fractured. In first world countries, primary care physicians ensure adherence to treatment to reduce fracture risk.

Straight forward. No issues on establishment of FLS. It was emphasized that there is no set menu for everyone to follow, but tailor fit to population established by the FLS in the community.

Recommendation 2:
Recommendation is straight forward, no issues identified.

Summary of Evidence

These recommendations were adapted from the guideline statements of the UK National Osteoporosis Guideline Group (NOGG) guideline and Scottish Intercollegiate Guideline Network (SIGN142).[1,2] A fracture liaison service is defined as a multidisciplinary model of care wherein patient identification, risk assessment, treatment, monitoring and patient education are all conducted within an integrated electronic healthcare network that is overseen by a coordinator and utilizes a dedicated database with built-in quality indicators.[1,3,4]

Both UK NOGG and SIGN142 recommend that patients who have experienced fragility fractures should be managed within a Fracture Liaison Service for fall and secondary fracture prevention based on evidence that models of care which provide identification, assessment and treatment initiation (i.e., Type A and B models) were more clinically effective and cost-effective in improving patient outcomes than Type C and D models with limited services (see Table 1).[1,5] Moreover, FLS that initiate pharmacological treatment, rather than recommend treatment for primary care initiation, were associated with higher rates of treatment initiation.[1,5]

Table 1. Secondary Prevention Models of Care[5]

Type	Features
Type A	(Coordinated approach to secondary fracture prevention) Identification, assessment and treatment of patients
Type B	(Treatment initiation responsibility of the primary care provider) Identification, assessment, and treatment only
Type C	(Less intensive intervention - no liaison co-coordinator) 1st component: Patient education about osteoporosis and lifestyle advice incl falls prevention 2nd component: Physician alert systems, assessment and treatment
Type D	Patient centered education only, no physician education

A 2012 meta-analysis of 42 studies (RCTs, cohort, cross-sectional and observational studies) compared the effectiveness of different FLS models (Type A to D) on rates of BMD testing, osteoporosis treatment initiation, adherence, re-fractures and cost-effectiveness.[5] FLS demonstrated a trend for increased BMD testing and treatment initiation with more intensive models. Although not analyzed due to an inadequate number of studies and significant variation in follow-up, Types A and B models of care were associated with higher rates of adherence (34% to 95%), a 15% reduction in fracture rates after 4 years of follow-up, and 37.2% reduction in hip fractures after 3 years of follow-up.

In a 2018 meta-analysis of 25 studies (2 RCTs, 7 controlled, and 16 uncontrolled observational studies), pooled analysis of RCTs and controlled studies showed a 22% improvement in adherence rates with FLS after a follow-up range of 3-48 months (Absolute Risk Difference, ARD 0.22; 95% CI 0.13 to 0.31; p≤0.05).6 FLS also significantly reduced the risk of refracture by 5% (ARD –0.05, 95% CI –0.08 to −0.03) and mortality by 3% (ARD -0.03, 95% CI -0.05 to -0.01).

A 2020 retrospective cohort study of 4 Swedish hospitals (N=21,083 patients) compared the incidence of recurrent osteoporotic fractures before and after the implementation of FLS in 2 hospitals versus control (2 hospitals without an FLS program).[7] In hospitals with FLS, implementation of FLS resulted in an 18% decrease in recurrent fractures (hazard ratio 0.82, 95% CI 0.73-0.92) while no significant change in recurrent fracture rate was observed in the hospitals without FLS.

Data from a recent study further support the SIGN142 and UK guideline recommendations. A 2021 meta-analysis of 16 cohort studies compared the effectiveness of FLS care in terms of subsequent fracture and mortality.[8] Overall, FLS care was associated with a significantly lower probability of subsequent fractures (Odds Ratio, OR 0.70, 95% CI: 0.52–0.93). No significant difference in

mortality was observed overall but a significantly lower probability of mortality was identified in 6 FLS cohort vs historical cohort comparisons (OR 0.65, 95% CI: 0.44–0.95).

UK NOGG recommends starting treatment promptly following a fragility fracture because the risk of refracture is highest immediately after a fracture and remains elevated throughout a patient's lifetime. It supports the statement of the Royal Osteoporosis society that secondary assessment and intervention should be initiated as soon as possible, and no later than 16 weeks post-fracture and that FLS should also initiate appropriate nonpharmacological interventions and provide a coordinated program for fall assessment and prevention.[1,9]

No harms or undesirable effects related to FLS were identified in the review.

Resource Implications

No direct cost studies on resource requirements for establishing an FLS program were identified in this review.

Experts suggest that the hospital administration should fund start-up expenses for FLS programs as part of a quality initiative in association with a musculoskeletal service line.[10] A business plan can be used to demonstrate cost savings based on preventable readmissions for secondary fractures to justify program implementation. The program is later integrated into the departmental or service line budget to include volume projections of office visits and associated ancillary income directly related to the FLS service (e.g., bone densitometry, anabolic or antiresorptive medications, and laboratory studies).[11]

The Scottish guidelines, SIGN142, identified several studies that evaluated the cost-effectiveness of Type A and B FLS models in terms of fracture prevention.[10] In Australia, Type A were found to be cost-effective in preventing non-vertebral secondary fractures with a cost per QALY of AUD 20,000-30,000.[2,12] In the US, the estimated annual savings with preventing secondary hip fractures with FLS amounted to US$ 30.8 million.[10]. In the UK, FLS care was cost-effective and associated with 18 fewer fractures vs usual care, resulting in 22 QALYs gained, 266 hospital bed days saved, and cost-savings of £312,000 from fractures avoided (per 1000 patients).[13]

A 2017 systematic review summarized the economic benefit and cost-effectiveness of FLS using data from 23 studies (16 cost-effectiveness studies, 2 cost-benefit analysis, 5 cost-saving analyses) conducted in Canada, Australia, USA, UK, Japan, Taiwan, and Sweden. Authors concluded that FLS was cost-effective and even cost-saving in comparison with usual care or no treatment, regardless of the program intensity or the country in which the FLS was implemented (cost per QALY of US$3023-$28,800 in Japan to $14,513-$112,877 in USA.[3]

Similar outcomes were noted by 2 recent cost-effectiveness studies published in 2022. In Spain, FLS was associated with 0.008 LYG and 0.082 QALY gained per patient. While FLS resulted in higher costs (€563.69 per patient) compared with standard care, an incremental cost-utility ratio of €6855.23 per QALY gained is projected over the 10-year horizon.[14] In Taiwan, a NMB (net monetary benefit) regression model was used to evaluate real-world cost-effectiveness in hip fracture patients who received hospital-based FLS vs. usual care. The FLS group had higher expenditures for osteoporosis-related medication than the usual care group due to increased patient adherence. FLS was found to be cost-effective by increasing refracture-free survival, hip refracture-free survival and overall survival when the willingness-to-pay threshold was >USD 65/gross domestic product per day.[15]

Acceptability and Applicability Issues

This review did not find any local studies on the acceptability, applicability and feasibility of FLS. Nevertheless, a highly coordinated FLS program has been shown to eliminate the care gap in a clinical and cost-effective manner,[11] and is highly recommended by recently published clinical guidelines.[1,2,16] Furthermore, multicomponent interventions with more active patient involvement, counseling and shared decision-making seem to have more positive effects on patient adherence and persistence to osteoporosis treatment.[17]

Barriers to the successful initiation and operation of an FLS program include 'turf battles' by specialty physicians over patient ownership as well as concern for potential lost income by individual practitioners or institutions.[18] Other challenges include a hierarchical culture that separates administrators and decision-makers from personnel within the FLS site, which can interfere with implementation by delaying allocation of essential resources. Logistical barriers (e.g., FLS site is in a different location) can impede effective collaboration between FLS teams.[19] At the hospital level, there may be budgetary reservations regarding compensation and infrastructure setup as well as long-term sustainability of the program.[18]

From a stakeholder perspective, several factors can positively impact the implementation of an FLS program - a strong evidence-based FLS that encourages stakeholder engagement and recognition of the relevance of the FLS; individual characteristics of FLS providers (e.g., coordinators' high self-efficacy, experience and knowledge of community resources), orthopaedic surgeons' leadership skills which can positively influence the perception of colleagues and organizational managers; and implementation of fall prevention programs with a strong patient-centered care approach. [19]

Advanced FLS programs are based primarily in first-world countries. In a developing country like the Philippines, health inequities largely depend on available resources (e.g., a program may be sound but financial issues limit the achievement of treatment goals). Thus, access to primary health care is a key determinant of health and equity; a government-backed program is the pragmatic approach. The UPM-PGH orthogeriatric multidisciplinary fracture management model and fracture liaison services has shown promising results in addressing fragility fractures, proving that FLS can work even in resource-poor settings.[20,21]

Research Gaps

To date, no RCTs have demonstrated the superiority of FLS in reducing fragility fracture risk. Conducting an RCT design might be inappropriate given the uncertainty regarding effectiveness based on data from qualitative studies.[5] It would also be extremely challenging, requiring a large sample size, and at least 4 years of follow-up. Ensuring fidelity to protocol would also be difficult as FLS requires multiple levels of engagements within the healthcare systems and adapts to changes in local and national modifications in health delivery, as well as availability of anti-osteoporosis medications.

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FOLLOW-UP AND CONTINUITY OF CARE

Question 15: Among adults receiving osteoporosis treatment, what is the appropriate interval between central DXA scans in monitoring treatment response?

Recommendation:

> Among adults receiving osteoporosis treatment, it is recommended that central DXA test should be done every 1-2 years especially in patients at high risk of fracture, then at longer intervals thereafter once definite satisfactory treatment response is achieved.
>
> ***(Strong recommendation, Moderate quality of evidence)***

Panel Considerations on the Recommendation

Clinical question is straightforward, no issues identified.

Summary of Evidence

These recommendations were adapted from the American Association of Clinical Endocrinologists / American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis – 2020 Update (AACE 2020) and Scottish Intercollegiate Guidelines Network 142 Management of Osteoporosis and the Prevention of Fragility Fractures (SIGN 142) guidelines.[1,3]

For patients on treatment or with a baseline evaluation near fracture intervention threshold, AACE 2020 guidelines recommend BMD measurement by DXA every 1-2 years until findings are stable or at a less frequent interval, depending on the patient's clinical condition.1 BMD testing every 1-2 years may be appropriate in recently postmenopausal women with increased rates of bone loss and women of any age with other disorders or medications that cause bone loss. This is based on evidence from a study that included 4957 women with normal BMD (femoral neck and total hip T-score ≥ −1.00 or higher) or osteopenia (T score bet −1.01 to −2.49) and with no history of hip or clinical vertebral fracture or treatment for osteoporosis and were followed prospectively for up to 15 years.2 The BMD testing interval was defined as the estimated time for 10% of women to make the transition to osteoporosis before having a hip or clinical vertebral fracture. Results showed that the estimated BMD testing interval was 16.8 years (95% confidence interval [CI], 11.5 to 24.6) for women with normal BMD, 17.3 years (95% CI, 13.9 to 21.5) for women with mild osteopenia, 4.7 years (95% CI, 4.2 to 5.2) for women with moderate osteopenia, and 1.1 years (95% CI, 1.0 to 1.3) for women with advanced osteopenia.

SIGN recommends repeat BMD measurements by DXA after an interval of 3 years to assess response to treatment in postmenopausal women on alendronic acid, ibandronic acid, zoledronic acid or denosumab therapy.[3] This recommendation is based on evidence from various studies that evaluated monitoring procedures and their ability to predict fracture risk.

In a post hoc study of the HORIZON-PFT, 7736 postmenopausal women who were randomized to either once-yearly intravenous zoledronic acid or placebo were analyzed to investigate the usefulness of measuring change in total hip BMD and procollagen type 1 amino-terminal propeptide

(PINP) for the assessment of fracture risk during zoledronic acid treatment.[4] For the yearly analyses, change in total hip BMD explained between 39% and 42% of the reduction in risk of new vertebral fracture. In the 3-year analysis total hip BMD explained 40% (95% CI, 30% to 54%) of the fracture risk reduction. The treatment effects for nonvertebral fracture were not statistically significant for the year-on-year analysis but 3-year change in total hip BMD explained 61% (95% CI, 24% to 156%) of treatment effect.

In another post hoc study, changes in DXA BMD as a predictor for fracture risk reduction was investigated using data from the FREEDOM trial, which included 7808 women who were randomly assigned placebo or denosumab 60 mg every 6 months.[5] Using standard approach, treatment effect was explained using percent changes in BMD obtained yearly at months 12, 24, or 36. A novel approach was also applied using estimated percent changes in BMD from baseline at the time of fracture occurrence in a time-dependent manner. Denosumab significantly increased total hip BMD by 3.2%, 4.4%, and 5.0% at 12, 24, and 36 months, respectively. The change in total hip BMD explained the effect of denosumab in reducing new or worsening vertebral fracture risk (35% [95% CI: 20%–61%] and 51% [95% CI: 39%–66%] accounted for by percent change at month 36 and change in time-dependent BMD, respectively) and explained reduction in nonvertebral fracture risk (87% [95% CI: 35% – >100%] and 72% [95% CI: 24% – >100%], respectively).

A post hoc analysis of data from the Fracture Intervention Trial (FIT), which included 6,459 women, showed that patients who lost 0–4% BMD at either spine or hip while on alendronate had a reduction of 60% in vertebral fracture risk [OR=0.40 95% CI: 0.16, 0.99] compared to placebo.[6] Patients who lost more than 4% BMD did not have a significant reduction in fracture risk. Patients who gained BMD (0% to 4%) during treatment had a comparable fracture risk reduction. Thus, women who adhere to alendronate should not stop treatment even if they lose BMD at either the hip or the spine after 1, or even 2, years of treatment and are still probably benefiting from a reduction in risk of vertebral fracture, except those who lost more than 4% a year. Repeated measurements of BMD over relatively short periods of time, such as 1 or 2 years, might not capture the factors responsible for the fracture risk reduction in patients on alendronate treatment.

The Monthly Oral Therapy with Ibandronate for Osteoporosis Intervention (MOTION) study enrolled 1760 postmenopausal women revealed that once-monthly ibandronate was clinically comparable to weekly alendronate and increased BMD after 12 months in both the lumbar spine and total hip. Mean relative 12-month changes were 5.1% and 5.5% in lumbar spine and 2.9% and 3.0% in total hip BMD with once-monthly ibandronate and weekly alendronate, respectively.[7] Emkey et al. revealed comparable efficacy of once monthly 150 mg ibandronate therapy in terms of BMD response.[8] The percentage of patients with mean lumbar spine and total hip BMD gains above baseline (responders) were 90% and 87%, respectively, for ibandronate and 92% and 90%, respectively, for alendronate.

Resource Implications

To date, there are no local or international studies on cost effectiveness of serial BMD testing by central DXA scan in monitoring treatment response.

Acceptability and Applicability Issues

Central DXA may not be readily available or accessible to some patients in certain locations, especially to those in the provinces. More frequent DXA measurement may not also be feasible for patients with financial constraints. This may lead to patient's non-compliance to medications and failure to identify patients who are not responding to treatment.

Research Gaps

There is limited data on the optimal interval for repeat central DXA testing for monitoring treatment response. Local studies are also lacking, and further research is needed including cost-effectiveness analyses.

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Question 16: Among patients with recent fragility fracture/s, should an immediate referral to bone specialist be done for better evaluation and management?

Recommendation:

It is recommended that patients with the following risk factors/conditions be referred to an osteoporosis specialist:

- patients with fragility fracture and/or subsequent fragility fractures
- BMD T-score ≤ − 3.5
- treatment with high dose glucocorticoids (≥7.5 mg/day of prednisolone or equivalent over 3 months) patients with co-morbidities such as CKD, endocrine and rheumatic diseases

(Strong Recommendation, High quality of evidence)

Panel Considerations on the Recommendation

Clinical question is straight forward, no issues identified.

Summary of Evidence

The AACE guidelines recommend referral to a clinical endocrinologist or other osteoporosis specialist when patients with normal BMD sustain fracture without major trauma, those who experience fragility fractures, those on therapy with recurrent fractures or continued bone loss without obvious treatable causes of bone loss, patients with unexpectedly low bone mineral density or has unusual features such as young age, unexplained artifacts on bone density, and unexplained laboratory studies, including high or low alkaline phosphatase and/or low phosphorus and patients with conditions such as decreased kidney function, hyperparathyroidism, or malabsorption.[1]

A systematic review done by Bell et al in 2013 was aimed to determine the effect of dedicated osteoporosis health professional on screening and treatment in outpatients presenting with acute low trauma fracture. Comparisons were made between those handled by the osteoporosis health professional (intervention) and patients receiving usual care, defined as sole management by the orthopedic surgeon or primary physician (control). Results showed an increase in BMD screening in the intervention group 58.2% vs 20.3% in the control group (OR 5.4, 95 % CI 4.3–6.9, P < 0.0001). The effect on treatment initiation showed a significantly increased rate of antiresorptive ± vitamin D therapy of 41.1% in the intervention groups vs 11.7% in the control groups (OR 5.3; 95 % CI 4.1–6.8, P < 0.0001). Two studies showed reduced fracture recurrence. There was also significantly increased referrals to a specialist bone clinic in the intervention group (OR 9.6, 95 % CI 6.2–14.6, P < 0.0001).[2]

The UK NOGG guidelines recommend osteoporosis specialist referral of very high-risk patients who may need first-line anabolic drug treatment, especially those with multiple vertebral fractures. Other indications include presence of risk factors such as a recent vertebral fracture (within the last 2 years), ≥ 2 vertebral fractures (whenever they have occurred), a BMD T-score ≤ − 3.5 and treatment with high dose glucocorticoids (≥7.5 mg/day of prednisolone or equivalent over 3 months)[3] or through a combination of clinical risk factors, resulting in very high fracture risk.

Patients at very high fracture risk may greatly benefit from a personalized treatment plan, for example, the two anabolic agents (teriparatide and romosozumab) initiated through secondary care by osteoporosis specialist.[3] Randomized clinical trials have shown that treatment with these anabolic agents result in rapid and greater fracture risk reductions as compared with antiresorptive treatments.[4,5]

Many studies have shown that prior fragility fracture is a well-established risk factor for a future fracture.[6,7,8,9,10,11,12] In a meta-analysis by Kanis et al, results showed that a previous fracture history was associated with a significantly increased risk of any fracture compared with individuals without a prior fracture (RR = 1.86; 95% CI = 1.75-1.98).[7]

In a population-based cohort study, 5039 individuals sustained one or more major osteoporotic fractures (MOF), of whom 1919 experienced a second MOF. The risk of a second MOF was highest immediately after the first fracture and thereafter decreased with time though remained higher than the population risk throughout follow-up. For example, 1 year after the first MOF the risk of a second fracture was 2.7 (2.4-3.0) fold higher than the population risk. After 10 years this risk ratio was 1.4 (1.2-1.6). The effect was more marked with increasing age.[12]

In a post hoc analysis of the MORE trial, it was shown that the incidence of new vertebral fractures at 3 years was significantly greater in women with the lowest baseline BMD *t* score (below 3.0) at the lumbar spine or femoral neck, compared to women in the other baseline BMD *t* score categories (see Appendix).[13]

Furthermore, the incidence of new nonvertebral fractures at 3 years was significantly different between women with baseline lumbar spine BMD t score of ≤3.0 compared to women with lumbar spine BMD T- scores between ≤2.5 and >3.0 (P 0.05, see Figure below), but was not different compared to women in the other groups of lumbar spine BMD T- scores (see Appendix).[13]

The estimated cost of referral to osteoporosis specialist in the Philippines depends on the setting be it private or public, pharmacologic treatment and procedure done. To date, there is no local study on the cost-effectiveness of referral to osteoporosis specialist for better evaluation and management.

It is important to consider timely referral to osteoporosis specialists for the benefit of the patients. If the case seems too complicated to handle, asking the opinion of experts in the field with regards management and other treatment options would be acceptable. There are increasing numbers of specialists in both private and public healthcare institutions within Metro Manila, however, in the provinces some areas still lack specialists. In these instances resorting to teleconsult will be an option.

Resource Implications

The estimated cost of referral to osteoporosis specialist in the Philippines depends on the setting be it private or public, pharmacologic treatment and procedure done. To date, there is no local study on the cost-effectiveness of referral to osteoporosis specialists for better evaluation and management.

Internationally, there is a study in 2017 in Australia. The total direct cost of osteoporosis in Australia in 2017 was estimated to be $3.44 billion (AUD 2017, USD 2.77 billion). Treatment of fractures accounted for 68% of total direct costs, and non-fracture management of osteoporosis accounted for 32%. Hip fractures accounted for the highest proportion (43%) of the total direct cost of fractures, although fractures at "other" sites accounted for 38.5%. Fractures among individuals aged 70 years

and older accounted for 74% of the direct costs (55% and 19% in women and men, respectively). Fracture costs in those with osteopenia accounted for 50% of direct fracture treatment costs.[14]

Acceptability and Applicability Issues

It is important to consider timely referral to osteoporosis specialists for the benefit of the patients. If the case seems too complicated to handle, asking the opinion of experts in the field with regards management and other treatment options would be acceptable. There are increasing numbers of specialists in both private and public healthcare institutions within Metro Manila, however, in the provinces some areas still lack specialists. In these instances, some would go online consultation or would travel far for the consult to resolve this issue.

Research Gaps

There is a need for education on osteoporosis and its management not only among primary care physicians but also the patients as well, especially those at the far-flung areas of our country. Once education is implemented, the problem is the availability of tests used in the screening and diagnosis of osteoporosis such as bone densitometry and bone markers. Finally when treatment is planned, the availability and cost effectiveness of the anti osteoporosis drugs remain a challenge.

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PREVENTION (LIFESTYLE AND NUTRITION, HORMONE REPLACEMENT THERAPY)

Question 17: Should at-risk PMW and older men receive calcium supplementation and/or Vitamin D supplementation for prevention of osteoporosis and fragility fractures?

Recommendation:

Among at-risk adults with normal FRAX and BMD scores, calcium and vitamin D supplementation is recommended for those who cannot meet country-specific reference standards.
(Strong recommendation, moderate quality of evidence)

Panel Considerations on the Recommendation

The panel initially pointed out the confusion on the definition of "supplementation": Does it imply that additional sources are being given via pill form and not from natural sources? This was answered by one of the EREs stating that the UK and RAGCP guidelines recommend that either a dietary or a supplementation source is valid. In the dietary part there is also supplementation with dietary sources. In both guidelines, vitamin D supplementation and dietary sources are discussed in a combined format. In this CPG, diet and supplementation are separated due to the clinical question sequence.

Another issue pointed out was on cost. The Philippine Osteoporosis program is not yet included in the omnibus health guidelines. Hence, out-of-pocket spending is a possibility for patients. A panel representative from DOH responded that procurement is possible if it's part of a DOH health program. Revisions will come after this CPG is completed hence it will be eventually part of the DOH health program. The DOH will use the "Life stage" approach. Another panel member added that it's good to include as a recommendation regardless of who will shoulder the expenses. This can encourage innovations on access to calcium + vitamin D (Example: incorporation into food products). The panel also suggested to rephrase "who do not meet" to "who cannot meet". The panel also suggested that the following topics be added in the discussion: 1. Philippine dietary reference standards for calcium and vitamin D, 2. Utilization of calcium citrate**.**

Summary of Evidence

The following recommendations are based on the guidelines from the UK National Osteoporosis Guideline Group (UK NOGG 2022), Royal Australian College of General Practitioners' 2017 guideline (RACGP) and the US Preventive Services Task Force (USPSTF) 2018 guideline.[1,2,3]

The UK NOGG guidelines recommend that an adequate intake of calcium (minimum 700 mg daily) is preferably achieved through dietary intake or otherwise by supplementation. Two meta-analyses on combined calcium and vitamin D supplementation show a reduction in hip, non-vertebral and vertebral fractures.[4,5] A meta-analysis of 6 RCTs (n=49,282) showed that a combination of vitamin

D(400-800 IU/day) and calcium(1000-1200 mg/day) reduces the risk of any fracture (RR 0.94, 95%CI 0.89-0.99) and hip fracture (RR 0.84 95%CI 0.72-0.97).[4]

The RACGP guidelines showed that institutionalized individuals at risk for deficiency will benefit more with calcium and vitamin D supplementation. Individuals on anti-osteoporosis treatment who have < 1300mg/day dietary calcium intake should be advised to have calcium and vitamin D supplementation. For non-institutionalized individuals, calcium and vitamin D supplementation is not recommended due to mixed evidences.[2] A systematic review of 20 RCTs (n=58,573) showed that calcium supplementation (with or without vitamin D) in older adults reduced the risk of any fracture (RR 0.89, 95% CI 0.81–0.96) and vertebral fracture (RR 0.86 95%, CI 0.74–1.00) but not for hip fracture (RR 0.95, 95% CI 0.76–1.18). However, in checking for bias using Egger's regression model and visual inspection of funnel plots, it is observed that data is biased towards risk reduction using calcium supplements for total (P=0.006), vertebral (P=0.002), and forearm fracture (P=0.06). This shows a possibility for publication bias.[6]

A Cochrane systematic review of 53 RCTs (n=91,791) showed that stand alone vitamin D supplementation did not reduce the risk of hip (RR 1.2, 95% CI 0.98–1.29) and any fracture (RR 1.03, 95% CI 0.96–1.11). A combination of calcium and vitamin D showed a minimal reduction in risk of hip fractures (RR 0.84, 95% CI 0.74–0.96). In a population setting, this data shows that non-institutionalized individuals will have one fewer hip fracture per 1000 older adults per year (95% CI 0 to 2) and institutionalized individuals will have nine fewer hip fractures per 1000 older adults per year (95% CI 2 to 14). Combination of calcium and vitamin D showed minimal reduction in risk of any fracture (RR 0.95, 95% CI 0.90 to 0.99).[7]

The USPSTF performed meta-analysis on 11 RCTs (n=51,419) and showed that compared to placebo, vitamin D intake was able to limit the incidence of total fracture incidence (ARD −2.26% 95%CI −4.53%to 0.00%) but was not associated with hip fracture (ARD −0.01% 95%CI, −0.80% to 0.78%). Calcium with vitamin D supplementation had no effect incidence of total fracture (ARD, −0.35% 95%CI, −1.02%to 0.31%) nor hip fracture (ARD −0.14% 95%CI, −0.34%to 0.07%).[3]

Other studies

A meta-analysis of eight studies with 30,970 participants met criteria for inclusion in the primary analysis, reporting 195 hip fractures and 2231 total fractures. Results showed that calcium plus vitamin D supplementation produced a statistically significant 15 % reduced risk of total fractures (SRRE, 0.85; 95% CI 0.73-0.98) and a 30 % reduced risk of hip fractures (SRRE, 0.70; 95% CI 0.56-0.87). Similar summary associations were noted on numerous sensitivity and subgroup analysis. Utilizing data from subgroup analysis of the Women's Health Initiative is one limitation of this meta-analysis.[8]

A meta-analysis was done aiming to determine if calcium with vitamin D has beneficial effects for postmenopausal women. Results showed that calcium with vitamin D supplementation increased the total bone mineral density of the lumbar spine (SMD 0.537; 95% CI: 0.227 to 0.847), arms (SMD 0.464; 95% CI: 0.186 to 0.741) and femoral neck (SMD 0.187; 95% CI: 0.010 to 0.364). Incidence of hip fracture was also reduced (RR 0.864; 95% CI: 0.763 to 0.979). Subgroup analysis revealed that vitamin D at doses < 400 IU d^{-1} significantly increases femoral neck BMD (SMD 0.335; 95% CI: 0.113 to 0.558). Dairy products enriched with calcium and vitamin D increases total (SMD 0.784; 95% CI: 0.322 to 1.247) and lumbar spine (SMD 0.320; 95% CI: 0.146 to 0.494) BMD.[9] Calcium supplementation, with concomitant vitamin D supplementation, is supported for patients at high risk of calcium and vitamin D insufficiency".[10]

Hazards of Calcium and vitamin D treatment

The hazards of calcium and vitamin D supplements were elaborated by several meta-analyses.[7,11,12] A Cochrane systematic review of 53 RCTs (n=91,791) showed that vitamin D and calcium supplements increased the risk for renal insufficiency or calculi (RR 1.17, 95% CI 1.03–1.34) and gastrointestinal symptoms (RR 1.04, 95% CI 1.00–1.08). The risk for cardiac events were also studied but varying findings were seen.

A meta-analyses of three placebo controlled trials showed that calcium and vitamin D increased the risk of myocardial infarction (RR 1.21 (95% confidence interval 1.01 to 1.44), P=0.04), stroke (1.20 (1.00 to 1.43), P=0.05), and composite of myocardial infarction or stroke (1.16 (1.02 to 1.32), P=0.02).[10] A meta-analysis of 18 RCTs (n=63,563) noted that calcium and vitamin D supplementation had no increased risk for MI (RR 1.08, 95% CI 0.92–1.26) or coronary heart disease (RR 0.92, 95% CI 0.73–1.15).[12]

An individual patient data (IPD) analysis of 8 RCTs (n=70,528) showed that supplementation of vitamin D with or without calcium leads to a 7% reduction in mortality (HR 0.93; 95% CI, 0.88–0.99). Risk of death was also reduced if vitamin D and calcium were given (HR 0.91; 95% CI, 0.84–0.98). A trial level meta-analysis of 24 RCTs (n=88,097) showed that vitamin D and calcium supplementation reduced mortality (OR 0.94;95% CI, 0.88–0.99). Vitamin D alone did not reduce mortality (OR 0.98 95% CI, 0.91–1.06).[13]

Resource Implications

The available evidence suggests that the intake of vitamin D/calcium-fortified foods or vitamin D/calcium supplements reduce the fracture risk (with resulting health benefits) and it is a cost-effective strategy which can even allow cutting costs regarding certain sub-populations. Nevertheless, more studies should be needed, especially observational. Eleven articles were included in total. On one hand, the identified studies suggest substantial benefits regarding fracture prevention, mortality, and life years and quality-adjusted life years gained. On the other hand, economical assessments reveal that the use of vitamin D/calcium-fortified foods or vitamin D/calcium supplements are cost-beneficial, at least for the population over aged 70 or with high fracture risk. In addition, these strategies seem to save direct costs, especially for elderly women with high fracture risk.[14]

Acceptability and Applicability Issues

The Philippine Academy of Family Physicians Clinical Pathway on Wellness for Older persons adopted the US Preventive Service Task Force recommendations on giving calcium and Vitamin D to at-risk elderly. A barrier to implementation is that the cost of calcium and vitamin D is not covered by medical insurance (e.g. Philhelath). It is also not part of the Primary Care Benefit Package of the Department of Health.

Research Gaps

It is suggested that economic evaluation studies be done.

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Question 18: Among PMW and older men, what doses of calcium and Vitamin D are associated with reduced fragility fracture risk?

Recommendation:

Among PMW and older men, supplementation with Vitamin D at 400 to 600IU/day and Calcium at 700 to 800 mg/day is recommended.
(Strong recommendation, moderate quality of evidence)

Panel Considerations on the Recommendation

The panel clarified regarding the clause “cannot meet through diet”, does this mean that this is the only time wherein supplementation is recommended? A panelist replied that yes, supplementation augments the calcium and vitamin D already present in the diet. Another point emphasized by the panel is the baseline checking of calcium and vitamin D levels. The rationale behind this is the addition of a dose on top of the daily requirement. A separate section for this in the diagnostics section will be discussed. The panel also noted that the target population is not clearly stated in the recommendation. A panelist pointed out that the PDRI is also for natural sources. PDRI is for diet, not supplementation. The issue on dose doubling of calcium and vitamin D was also raised since a supplementary dose is recommended on top of the daily dose. Nutritional needs should be addressed first before supplementation. It was also suggested that the clinical question on diet.

Summary of Evidence

The following recommendations are based on the guidelines from the UK National Osteoporosis Guideline Group (UK NOGG) and Royal Australian College of General Practitioners’ 2017 guideline (RACGP).[1,2] The UK NOGG guidelines recommend that for patients who are at risk or identified to have vitamin D insufficiency, at least 800 IU/day of vitamin D should be consumed. A meta-analysis of 29 RCTs (n=63,897) showed that calcium doses more >1200 mg and vitamin D doses >800IU produced better treatment outcomes.[3] Limited information exists regarding vitamin D supplementation alone and reduction of fracture incidence, although it may reduce risk of falls.[4] A patient pooled analysis (n=68,500) showed that vitamin D given alone at doses of 10-20 µg/day did not decrease the incidence of fractures (RR 1.01, 95% CI 0.92 to 1.12).[5]

The RACGP guidelines showed that institutionalized individuals at risk for deficiency will benefit more with calcium and vitamin D supplementation. Individuals on anti-osteoporosis treatment who have <1300mg/day dietary calcium intake should be advised to have calcium and vitamin D supplementation. The recommended dietary intake of vitamin D is 1300 mg per day for women older than 50 years of age, 1000 mg per day for men 50–70 years of age, and 1300 mg per day for men older than 70 years of age.[4]

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Question 19: Among PMW and older men, what is the benefit of physical activity in the prevention of osteoporosis and fragility fractures?

Recommendation:

> Among PMW and older men, regular physical activities using a combination of exercise types *(such as weight bearing, balance training, flexibility or stretching exercises, endurance and progressive strengthening exercises)* are recommended to increase BMD and reduce the risk of fragility fractures.
>
> ***(Strong recommendation, High quality of evidence)***

Panel Considerations on the Recommendation

The panel noted a lack of coherence between the clinical question and the recommendation. The clinical question asks about the benefit of physical activity, but the recommendation states the type of physical activity. One of the ERE's suggested that the clinical question be re-phrased so that the outcome (prevention of osteoporosis and fragility fractures) comes first.

Another concern was the lack of connection between the types of exercise and the outcomes presented. An ERE noted that based on the forest plots of meta-analyses, multiple types of exercises have the greatest benefits. The main outcomes of these studies are BMD. Data regarding the reduction of fractures was also sought by the panel. An ERE stated that the RAGCP guideline has an outcome of fragility fracture reduction. The UK NICE guideline has an outcome of BMD.

In the recommendation, the benefit is not clear. The panel suggested that the phrases "improve BMD" and "reduction of fragility fracture risk" be put as an outcome since it more directly reflects the evidence presented. The definition of physical activity and exercise was another concern of the panel. Physical activity refers to any physical movement while exercise refers to a more concise and structured body movements. The clinical question is about physical activity, but the recommendation tackles forms of exercise . Hence, there is an issue about indirectness of evidence. An ERE then responded that the discrepancy is due to the data available. Upon literature search, physical activity was typed on the search bar however the studies that came up discussed mainly about exercise. A panelist also suggested that "Physical exercise" be used since it reflects the evidence presented.

A question was also raised if the recommendation focuses on primary or secondary prevention. An ERE responded that primary prevention is the focus since the population in the studies had no disease yet. A panelist pointed out an article showing that high impact exercise does not improve BMD, but high force does. An ERE responded that the recommendations did not consider high impact exercises, it focused mainly on multiple exercises. A panelist pointed out that exercise prescriptions need to be specific. It was suggested that an exercise menu table containing the different exercise prescriptions be added as an annex to the guideline. Walking is the most prescribed exercise however it was not discussed. A panelist inquired if the evidence shows weight bearing exercise? An ERE responded that weight bearing exercises were not discussed. It is better that a general recommendation be written and the exercise types be elaborated in the discussion.

Summary of Evidence

These recommendations were adapted from the guideline statements of the UK National Osteoporosis Guideline Group (NOGG), Scotland Intercollegiate Guideline Network 2020 guideline (SIGN 142) and Royal Australian College of General Practitioners' 2017 update.[1,2,3] Exercise, especially combinations of different exercise types, are associated with modest improvements in bone density and a reduced risk of fragility fractures.

Evidence from 2011 Cochrane review (43 RCTs and 4,320 women) showed that any exercise type was associated with minimal improvements in bone density at the spine (MD 0.85 95% CI 0.62 to 1.07) and femoral neck (MD -0.08 95% CI -1.08 to 0.92), a minimal reduction in fracture risk (OR 0.61 95% CI 0.23 to 1.64) but a slight worsening of total hip BMD (MD 0.41 95% CI -0.64 to 1.45) compared to control.[4] Other meta-analyses also demonstrated that combining impact exercise with resistance exercises was effective at reducing bone density loss at the lumbar spine and femoral neck, while combination of aerobics and high-intensity resistance training showed positive benefits on BMD decline.[5,6] Combination exercise programs were most effective intervention for improving BMD at the spine was (MD 3.22; 95% CI 1.80 to 4.64). Furthermore, combination exercises have been associated with positive effects on physical function, pain and vitality measures.[7]

A recent 2020 meta-analysis of 74 studies representing 5,112 early and late post-menopausal women confirmed the positive effects of different types of exercise on BMD at the lumbar spine (OR 0.42 95% CI 0.23 to 0.61), femoral neck (MD 0.35 95% CI 0.19 to 0.51) and total hip (MD 0.34 95% CI 0.14 to 0.53). Analysis revealed no significant differences between weight-bearing, direct resistance training or combination exercises for all BMD outcomes and postulated that exercise may be more beneficial during the early phase of menopause, with respect to trabecular bone loss.[8]

Data on the effect of specific types of exercise were reviewed in several meta-analyses. Static weight bearing exercise showed a significant reduction in hip BMD decline (MD 2.42, 95% CI, 0.73 to 4.10) based on a single study of single leg standing. Compared with sedentary lifestyle or placebo exercise, low-force dynamic weight bearing exercise (e.g., walking and tai chi) has been associated with improvement in spine BMD.[4,6] High-force dynamic weight bearing exercise (e.g., jogging and running) showed no impact on improving BMD at any site [4,5] Non-weight bearing exercise was not associated with improvement in any BMD outcomes if done with low force but high-force non-weight-bearing exercise like progressive resistance strength training using high loads have shown improvement in spine BMD decline (MD 0.86, 95% CI 0.58 to 1.13) and was most effective for improving femoral neck BMD decline (MD 1.03, 95% CI 0.24 to 1.82).[4]

In general, exercise may reduce the risk of fall-related fractures (RR 0.60, 95% CI 0.45 to 0.84) in older adults.[9] However, only combination exercise has been shown to reduce the risk of any type of fracture (OR 0.33, 95% CI, 0.13 to 0.85) in post-menopausal women based on limited data.[4,10] No other harms data were reported for physical activity or exercise in the primary prevention of osteoporosis and fragility fractures.

Resource Implications

No studies were found that tested the cost-effectiveness of exercise as an intervention for osteoporosis.

Acceptability and Applicability Issues

Providing health education regarding physical activity may easily be incorporated during patient consultation in the primary care setting. Patient education regarding exercise and its value in

preventing fragility fractures among other chronic illnesses, may be included as part of wellness and preventive care plan for the post-menopausal women. Possible barriers to implementation of physical activities include presence of pain, fear of falling, bad weather, lack of caregiver and lack of knowledge on the appropriate exercises. Apart from recognizing the existence of some modifiable personal factors, patients generally demand: more knowledge and education on exercise, including the pros and cons in the context of their disease, and coherence of messages received, together with better monitors that accompany them in their coping with disease and exercise.[11] personal health factors that could be important barriers to walking and other physical activity were common. If these barriers are ignored, patients may think their providers are giving them advice that is insensitive to their difficulties or may struggle unsuccessfully to cope with them. However, if the type of barriers we elicited are specifically acknowledged and presented to patients it can motivate them to do it to attain quality of life.[12]

Research Gaps

Local studies on the effectiveness, safety, cost-effectiveness as well as qualitative data on the acceptability, applicability and feasibility of recommending physical activity for primary prevention of osteoporosis and fragility fractures are lacking.

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Question 20: Among PMW and older men, does smoking cessation prevent osteoporosis and fragility fractures?

Recommendation:

Among postmenopausal women and older men, smoking cessation is recommended to reduce risk of osteoporotic fractures.
(Strong recommendation, Moderate Quality of evidence)

Panel Considerations on the Recommendation

The panel suggested the inclusion of post-menopausal women and older men in the recommendation to have coherence with the clinical question. The evidence shows that it takes 8 to 10 years of smoking cessation to see the effect of decreased fracture risk. However, the evidence also shows that the immediate effect of smoking cessation is the enhancement of bone health. Is there a way to reconcile this discrepancy in evidence? An ERE points out that there is no direct evidence, only association studies are done. There was also no BMD monitoring done. The main outcome of the studies is on fracture risk (osteoporotic and hip fracture).

Summary of Evidence

These recommendations were adapted from the UK National Osteoporosis Guideline Group (UK NOGG 2022), Scotland Intercollegiate Guideline Network 2020 guideline (SIGN 2021) and the Royal Australian College of General Practitioners' 2017 guideline (RACGP).[1,2,3] Recommendations from the 3 clinical practice guidelines on smoking cessation are based on observational studies that established correlations between smoking and low bone mineral density and increase in risk for osteoporosis fractures.[1,2,3]

A systematic review and meta-analysis of 10 large prospective cohort studies which included 59,232 men and women, found that current smoking was associated with significantly increased risk for any fracture (RR 1.25; 95% CI 1.15 – 1.36), osteoporotic fractures (RR 1.29; 95% CI 1.17 – 1.43) and hip fracture (RR 1.84; 95% CI 1.53 – 3.33). Adjusted for BMD, risks are slightly lower at 1.13 (95% CI 1.00 – 1.28) for osteoporotic fractures and 1.6 (95% CI 1.27 – 2.02) for hip fracture. Risks were also significantly increased for those with history of smokers but lower than for current smokers.[4] SIGN 2021 recommends smoking cessation for all smokers to reduce the risk for fragility fractures [2] and consider fracture-risk assessment for smokers over age 50 years, particularly in the presence of other risk factors. The RACGP recommends cessation of smoking for all postmenopausal women and men over 50 years of age.[3]

The UK NOGG 2022 included results as evidence base from a meta-analysis of prospective studies among women and a 10-year prospective study among 1033 women. A meta-analysis that included 359,468 women, found that risk for hip fracture was higher among current smoker (relative to never smokers) (RR 1.30 95%CI 1.16-1.45), lower for those who have quit smoking for 10 years (RR 0.70 95% CI 0.70-0.90) though not significantly different in low-dose smokers (< 15 cigarettes/day) (RR 1.11 95%CI 0.89 – 1.33).[5] Among the 1033 women who followed up for 10 years, current smoking was significantly associated with increased risk for any fracture (HR 1.32 95%CI 1.01-1.73) and osteoporotic fractures (HR 1.49 95%CI 1.11-1.98) but not significantly associated with increased risk of hip fracture (HR 1.25; 95%CI 0.78-2.02).[6]

Resource Implications

Direct evidence of the cost-effectiveness of smoking cessation interventions on preventing osteoporosis and fragility fractures is lacking. Smoking cessation intervention may entail behavioral counseling or nicotine replacement therapy (NRT) alone or these two in combination. Implementation may require training of clinic staff.

A recent systematic review (2019) of 9 cost-effectiveness studies (N=13,452) regarding community-based smoking cessation interventions including primarily quit lines or telephone counseling. Others were self-help via internet or postal mail, and NRT. Community-based interventions may have lower cessation (or quit) rates than clinic-based interventions but can engage more smokers including those who are underserved. Overall, when combining all studies, cost per quit ranged from $5 to $2,040. Based on subgroup analyses, cost per quit ranged from $102.44 for monotherapy (2 weeks of nicotine patch only) to $2,040 for combination therapy (6weeks), from $5 for basic internet to $1,882 for enhanced internet plus phone, and, in terms of duration, from $883 for 4 weeks to $2,040 for 8 weeks.[7]

Acceptability and Applicability Issues

Screening for smoking may easily be integrated in regular patient consultation by asking for current smoking and intensity (in pack/years) during history taking. The USPSTF recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and pharmacotherapy for cessation to nonpregnant adults who use tobacco.[8] A brief behavioral intervention (5 As) utilized in smoking cessation can be conducted within 3-5 minutes and includes assessing for current tobacco use, willingness to make a quit attempt among smokers and brief counseling and medication, if necessary.[9] Cost of medication may be a barrier to a smoker's compliance to treatment. Varenicline which costs 99.75 pesos is taken for at least 12 weeks.

Research Gaps

Direct evidence of the effectiveness of smoking cessation interventions on reducing risk of fragility fractures is lacking. Randomized controlled trials may establish effectiveness of particular interventions in preventing fragility fractures among smokers.

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Question 21: Among PMW and older men, what diet is effective in the prevention of osteoporosis?

Recommendation:

Among PMW and older men, a balanced diet or nutrient-dense diet is recommended to prevent osteoporosis and fragility fractures.
(Strong recommendation, Moderate Level of Evidence)

Panel Considerations on the Recommendation

A panelist suggested that the recommendation be rephrased to have coherence with the clinical question. Another panelist pointed out the need to promote the utilization of probiotics and omega-3 fatty acids to improve nutrient absorption. Inquiry regarding the inclusion of "Pinggang Pinoy" was also pointed out because it is not seen in the evidence.

A panelist inquired if a health and nutrition dense/balanced diet will be placed in the discussion. An ERE responded that it will be placed in the discussion. A healthy diet is rich in vegetables, fruits, fish, poultry, and whole grains. Nutrient-dense diet dwells on enhancement of absorption. It is thus important to include the factors that increase the absorption of bone-forming minerals. Another concept that needs to be discussed are the factors that excrete nutrients from bone. Examples of these factors are presence of oxalates, phytates, nutrient to nutrient interaction of Calcium and proteins and caffeine. Food preparation and cooking also needs to be discussed.

Summary of Evidence

These recommendations were adapted from the UK National Osteoporosis Guideline Group (UK NOGG 2022), Scotland Intercollegiate Guideline Network 2020 guideline (SIGN 2021) and the Royal Australian College of General Practitioners' 2017 guideline (RACGP).[1,4,9]

The UK National Osteoporosis Guideline Group recommends a "healthy, nutrient-based diet".[1] Recommendations were based on evidence from 1 meta-analysis and 1 randomized controlled trial (RCT). A 2019 meta-analysis of 10 cohort and cross-sectional studies evaluated the association between dietary pattern and osteoporosis risk and found a modest reduction in risk of low BMD (Odds Ratio, OR 0.82; 95% CI 0.69 to 0.98; p=0.028), fracture at any site (OR 0.79; 95% CI 0.66 to 0.93; p=0.007) and of hip fracture (OR 0.71; 95% CI 0.55 to 0.91; p=0.007) in study participants on "healthy" diet as well as a reduction in risk for low BMD in participants on a "milk/dairy" diet (OR 0.59; 95% CI 0.50 to 0.68; p<0.0001)[2] Healthy diet was characterized as high in vegetables and fruits, fish, poultry, and whole grains. Pooled results showed estimates of effect with narrow confidence intervals, indicating precision in estimates but with high heterogeneity. Furthermore, inclusion of subjects <25 years in some dietary studies precludes generalizability in the older populations. In contrast, a diet high in processed meat, refined sugar and soft drinks was associated with an increased risk for low BMD.[6] Supporting evidence from a well-conducted RCT trial was also discussed, wherein consumption of a 30-day calcium-rich DASH diet resulted in a reduction in bone turnover, as measured by osteocalcin and C-terminal telopeptide of type I collagen.[3]

The 2021 Scotland Intercollegiate Guideline Network guideline recommends a balanced diet for bone health.[3,4] The evidence base includes 3 studies: 1 Meta-analysis of Cohort Studies and 2 Cross-sectional Studies. The first study is a well-conducted large Canadian retrospective cohort

study (N=5,188) that compared a nutrient-dense diet (i.e., intake of fruits, vegetables, and whole grains) to an energy-dense diet (i.e., intake of soft drinks, potato chips, French fries, hamburger and bacon, ice cream and doughnuts).[4,5] The nutrient-dense diet was associated with a reduced risk in fracture per 1 SD of women overall (Hazard Ratio, HR 0.86; 95% CI 0.76 to 0.98) with a lower risk of fracture in older women aged >70 years but not in women < 70 years(HR 0.82, 95% CI: 0.71 to 0.96, vs. HR 0.97, 95% CI: 0.76 to 1.24, respectively). The differential effects in men also did not reach statistical significance (HR 0.83; 95% CI 0.64 to 1.08).[5] The age effect may be related to a threshold effect, indicating that food choices matter more in older individuals. Lack of dietary variety may lead to inadequate intake of particular nutrients.[5] The second study is a cross-sectional study of 3236 scottish women aged 50-59 found that a healthy meal pattern (fruit, vegetables, rice, pasta, white meat, oily fish and dairy products except milk) was associated with decreased bone resorption (Pearson's r = -0.081, P<0.001). Intake of processed (Pearson's r = -0.056, P<0.001) and snack food (Pearson's r = -0.044, P<0.001) was associated with lower femoral neck BMD.[6] The third study is a cross-sectional study done on 220 adult Greek women shows that intake of a diet with high fish, olive oil and low red meat content was positively associated with lumbar spine bone mineral density (standardized **β**-coefficient= 0.185, P = 0.017) and total body bone mineral content (standardized **β**-coefficient= 0.140, P = 0.048).[7] Two guidelines, the UK National Osteoporosis Guideline Group (NOGG 2022) and the Royal Australian College of General Practitioners (RACGP 2018), recommended an adequate intake of dietary calcium for postmenopausal women and men over 50 years of age.

The UK NOGG 2022 based its recommendation on RCTs of calcium and Vit D supplementation stating that dietary sources of calcium are the preferred option in clinical practice. RACGP 2018 included in its diet and lifestyle recommendations, adequate calcium and protein intake for all post-menopausal women and men over 50 years of age. The evidence base, however, showed contradicting results in terms of association between dietary calcium intake and fracture risk**.**[11] The SIGN guideline included a recommendation for adequate dietary calcium consumption to meet reference intake levels of 700 mg/day in adults as a Good Practice Point. Good practice points are recommended best practice based on the clinical experience of the guideline development group. The evidence base included 4 meta-analyses of well-conducted observational studies, mostly cohort, which concluded that dietary calcium has no effect on fracture risk.[3]

Recent studies also present conflicting evidence on high-protein diet and its effectiveness in improving BMD and reducing hip fracture. In a 2019 meta-analysis of both observational and interventional studies, subgroup analysis of 5 cohort studies presenting fracture risk data found no significant association between increased total protein intake and fracture risk (RR 0.94; 95% CI 0.72 to 1.23; P=0.30).[10] No significant association between protein supplementation and BMD was also observed for lumbar spine BMD and femoral neck BMD using linear and non-linear modeling. In contrast, a separate 2019 meta-analysis of 4 cohort studies on older adults (65 years and above) showed a modest reduction in hip fracture risk (HR of 0.89;95% CI 0.84 to 0.94; *p*<0.001) among participants with high protein intake (> 0.8 g/kg body weight/day) compared to participants with low protein intake (<0.8 g/kg body weight/day) after a follow-up period of 1-11 years.[11]

Resource Implications

No studies evaluating the cost-effectiveness of dietary modification as an intervention for osteoporosis prevention were found in this review. Nevertheless, food options that can be used to prepare nutrient-dense or balanced meals such as vegetables, fruits and grains are widely available in the country and can be easily accessed.

Food-insecure households, however, may be placed at a disadvantage if a healthy diet is implemented as a non-pharmacologic intervention for osteoporosis and fragility fracture prevention.

Food insecurity is defined as the state in which people are at risk of or suffering from inadequate consumption of food and inability to meet nutritional requirements due to physical unavailability of food, lack of social or economic access to adequate food, and/or inadequate food utilization (Global Forum on Food Security).[12] Based on the 2019 Expanded National Nutrition Survey, food-insecure households in the Philippines were as high as 64%, overall. More than 50% of urban households and almost 70% of rural households are food insecure. Food insecurity can be as high as 87% among households belonging to the poorest wealth quintile.[12]

Acceptability and Applicability Issues

Dietary advice can be easily incorporated during doctor-patient consultations in the primary care setting. Patient education on what constitutes a healthy diet and its value in preventing fragility fractures as well as other chronic illnesses, may be included as part of a wellness and preventive care plan for postmenopausal women and elderly men. The Food and Nutrition Research Institute had developed infographics on balanced diet for older adults.[13]

Maintaining a healthy diet is a behavior. Thus, dietary modification may require behavioral counseling in the primary care setting. Behavioral counseling techniques such as motivational interviewing or counseling will require the acquisition of necessary skills. In the Women's Health Initiative Dietary Modification Trial, the intervention utilized an intensive behavioral program that consisted of 18 group sessions led by trained nutritionists.[8] The intervention emphasized self-monitoring techniques and introduced other tailored and targeted strategies, such as motivational interviewing to lower fat intake throughout the intervention period.[5]

Research Gaps

Strong clinical evidence for nutritional influences on fracture risk is lacking as there are few long-term intervention studies on this topic. The current body of evidence is based mostly on observational studies, which do not prove causality and may be subject to confounding.[3,4] Local studies on the effectiveness of diet in reducing the risk of osteoporosis and fragility fractures are lacking. Randomized controlled trials utilizing the FNRI Pinggang Pinoy for older adults as intervention may be conducted in the future to strengthen the evidence base for application in the Philippine context.

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ROLE OF MHT IN PREVENTION OF OSTEOPOROSIS

Question 22: Should at-risk postmenopausal women receive (MHT) for the prevention of fragility fractures? What is the duration of use for MHT?

Recommendation 1:

Among at risk peri and postmenopausal women with climacteric symptoms but without contraindications to MHT, it is recommended that MHT be given for a minimum duration of 2 years but not longer than 3 years to reduce fracture risk.
(Strong recommendation, High quality of evidence)

Recommendation 2:

Among at-risk peri and post-menopausal women with climacteric symptoms but with contraindications to MHT, MHT is not recommended.
(Strong recommendation, High quality of evidence)

Panel Considerations on the Recommendations

A panelist commented that the clinical question asked for the clinical outcome of osteoporosis prevention. However, since all the evidence reviewed mainly had the outcome of fracture risk reduction, it was agreed upon to use “prevention of fragility fractures” instead of “prevention of osteoporosis”. Women with menopausal climacteric symptoms benefit from HRT. However, concern about women without menopausal signs was raised. Is MHT recommended? Another issue raised was the study population used in the evidence reviewed. Considering the risk-benefit of MHT, it is not recommended as a first line treatment for osteoporosis? Other studies comparing MHT vs other osteoporosis treatment regimen was brought up. Evidence showed MHT’s relative safety for population aged 50-59 years old. However, concern on its safety in different age groups was raised. Since there was no consensus regarding the strength of recommendation after 3 rounds of voting, Delphi technique was used. After Delphi Technique was done, the consensus panel agreed that the clinical question and recommendation on duration of MHT use can be integrated in this recommendation.

All the evidence reviewed mainly had the outcome of fracture risk reduction, hence this was the outcome used instead of “prevention of osteoporosis”. Estrogen-only menopausal hormone therapy increases the risk of endometrial cancer for patients with an intact uterus hence a combination therapy is recommended. However, hysterectomized women (either surgical or medical) can take either combination or single hormone therapy regimens. MHT may be unsuitable for some women especially for those that increase risk for cardiovascular and thromboembolic disease, increase some types of cancer (endometrial CA). It is suggested that the recommendations be stratified into at-risk peri and post-menopausal women with climacteric symptoms with or without contraindications to MHT. All data from the systemic review and meta-analyses used the study population from the Women’s Health Initiative study. These were women with climacteric symptoms. MHT is not recommended as first line treatment due to the risks and the availability of other modes of treatment. However, all the evidence compared MHT to placebo and there were significant

findings of improvement in terms of the outcome of fracture risk reduction. There are also other studies that compared MHT to other medications for osteoporosis, however it proved to be inferior in terms of efficacy. Hence, the recommendation will only state if it's recommended or not. After evidence review, the majority of the studies compared MHT with placebo. However, there are other studies that compared MHT to other treatment regimens.

Summary of Evidence

The following recommendations were based from the 2022 hormone therapy position statement of The North American Menopause Society (NAMS 2022)[2].

Multiple meta-analyses have shown that menopausal hormone therapy (MHT) in postmenopausal women reduces the risk of fractures. A meta-analysis of 107 RCTs (n=193,987) showed that compared to placebo, estrogen with progesterone treatment reduces the risk for hip (RR 0.72, 95% CI 0.53-0.98), non-vertebral (RR 0.78, 95% CI 0.68-0.89) and vertebral fractures (RR 0.65, 95% CI 0.46-0.92) after a mean treatment duration of 27.7 months.[3] A meta-analysis of 28 RCTs (n=33,426) showed that hormone replacement therapy reduces the risk for total (RR 0.74, 95% CI 0.69-0.80), hip (RR 0.72, 95% CI 0.53-0.98) and vertebral fractures (RR 0.63, 95% CI 0.44-0.91).[4]

In terms of osteoporosis prevention, HRT was shown to decrease the risk of fractures.[5] A systematic review shows that estrogen therapy for osteoporosis reduces the risk for all (RR 0.54, 95% CI 0.18-1.60) and vertebral(RR 0.12, 95% CI 0.01-1.98) fractures.[5] A systematic review shows that menopausal hormone therapy (MHT) decreases the risk of vertebral and hip fractures for post-menopausal women not having osteoporosis.[1] A meta-analysis of 8 RCTs (n=15,795) shows that raloxifene treatment decreases the risk of vertebral(RR 0.61 95% CI 0.44-0.80), non-vertebral(RR 0.90 95% CI 0.65-1.21) and hip fractures(RR 0.94 95% CI 0.31-2.67). [6] Combined analysis of 25,389 postmenopausal women (age 50-79) enrolled in the 2 Women's Health Initiative hormone therapy trials showed that MHT decreases the risk of any fracture(RR 0.72 95% CI 0.65-0.78), major osteoporotic fracture(RR 0.60 95% CI 0.53-0.69) and hip fracture(RR 0.66 95% CI 0.45-0.96) compared to placebo.[7] A systematic review shows that the risk of all clinical fractures is decreased by either combined continuous(RR 0.78 95% CI 0.71-0.86) or estrogen-only(RR 0.73 95% CI 0.65-0.80) hormone therapy.[8]

A systematic review and meta-analysis of 20 RTC's (n=39,145) and 3 cohort studies (n=1,155,410) showed that fracture risks can be decreased with the use of estrogen-only (Risk difference (RD) -388, 95% CI -489 to -277) and estrogen + progesterone (RD -230, 95% CI -372 to -66) compared to placebo.[26]

Duration of MHT use

Five to seven years of menopausal hormone therapy (MHT) significantly decreased the incidence of spine, hip, and nonvertebral fractures, according to a meta-analysis and systematic review that predominantly used the Women's health initiative trial as their main data source.[3,4]

A meta-analysis of 107 RCTs (n=193,987) showed that compared to placebo, estrogen with progesterone treatment reduces the risk for hip (RR 0.72, 95% CI 0.53-0.98), non-vertebral (RR 0.78, 95% CI 0.68-0.89) and vertebral fractures (RR 0.65, 95% CI 0.46-0.92) after a mean treatment duration of 27.7 months.[3]

A meta-analysis of 28 RCTs (n=33,426) showed that hormone replacement therapy reduces the risk for total (RR 0.74, 95% CI 0.69-0.80), hip (RR 0.72, 95% CI 0.53-0.98) and vertebral fractures (RR 0.63, 95% CI 0.44-0.91).3 Subgroup analysis also showed MHT reduces the risk for total fractures for women <60 years old (RR 0.55, 95% CI 0.44-0.68) and >60 years old (RR 0.77, 95% CI 0.71-0.84). Women aged <60 years old also had significantly lower risk of total fractures compared to those aged 60 years old and above (p=0.003). MHT types in this study were conjugated equine estrogens (CEE) or estradiol. Total fracture risk was reduced with use of either CEE(RR 0.77, 95% CI 0.71-0.83) or estradiol (RR 0.55, 95% CI 0.44-0.70). If CEE and estradiol are compared, estradiol leads to a lower risk of total fracture (P=0.01). Patients who were followed-up less than 36 months after treatment showed greater reduction in total fracture risk compared to patients that followed-up after 36 months (P=0.003). MHT was also not associated with any increase of cancer incidence (RR 0.99, 95% CI 0.81-1.22). However, higher incidence of thrombus was associated with hormone therapy (RR 3.22, 95% CI 2.02-5.14).[4]

Multiple randomized control trials have shown that MHT treatment at an average of 5 to 7 years can decrease the risk of fractures.[5] One RCT and 1 Controlled clinical trial (n=6,828) shows that after an average of 4 years treatment with raloxifene, there was decreased incidence of clinical(RR 0.58, 95% CI 0.43-0.79) and radiographic(RR 0.64, 95% CI 0.53-0.76) vertebral fracture compared to placebo.[6-19] Two RCTs utilized the data from the Women's health initiative randomized trial to determine the ideal duration of MHT. The first RCT (n=16,608) shows that after an average of 5.6 years treatment with Estrogen-progestin, there was decreased incidence of clinical(RR 0.76, 95% CI 0.69-0.83) and hip(RR 0.67, 95% CI 0.47-0.96) fracture compared to placebo.[20] The second RCT (n=10,739) shows that after an average of 7.1 years treatment with Estrogen, there was decreased incidence of clinical(RR 0.71, 95% CI 0.64-0.80) and hip(RR 0.65, 95% CI 0.45-0.94) fracture compared to placebo.[21]

A population based, nested case control study involving 78,294 women aged 45-75 years old aimed to compare the various categories of MHT treatment duration. The main outcome of the study was fracture risk. Results show that HRT use of more than 20 months results in significant reduction of fracture risk for all (OR 0.80 95%CI 0.65-0.99, p=<0.05) and current (OR 0.71 95%CI 0.55-0.90, p=<0.05) users. MHT use of more than 20 months results in significant reduction of fracture risk for women aged 56-65 y/o (OR 0.63 95%CI 0.42-0.94, p=<0.05) and 66-75y/o (OR 0.56 95%CI 0.32-0.99, p=<0.05).[22]

A randomized, double blind-masked, placebo-controlled, clinical trial involving 495 women enrolled in Postmenopausal Estrogen/Progestin Interventions (PEPI) RCT showed that MHT use of more than 3 years results in lesser increase in adjusted and unadjusted BMD compared to placebo.[23]

A prospective epidemiological risk factor study involving 347 healthy postmenopausal women with normal bone mass aimed to determine if there are long term benefits after giving MHT for 2-3 years in the early postmenopausal years. The main outcomes used in the study are osteoporotic fractures. Results show that MHT use of 2 to 3 years results in an increase of forearm (Mean Difference (MD) 6.2 95% CI 5.1-7.3) and spine (MD) 8.9 95% CI 6.3-11.4) BMD compared to placebo.[24]

A meta-analysis of prospective and retrospective studies aimed to determine the association between the timing of MHT and development of breast cancer. A total of 58 studies were found, 24 were prospective and 34 were retrospective. A total of 568,859 women were identified and 143,887 of these were postmenopausal women with invasive breast cancer (Identified as "Cases"). The results show that for a treatment duration of 1 to 4 years, breast cancer risk is increased for women taking Estrogen + Progesterone (RR 1.60, 95% CI 1.52-1.69) and Estrogen only (RR 1.17, 95% CI 1.10-1.26) MHT. The risk was increased for 5-14 year treatment duration both for Estrogen + Progesterone (RR 2.08, 95% CI 2.02-2.15) and Estrogen only (RR 1.33, 95% CI 1.28-1.37) users.[25]

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Question 23: When should menopausal hormone therapy be initiated to reduce fracture risk?

Recommendation:

Among women younger than 60 years of age, initiation of MHT may be of greater benefit in fracture risk reduction.
(Strong recommendation, High Quality of Evidence)

Panel Considerations on the Recommendation

A recommendation by a panel member on definition of “early vs late postmenopausal women”.
Issue on direct and indirect costs of MHT was raised. Table on medication costs are available.
There is non-congruence of outcome and evidence presented hence it is suggested that the clinical question be rephrased.
Is the perimenopausal period included?
The age 60 years old is the cut-off. Early is <60y/o and Late is >60y.o. The direct costs of MHT is presented in the table showing the medication prices. Indirect costs include diagnostics for monitoring of MHT treatment. Mammography is indicated independent of HRT use and it is indicated for women > 40y.o. The BIRADS score dictates the frequency of mammograms for surveillance. The perimenopausal period did not have any studies. The climacteric symptoms of osteoporosis can occurs a year prior to the actual onset of menopause. This is the main reason why MHT is recommended for climacteric symptoms.

Summary of Evidence

The following recommendations were based from the 2022 hormone therapy position statement of The North American Menopause Society (NAMS 2022)[2].

Osteoporosis incidence is reduced in users of hormone therapy when compared to non-users when it is started ideally during the perimenopause and continued until age sixty.[1] In the absence of contraindications, in women aged younger than 60 years or within 10 years of menopause onset, systemic hormone therapy is an appropriate therapy to protect against bone loss.[2] A RCT involving 27,347 postmenopausal women aged 50 to 79 years showed that absolute risks of adverse events for estrogen + progesterone treatment were lower in younger women: women aged 50 to 69 years had 12 more adverse events per 10,000 person-years, whereas those aged 70 to 79 years had 38 more compared to placebo. In the estrogen alone group, women aged 50 to 59 years had 19 fewer adverse events per 10,000 person-years, and women aged 70 to 79 years had 51 more adverse events.[3]

A Meta-analysis of prospective and retrospective studies aimed to determine the association between the timing of MHT and development of breast cancer. A total of 58 studies were found, 24 were prospective and 34 were retrospective. A total of 568,859 women were identified and 143,887 of these were postmenopausal women with invasive breast cancer (Identified as “Cases”). The remaining 424,972 were women with no breast cancer (Identified as “Controls”). Results showed that all MHT preparations, except vaginal estrogens, was linked to increased breast cancer risk. Women using Estrogen + progesterone had higher breast cancer risk compared to estrogen alone. After prospective follow-up of 108,647 postmenopausal women, it was found that the mean age of breast cancer development was at 65 years old and 51% had used MHT.[4]

Subgroup analysis of a Meta-analysis showed that the risk of total fractures is lower in patients that are less than 60 years old (RR 0.55, 95% CI 0.44-0.68, P<0.05) compared to those who are more than 60 years old (RR 0.77, 95% CI 0.71-0.84, P<0.05).[5]

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Question 24: Which hormone preparation should be used for fracture risk reduction?

Recommendation:

Among hysterectomized PMW, it is recommended to give estrogen only replacement therapy for fracture risk reduction. Addition of progestins is recommended for women with intact uterus to prevent endometrial pathology.

(Strong recommendation, High Quality of Evidence)

Panel Considerations on the Recommendation

A panelist suggested that the recommendation be rephrased to have coherence with the clinical question. *Best to use "hysterectomized" than "without uterus" in the recommendation.*

Summary of Evidence

The following recommendations were based from the 2022 hormone therapy position statement of The North American Menopause Society(NAMS 2022)[2].

The 2022 NAMS guidelines show that there are three types of hormone preparations that can be used for HRT: estrogen, estrogen + progestin (progestogens) and tissue-selective estrogen complex.[2]

There are 4 types of estrogen formulations: Conjugated equine estrogen (CEE), synthetic conjugated estrogens (CE), micronized 17β-estradiol, and ethinyl estradiol. CEE, along with estrone sulfate, is isolated from the urine of pregnant mares. Synthetic conjugated estrogens are composed of estrone sulfate, equilin sulfate, and estradiol sulfate. Micronized 17β-estradiol has a chemical structure identical to the estradiol from the ovaries. Ethinyl estradiol is a type of synthetic estrogen commonly combined with progestin to produce hormone contraceptives. The dosing of estrogen should meet the appropriate therapeutic goal. The lowest effective dose should be used. The route of administration can be in the form of oral, transdermal patches, sprays, gels, and vaginal rings. Oral preparation is commonly used to address vasomotor menopausal symptoms. Non-oral routes bypass the first-pass hepatic effect however safety is still unknown.[2]

Progestogens are administered with estrogen in women with intact uterus. Examples include Medroxyprogesterone acetate (MPA), norethindrone acetate (NETA), and micronized progesterone (MP). Progestogen is indicated for menopausal women to prevent endometrial overgrowth and decrease the risk for endometrial cancer during estrogen therapy (ET). Chronic exposure to estrogen alone increases the risk for endometrial hyperplasia or cancer. Endometrial protection is ensured if proper dose and duration of progestogen is used.[2]

A systematic review shows that daily CEE+MPA treatment was linked to a risk of endometrial cancer like placebo (HR 0.81, 95% CI 0.48-1.36).[3] CEE+MPA was also shown to reduce the risk of endometrial cancer after an average of 13 years follow-up (HR 0.67, 95% CI 0.49-0.91).[4] A meta-analysis also showed that noncontinuous HRT increases the risk for endometrial cancer (RR 1.2, 95% CI 1.06-1.35). Continuous HRT decreases the risk (RR 0.73, 95% CI 0.65-0.82) for endometrial cancer.[5] In order to prevent endometrial hyperplasia, the ideal dose for oral MP is 200 mg/d for 12-14 d/mo.[6,7]

Tibolone is a progesterone derivative with both estrogenic and progestogenic effects. It has been determined to increase bone mineral density like that of estrogen replacement therapy.[8] However, as regards the outcome of reducing risk for fragility fractures, no data was available supporting its effectiveness in comparison with bisphosphonate and non-bisphosphonate therapy.[9]

One RCT and 1 Controlled clinical trial (n=6,828) shows that after an average of 4 years treatment with raloxifene, there was decreased incidence of clinical (RR 0.58, 95% CI 0.43-0.79) and radiographic (RR 0.64, 95% CI 0.53-0.76) vertebral fracture compared to placebo.[10-23]

Two RCTs utilized the data from the Women's health initiative randomized trial to determine the ideal duration of MHT. The first RCT (n=16,608) shows that after an average of 5.6 years treatment with Estrogen-progestin, there was decreased incidence of clinical (RR 0.76, 95% CI 0.69-0.83) and hip (RR 0.67, 95% CI 0.47-0.96) fracture compared to placebo.[24] The second RCT (n=10,739) shows that after an average of 7.1 years treatment with Estrogen, there was decreased incidence of clinical (RR 0.71, 95% CI 0.64-0.80) and hip(RR 0.65, 95% CI 0.45-0.94) fracture compared to placebo.[25] Subgroup analysis shows that total fracture risk can be decreased by both Conjugated equine estrogen(RR 0.77, 95% CI 0.71-0.83, P<0.05) and Estradiol (RR 0.55, 95% CI 0.44-0.70, P<0.05).[26]

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Question 25: What are the safety issues of MHT?

Recommendation:

> Transdermal estrogen is recommended over oral estrogen to decrease the risk of VTE.
> *Strong recommendation, High Quality of Evidence*

Panel Considerations on the Recommendation

A panelist suggested that the recommendation be rephrased to have coherence with the clinical question. To avoid duplication, the discussion on addition of progestins for women with intact uterus may be placed in the clinical question 12. A research gap regarding the cost and feasibility of transdermal estrogen was also raised.

Summary of Evidence

The following recommendations were based from the 2022 hormone therapy position statement of The North American Menopause Society (NAMS 2022)[2].

A systematic review showed that continuous estrogen + progesterone hormone therapy increases the risk for multiple diseases. Combined continuous and estrogen therapy increases the risk of coronary events (RR 1.89, 95% CI 1.15-3.10), stroke (RR 1.46, 95% CI 1.02-2.09), venous thromboembolism (VTE) (RR 4.28, 95% CI 2.49 to 7.34), breast cancer (RR 1.27 , 95% CI 1.03-1.56), death from lung cancer (RR 1.74 , 95% CI 1.18-2.55) and gallbladder disease (RR 1.64, 95% CI 1.30-2.06). Estrogen only hormone therapy increases the risk of coronary events (RR 0.94, 95% CI 0.78-1.13), stroke (RR 1.33, 95% CI 1.06-1.67), VTE (RR 2.22, 95% CI 1.12-4.39), breast cancer (RR 0.79, 95% CI 0.61-1.01) and gallbladder disease (RR 1.78 , 95% CI 1.42-2.24).[3]

A Meta-analysis of prospective and retrospective studies aimed to determine the association between the timing of MHT and development of breast cancer. A total of 58 studies were found, 24 were prospective and 34 were retrospective. A total of 568,859 women were identified and 143,887 of these were postmenopausal women with invasive breast cancer (Identified as “Cases”). The remaining 424,972 were women with no breast cancer (Identified as “Controls”). Results showed that all MHT preparations, except vaginal estrogens, was linked to increased breast cancer risk. Women using Estrogen + progesterone had higher breast cancer risk compared to estrogen alone. After prospective follow-up of 108,647 postmenopausal women, it was found that the mean age of breast cancer development was at 65 years old and 51% had used MHT.[4]

The table below summarizes the relationship between breast cancer risk, MHT duration and preparation. The results show that prolonged MHT administration increases the risk of breast cancer.[4]

Table : Duration of MHT preparation and corresponding risk of developing breast cancer

Duration	MHT Preparation	Relative Risk of Breast Cancer (RR [95% CI])
1-4yrs	Estrogen + Progesterone	1.60 (1.52-1.69)
	Estrogen Only	1.17 (1.10-1.26)
5-14yrs	Estrogen + Progesterone	2.08 (1.52-1.69)
	Estrogen Only	1.33 (1.28-1.37)

A systematic review and meta-analysis of 20 RTC's (n=39,145) and 3 cohort studies (n=1,155,410) showed that MHT treatment significantly increases the risk of certain diseases. Estrogen only therapy significantly increases the risk of gallbladder disease (RD 377, 95% CI 234 to 540), stroke (RD 79, 95% CI 15 to 159), urinary incontinence (RD 885, 95% CI 659 to 1135), venous thromboembolism (RD 77, 95% CI 19 to 153) and all-cause mortality (RD 21, 95% CI -57 to 109) compared to placebo. Estrogen + Progesterone therapy also significantly increases the risk of gallbladder disease (RD 260, 95% CI 169 to 364), stroke (RD 52, 95% CI 12 to 104), urinary incontinence (RD 562, 95% CI 412 to 726), venous thromboembolism (RD 120, 95% CI 68 to 185) and all-cause mortality(RD 4, 95% CI -46 to 61) compared to placebo.[5]

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Question 26: Among at-risk postmenopausal women, should SERMS be considered an alternative to MHT for prevention of osteoporosis?

Recommendation:

Among women at risk of breast cancer, raloxifene is recommended as an alternative to MHT to reduce the risk of vertebral fractures.

(Strong recommendation, High Quality of Evidence)

Panel Considerations on the Recommendation

Raloxifene can worsen the climacteric symptoms in how many percent? The main indication for MHT use is climacteric symptoms (hot flushes). A study by Gennari et al in 2010 showed that SERMS only increase the vasomotor symptoms of menopause. SERMS can decrease the risk for fragility fractures. Once MHT is discontinued, patients will need to be shifted to SERMS.

Summary of Evidence

The following recommendations were based from the 2022 hormone therapy position statement of The North American Menopause Society (NAMS 2022)[2].

Selective estrogen receptor modulators (SERMs) are a class of drugs that target intracellular estrogen receptors in target organs. SERMs can function either as estrogen agonists or antagonists. There are 2 main classes of SERMs: triphenylethylene derivatives (tamoxifen and toremifene) and benzothiopene derivatives (raloxifene ospemifene, lasofoxifene, bazedoxifene and arzoxifene). Tamoxifen is commonly used to treat breast cancer. Raloxifene is used to treat and prevent osteoporosis and prevent breast cancer.[3] Multiple RCTs have shown that taking raloxifene at 60mg daily is effective in the treatment of osteoporosis and vertebral fractures.[4]

Multiple meta-analyses have shown that raloxifene decreases the risk of fractures in postmenopausal women. Meta-analysis has shown that raloxifene decreases the risk for vertebral (RR 0.60, 95% CI 0.50-0.70, P<0.01) and non-vertebral fractures(RR 0.92, 95% CI 0.79-1.07, P= 0.27). Raloxifene also increases the bone density with prolonged use. This increase in bone density is independent of dose. In the final year of raloxifene treatment, there was a noted increase in bone density compared to placebo (Weighted mean difference WMD 1.33, 95% CI 0.37-2.30, P= 0.01). After 2-3 years of raloxifene treatment, there was also noted increase in the bone density of the lumbar spine (WMD 2.51, 95% CI 2.21-2.82, P<0.01) and hip (WMD 2.11, 95% CI 1.68-2.53, P<0.01) compared to placebo. Increase in forearm bone density (WMD 2.05, 95% CI 0.71-3.39, P<0.01) compared to placebo was also observed after 2 years of raloxifene treatment.[5] A systematic review shows that raloxifene decreases the risk for vertebral fractures (RR 0.66, 95% CI 0.48-0.90), but not nonvertebral (RR 0.99, 95% CI 0.86-1.13), hip (RR 0.86, 95% CI 0.65-1.15) or wrist (RR 0.97, 95% CI 0.74-1.26) fractures compared to placebo.[6] A meta-analysis of 5 RCTs (n=244) showed that raloxifene improves the BMD levels of post-menopausal women compared to placebo (WMD 33.88, 95% CI 10.93-56.84, p=0.004) in postmenopausal women with end stage renal disease.[7] A Meta analysis of 7 RCTs (n=4054) showed that there is no difference in terms of reduction of total(RR 1.12, 95% CI 0.75-1.68, p=0.58), vertebral(RR 1.30, 95% CI 0.66-2.54, p=0.45), non-vertebral(RR 0.95, 95% CI 0.54-1.58, p=0.87) fracture between alendronate and raloxifene in postmenopausal women.[8]

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Question 27: How are adverse events monitored in women receiving MHT for osteoporosis prevention?

Recommendation:

1. Among women on MHT who are at risk of breast cancer, it is recommended for them to undergo annual mammograms.
2. Among women with postmenopausal bleeding on MHT, it is recommended for them to undergo transvaginal ultrasound.
3. Among women on MHT, it is recommended that they be monitored for signs and symptoms of venous thromboembolism, cardiovascular and cerebrovascular diseases.

(*Strong recommendation, High Quality of Evidence)*

Panel Considerations on the Recommendation

A research gap regarding the correlation of breast ultrasound and mammogram in detection of breast masses was identified. It is suggested that the risks should not only be evaluated but also monitored. The specific signs and symptoms should be elaborated in the discussion. A panel mentioned on the frequency of diagnostic tests for monitoring and evaluation should be indicated. Women not on HRT but who have bleeding will need trans-vaginal ultrasound. A clarification on the difference between cyclical and continuous MHT was suggested to be included in the manuscript. A combination of breast ultrasound and mammogram is useful in screening for breast mass. However, there is no available local research data to support it.

Summary of Evidence

The following recommendations were based on the 2022 hormone therapy position statement of The North American Menopause Society (NAMS 2022)[2].

Hematologic Markers

A study on Anti-Mullerian Hormone (AMH) levels as a predictor of early bone loss as correlated with bone mineral density measurement in the early perimenopausal period very clearly illustrates 0.22% decline in bone mineral content at pre-menopause, 0.43% in early menopause and an additional 0.50% decline in late menopause, all of which were found to be significant ($p<0.001$).[3]

Bone Mineral Densitometry (BMD)

Women on MHT should be evaluated for osteoporosis risk using bone dual x-ray absorptiometry (DXA) after at least 2 years of therapy and thereafter especially with cessation of use.[4] Women on MHT should be made aware that their risk of developing osteoporosis changes once MHT is discontinued. The benefits of preventing bone loss is persistent if treatment is continued, but it quickly disappears when medication is stopped. Markers of bone turnover returned to pretreatment levels after a few months, whereas BMD decreased within 1 to 2 years of stopping medication.[5]

Annual Mammogram

A cohort study composed of 98,995 women aimed to determine if menopausal hormone therapy (MHT) is associated with mammographic density and breast cancer risk. Results show that women currently undergoing MHT had higher mammographic density (Mean percent mammographic density (MPMD) 33%, 95% CI 31%-35%) compared to past (MPMD 29%, 95% CI 27%-31%) and never users (MPMD 24%, 95% CI 22%-36%). Mediation analysis also showed that MHT use increases the risk of breast cancer compared to non-users (OR 1.67, 95% CI 1.04 to 2.68).[6]

Trans-Vaginal Ultrasound

A cohort study composed of 488 women aimed to determine the risk of malignancies among asymptomatic postmenopausal women with thickened endometrium. The median endometrial thickness based on trans vaginal ultrasound was 8mm (range 6-30mm). Multivariate analysis shows that a positive Doppler flow signal on TVS independently increases the odds of detecting endometrial intraepithelial neoplasia (EIN)/carcinoma (OR 8.0, 95% CI 1.45 to 45.1) and carcinoma (OR 16.0, 95% CI 1.3 to 192.8). After an average follow-up of 45 months, carcinoma was noted in 2.8% of women with thickened endometrium.[7] A narrative review regarding the surveillance and care of gynecologic cancer survivors suggests that trans-vaginal ultrasound be done every 6 months for the first year and annually thereafter.[8]

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DISCUSSION

Local epidemiological data are scarce and outdated. Developing Asian countries have limited epidemiological data on large-scale research or real-world disease registries.[AUDIT2013] This creates a competition for source of funding because government entities prioritize budgets toward infectious and communicable diseases where epidemiologic data is more robust. Without determining the magnitude of disease epidemiology of osteoporosis, it is difficult to lobby with health and policymakers to direct resources to primary, secondary, and tertiary prevention of osteoporosis-related health concerns.

Burden of disease is expected to be more pronounced in the near future as the old population is expected to triple in size. Increasing education and dissemination of osteoporosis, improving resource allocation, and paying more attention on screening and treatment of osteoporosis could help reduce the global burden of disease attributable by low bone mineral density and fracture, especially in low-middle and middle sociodemographic index (SDI) countries and territories.[SHEN2022]

Dissemination, Monitoring and Evaluation

The steering committee will submit to the Department of Health the completed CPG manuscript. The Disease Prevention and Control Bureau of DOH will send copies of this manuscript to other health maintenance organizations, PhilHealth and other industry partners. A memorandum will also be released by DOH so that all stakeholders will be notified of this CPG's publication.
This CPG will also be presented during conferences and annual conventions of various medical societies. This guideline will also be disseminated to various medical schools in the country with the aim of its integration into the current Doctor of Medicine degree curriculum. A simplified version of this CPG will also be generated by DOH in order to be accessible to the general public and other health care institutions.

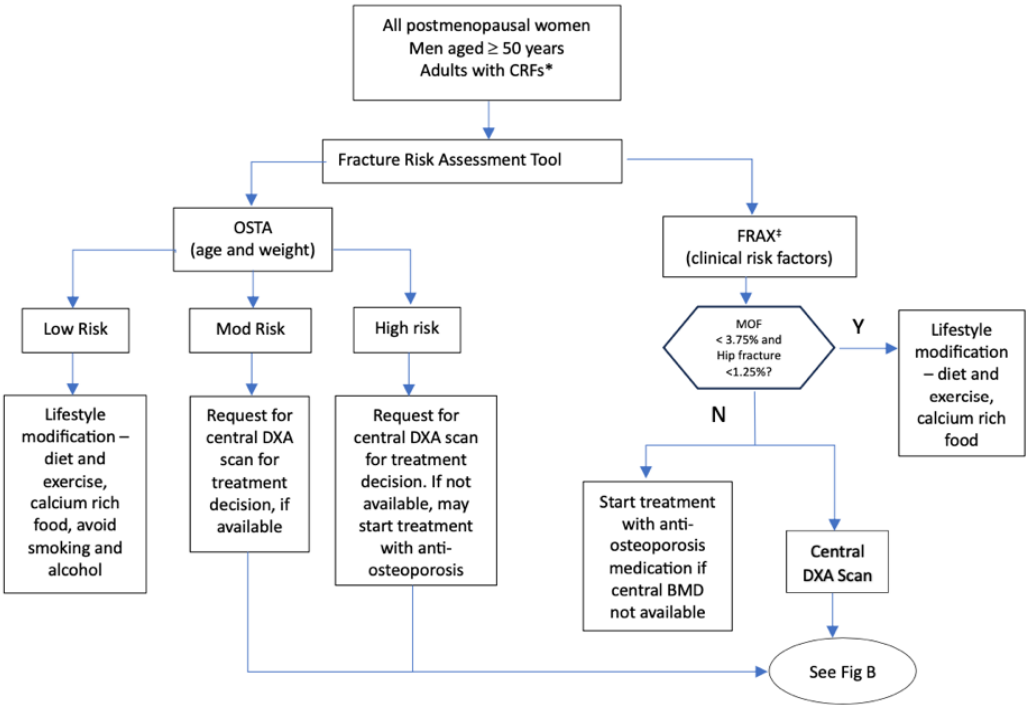
Recommendations for Guideline Development and Update

This CPG will be updated after three years or earlier in order to present more recent evidence. Surveys and focused group discussions with end-users of this guideline will be also done in order to accurately capture their preferences and other views. Cost-evaluation, feasibility and health economic outcomes studies will also be done in order to evaluate the impact of this guideline from a budget and financial standpoint.

Implementation

The following algorithms can be used for the implementation of this CPG:

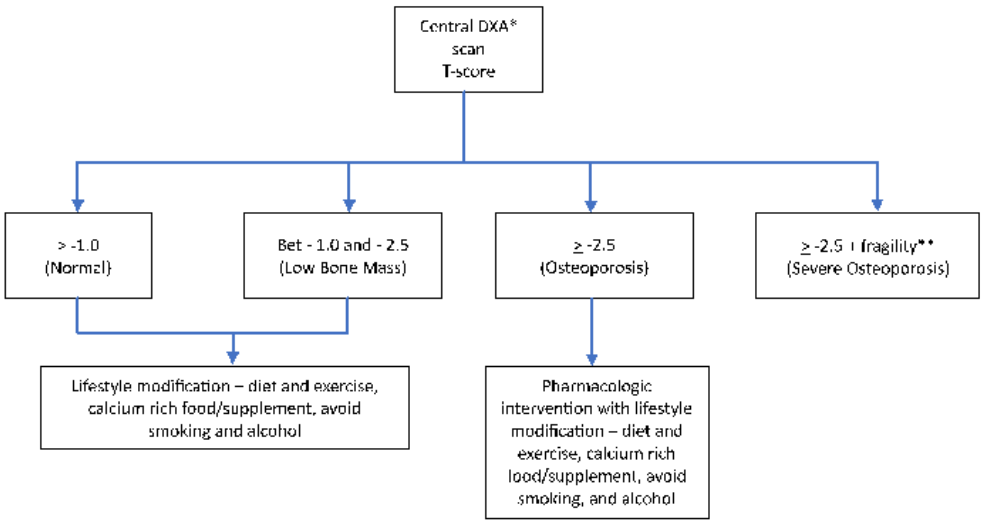
Figure A: Primary Prevention of Bone Loss



**Clinical Risk Factors that increase the risk of osteoporosis include:* advanced age (>70 years), previous fragility fracture, menopause or untreated early menopause, parental history of osteoporosis and/or fractures, excessive alcohol consumption (>3.5 units per day), smoking, frailty or low level of physical activity, coexisting illnesses, and certain medications.
Comorbidities: diabetes, hyperparathyroidism or other endocrine diseases, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, malabsorption, institutionalized patients with epilepsy, chronic liver disease, neurological disease (Alzheimer's, Parkinson's, multiple sclerosis, stroke), moderate to severe chronic kidney disease, bronchial asthma, human immunodeficiency virus
Medications: glucocorticoids, antidepressants, anti-epileptic agents (i.e. enzyme-inducing drugs), aromatase inhibitors, GnRH agonists for prostate cancer, PPIs, thiazolidinediones, anticoagulants, methotrexate, thyroid hormones

*FRAX clinical risk factors:
Age, gender, weight, height, parental history of hip fracture, personal history of fracture, glucocor0coid use, rheumatoid arthri0s, secondary cause of bone loss, current smoking, alcohol intake of ≥ 3 units per day, ± femoral neck BMD using central DXA

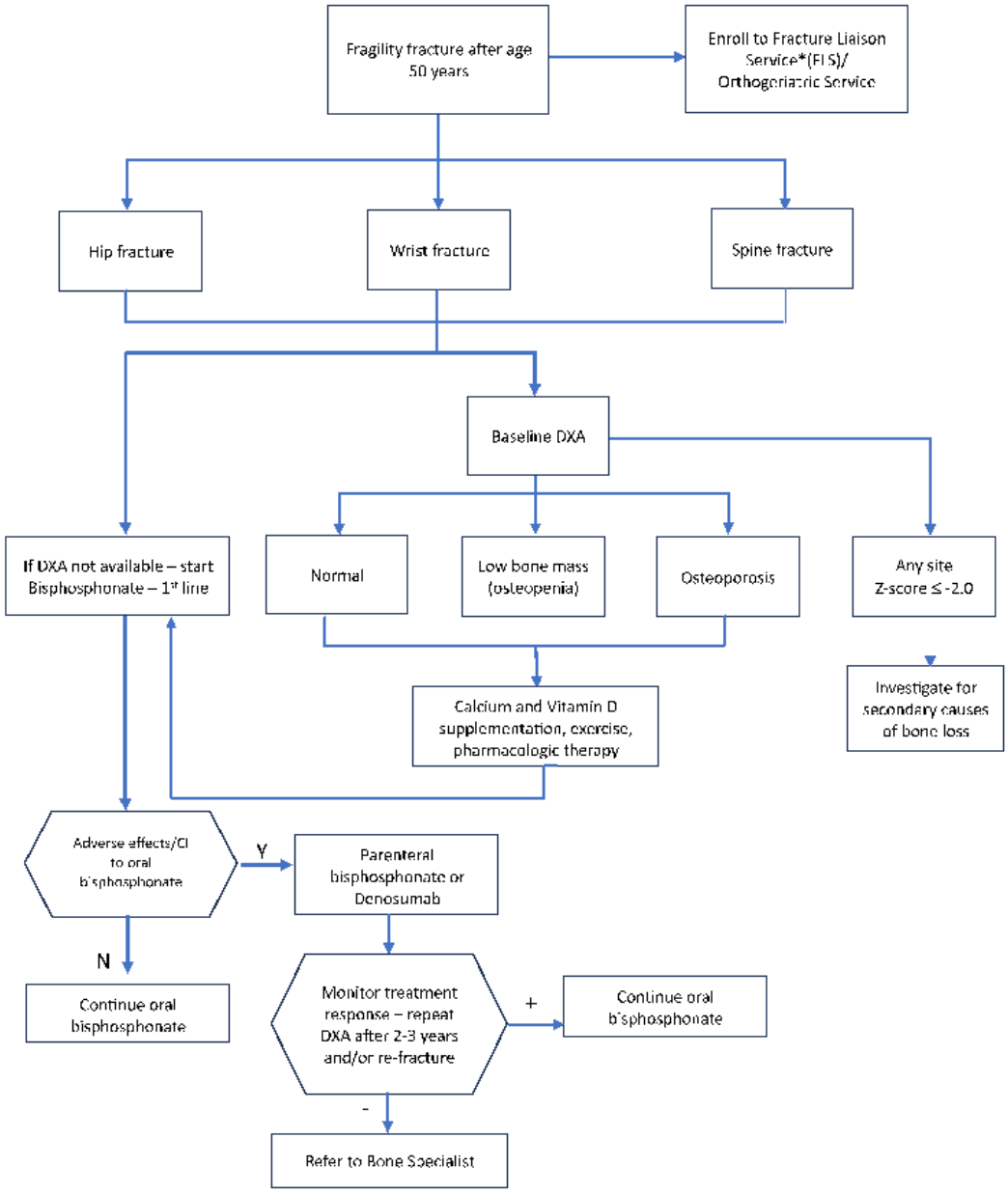
Figure B: WHO classifica0on criteria for BMD and management approach



*Region of interest: lumbar spine (L1 to L4), femur (total and/or neck), 1/3 radius
** Referral to osteoporosis specialist

Follow-up requests on BMD should be given in the ff. circumstances:
a. monitor interval change that will need an0-osteoporosis medica0on or
b. pa0ents who con0nue to loose bone or con0nues to sustain fracture despite pharmacologic therapies

Figure C: Algorithm on Secondary fracture prevention



*FLS – enables timely fracture and falls risk assessment, investigation, treatment, and monitoring

APPENDIX

A. Search Strategy - Pubmed

Search number	Query	Filters	Results	Time
15	((((((((((("Guideline" [Publication Type]) OR "Practice Guideline" [Publication Type]) OR "Consensus"[Mesh]) OR ("Consensus Development Conference, NIH" [Publication Type] OR "Consensus Development Conference" [Publication Type])) OR (consensuses[ti] or consensus[ti])) OR "position statement"[ti]) OR "position statements"[ti]) OR "practice parameter"[ti]) OR "practice parameters"[ti]) OR "appropriate use criteria" [ti]) OR "appropriateness criteria" [ti]) OR (("guidance statement"[ti]) OR "guidance statements"[ti])) OR (guideline[ti] or guidelines[ti])) AND (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)	in the last 5 years	309	22:43:39
14	((((((((((("Guideline" [Publication Type]) OR "Practice Guideline" [Publication Type]) OR "Consensus"[Mesh]) OR ("Consensus Development Conference, NIH" [Publication Type] OR "Consensus Development Conference" [Publication Type])) OR (consensuses[ti] or consensus[ti])) OR "position statement"[ti]) OR "position statements"[ti]) OR "practice parameter"[ti]) OR "practice parameters"[ti]) OR "appropriate use criteria" [ti]) OR "appropriateness criteria" [ti]) OR (("guidance statement"[ti]) OR "guidance statements"[ti])) OR (guideline[ti] or guidelines[ti])) AND (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)		1,360	22:43:04
13	((((((((((("Guideline" [Publication Type]) OR "Practice Guideline" [Publication Type]) OR "Consensus"[Mesh]) OR ("Consensus Development Conference, NIH" [Publication Type] OR "Consensus Development Conference" [Publication Type])) OR (consensuses[ti] or consensus[ti])) OR "position statement"[ti]) OR "position statements"[ti]) OR "practice parameter"[ti]) OR "practice parameters"[ti]) OR "appropriate use criteria" [ti]) OR "appropriateness criteria" [ti]) OR (("guidance statement"[ti]) OR "guidance statements"[ti])) OR (guideline[ti] or guidelines[ti])		149,071	22:42:50
12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11		109,286	22:42:27
11	bone fragility[Title/Abstract]		2,670	22:41:36
10	osteopenic[Title/Abstract]		2,383	22:40:17
9	osteoporotic[Title/Abstract]		21,298	22:40:08
8	fragility fracture[Title/Abstract]		2,008	22:39:37
7	osteoporotic fractures[Title/Abstract]		5,650	22:39:06
6	osteoporotic fracture[Title/Abstract]		3,268	22:38:47
5	osteoporosis[MeSH Terms]		60,265	22:32:35
4	osteopenia[Title/Abstract]		10,453	22:23:33
3	low bone density[Title/Abstract]		1,029	22:23:25
2	fragility fractures[Title/Abstract]		3,286	22:23:14
1	osteoporosis[Title/Abstract]		77,816	22:22:59

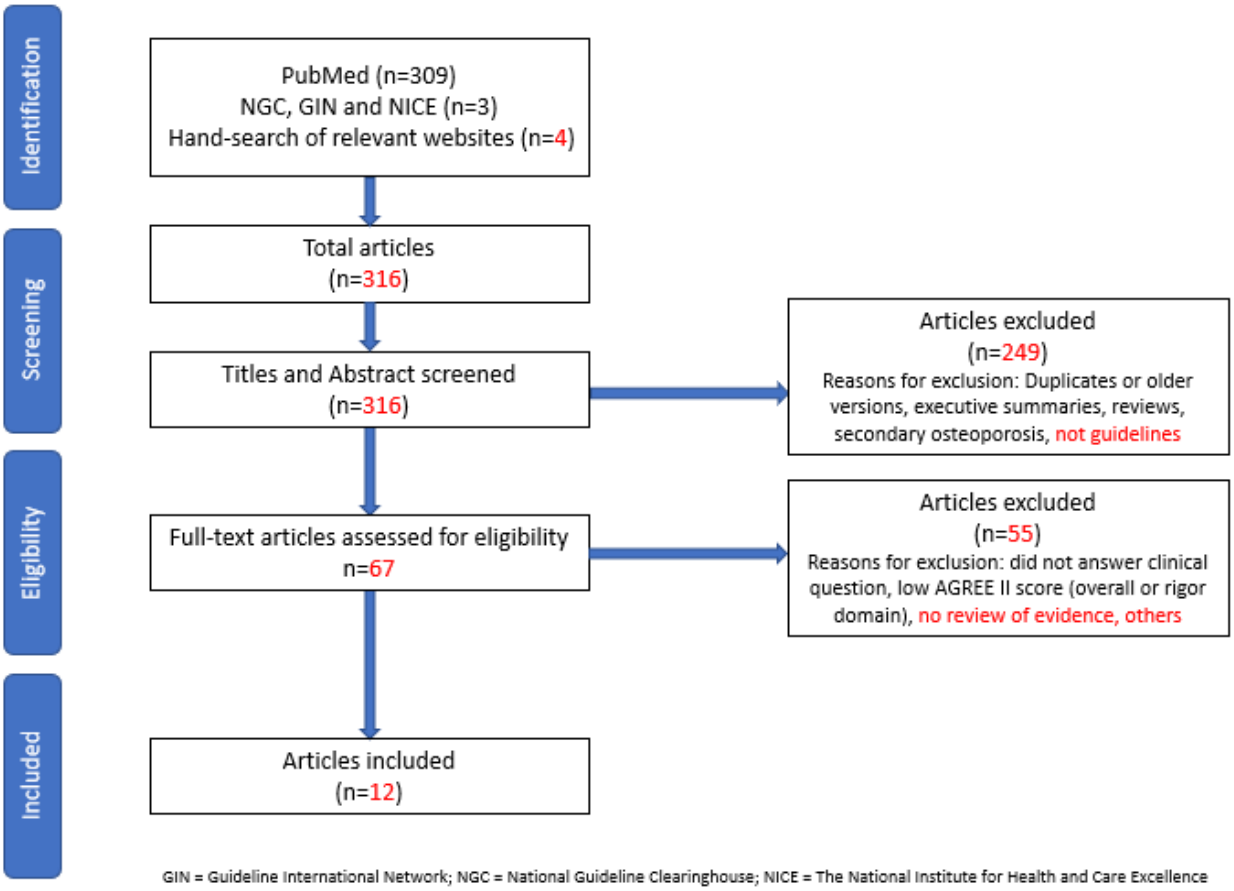
Other Databases

Database	Search String Used
National Guideline Clearinghouse	Osteoporosis
Guidelines International Network	Osteoporosis
The National Institute for Health and Care Excellence	Osteoporosis
Other Websites: ● American Academy of Family Physicians (AAFP) ● American Academy of Orthopedic Surgeons (AAOS) ● American Association of Clinical Endocrinologists (AACE) ● American Association of Neurological Surgeons (AANS) ● American College of Obstetricians and Gynecologists (ACOG) ● American College of Radiology (ACR) ● American Society for Bone and Mineral Research (ASBMR) ● American Society of Neuroradiology (ASNR) ● American Society of Spine Radiology (ASSR) ● Canadian Agency of Drugs and Technology in Health ● Canadian Interventional Radiology Association (CIRA) ● Cochrane Library ● Congress of Neurological Surgeons (CNS) ● International Osteoporosis Foundation - European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (IOF-ESCEO) ● International Society for the Advancement of Spine Surgery (ISASS) ● National Osteoporosis Guideline Group (NOGG) ● North American Menopause Society (NAMS) ● North American Spine Society (NASS) ● Scottish Intercollegiate Guidelines Network (SIGN) ● Society of Interventional Radiology (SIR) ● Society of NeuroInterventional Surgery (SNIS) ● The Royal Australian College of General Practitioners (RACGP) ● US Preventive Services Task Force (USPSTF)	Osteoporosis

B. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
a. National or international clinical practice guideline on primary osteoporosis in women and/or post-menopausal women b. Evidence-based guideline with evidence tables, recommendation statements and ratings on the quality and strength of evidence c. Guideline covers one or more key topics on osteoporosis including prevention, screening, diagnosis, treatment, surgery, continuity of care, prognosis d. Peer-reviewed and published (in text or online) e. Written in English or with English translation f. Published within the last five years (2017-2022) g. Evidence-based CPG only; must include a report on systematic literature searches and explicit links between recommendations and supporting evidence	a. Consensus statements or non-evidence-based guidelines b. CPG on secondary causes of osteoporosis or pediatric osteoporosis c. Non-English guidelines d. Non-peer-reviewed guidelines and grey literature e. For duplicate guidelines (e.g., update or revision of a previous CPG), only the most current CPG will be considered f. CPG written by a single author g. Non-evidence-based CPG or CPG published without references

C. PRISMA Flow Diagram of Guidelines Included in the ADAPTE Methodology



▼

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

D. Summary of Characteristics of Source Guidelines

Title	Code	Publisher	Country/ Language	Publication Date	End of Search Date	Recommendation Standards	AGREE II Score (Rigor)
American Association of Clinical Endocrinologists/ American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2020 update	**AACE**	American Association of Clinical Endocrinologists (AACE)/ American College of Endocrinology (ACE)	US/ English	January 2020	NA	AACE Protocol	87.08
Management of Distal Radius Fractures. Evidence Based Clinical Practice Guidelines	**AAOS**	American Academy of Orthopedic Surgeons	US/ English	2021	Feb 2020	GRADE	93.8
Management of Hip Fractures in Older Adults: Evidence Based Clinical Practice Guidelines	**AAOS**	American Academy of Orthopedic Surgeons	US/ English	2021	Jul 2021	GRADE	90.3
Consensus evidence-based clinical practice guidelines for the diagnosis and treat-to-target management of osteoporosis in Africa: an initiative by the African Society of Bone Health and Metabolic Bone Diseases	**AFRICAN**	International Osteoporosis Foundation and National Osteoporosis Foundation/ Archives of Osteoporosis	Africa/ English	2021	April 2021	Oxford Centre for Evidence-based Medicine (OCEBM)	88.88
Secondary fracture prevention: Consensus clinical recommendations from a multistakeholder coalition	**ASBMR**	American Society for Bone and Mineral Research/ Journal of Bone and Mineral Research	Boston, USA/ English	2019	N/A	N/A	96.9
The Belgian Bone Club 2020 guidelines for the management of osteoporosis in postmenopausal women	**BBC**	Belgian Bone Club/ Elsevier	Belgium/ English	May 2020	June 2019	Oxford Centre for Evidence-based Medicine (OCEBM)	90.63

Diagnostic, Treatment, and Follow-up of osteoporosis - position statement of the Latin American Federation of Endocrinology	**Latin America**	Latin American Federation of Endocrinology Springer	Latin America/ English	June 2021	2020	Scottish Intercollegiate Guideline Network and International Center for Allied Health Evidence	82.29
North American Menopause Society 2022	**NAMS 2022**	North American Menopause Society	English	Jul 2022	No mention	No mention	85.4
Royal Australian college of General Practitioners	**RACGP**	Royal Australian college of General Practitioners	Australia/English	2017	Feb 2016	National Health and Medical Research Council	82.29
SIGN 142 Management of osteoporosis and the prevention of fragility fractures	**SIGN**	Scottish Intercollegiate Guidelines Network (SIGN)/NHS Scotland	Scotland/ English	January 2021	2018	GRADE	88.80
UK Clinical Guideline for the prevention and treatment of osteoporosis	**UK NOGG**	National Osteoporosis Guideline Group	UK/ English	2022	Sept 2020	GRADE	95.83
Screening for Osteoporosis to Prevent Fractures: US Preventive Services Task Force Recommendation Statement	**USPSTF**	US preventive Services Task Force/American Medical Association	US/English	June 2018	April 2015	USPSTF criteria	90.83

E. CPG Clinical Questions in PICO Framework

SCREENING AND CLINICAL ASSESSMENT

Clinical Question	PICO
1. Among the adult population, who should be screened for osteoporosis?	Population: adults Intervention: screening tools Outcomes: osteoporosis
2. Among the adult population, what factors increase the risk of osteoporosis?	Population: adults Intervention: risk factors Outcomes: osteoporosis
3. What tool should be used for osteoporosis screening?	Population: adults Intervention: risk assessment tools Outcomes: osteoporosis
4. What is the clinical presentation of osteoporosis?	Population: adults Intervention: clinical presentation Outcomes: osteoporosis

DIAGNOSIS

Clinical Question	PICO
5.Among at-risk PMW and older men, should bone mineral density measurement by dual energy x-ray absorptiometry be used to diagnose osteoporosis?	Population: at-risk PMW and old men Intervention: central DXA Comparison: no DXA Outcomes: osteoporosis diagnosis

PHARMACOLOGIC MANAGEMENT

Clinical Question	PICO
6. Among PMW with osteoporosis, is alendronate, ibandronate, zoledronate, denosumab, raloxifene effective in reducing vertebral, non-vertebral, hip fractures compared to placebo?	Population: PMW with osteoporosis Intervention: anti-resorptives Comparison: PBO Outcomes: reduction in vertebral, non-vert, hip fractures
7. Among PMW with severe osteoporosis, is teriparatide, abaloparatide, and romosozumab effective in reducing	Population: PMW with severe osteoporosis Intervention: bone forming agents and duration of use Comparison: PBO

vertebral, non-vertebral, hip fractures compared to placebo? How long should treatment duration be?	Outcomes: reduction in vertebral, non-vert, hip fractures

NONPHARMACOLOGIC MANAGEMENT

Clinical Question	PICO
8. Among PMW women with osteoporosis, should Calcium and Vitamin D be given as supplement to reduce fragility fracture risk?	Population: Postmenopausal women diagnosed with osteoporosis Intervention: Calcium and Vitamin D supplementation Comparison: No supplementation Main outcomes: Incidence of fragility fracture
9. Among PMW with osteoporosis and fragility fractures, should levels of calcium and vitamin D be within normal before initiation of anti-resorptive therapy?	Population: Post-menopausal women with osteoporosis Intervention: Bisphosphonates and low calcium or Vitamin D levels Comparison: Bisphosphonates and normal calcium and vitamin D levels Main outcomes: Efficacy (vertebral, nonvertebral and hip fractures) and adverse events

SURGICAL MANAGEMENT

Clinical Question	PICO
10. Among patients with previous fragility fractures, what is the effect of pharmacologic intervention on the risk of having a subsequent or second fracture?	Population: Patients with fragility fractures Intervention: Immediate initiation of pharmacologic therapy Comparison: No pharmacologic therapy Outcomes: Subsequent/secondary fractures
11. Among patients with acute displaced fragility fractures of the distal radius, is early surgical intervention superior to conservative management to improve functionality?	Population: adults with displaced fragility fractures of distal radius Intervention: early surgical intervention Comparison: late surgical intervention OR no surgical intervention Outcomes: improved function
12. Among patients who have painful osteoporotic compression fractures of the spine, is kyphoplasty superior to nonsurgical management for controlling pain and improvement of quality of life (QOL)?	Population: Patients with painful osteoporotic compression fractures of the spine Intervention: Kyphoplasty Comparison: Conservative treatment/standard of care Outcomes: Pain control, quality of life and adverse events

13. Among patients who sustained fragility fractures of the hip, is early surgical intervention superior to delayed surgical intervention in improving overall survival, morbidity, mortality, and functionality of patients?	Population: patients with fragility hip fracture Intervention: early surgical intervention Comparison: delayed surgical intervention Outcomes: improvement in survival, morbidity, mortality, and functionality
14. In patients with previous osteoporotic fragility fracture, will enrollment in a secondary fracture prevention program or fracture liaison service (FLS) improve treatment adherence and prevent re-fractures?	Population: Patients with previous osteoporotic fragility fracture Intervention: Secondary fracture prevention program (Fracture Liaison Service) Comparison: No secondary fracture prevention program (Fracture Liaison Service) Outcomes: Adherence to osteoporosis therapy and refracture Setting: Inpatient and outpatient

FOLLOW-UP CARE

Clinical Question	PICO
15. Among adults receiving osteoporosis treatment, what is the appropriate interval between central DXA scans in monitoring treatment response?	Population: adults Intervention: osteoporosis medication Comparator: Outcomes: treatment response
16. Among adults with recent fragility fracture, what factors should be considered when recommending referral to an osteoporosis specialist?	Population: adults with fragility fracture Intervention: referral to specialist Comparison:no referral Outcomes: evaluation and management

PREVENTION (LIFESTYLE AND NUTRITION)

Clinical Question	PICO
17. Among at-risk PMW, should calcium and/or Vitamin D supplementation be given for prevention of osteoporosis and fragility fractures?	Population: at-risk PMW Intervention: calcium and/or vitamin D supplementation Comparison: no calcium/vitamin D supplement Outcomes: osteoporosis and fragility fractures
18. Among PMW, what doses of calcium and Vitamin D are associated with reduced fragility fracture risk?	Population: PMW Intervention: doses of Ca and vitamin D Comparison: no Ca and vitamin D Outcomes: fragility fracture risk reduction

19. Among PMW, what is the benefit of physical activity in the prevention of osteoporosis and fragility fractures?	Population: POMW Intervention: physical activity Comparison: no physical activity Outcomes: prevention of osteoporosis and fragility fractures
20. Among PMW and older men, does smoking cessation prevent osteoporosis and fragility fractures?	Population: PMW and old men Intervention: smoking cessation Comparison: continue smoking Outcomes: prevention of osteoporosis and fragility fractures
21. Among PMW and older men, what diet is effective in the prevention of osteoporosis?	Population: PMW and old men Exposure: diet Outcomes: prevention of osteoporosis

PREVENTION (HORMONE REPLACEMENT THERAPY)

Clinical Question	PICO
22. Should at-risk peri- and postmenopausal women receive menopausal hormone therapy (MHT) for the prevention of fragility fractures? For how long will the duration of use be?	Population: at-risk PMW Intervention: Duration of use of mHT Comparison: none Outcomes: reduction in fracture risk
23. When should MHT be initiated to reduce fracture risk?	Population: at-risk PMW Intervention: timing of MHT Comparator: none Outcomes: fragility fracture reduction
24. Which hormone preparation should be used in PMW for fracture risk reduction?	Population: at-risk PMW Intervention: hormone preparation Comparison: no hormone Outcomes: fracture risk reduction
25. What are the safety issues of MHT in peri-and postmenopausal women?	Population: peri- and postmenopausal women Exposure: MHT Outcomes: safety
26. Should SERMS be given as an alternative to MHT for osteoporosis fracture risk reduction?	Population: at-risk PMW Intervention: SERMs Comparison: no SERMs Outcomes: osteoporosis
27. How are adverse events monitored in women receiving MHT for osteoporosis fracture risk reduction?	Population: at-risk PMW Exposure: MHT Outcomes: adverse events

G. Summary of Guideline Content

A check (✓) indicates discussion of the clinical question in the source guideline												
	1 AACE	**2 AAOS**	**3 AAOS**	**4 African**	**5 ASBMR**	**6 BBC**	**7 LatAm**	**8 NAMS**	**9 RAGCP**	**10 SIGN**	**11 UK NOGG**	**12 USPSTF**
Screening												
Among the adult population, who should be screened for osteoporosis?											✓	
Among the adult population, what factors increase the risk for osteoporosis?											✓	
Among adult population, what tool should be used for osteoporosis screening?												✓
Among adult population, what is the clinical presentation of osteoporosis?											✓	
Diagnosis												
Among at-risk PMW, should bone mineral density measurement using dual energy x-ray absorptiometry be used to diagnose osteoporosis?	✓					✓				✓		✓
Management – Pharmacologic												
Among PMW with osteoporosis, is alendronate, ibandronate, zoledronate, denosumab, raloxifene effective in reducing vertebral, non-vertebral, hip fractures compared to placebo?	✓											
Among PMW with severe osteoporosis, is teriparatide, abaloparatide, and	✓						✓			✓	✓	

romosozumab effective in reducing vertebral, non-vertebral, hip fractures compared to placebo? How long should treatment duration be?												
Management – Non-Pharmacologic												
Among PMW women with osteoporosis, should Calcium and Vitamin D supplement be given to reduce the risk of fragility fractures?				✓	✓	✓					✓	
Among PMW with osteoporosis, should serum calcium and vitamin D levels be normal before initiation of anti-osteoporosis medication?	✓									✓	✓	
Surgical Management												
Among patients with previous fragility fractures, what is the effect of pharmacologic intervention on the risk of having a subsequent or second fracture?										✓		
Among patients with acute displaced fragility fractures of the distal radius, is early surgical intervention superior to conservative management to improve functionality?		✓										
Among patients who have painful osteoporotic compression fractures of the spine, is kyphoplasty superior to nonsurgical management for controlling pain and improvement of quality of life (QOL)?										✓		
Among patients who sustained fragility fractures of the hip, is early surgical intervention superior to delayed surgical intervention in improving overall survival,			✓									

morbidity, mortality, and functionality of patients?												
Among patients with previous osteoporotic fragility fracture, will enrollment in a secondary fracture prevention program or fracture liaison service (FLS) improve treatment adherence and prevent re-fractures?										✓	✓	
Follow-up Care												
Among PMW receiving osteoporosis treatment, what is the appropriate interval between central DXA scans in monitoring treatment response?	✓									✓		
Among patients with recent fragility fracture, should an immediate referral to an osteoporosis specialist be done for better evaluation and management?	✓										✓	
Prevention												
Among at-risk PMW and old men, should calcium and/or Vitamin D supplementation be recommended for prevention of osteoporosis and fragility fractures?									✓		✓	
Among PMW and old men, what doses of calcium and Vitamin D are associated with reduced fragility fracture risk?											✓	✓
Among PMW and old men, what is the benefit of physical activity in the prevention of osteoporosis and fragility fractures?									✓		✓	
Among PMW and old men, does smoking cessation prevent osteoporosis and fragility fractures?									✓	✓	✓	

Among PMW and old men, what diet is effective in the prevention of osteoporosis?									✓	✓	✓	
Prevention - MHT												
Among at-risk postmenopausal women, should menopausal hormone therapy (MHT)be recommended to prevent fragility fractures? For how long will the duration of use be?								✓				
Among at-risk postmenopausal women, when should MHT be initiated to reduce fracture risk?								✓				
Among at-risk postmenopausal women, what hormone preparation should be used for fracture risk reduction?								✓				
Among peri- and postmenopausal women, what are the safety issues of MHT?								✓				
Among at-risk PMW, should SERMS be given as an alternative to MHT for the prevention of osteoporosis?								✓				
Among at-risk PMW on MHT for osteoporosis prevention, what adverse events should be monitored?								✓				

1- AACE 2021, 2 - AAOS distal radial fracture, 3 - AAOS hip fracture, 4. African, 5. ASBMR, 6. Belgian Bone Club, 7. Latin America Federation of Endocrinology, 8. RACGP, 9. SIGN, 10. UK NOGG 2021, 11. USPSTF

H. AGREE II Scores of Source Guidelines

Source Guideline	Scope and Purpose	Stakeholder Involvement	Rigor of Development	Clarity of Presentation	Applicability	Editorial Independence	Overall Assessment
AACE/ACE (2020)	96.53	85.42	87.08	97.22	72.39	93.75	98.61
AAOS (2021) Distal Radius	100	87	93.8	94.4	69.4	69.4	83.3
AAOS (2021) Hip	100	66.7	90.3	94.4	62.5	69.4	83.3
AFRICAN (2021)	98.15	85.19	88.89	94.44	54.17	38.89	78.9
ASBMR (2019)	86.11	72.22	90.63	100	81.25	87.5	88
BBC (2020)	100	77.77	79.17	75	95.83	100	87.9
Latin America (2022)	97.22	80.56	82.29	94.44	89.58	87.5	83.33
NAMS (2022)	94.4	75	85.4	91.7	64.6	87.5	83.1
RACGP (2017)	98.15	94.44	82.29	98.61	76.04	54.17	83
SIGN 142 (2021)	95.83	94.44	88.80	98.61	81.77	95.83	92.55
UK NOGG (2021)	94.44	94.44	83.33	94.44	79.17	91.67	95.83
USPSTF (2018)	95.53	88.89	90.83	86.67	85.83	85	77.78

2023 OSTEOPOROSIS CPG GUIDELINE DEVELOPMENT GROUP

Steering Committee

Chair: Julie Li-Yu, MD (OSPFI)
Co-Chair: Emmanuel C. Perez, MD (PRA)
Members: Monica Therese Cating-Cabral, MD (PCEDM)
Angela G. Sison-Aguilar, MD, (POGS)
Irewin A. Tabu, MD (POA)
Cheridine Oro-Josef, MD (PAFP)

Technical Working Group

Technical Adviser: Noel Espallardo, MD (Epidemiologist/ Family Medicine)
Technical Writers: Angeli Wyson-Wong, MD (Epidemiologist/ Pediatrician)
Irvin Paul G. Parada, MD (General Practitioner)

Evidence Review Experts:

Angela G. Sison-Aguilar, MD (Obstetrician)
Joy Bautista, MD (Obstretrician)
Ma. Eunice M. Co, MD (Rheumatologist)
Seuriane Sean Española, MD (Family Medicine Specialist)
Eizelle Fernandez, MD (Rheumatologist)
Juliet Gabat-Tan, MD (Endocrinologist)
Tricia Guison-Bautista, MD (Family Medicine Specialist)
Lenore Lugue-Lizardo, MD (Rheumatologist)
Ma. Eva Irene Maglonzo, MD (Family Medicine Specialist)
Edmund Martinez, MD (Physiatrist)
Daisy Medina, MD (Endocrinologist)
Queenie Ngalob-Samonte, MD (Endocrinologist)
Nathaniel Orillaza, MD (Orthopedic)
Mary Ruth A. Padua, MD (Orthopedic)
Joseph Patricio, MD (Rheumatologist)
Jonathan Ronquillo, MD (Orthopedic)
Ma. Carrissa Abigail Roxas-Panuda, MD (Endocrinologist)
Hannah Urbanozo-Corpuz, MD (Endocrinologist)

Consensus Panel

Anne Annette Raso, MD (Osteoporosis Society of the Phils Foundation, Inc)
Cheryl dela Cruz-Tan, MD (Philippine Rheumatology Association)
Lora May Tan-Tinhay, MD (Philippine College of Endocrinology, Diabetes, and Metabolism)
Alejandro Pineda Jr, MD (Philippine Academy of Family Physicians)
Louie Gaston, MD (Philippine Orthopedic Association)
Gladys Tanangonan, MD (Philippine Obstetrics and Gynecology Society)
Bee Giok Tan-Sales, MD (Philippine Academy of Rehabilitation Medicine)
Regina P. Barba, MD (Philippine College of Physicians)
Leila Ferrer, MD (Philippine College of Geriatric Medicine)
Ms.Pacita Alano (Department of Health)
Ma. Bernadette Platon, RND (Nutrition Dietetics Association of the Phils)
Charisse D. Banaag, MD (Philippine Health Insurance Corporation)
Maila Cabero, MD – (Philippine College of Radiology)
Marie Rhiamar Sauler-Gomez, MD (Philippine Society of Nuclear Medicine)
Ms. Joselyn T. Li – Patient

External Reviewers

Arvin L. Dalumpines, MD (Internist, Certified Specialist of the Philippine Society of Hypertension)
Nenancia Ranali Nirena Palma-Mendoza, MD (Family Medicine Specialist)
Wenceslao S. Llauderes, MD (Geriatrician, Nuclear Medicine Specialist)

CONFLICT OF INTEREST DECLARATION AND FUNDING AGENCY

The 2023 Philippine Osteoporosis Clinical Practice Guidelines is a self-funded, joint undertaking of the Osteoporosis Society of the Philippines Foundation, Inc. and joined by the Philippine Academy of Family Physicians, Philippine College of Endocrinology, Diabetes and Metabolism, Philippine Orthopedic Association, Philippine Obstetrics and Gynecological Society and Philippine Rheumatology Association

Steering Committee

NAME	AFFILIATION	CONFLICT OF INTEREST
Julie Li-Yu, MD	Osteoporosis Society of the Philippines Foundation, Inc. University of Santo Tomas Hospital Chinese General Hospital and Medical Center	No COI
Angela C. Sison-Aguilar, MD	Philippine Obstetrics and Gynecology Society Philippine General Hospital	No COI
Irewin A. Tabu, MD	Philippine Orthopedic Association Philippine General Hospital	No COI
Emmanuel Perez, MD	Philippine Rheumatology Association De La Salle University Medical Center	No COI
Monica Therese Cating-Cabral, MD	Philippine College of Endocrinology Diabetes and Metabolism St Luke's Medical Center BGC	No COI
Cheridine Oro-Josef, MD	Philippine Academy of Family Physicians Marikina Doctors Hospital and Medical Center	No COI

Technical Working Group

NAME	AFFILIATION	CONFLICT OF INTEREST
Angeli Wyson-Wong, MD	The Medical City Pangasinan	No COI
Irvin Paul G. Parada, MD	Magsaysay Medical Healthcare, Inc. Viacrucis Infirmary	No COI
Ma. Eunice M. Co, MD	Fe del Mundo Medical Center	No COI
Eizelle Fernandez, MD	De La Salle University Medical Center EAC Medical Center-Cavite Gentri Medical Center and Hospital Tanza Specialist Medical Center	No COI
Lenore Lugue-Lizardo, MD	Fatima Medical Center Veterans Memorial Medical Center Rizal Medical Center	No COI
Joseph Patricio, MD	Ilocos Training and Regional Medical Center Lorma Medical Center Bethany Hospital	No COI
Irene Maglonzo, MD	University of Santo Tomas Hospital Qualimed Manila UP-PGH	No COI
Tricia Guison-Bautista, MD	University of Santo Tomas Quirino Memorial Medical Center Rizal Medical Center	No COI

Seuriane Sean Española, MD	Southern Philippines Medical Center	No COI
Queenie Ngalob-Samonte MD	Medical Mission Group - Aklan	No COI
Mary Ruth Padua, MD	University of the Philippines Manila - Philippine General Hospital The Medical City Ortigas Cardinal Santos Medical Center Diliman Doctors Hospital	No COI
Juliet Anne Gabat-Tan, MD	Medical Center Manila	No COI
Nathaniel Orillaza Jr, MD	University of the Philippines Manila - Philippine General Hospital Quirino Memorial Medical Center Cardinal Santos Medical Center	No COI
Ma Carrissa Abigail Roxas-Panuda, MD	Metro Davao Medical and Research Center	No COI
Jonathan Ronquillo, MD	De La Salle University Medical & Health Sciences Institute Asian Hospital and Medical Center Focus Athletics/Medical - Alabang	No COI
Daisy Medina, MD	Batangas Medical Center AMOSUP Seamen's Hospital Manila	No COI
Joy Bautista, MD	Manila Doctors' Hospital Ateneo School of Medicine and Public Health	No COI
Hannah Urbanozo-Corpuz, MD	Lorna Medical Center Ilocos Training and Regional Medical Center	No COI
Edmund Martinez, MD	Hospital of Infant Jesus Manila	No COI

	San Juan de Dios Hospital Philippine Heart Center	

Consensus Panel

Name	Affiliated Society/Stakeholders	Conflict of Interest
Anne Annette Raso, MD	Osteoporosis Society of the Philippines Foundation, Inc.	No COI
Cheryl dela Cruz-Tan, MD	Philippine Rheumatology Association	No COI
Lora May Tinhay, MD	Philippine College of Endocrinology Diabetes and Metabolism	No COI
Alejandro Pineda, Jr, MD	Philippine Academy of Family Physicians	No COI
Louie Gaston, MD	Philippine Orthopedics Association	No COI
Gladys Tanangonan, MD	Philippine Obstetrics and Gynecological Society	No COI
Bee Giok Tan-Sales, MD	Philippine Academy of Rehabilitation Medicine	No COI
Regina Barba, MD	Philippine College of Physicians	No COI
Leila Ferrer, MD	Philippine College of Geriatric Medicine	No COI
Maila Cabero, MD	Philippine College of Radiology	No COI
Marie Rhiamar Sauler-Gomez, MD	Philippine Society of Nuclear Medicine	No COI
Ms. Pacita Alano	Department of Health	No COI

Ma. Bernadette Platon, RND	Nutrition Dietetics Association of the Phils	No COI
Charisse D. Banaag, MD	Philippine Health Insurance Corporation	No COI
Ms. Joselyn T. Li	Patient Representative	No COI

External Reviewers

Name	**Affiliated Society/Stakeholders**	**Conflict of Interest**
Arvin L. Dalumpines, MD	University of Santo Tomas	No COI
Nenancia Ranali Nirena Palma-Mendoza, MD	Pamantasan ng Lungsod ng Muntinlupa-Ospital ng Muntinlupa	No COI
Wenceslao S. Llauderes, MD	Jose Reyes Memorial Medical Center	No COI

EXTERNAL REVIEW

External Reviewer: Arvin L. Dalumpines, MD, FPCP, CSPH

The 2023 CPG on Osteoporosis presents to us a good local reference on the screening, diagnosis, management, and prevention of osteoporosis. As an end-user being a practicing Internist, it has highlighted the most important questions that we can encounter in our day-to-day practice. Looking from the perspective of a primary care provider, the working body can also reconsider several specific points:

1. A concise summary in the form of several flow charts or algorithms for decision-making (one for screening, one for diagnosis, one for prevention, etc.) can be included in the appendix, which will serve as a quick reference tool in the clinics.

2. In the publication of the CPG, the group can format the guideline to show “essential” (the minimum applicable standard of care) and “optimal” (the best ideal choice if and when the resources are available) to simplify and ensure accessibility to the different recommendations to be applied by the clinicians whether they are practicing in NCR or in smaller hospitals in the provinces. This was the format used in the latest guidelines by the International Society of Hypertension to be accessible to different levels of practice.

3. In line with the title “...CPG on Screening, Diagnosis, Management, and Prevention...” it would be better to reorganize the clinical questions in that same sequence to give a better flow of discussion, i.e., how to diagnose osteoporosis once the screening shows a high-risk patient.

4. In the recommendation to answer Clinical Question # 4 referring to “clinical presentation of osteoporosis”, should smoking and alcohol consumption be deleted since these are actually risk factors that were already included in the answer to Clinical Question #2?

5. In the recommendation to answer Clinical Question # 8 regarding smoking cessation, a cross-reference or citation regarding local CPG on smoking cessation can be included so the reader can easily access and utilize it.

6. In the recommendation to answer Clinical Question # 5, it is good to emphasize the possible hazards or adverse effects of calcium and vitamin D supplements.

7. In the recommendation to answer Clinical Question # 9 regarding diet, a specific list or table of food and food products can be included so that clinicians can advise what these specific food or food products are.

8. In the second recommendation to answer Clinical Question # 10, can the specific risks be listed in the same sentence?

9. In the recommendation to answer Question # 11, “Among women younger than 60 years...”, it would be better to particularly state again “peri- and PMW” so as not to cause confusion that all women <60 years old will benefit from MHT.

10. In the recommendation to answer Clinical Question # 13 “What are the safety issues of MHT...”, a first statement to directly answer the question is more appropriate, followed by a second

recommendation statement on using transdermal estrogen to reduce VTE risk.

11.Clinical Question #16 and its recommendations (on Diagnosis) are better placed immediately after the section on Prevention. It is noteworthy to read the 4th recommendation, especially for physicians in areas wherein DXA is not readily available.

12.In relation to the recommendation presented for Clinical Question # 18, can the recommendation statement itself already include the WHO classification and the AACE criteria? Or is it better to be included in the statement of the recommendation for Clinical Question # 16 regarding Diagnosis instead?

13.Since it is uncommon for us to have access and coordination with specialists in the field of Osteoporosis, the OSPFI can publish an accessible list of their specialists (including clinic address, e-mail, or contact numbers) to whom primary care physicians or other specialists can refer their patients for further evaluation and management.

14.In the recommendation to answer Clinical Question # 20, is there a recommendation regarding the frequency of monitoring serum Vitamin D and Calcium levels?

15.With regard to the recommendations on surgical interventions, what would be the recommendation if the patient is a poor surgical candidate (i.e., very high cardiac risk patient)?

16.In relation to Question 26, what would be our option for follow-up among patients receiving osteoporosis treatment if DXA is unavailable?

Overall, the comprehensive guideline is well-detailed and addresses common clinical questions that a clinician may encounter when dealing with osteoporosis prevention, screening, and treatment. Several issues were addressed and discussed. Recommendations were backed by evidence from updated clinical studies. This is truly an invaluable reference in our practice as primary care physicians or internists, especially in line with the government and the Department of Health's transition to Universal Health Care.

External Reviewer: Nenacia Ranali Nirena P. Mendoza, MD, FPAFP

Congratulations to the CPG team for the fruit of all the hard work placed into drafting this CPG. Thank you for this opportunity to review the CPG manuscript.

Here are my comments/recommendations for your consideration:

A. Panel considerations
Please consider rewriting/modifying the panel considerations for each CPG question, to reflect NOT so much the proceedings of the panel meetings, but rather the relevant issues or considerations raised by the panelists which could affect the interpretation/implementation of the recommendations.

Sharing here sample consensus issues (panel considerations) from the COVID-19 Living CPG

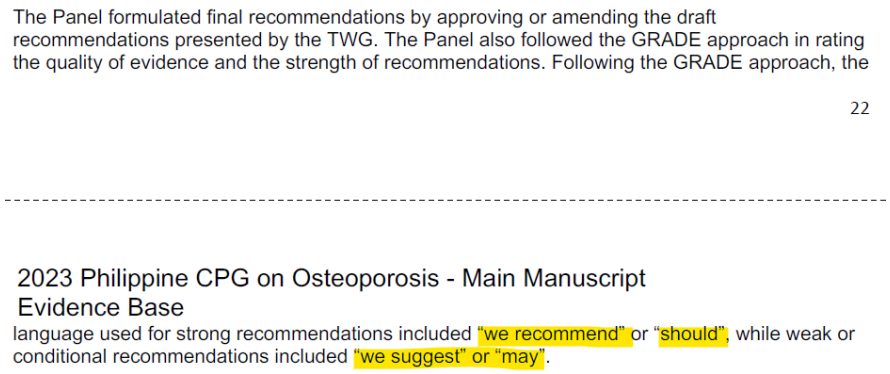
Recommendations	Certainty of Evidence	Strength of Recommendation
We suggest the use of molnupiravir within 5 days of symptom onset in adult patients with COVID-19 infection who are non-oxygen requiring and with at least one risk factor* for progression. *Risk factors for progression include: age >60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, serious heart conditions, or diabetes mellitus	Very low	Weak
We suggest against the use of molnupiravir among children with COVID-19.	Very low	Weak

Consensus Issues
Molnupiravir showed no significant benefit on critical outcomes (all-cause mortality, clinical improvement, need for hospitalization, and serious adverse events). Although there is evidence of benefit on the subgroup analysis of the need for hospitalization on unvaccinated participants, the panel took into consideration that the study on vaccination may not be reflective of the vaccination status in our country since 90% of the participants in the study are vaccinated with three doses. Another consideration is the duration of the last dose of vaccination since immunity may wane depending on the time it was given. The panel also noted that there is benefit on subgroup analysis on all-cause mortality among the mild to moderate non-hospitalized patients. However, because of the current definition of moderate COVID-19 in our guideline, the panel emphasized that the studies only included the non-oxygen requiring participants, hence specifying it as part of the recommendation to avoid confusion.

Children are a vulnerable population since there is no evidence for the use of molnupiravir and there is still no FDA recommendation for the use of molnupiravir in children with COVID-19, suggesting against the use of molnupiravir will be beneficial for children.

B. Statement of Recommendations

1. Consider using the same format for statement of recommendations for all questions, as stated in your methodology


The Panel formulated final recommendations by approving or amending the draft recommendations presented by the TWG. The Panel also followed the GRADE approach in rating the quality of evidence and the strength of recommendations. Following the GRADE approach, the

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language used for strong recommendations included "we recommend" or "should", while weak or conditional recommendations included "we suggest" or "may".

Recommendations for questions 2 and 4 may be revised as follows:
For question 2: We recommend screening for the following risk factors:….
For question 4: Patients who present with the following ……. should be suspected (or a better term) to have osteoporosis

2. Please clarify the population of the recommendation for question 6.
Are these ALL PMW and older men, regardless of risk status and FRAX or BMD scores? If so, this is not congruent with recommendation for question 5, which offers supplementation only to those who are at risk and do not meet country-specific standards

3. For recommendation 2 under question 15, consider including the recommended frequency for dong TVS

4. For question no. 11, consider adding qualifiers for the population… As it is stated, any woman younger than 60 (teens, young adults in 20s and 30s) can be given MHT

5. For question no. 13, include the population in the actual recommendation

C. Executive Summary
Consider adding a note on the implication/explanation of the certainty of evidence and strength of recommendations… Some readers do not go beyond the executive summary

D. Recommended tools and tests
Consider including footnotes in the manuscript directing the reader/end user to website/material where they can get information on how to administer/interpret tools/tests recommended in the CPG, eg FRAX, BMD, etc.

Alternatively, a separate section with instructions how to use these tools can be included in the supplementary appendix

E. Format

Please improve formatting to make it uniform across the document, there are sections with different font, spacing and alignment (left aligned or justified)

Panel Considerations

After initial panel discussion, it was suggested that changes be made in the recommendations. It was suggested that all post-menopausal women be included and mentioned first. This is because osteoporosis is more common in women. The line “All postmenopausal women” captures both natural and surgical menopause. Data from a study in Taiwan, which is nearest to the Philippines, shows that men >50 years old are included in osteoporosis screening. Hence, men >/= 50 years old should be also included. The line “adults with clinical risk factors” capture the following: women and men with personal history of fractures, parental history of hip fractures, low body mass index, inflammatory arthritis, medications that affect bone health, alcoholism, current smokers, etc.

Summary of Evidence

The following recommendations were based from the UK clinical guideline for the prevention and treatment of osteoporosis (UK NOGG 2022) and the development of the Asia Pacific Consortium on Osteoporosis (APCO) Framework: clinical standards of care for the screening, diagnosis, and management of osteoporosis in the Asia-Pacific region.[1,2]

Both guidelines recommended screening men age ≥ 50 and postmenopausal women with fragility fracture. The guidelines suggest health evaluation for those with clinical risk factors, specifically FRAX assessment and BMD measurement with timely referral and drug treatment if indicated.

UK NOGG 2022 recommends, as part of screening, vertebral fracture assessment for postmenopausal women or men age ≥ 50 years old with the following characteristics: history of ≥ 4 cm height loss, kyphosis, recent or current long-term oral glucocorticoid therapy, a BMD T-score ≤ − 2.5 at either the spine or hip, or in cases of acute onset back pain with risk factors for osteoporosis.[1]

APCO recommends bone health assessment to individuals with hip fractures, clinical or morphometric vertebral fractures and non-hip, non-vertebral major fractures. Two guidelines proposed bone health assessment and Identification of fall risks to patients taking drugs associated with bone loss and/or with increase fracture risk and/or with conditions associated with bone loss.[2]

External Reviewer: Wenceslao Llauderes, MD

Department of Health designated Jose R. Reyes Memorial Medical Center as the National Specialty Center for Geriatric Health.

This responsibility has an important role in the implementation of Universal Health Care especially addressing the urgent needs of elderly patients across the country. This National leadership designation in Geriatric health will address the morbidity and mortality of geriatric cases and ensuring proper coordination across facilities for delivery of quality services across the continuum of care.

It was stated in the recent Global Burden of Disease Study that majority of the fractures occurred in the older population particularly attributed to osteoporotic fractures.
Hence, as mandated in the general expectations for being a National Specialty Center, the following services should be provided as follows:

End referral of service network for Geriatric Center with Multi - disciplinary training: has the highest level of clinical services, fellowship program, training for geriatricians and gerontologist, and research, training of geriatric nurse/s and CGA for geriatric nurse, social worker, midwifery and other allied health personnel at the same provides necessary capacity building training to hospitals/facilities with Advanced Comprehensive and Basic Geriatric Health Services.

This Clinical Practice Guidelines on screening, diagnosis and management of osteoporosis will be definitely of importance in rolling out our mandate to provide quality and comprehensive care among our elderly patients.