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Original Article

Asia—pacific consensus on osteoporotic fracture prevention in postmenopausal women with low bone mass or osteoporosis but no fragility fractures

Chun-Feng Huang [a,b,c], Jung-Fu Chen [d], Ian R. Reid [e], Wing P. Chan [f,g], Peter Robert Ebeling [h], Bente Langdahl [i], Shih-Te Tu [j], Toshio Matsumoto [k], Ding-Cheng Chan [l,m], Yoon-Sok Chung [n], Fang-Ping Chen [o], E Michael Lewiecki [p], Keh-Sung Tsai [q], Rong-Sen Yang [r], Seng Bin Ang [s], Ko-En Huang [t], Yin-Fan Chang [u], Chung-Hwan Chen [v,w,x], Joon-Kiong Lee [y], Hsin-I Ma [z], Weibo Xia [aa], Ambrish Mithal [ab], David L. Kendler [ac], Cyrus Cooper [ad], Jawl-Shan Hwang [ae,**], Chih-Hsing Wu [u,af,ag,*]

[a] *Division of Family Medicine, En Chu Kong Hospital, New Taipei City, Taiwan*
[b] *Faculty of Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan*
[c] *Department of Leisure Services Management, Chaoyang University of Technology, Taichung, Taiwan*
[d] *Division of Metabolism and Endocrinology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan*
[e] *Department of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand*
[f] *Department of Radiology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*
[g] *Department of Radiology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan*
[h] *Department of Medicine, School of Clinical Sciences, Monash University, Clayton, Victoria, Australia*
[i] *Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark*
[j] *Division of Endocrinology and Metabolism, Department of Internal Medicine, Changhua Christian Hospital, Changhua, Taiwan*
[k] *Fujii Memorial Institute of Medical Sciences, Tokushima University, Tokushima, Japan*
[l] *Department of Geriatrics and Gerontology, National Taiwan University Hospital, Taipei, Taiwan*
[m] *Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*
[n] *Department of Endocrinology and Metabolism, Ajou University School of Medicine, Suwon, South Korea*
[o] *Keelung Osteoporosis Prevention and Treatment Center, Chang Gung Memorial Hospital, Keelung, Taiwan*

* Corresponding author. Institute of Gerontology, College of Medicine, National Cheng Kung University, Tainan, Taiwan.
** Co-corresponding author.

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[p] New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM, USA
[q] Superintendent Office, Far Eastern Polyclinic of Far Eastern Medical Foundation, Taipei, Taiwan
[r] Department of Orthopaedics, National Taiwan University Hospital, Taipei, Taiwan
[s] Menopause Unit and Family Medicine Service, KK Women's and Children's Hospital, Singapore, Singapore
[t] Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan
[u] Department of Family Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[v] Orthopaedic Research Center and Department of Orthopedics, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
[w] Regeneration Medicine and Cell Therapy Research Center and Musculoskeletal Regeneration Research Center, Kaohsiung Medical University, Kaohsiung, Taiwan
[x] Department of Orthopedics, Kaohsiung Municipal Ta-Tung Hospital and Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
[y] Beacon Hospital, Petaling Jaya, Selangor, Malaysia
[z] Department of Neurological Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
[aa] Department of Endocrinology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China
[ab] Division of Endocrinology and Diabetes, Medanta the Medicity, Gurgaon, Haryana, India
[ac] Department of Medicine (Endocrinology), University of British Columbia, Vancouver, British Columbia, Canada
[ad] Oxford National Institute for Health Biomedical Research Centre, University of Oxford, Windmill Road, Oxford, United Kingdom
[ae] Division of Endocrinology and Metabolism, Department of Internal Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan
[af] Department of Family Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[ag] Institute of Gerontology, College of Medicine, National Cheng Kung University, Tainan, Taiwan

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Postmenopausal women are at significant risk for osteoporotic fractures due to their rapid bone loss. Half of all postmenopausal women will get an osteoporosis-related fracture over their lifetime, with 25% developing a spine deformity and 15% developing a hip fracture. By 2050, more than half of all osteoporotic fractures will occur in Asia, with postmenopausal women being the most susceptible. Early management can halt or even reverse the progression of osteoporosis. Consequently, on October 31, 2020, the Taiwanese Osteoporosis Association hosted the Asia—Pacific (AP) Postmenopausal Osteoporotic Fracture Prevention (POFP) consensus meeting, which was supported by the Asian Federation of Osteoporosis Societies (AFOS) and the Asia Pacific Osteoporosis Foundation (APOF). International and domestic experts developed ten applicable statements for the prevention of osteoporotic fractures in postmenopausal women with low bone mass or osteoporosis but no fragility fractures in the AP region. The experts advocated, for example, that postmenopausal women with a high fracture risk be reimbursed for pharmaceutical therapy to prevent osteoporotic fractures. More clinical experience and data are required to modify intervention tactics.

Introduction

The world's population is rapidly aging, which is increasingly recognized as a significant public health burden, especially in the Asia—Pacific (AP) region due to its substantial population base.[1] The World Health Organization (WHO) anticipated in 2004 that osteoporosis would cause nearly 9 million fractures worldwide, with 2.5 million and 1.6 million occurring in the Western Pacific and Southeast Asian regions, respectively.[2] By 2050, Asia is expected to account for half of all hip fractures worldwide.[3] The annual number of hip fractures is anticipated to increase 2.28-fold

from 1.12 million in 2018 to 2.56 million in 2050.[3] As a result, the threat of bone health hazards in the AP region will expand in the following decades, necessitating the development of optimum diagnostic and monitoring measures to limit this risk.

Osteoporotic fractures (also known as fragility fractures) are prevalent causes of disability and death in the elderly, as well as significant contributors to medical care expenses.[3,4] Hip fractures have grown by 2–3 times in most Asian countries over the previous three decades.[3,5] Consequently, preventing osteoporotic fractures is crucial for both clinical and public health. In the AP region, osteoporosis is significantly underdiagnosed and undertreated, even in high-risk patients with fragility fractures.[5–7] Osteoporosis and osteopenia (low bone mass) are defined by a bone mineral density (BMD) T-score measured by dual-energy X-ray absorptiometry (DXA) (specifically, a BMD T-score at or below −2.5 indicates the former, and a T-score between −1.0 and −2.5 indicates the latter), but BMD is only one of several important risk factors for fragility fractures.[4,8] People with osteopenia are responsible for the vast majority of fragility fractures.[9] Women who have previously fractured due to fragility are more likely to fracture again.[10] Osteoporotic fractures can cause kyphosis, prolonged discomfort, a loss of self-esteem, an increased risk of death, a dependent living situation, and a poor quality of life.[11] As a result, the importance of osteoporotic fracture prevention in postmenopausal women cannot be emphasized more.

To draw attention to the prevention of osteoporotic fractures in postmenopausal women with low bone mass or osteoporosis but no fragility fractures, and to establish a consistent intervention method, the Taiwanese Osteoporosis Association (TOA) hosted a "Postmenopausal Osteoporotic Fracture Prevention (POFP) in Asia–Pacific" meeting in Taipei on October 31, 2020, with experts from the AP region to review the standard strategies for preventing osteoporotic fractures. The meeting was endorsed by the Asian Federation of Osteoporosis Societies (AFOS) and the Asia Pacific Osteoporosis Foundation (APOF). The conclusion of this meeting is reported in the manuscript.

Methods

To establish consensus recommendations, osteoporosis specialists from the countries of the AP region (Australia: Peter Robert Ebeling; Canada:David L Kendler; China: Weibo Xia; Denmark: Bente Langdahl; India: Ambrish Mithal; Japan: Toshio Matsumoto; Malaysia: Joon-Kiong Lee; Singapore: Seng Bin Ang; South Korea: Yoon-Sok Chung; Taiwan: Wing P. Chan, Jawl-Shan Hwang, Chih-Hsing Wu, Keh-Sung Tsai, Chun-Feng Huang, Ding-Cheng Chan, Fang-Ping Chen, Jung-Fu Chen, Shih-Te Tu, Ko-En Huang, Yin-Fan Chang, Hsin-I Ma, Chung-Hwan Chen and Rong-Sen Yang; United Kingdom: Cyrus Cooper; United States: E Michael Lewiecki, and New Zealand: Ian R Reid) were invited to achieve an agreement through review and revise the statements given before and during the meeting. All panelists took part in a preview to formulate recommendation statements. The panel examined the most recent data on the osteoporotic fracture prevention approach for postmenopausal women. Finally, the experts debated each assertion in depth before reaching a consensus through agreement.

Results

Experts on the POFP committee agreed that, due to the rapidly aging population in the AP region, the demand for osteoporosis fracture prevention, particularly among postmenopausal women with low bone mass or osteoporosis but no fragility fractures, is increasing significantly. As a result, it is promising that nations in the AP area are presently actively formulating the fracture prevention intervention guideline. Furthermore, the AP specialists agreed that enhancing osteoporosis screening and treatment was generally necessary for the AP region, but those specific modifications were required to improve their fitness for the area. The following recommendations were made.

Statement 1. *Postmenopausal women without a history of fragility fractures who are at high risk for fractures may use pharmacological therapy for the prevention of fractures.*

- The experts recommended the use of pharmaceutical regimens for the prevention of osteoporotic fracture in postmenopausal women with an increased risk of fracture, low bone mass, or osteoporosis, but no history of fragility fracture.
- The majority of patients presenting with fractures have BMD within the osteopenic range, as the osteopenic population is numerically greater than the osteoporotic population. Although an osteopenic T-score does not necessarily indicate the need for treatment, a high risk for future fractures as determined by risk calculators (e.g. FRAX) may indicate the necessity for osteoporosis treatment.

Statement 2. *For the prevention of fragility fractures in postmenopausal women, raloxifene, alendronate, and risedronate are well-recognized options.*

- The experts agreed that raloxifene, alendronate, and risedronate will prevent osteoporotic fractures in postmenopausal women with low bone mass or osteoporosis.

Statement 3. *In postmenopausal women with low bone mass or osteoporosis, zoledronic acid is effective in the prevention of fragility fractures.*

- The experts concluded that zoledronic acid could be used for the prevention of fractures in postmenopausal women with low bone mass (osteopenia) or osteoporosis who have not experienced a fragility fracture in the past.

Statement 4. *Denosumab and Romosozumab can be considered for postmenopausal women who have a high fracture risk but have not previously suffered from fragility fractures.*

- The experts agreed that denosumab and romosozumab are options for postmenopausal women with

osteoporosis who are at high or very high risk of fracture but have never had a fragility fracture, especially if they are intolerant to bisphosphonates.

Statement 5. *Menopausal hormone therapy (MHT) is* supported *by substantial data for the prevention of fragility fractures, however, it should be utilized with caution in clinical practice.*

- The experts concluded that MHT may be used for fracture prevention in postmenopausal women with osteopenia or osteoporosis, with a careful balancing of benefits and hazards.

Statement 6. *Ibandronate, tibolone, bazedoxifene, lasofoxifene, teriparatide, and abaloparatide have limited evidence for prevention of fragility fractures in postmenopausal women with low bone mass or osteoporosis but no fragility fractures.*

- The experts concurred that the evidence for ibandronate, tibolone, bazedoxifene, lasofoxifene, teriparatide, and abaloparatide for the prevention of fragility fractures in postmenopausal women is limited.
- Teriparatide and abaloparatide show more convincing evidence of efficacy than ibandronate, tibolone, bazedoxifene, and lasofoxifene.

Statement 7. *The evaluation of efficacy in the prevention of fragility fractures can be determined by the changes in bone turnover markers, BMD, radiography, and clinical fracture.*

- Experts agreed that changes in bone turnover markers, BMD, and the absence of subclinical or clinical fractures can be utilized to assess the efficiency of osteoporosis fracture prevention.

Statement 8. *In individuals at high fracture risk, pharmacological therapies for prevention of osteoporotic fractures should be reimbursed.*

- Experts agreed that changes in bone turnover markers, BMD, and the absence of subclinical or clinical fractures can be utilized to assess the efficiency of osteoporosis fracture prevention.
- The AP area has differing reimbursement limits for various pharmaceuticals, which are determined by factors such as the country's finances, aging population, prescription costs, and fracture surgery expenses, all of which influence cost-effectiveness and policy design.[12,13]

Statement 9. *Long-term treatment options, safety, efficacy, budget impact, ethnic differences, and pharmaceutical comparisons for prevention of osteoporotic fracture require additional investigation.*

- Experts agreed that more research is needed into long-term treatment strategies, safety, efficacy, financial impact, ethnic disparities, and pharmacological comparisons for the prevention of osteoporotic fractures.

Statement 10. *Nonpharmacological management strategies are essential and should be used in combination with pharmacological treatments.*

- Experts agreed that nonpharmacological management strategies such as calcium and vitamin D supplementation, weight-bearing exercise, muscle strengthening, and fall prevention are critical and should be used in conjunction with pharmaceutical therapies.
- However, there are unmet needs in the evaluation of nonpharmacological and pharmacological treatment for fracture prevention, such as long-term safety and efficacy, cost-effectiveness, ethnic impacts, and stratification studies.

Fig. 1 depicts a flow chart of fracture risk assessment, intervention, and efficiency evaluation in postmenopausal women, as concluded by the POFP consensus meeting.

Discussion

The most common type of osteoporosis, postmenopausal osteoporosis, affects a significant number of postmenopausal women and worsens with age.[10] As women's life expectancy in the AP region rises, so will the number of women at risk for osteoporotic fractures during the next few decades.[3] It emphasizes the need for osteoporotic fracture prevention in postmenopausal women. Following discussions at this expert consensus meeting, we developed recommendations and statements for the prevention of osteoporotic fractures in AP postmenopausal women, especially those with low bone mass or osteoporosis but no fragility fracture.

There is currently no universal agreement on who should begin pharmacological osteoporosis treatment and when.[14] As a result, several national guidelines recommend that postmenopausal women who have previously experienced a fragility fracture be evaluated for pharmacological therapy, as these occurrences are linked to an increased risk of repeat fractures.[15] Furthermore, the FRAX fracture risk assessment tool has added the "high" or "very high" fracture risk category and suggested that antiosteoporosis medications be offered to these individuals.[16,17] So, in postmenopausal women who have not previously fractured, the intervention threshold might be set at the FRAX-based age-specific fracture probability corresponding to a person (of the same age) who has previously fractured.[18,19] Interventions solely based on BMD T-scores have been demonstrated to be ineffective because fracture risk varies widely among regions and ethnicities, even at the same T-score.[20,21] Furthermore, the T-score for fracture risk is strongly related to age.[22] As a result, the POFP consensus meeting examined the various indications for pharmaceutical osteoporosis treatment in postmenopausal women.

Bisphosphonates (such as alendronate, risedronate, ibandronate, and zoledronate) have been the cornerstone of osteoporosis treatment for the past three decades.[23] Alendronate treatment was associated with a nearly 50% reduction in new vertebral fractures, a reduction in the progression of vertebral abnormalities, and a reduction in

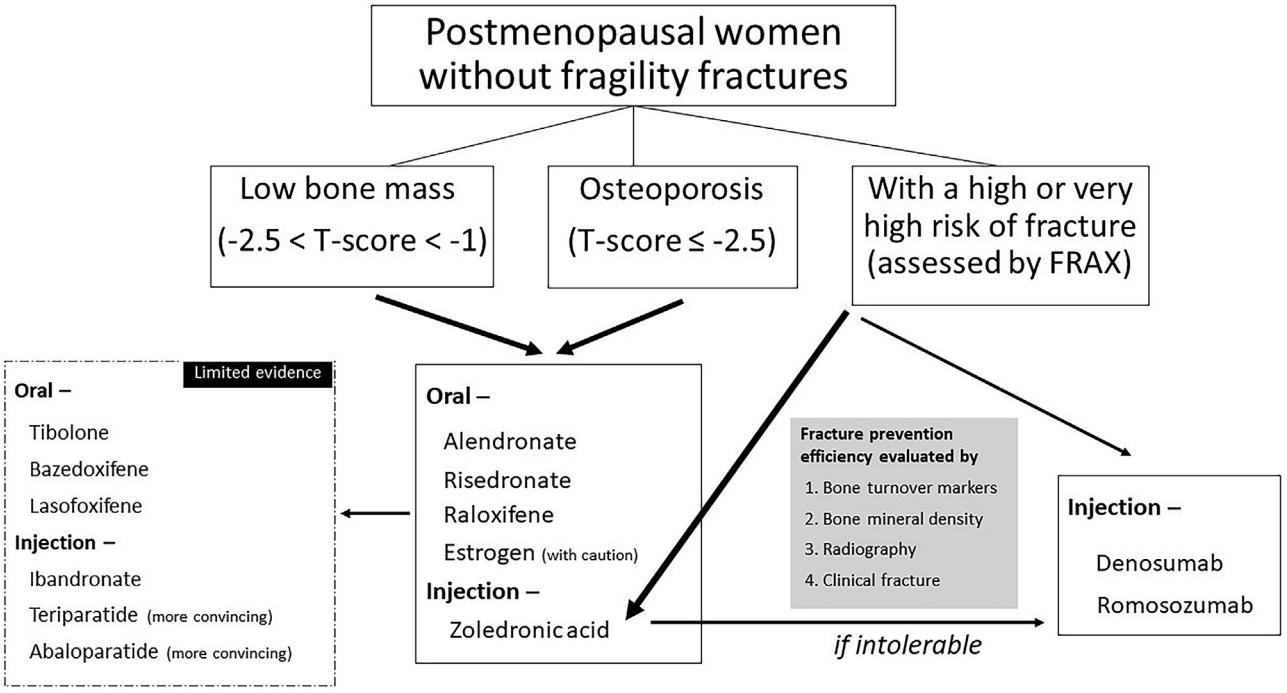

Figure 1 The Asia—Pacific POFP consensus meeting concluded with a flowchart of risk assessment, intervention, and efficacy evaluation for postmenopausal women without fragility fractures. POFP: Postmenopausal Osteoporotic Fracture Prevention.

height loss.[24] The relative risk of new radiographic (morphometric) vertebral fractures, clinical vertebral fractures, hip fractures, and wrist fractures was reduced by about 50% in a study of postmenopausal women with at least one previous vertebral fracture.[25] Furthermore, women who did not have prevalent vertebral fractures but had a baseline hip BMD T-score of −2.5 or below had a substantial reduction in clinical fractures.[26] Risedronate was found to reduce the incidence of vertebral and nonvertebral fractures in postmenopausal women with prevalent vertebral fractures by 40—50% and 30—36%, respectively.[27] The relative risk reduction for hip fracture was 30% for all women allocated risedronate and 40% for those with osteoporosis aged 70—79 years.[27] According to pooled data from studies looking at the long-term efficacy of ibandronate, dosages corresponding to the annual total exposure of 10.8 mg (containing 150 mg oral monthly and 3 mg quarterly i. v.) significantly reduced the risk of nonvertebral fractures.[28] However, there is no direct evidence of intravenous ibandronate's anti-nonvertebral fracture efficacy from RCTs with fracture as the primary endpoint. Zoledronate, administered intravenously at a dose of 5 mg every 18 months, has been shown to significantly reduce both vertebral (RR 0.46) and nonvertebral fracture risk (HR 0.66) for primary prevention of postmenopausal osteoporosis and will help improve primary prevention management of postmenopausal osteoporosis due to its superior anti-fracture efficacy and good safety.[29] Zoledronate is the only drug with different doses for low bone mass and osteoporosis (5 mg every 18 months vs. 5 mg every 12 months) in the prevention of osteoporotic fractures.

Denosumab decreases bone resorption by binding to the receptor activator of nuclear factor-κB ligand (RANKL) and blocking the interaction between RANKL and its receptor RANK.[30] In postmenopausal women with osteoporosis, denosumab significantly reduced the risk of new radiographic vertebral fractures (RRR 68%), hip fractures (RRR 40%), and nonvertebral fractures (RRR 20%).[31] Romosozumab has been shown to have a dual effect on bone formation based on sclerostin inhibition, resulting in increased bone formation and decreased bone resorption.[32] When romosozumab was compared to placebo in postmenopausal women with a T-score between −2.5 and −3.5 at the total hip or femoral neck, the rapid and significant increases in BMD were associated with a lower risk of new vertebral and clinical fractures at 12 months.[33] Teriparatide's bone-forming impact is mediated by osteoblast activation, which results in new bone tissue and thus increases in bone mass and bone strength.[34] Teriparatide was studied in a pivotal randomized controlled trial in postmenopausal women with severe osteoporosis, and the results revealed a significant reduction in vertebral fractures (RRR 65%), moderate/severe vertebral fractures (RRR 90%), multiple vertebral fractures (RRR 77%), and nonvertebral fractures (RRR 35%).[35]

Women who received MHT for two to three years had a 52% lower incidence of osteoporotic fractures even after therapy was stopped.[36] Women using oral estrogen and medroxyprogesterone acetate, on the other hand, had a higher risk of venous thromboembolism.[37] Except for vaginal estrogens, all MHT types were likely related to higher breast cancer risks, which grew steadily with the duration of use and were greater for estrogen-progestogen preparations than for estrogen-only preparations.[38] Selective estrogen receptor modulators, such as raloxifene, function similarly to estrogens on bone tissue in that they

bind to skeletal estrogen receptors, hence decreasing bone resorption by preventing the release of RANKL.[39] In addition, they act as estrogen antagonists on breast tissue, which has been associated with a reduced risk of breast cancer in postmenopausal women with osteoporosis. Raloxifene reduces not only the risk of vertebral fractures but also the risk of nonvertebral fractures significantly.[39] Finally, to reduce the risk of fracture, a treatment strategy that includes both nonpharmacologic, such as calcium and vitamin D supplements, weight-bearing exercise, muscle strengthening, and fall prevention, and pharmacologic therapy should be followed.[40]

Conclusion

In the AP region, there is still a significant intervention gap for the prevention of osteoporotic fractures in postmenopausal women with low bone density or osteoporosis but no fragility fractures. Following a thorough examination and debate, the POFP experts agreed that the ten consensus statements are appropriate in the AP region and that additional effort is required to promote effective strategies to prevent fractures. More clinical experience and data are needed to provide feedback for future improvements in osteoporotic fracture prevention.

Declaration of competing interest

Chih-Hsing Wu received honoraria for lectures, attending meetings, and/or travel from Eli Lilly, Roche, Amgen, Merck, Servier laboratories, GE Lunar, Harvester, TCM Biotech, and Alvogen/Lotus.
E Michael Lewiecki is an investigator, consultant, and speaker for Amgen, and an investigator for Radius.

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