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Management of Osteoporosis Medication after Osteoporotic Fracture

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The aim of this study was to provide helpful information for use in selection of an appropriate medication after osteoporotic fractures through conduct of a literature review. In addition, a review of the recommendations of several societies for prevention of subsequent fractures was performed and the appropriate choice of medication for treatment of atypical femur fractures was examined. Clinical perspective was obtained and an updated search of literature was conducted across PubMed and MEDLINE and relevant articles were selected. The articles were selected manually according to relevance, and the references for identified articles and reviews were also evaluated for relevance. The following areas are reviewed: Commonly prescribed osteoporosis medications: BPs (bisphosphonates), denosumab, and SERMs (selective estrogen receptor modulators) in antiresorptive medications and recombinant human parathyroid hormone teriparatide, recently approved Romosuzumab in anabolic agents, clinical practice guidelines for the management of osteoporosis, osteoporotic fracture, and atypical femur fracture. Most medications for treatment of osteoporosis do not delay fracture healing and the positive effect of teriparatide on fracture healing has been confirmed. In cases where an osteoporotic fracture is diagnosed, risk assessment should be performed for selection of very high-risk patients in order to prevent subsequent fractures, and administration of anabolic agents is recommended.

Key Words: Osteoporotic fracture, Medication review, Clinical practice guideline

INTRODUCTION

The incidence of osteoporotic fractures is increasing yearly due to the increase in life expectancy and the resulting aging population. Global life expectancy increased by more than six years between 2000 and 2019–from 66.8 years in 2000 to 73.4 years in 2019, and this trend is expected to continue in the coming decades[1]. Hip fracture is a major osteoporotic fracture; 1.66 million cases were reported in 1990, which will increase to 6.26 million by 2050, and 51.1% of hip fractures worldwide are expected to occur in Asians[2]. The resulting socioeconomic cost is also expected to show a steep increase.

Fractures caused by osteoporosis are associated with an increased risk of further fractures and complications.

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Several studies have demonstrated that a history of fractures is a major risk factor for future fractures, and the relative risk of subsequent fractures is increased by 2.1 times during the entire follow-up period in patients with a history of fractures compared to the risk in patients without a history of fractures[3]. The relative risk is highest in the first year after the first fracture, and a remarkable increase during a 15-year follow-up period was reported[4]. Therefore, evaluation of osteoporosis and fracture risk is essential in patients with a history of fractures[3]. Nevertheless, according to findings reported from several research studies, measures to prevent further fractures are implemented in less than 20% of patients with fragility fractures, indicating that patients are not provided adequate evaluation and treatment[5]. Therefore, treatment for fracture healing along with medications for prevention of secondary fractures is necessary and should be started as soon as possible in patients with osteoporotic fractures.

A review of literature on the effects of osteoporosis medication on healing of fractures was conducted. In addition, a review of the recommendations of several societies for prevention of subsequent fractures was conducted and the appropriate choice of medication for treatment of atypical femur fractures (AFFs) was examined.

MATERIALS AND METHODS

In this study, the medications prescribed most often for treatment of osteoporosis, bisphosphonates (BPs), denosumab, and selective estrogen receptor modulators (SERMs) in antiresorptive medications and recombinant human parathyroid hormone (PTH) teriparatide, and recently approved Romosuzumab in anabolic agents, as well as clinical practice guidelines for management of osteoporosis, osteoporotic fracture, and AFF were reviewed. A primary search was conducted across PubMed and MEDLINE and relevant articles were selected without limitation according to publication date. Secondary selection of the articles was performed manually according to relevance, and the references for identified articles and reviews were also evaluated for relevance.

RESULTS

1. Effects of Osteoporosis Medication on Fracture Healing

There are no unequivocal conclusions on whether there is a delay in the healing of osteoporotic fractures compared to fractures with normal bone density; however, a higher rate of complications, including implant failure, non-union, and re-fracture has been reported for osteoporotic fractures[6,7]. Therefore, pharmacological interventions that promote fracture healing and implant fixation are expected to be helpful in reducing the prevalence of comorbidity of osteoporosis.

1) Bisphosphonates

Evaluation of the possible negative effects of osteoporosis medications, especially BPs, on fracture healing has been extensive. BPs have a selective inhibitory effect on osteoclasts, which play an important role in remodeling calluses into cortical bones; therefore, theoretically, indirect fracture healing can be delayed or impeded by inhibition of bone turnover due to use of BPs. The fact that many clinicians take a passive position in prescribing drugs for treatment of osteoporosis after fractures due to these concerns has been confirmed. However, no study has reported that administration of BPs has a negative effect on fracture healing. According to a meta-analysis of eight randomized control trials conducted on 2,508 patients, no clinical difference regarding the time required for fracture healing through external callus formation with the use of BPs was observed in short-term or long-term observations[8]. Findings from the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial, which aimed to evaluate the effect of BPs on fracture healing, showed that there was no relevant delay in fracture healing with administration of zoledronic acid in patients with hip fractures. This result was confirmed even when the drug was administered immediately after surgery. Results of a multiple regression analysis showed that there was no significant relationship between the timing of zoledronic acid administration and the delay of fracture healing[9]. Findings of another study demonstrated that taking alendronate for one year was effective in preventing bone loss without delaying fracture healing[10,11]. In contrast to those reports, clinical studies on patients who were taking BPs prior to the fracture reported on the possibility of delayed fracture healing. A retrospective review of 196 consecutive patients with a fracture of the distal radius reported that the time to reach radiographic union was statistically longer than that of individuals who were not on a BP prior to the fracture (55 vs. 49 days, P=0.03)[12], but without clinical significance, and in a prospective study of 105 patients with osteoporotic spinal fracture, an intravertebral cleft sign, indicating delayed fracture healing, was more common in patients with prior use

of BP than those without (30% vs. 20.5%, $P<0.05$)[13]. However, both studies still reported that clinical outcomes such as Oswestry Disability Index scores and pain ratings on the visual analogue scale (VAS) at three months post-fracture are apparently not impacted by BPs.

Several experimental/clinical studies have reported that administration of systemic BPs caused an increase in screw removal resistance and local application of BPs by coating the surface of the screw or injection to the fracture site can increase implant-osseointegration[14-17]. These results are based on the fact that the initial fixation force of the cortical bone-screw bond is strong but decreases over time, while the initial fixation force of the cancellous bone-screw bond is weak, but shows gradual improvement over time[18]. In clinical practice, where early load bearing is permitted before fracture healing is complete, even if there is no immediate occurrence of mechanical failure in such circumstances, gradual collapse may occur due to accumulated damage along with bone resorption around the screw due to micro-instability[19]. In the competition between the destructive and repair processes, administration of BPs promotes formation of bone around the screw and reduces bone resorption, aiding in fixture endurance until fracture healing is achieved.

According to the findings of an experimental study, osteoblasts can function without coupling with osteoclasts at the fracture site, unlike bone resorption and bone formation, which are coupled during the ordinary remodeling process. That is, the intrinsic osteoclast inhibitory effect of BPs works while preserving the function of osteoblasts at the fracture healing site, and the overall net effect acts in an anti-catabolic or anabolic direction, providing a theoretical basis for the assertion that it does not have a negative effect on the fracture healing process[15].

2) Denosumab

Denosumab, a potent inhibitor of osteoclast mediated bone resorption, is expected to have properties that are similar to those of BPs with respect to fracture healing[20]. Findings from animal studies have confirmed that denosumab has no negative effect on fracture healing or early callus formation. However, administration of denosumab showed an association with delayed callus remodeling compared to the control group, but further improvement of callus strength and stiffness was reported[21]. Findings from the Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 months (FREEDOM) trial, which included 199 patients with a non-vertebral fracture, demonstrated that administration of denosumab does not delay fracture healing and is not associated with other complications. Results on the use of denosumab, which has a greater antiresorptive effect than BPs, demonstrated that antiresorptive treatment does not interfere with fracture healing[22].

3) Selective estrogen receptor modulator

SERMs are known to inhibit bone resorption through downregulation of osteoclast activity via TGF-β3. Animal studies have reported that it does not have a negative effect on the fracture healing process and has a positive effect on fracture healing by improving callus formation, resistance, and elasticity[23,24]. However, to date, no study evaluating the effect of SERMs on fracture healing in humans has been reported. In clinical practice, the use of SERMs may be considered in patients in whom the use of BPs or denosumab is restricted.

4) Parathyroid hormone

Several animal studies have reported on the excellent effect of PTH, a representative osteogenesis promoter, on osteogenesis. According to the findings of a rat fracture experiment, the use of intermittent PTH (1-34)/kg/day led to an increase in mechanical strength through callus formation[25]. Histologically, an increase in the density of trabecular bone around implants was confirmed with the use of PTH, suggesting that the initial fixation strength and osteointegration of orthopedic implants could be increased[26].

There is significant experimental evidence regarding the impact of teriparatide on fracture healing; currently, it is the only medication for treatment of osteoporosis for which a randomized controlled trial (RCT) on fracture healing has been completed[20]. In a prospective, randomized, double-blind study of 102 postmenopausal women with distal radius fracture who received conservative treatment, the time required for fracture healing was 7.4 weeks with teriparatide 20 μg/day, 8.8 weeks with teriparatide 40 μg/day, and 9.1 weeks in the placebo group. Shorter time to healing was observed in the teriparatide-administered group[27].

In addition, findings from a study evaluating the time for fracture healing, pain, and functional recovery for pelvic bone fractures confirmed significant acceleration of fracture healing (7.8 weeks [with administration of 100 μg/day of PTH] vs. 12.6 weeks [control group]; $P<0.001$), positive effects on clinical outcomes, such as pain (VAS score) and function, and better results for the Timed Up and Go test[28]. Therefore, teriparatide would be a promising treatment for fractures and nonunion, and these results are consistent with those of preclinical investigations demonstrating that teri-

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paratide promotes fracture healing[29].

5) Romosozumab

Romosuzumab, a recently approved drug containing humanized monoclonal antibody to sclerostin, has a dual effect of accelerating bone formation and suppression of bone resorption through activation of the Wnt signaling pathway, where osteoblasts are stimulated while osteoclasts are inhibited. In an experimental study of a rat model of postmenopausal osteoporosis, significantly increased bone formation was observed on the trabecular, periosteal, endocortical, and intracortical surfaces in the group that was administered a sclerostin antibody compared to the control group. Increased bone mass and strength were observed compared not only to the control group but also when compared to a normal rat model[30]. Findings from another study of rat models with femoral fractures confirmed an increase in the callus volume around the screw of more than 30% and an increase in the screw pull-out force of more than 50% in the group that was administered sclerostin antibody compared to the control group; these anabolic effects were observed in both untraumatized bones and fractured bones[31]. A number of other animal studies have also reported positive results in fracture healing and reduction of gap defects, as well as an increase in the mechanical strength of the callus with use of the sclerostin antibody. According to the findings from a few clinical studies with human subjects, use of romosozumab did not result in accelerated fracture healing or improvement of the fracture-healing-related clinical and radiographic outcomes[32,33]. However, to date, clinical studies on romosuzumab are still lacking and conduct of further studies will be necessary.

Overall, no studies suggesting that treatment of osteoporosis has a negative effect on fracture healing have been reported. Many studies have demonstrated that medications for treatment of osteoporosis, especially those that promote bone formation, accelerate fracture healing. The timing of drug administration is also expected to affect the healing of fractures; however, several studies have reported inconsistent results. One study reported that administration of osteoporosis treatment had no effect on fracture healing even when administered immediately after a fracture[9,34]. However, in another experimental study, higher strength of osseointegration was observed in the group of patients who received treatment within a certain period of time after the fracture[35]. Conduct of further research on this topic will be needed. In addition, the effects of each drug differ according to the fracture site (e.g., radius, tibia, or hip) and the type of bone (cortical or cancellous bone); therefore, this factor should be considered. Although it is known that BPs do not have a negative effect on fracture healing and clinical outcomes in fractures of the distal radius and hip, studies on spine fractures are insufficient. Denosumab is also known to have no negative effects on non-vertebral fractures. According to findings from a recent study on hip fractures, positive results regarding pain and function were confirmed in patients treated with teriparatide, and similar results were reported in an RCT comparing the effect of teriparatide with that of alendronate in patients with vertebral fractures[36]. There is no consensus on whether the results from use of a certain medication on a specific site can be equally applied to other sites. Nevertheless, considering that medications for treatment of osteoporosis do not have a negative effect on fracture healing and increase the risk of subsequent fractures after the initial fracture, administration of osteoporosis medications is necessary in patients with osteoporotic fractures (Table 1).

Table 1. Effect of Currently Available Osteoporosis Treatments on Bone Repair

Agent	Clinical evidence
Bisphosphonate	No clinically detectable delay to fracture healing via external callus formation following bisphosphonates treatment (I)* Improved implant fixation/osteointegration with local, systemic application (II)*
Denosumab	No delay to fracture-healing or contribute to other complications (II)*
SERMs	None
Teriparatide	Accelerate fracture healing by enhancing callus formation (pelvic fracture and distal radial) (II)* Improved radiographic fracture healing and reduced complication rates of a hip fracture (III)* Aid fracture healing in patients with AFF (IV)*
Romosuzumab	Does not accelerate fracture healing nor improve the fracture-healing-related clinical and radiographic outcomes (II)* Increased callus volume around and the screw pull-out force (III)*

* Level of evidence.
SERMs: selective estrogen receptor modulators, AFF: atypical femur fracture.

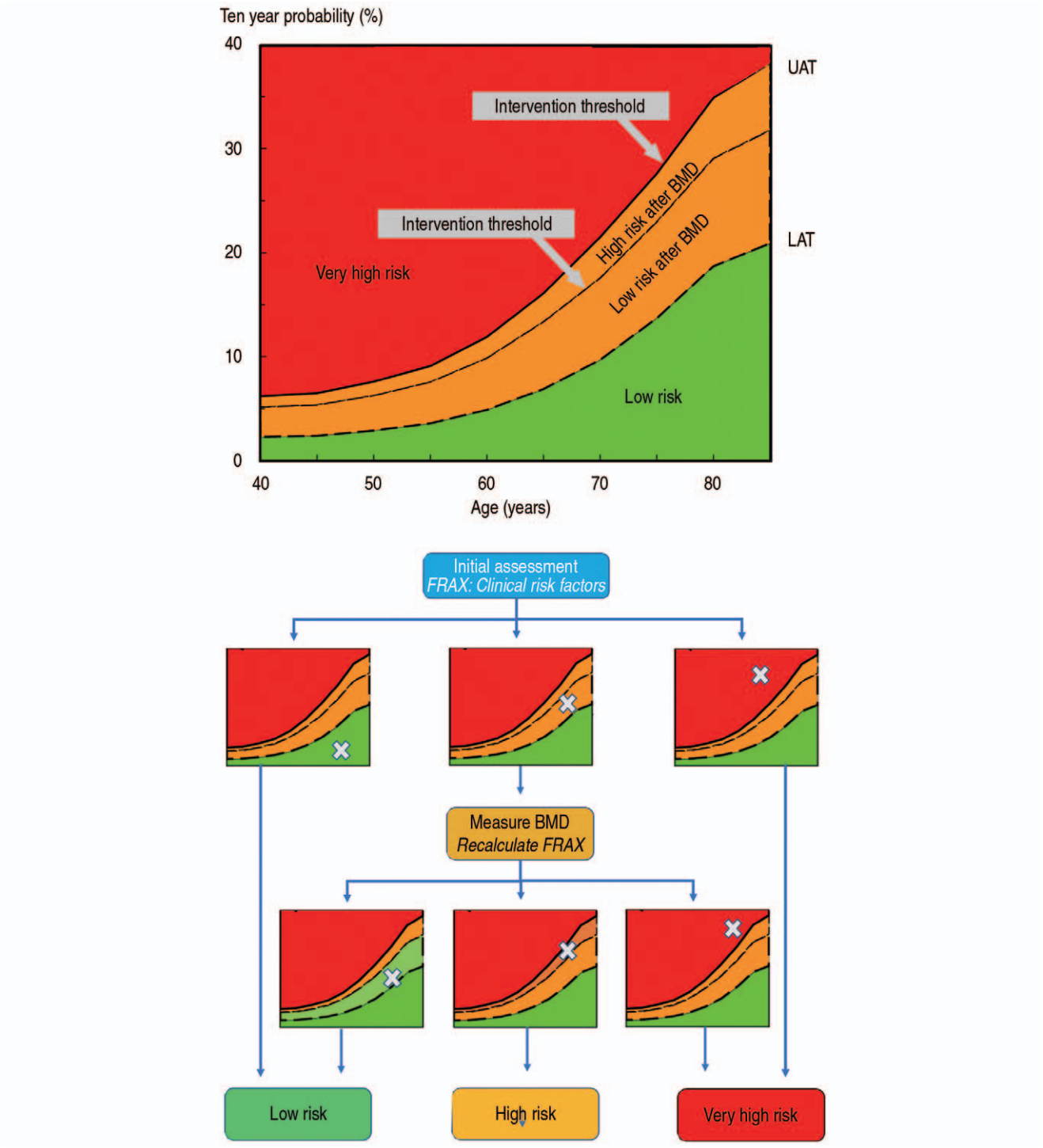

Fig. 1. Fracture risk according to the FRAX tool in postmenopausal women. The initial risk assessment used the FRAX tool with clinical risk factors alone and without bone mineral density (BMD). Assessment guidelines were based on the 10-year probability of a major osteoporotic fracture (%). The lower assessment threshold (LAT) set by FRAX were based on the 10-year probability (%) of a major osteoporotic fracture equivalent to that in women without clinical risk factors. The upper assessment threshold (UAT) was set at 1.2 times the intervention threshold. A BMD test is recommended for individuals where the probability assessment lies in the orange region. Adapted from the study by Kanis et al.[39] (Osteoporos Int. 2020;31:1-12) under the terms of the Creative Commons Attribution Non-Commercial (CC BY-NC 4.0) license.

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2. Medical Management for Prevention of Future Fractures after Osteoporotic Fracture

For the treatment of osteoporotic fractures, as in the treatment of patients with general osteoporosis, the appropriate choice of drug through assessment of fracture risk is essential. Each society or country has established various guidelines and there are subtle differences in the criteria for each of these guidelines. Among them, the most widely cited and utilized guidelines are those for AACE/ACE (American Association of Clinical Endocrinology/American College of Endocrinology), Endocrine Society, and ESCEO/IOF (European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases/International Osteoporosis Foundation). According to AACE/ACE, "very high risk" individuals are patients with an extremely high risk of fracture, including those with a recent fracture (e.g., within the past 12 months), those in whom fractures occurred while on approved osteoporosis therapy, multiple fractures, fractures that occurred while on drugs causing skeletal harm (e.g., long-term glucocorticoids), those with a very low T-score (e.g., less than –3.0), high risk of falls or history of injurious falls, and those with a very high probability of fracture according to FRAX (e.g., major osteoporosis fracture >30%, hip fracture >4.5%) or other validated fracture risk algorithms. In addition, according to the Endocrine Society "very high risk" includes multiple spine fractures and a bone mineral density (BMD) T-

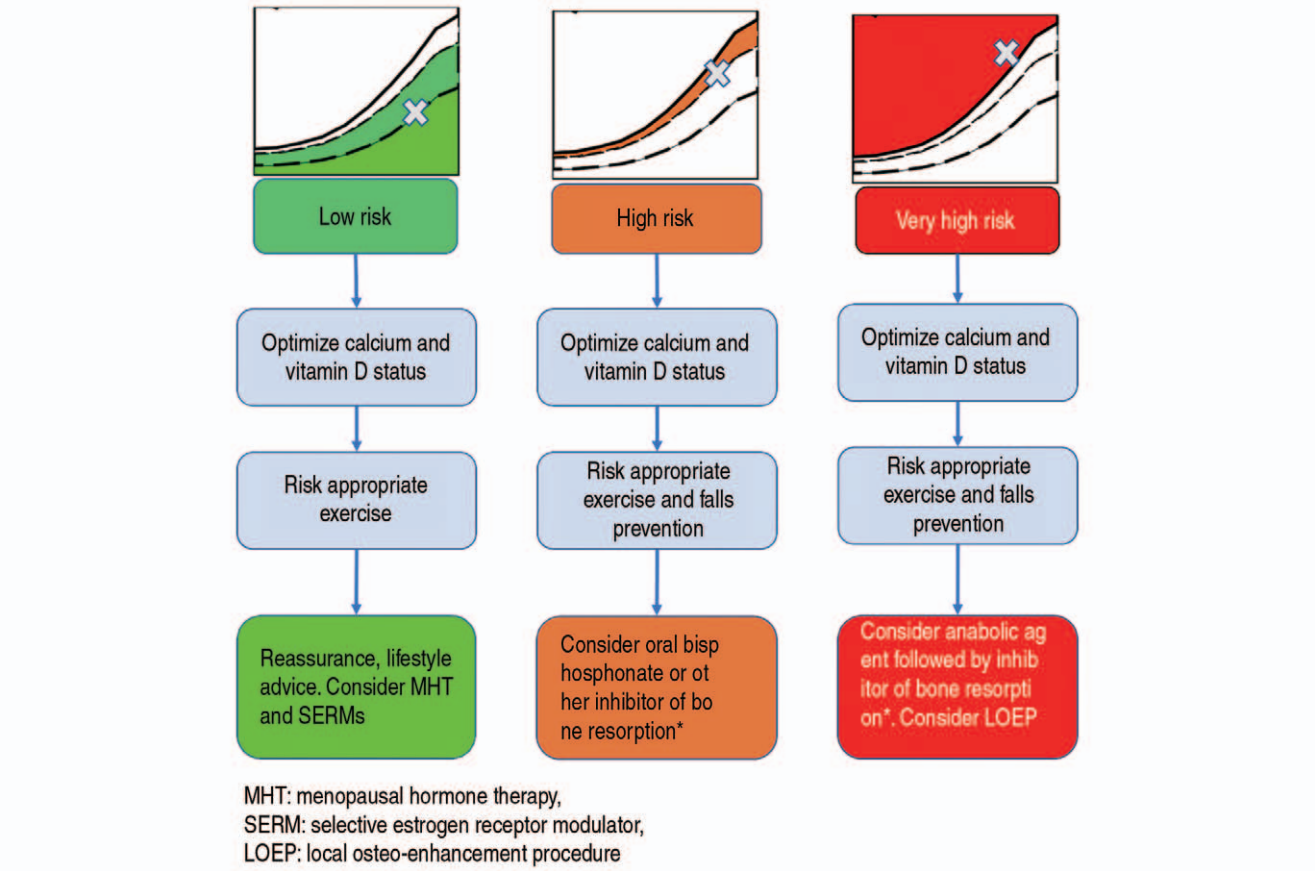

Fig. 2. Treatment pathways according to the categorization of fracture risk. The FRAX probability in the red zone indicates very high risk, where an initial course of anabolic treatment followed by antiresorptive therapy may be appropriate. The FRAX probability in the green zone suggests low risk; lifestyle modifications, calcium and vitamin D nutrition, and menopausal hormone treatment should be considered in these cases. The FRAX probability in the intermediate (orange) zone should be followed by bone mineral density (BMD) assessment and recalculation of FRAX probability including femoral neck BMD. After recalculation, the risk may be in the red (very high risk), orange (high risk, which suggests initial antiresorptive therapy) or green (low risk, either in the original green zone or in the original orange zone but below the intervention threshold) zones. Note that patients with a prior fragility fracture are designated at high risk or possibly at very high risk depending on the FRAX probability. Adapted from Kanis et al.[39] (Osteoporos Int. 2020;31:1-12) under the terms of the Creative Commons Attribution Non-Commercial (CC BY-NC 4.0) license.

score at the hip or spine of 2.5 or below. The ESCEO/IOF recommend expressing fracture risk as an absolute value within 10 years; this fracture risk is determined by several factors, including age and life expectancy[37]. The Fracture Risk Assessment Tool (FRAX) is widely used for stratifying the risk of major osteoporotic fractures, including fractures of the spine, hip, forearm, and humerus, within 10 years by synthesizing BMD and risk factors for clinical fractures. According to the European Society guidance, FRAX evaluation is recommended for postmenopausal women with a history of fragility fracture, and those who fall below the lower assessment threshold are classified as low risk[38]. Fracture risk falling above the upper assessment threshold is classified as a group requiring treatment, and when it falls between the upper and lower assessment thresholds, re-evaluation of the fracture risk should be performed through BMD evaluation. Intervention thresholds correspond to the FRAX-based 10-year probability (%) of a major osteoporotic fracture equivalent to women with a previous fracture and average body mass index (BMI) with no other clinical risk factors (without BMD). The lower assessment thresholds are based on the 10-year probability (%) of a major osteoporotic fracture equivalent to women with an average BMI and without clinical risk factors (without BMD). The upper assessment threshold was set at 1.2 times the intervention threshold. The intervention threshold is age-dependent and increases with age

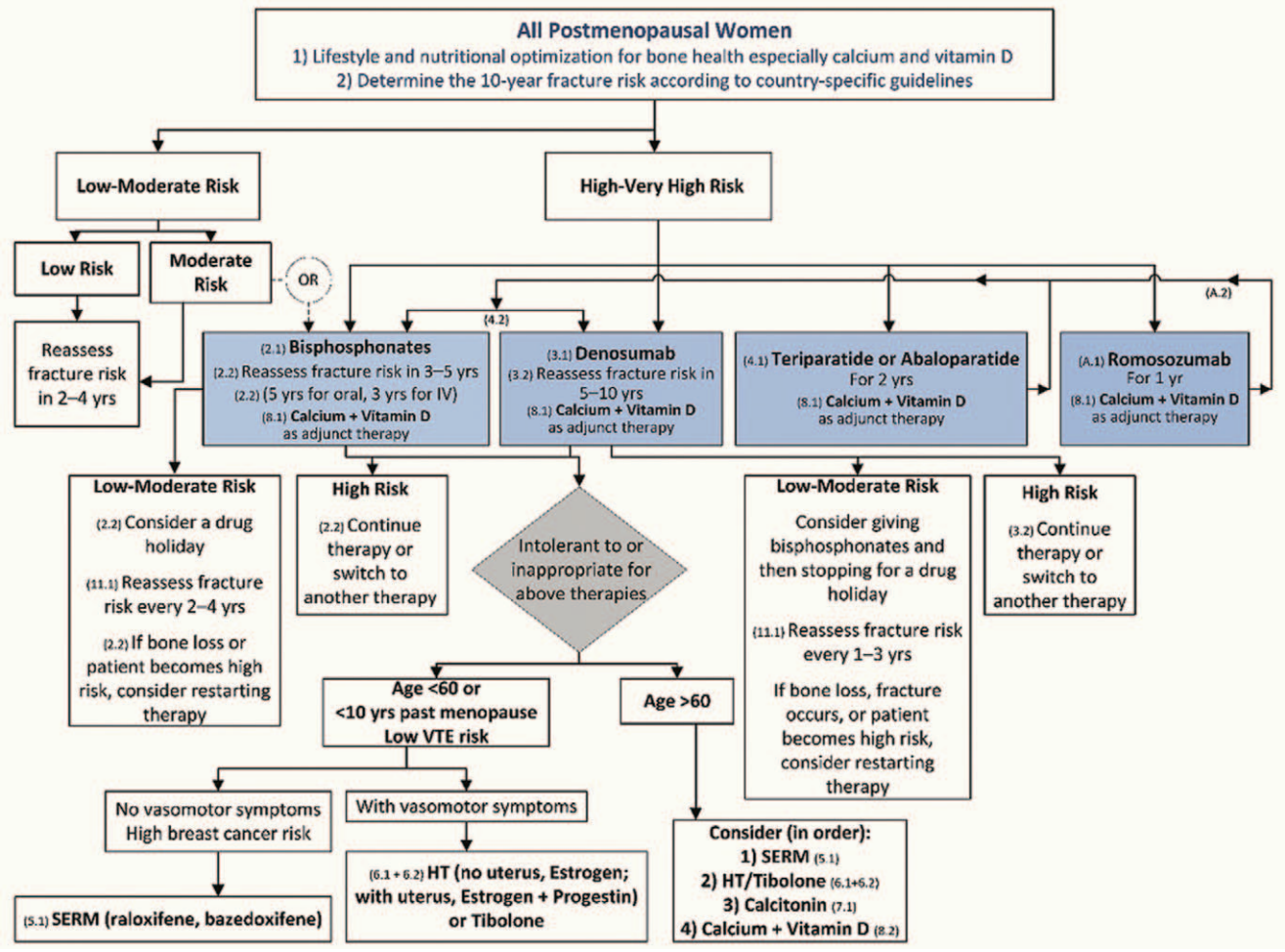

Fig. 3. Algorithm for the management of postmenopausal osteoporosis. Fracture risk was determined by the FRAX tool with lumbar spine and hip bone mineral density (BMD). Risk categories: (1) low risk: no prior hip or spine fractures, a BMD T-score at the hip and spine both above –1.0, a 10-year hip fracture risk <3%, and 10-year risk of major osteoporotic fractures <20%; (2) moderate risk: no prior hip or spine fractures, a BMD T-score at the hip and spine both above –2.5, and 10-year hip fracture risk <3% or risk of major osteoporotic fractures <20%; (3) high risk: a prior spine or hip fracture, a BMD T-score at the hip or spine of –2.5 or below, 10-year hip fracture risk ≥3%, or risk of major osteoporotic fracture risk ≥20%; and (4) very high risk: multiple spine fractures and a BMD T-score at the hip or spine of –2.5 or below. Adapted from Shoback et al.[44] (J Clin Endocrinol Metab. 2020;105:dgaa048) with permission of Oxford University Press.

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(Fig. 1)[39]. The same criteria can be applied to men. For patients classified as the very high-risk group whose probability of fracture is 1.2 times the intervention threshold after a FRAX assessment, administration of antiresorptive agents after anabolic agents is recommended, antiresorptive therapy is recommended for the high-risk group, and lifestyle modification, calcium, and vitamin D nutrition, as well as administration of menopausal hormone is recommended for the low-risk group (Fig. 2)[39]. Among the guidelines described above, the FRAX tool is easy to understand visually and would provide the most accessible risk stratification without implementing BMD. However, data on the 10-year probability (%) of major osteoporotic fractures in women with a history of previous fracture, average BMI, and without clinical risk factors are required in order to apply the intervention threshold in the manner suggested in the European guidelines, but such data are not available in every country. Therefore, application of this method is difficult.

Hip fractures correspond to the high/very high-risk group, and, accordingly, administration of antiresorptive treatment and anabolic agents is required for high-risk and very high-risk patients, respectively. Alendronate and risendronate (BPs) inhibit bone resorption, subsequently reducing the incidence of fractures[11,40]. As demonstrated in the HORIZON Recurrent Fracture Trial, use of zoledronic acid also results in improvement of hip BMD in patients with low-energy hip fractures when administered within 90 days after the surgical repair of a hip fracture, and a significant reduction of the occurrence of vertebral, non-vertebral, and hip fractures resulting in mortality[41]. Administration of teriparatide results in an increase of the BMD of the proximal femur and a reduced risk of hip fractures[42]. According to a study of patients with unstable intertrochanteric fractures, short-term daily treatment with teriparatide resulted

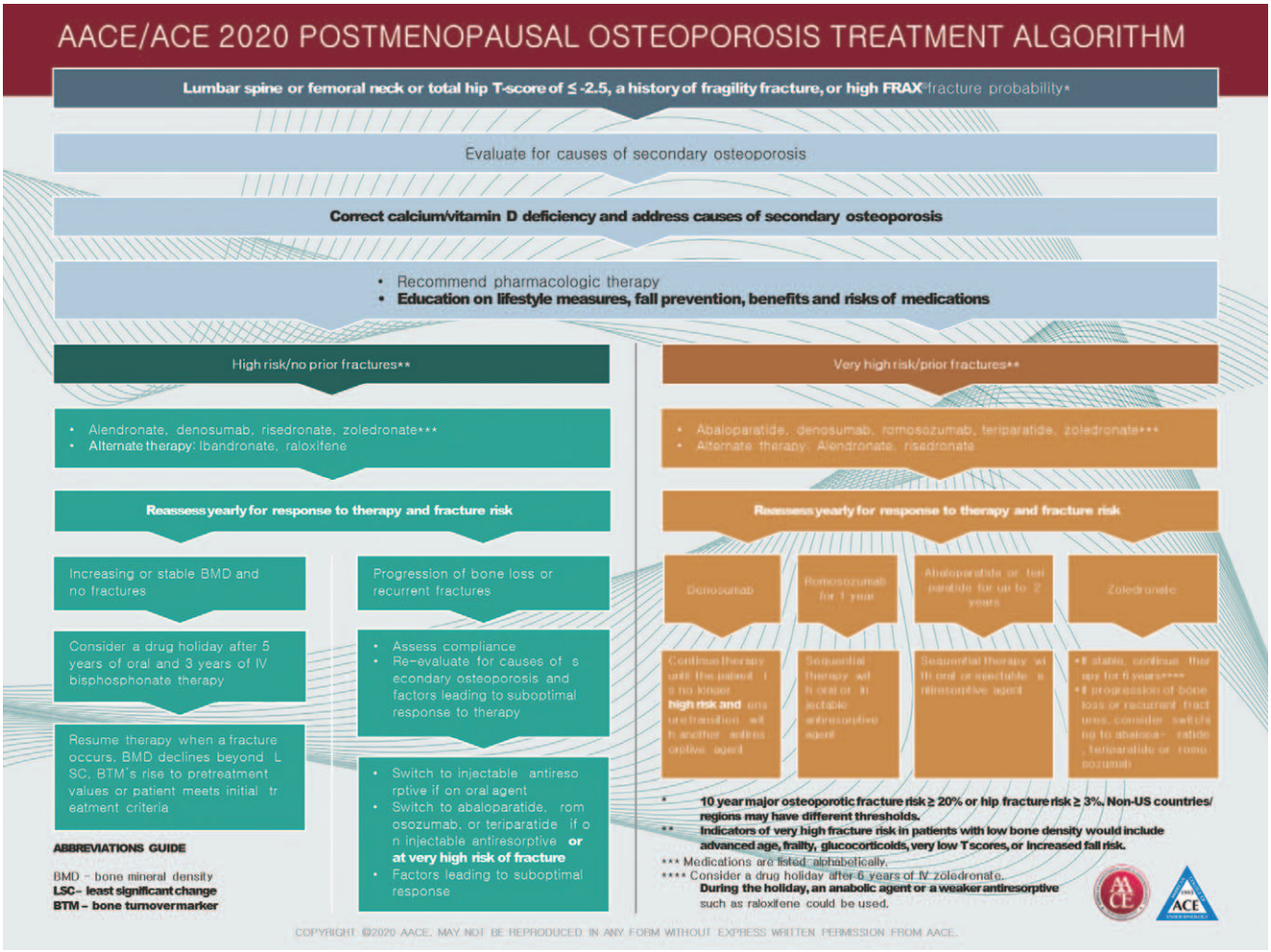

Fig. 4. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis–2020 update. Adapted from Camacho et al.[45] (Endocr Pract. 2020;26(Suppl 1):1-46) with permission of Elsevier.

in significant improvement of postoperative functional outcomes (Harris hip score, P=0.02) and reduced postoperative pain (VAS score, P=0.008), time required for fracture healing (14.8 weeks vs. 12.1 weeks, P=0.002), and complication rates compared to the control group[43]. The recently updated guidelines from the Endocrine Society recommend the use of romosuzumab, which has recently been approved by the U.S. Food and Drug Administration and the European Medicines Agency, along with teriparatide, in patients who require an anabolic agent (Fig. 3, 4)[44,45].

3. Medical Management of Patients after AFFs

Due to its low incidence, the number of studies on AFF are limited. Therefore, other than the administration of teriparatide, there is no evidence-based indication for the reduction of typical fragility fractures in osteoporotic patients with AFF. However, several studies have reported that teriparatide promotes fracture healing in surgically treated AFF. However, non-unions still occur, and no studies on the effectiveness of teriparatide for the complete and non-healing of AFF have been reported. In addition, similar results were obtained with conservatively treated incomplete AFF[46-48], According to findings from a systematic review and recommendations from the European Calcified Tissue Society, if AFF is observed during use of BP or denosumab, those medications should be discontinued in order to prevent the progression of AFF or the occurrence of AFF on the contralateral side[49]. However, regarding denosumab, abrupt discontinuation of the drug may lead to a rebound effect[50,51]. BPs or SERMs should be administered in a short course in order to prevent the rebound effect in surgically treated AFF, except in cases where there

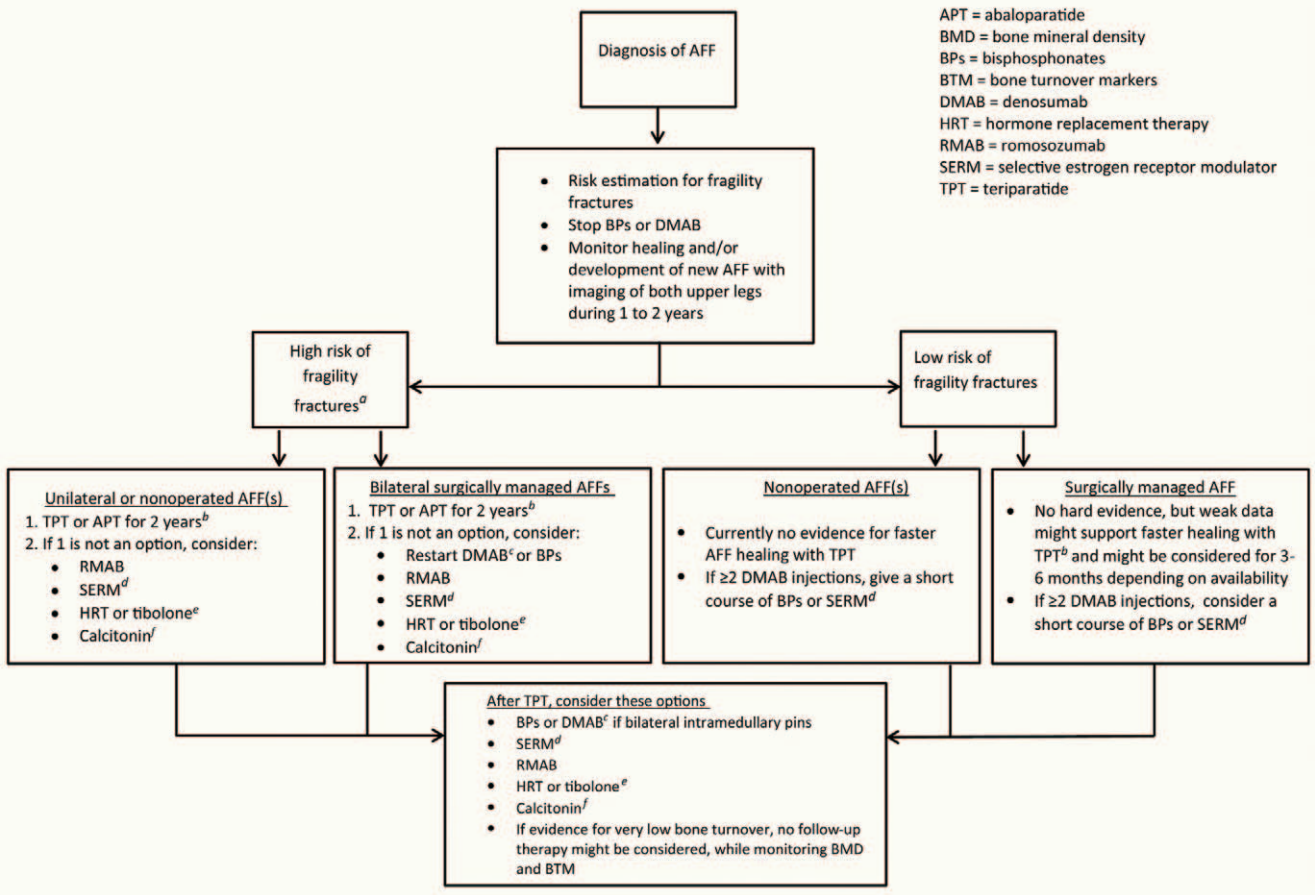

Fig. 5. Decision tree with considerations for medical management after atypical femur fracture (AFF). [a]Definition may vary across countries, e.g., a hip bone mineral density (BMD) T-score ≤−2.5 standard deviation, older age (70-75 years), a recent fragility fracture, other strong risk factors for fracture, or a FRAX fracture risk score that is above country-specific thresholds. [b]Switching denosumab to teriparatide may result in progressive BMD loss. [c]Be aware that antiresorptive therapy may be needed after stopping denosumab. Adapted from van de Laarschot et al.[49] (J Clin Endocrinol Metab. 2020;105:1682-99) with permission of Oxford University Press.

is no prevalent vertebral fracture and the risk of fracture is low, or only one or two administrations have been performed.

Administration of BPs and SERMs should be avoided in cases of conservatively managed incomplete AFF or contralateral AFF. Cessation of BP lasting longer than three years can lead to an increased risk of hip or vertebral fractures; therefore, caution is necessary. Although there is no clear evidence indicating that administration of teriparatide can promote fracture healing in surgically treated AFF, it is suggested that it can be helpful. Administration of BPs or denosumab may be continued for prevention of fragility fractures in surgically managed bilateral AFF. In patients with AFF who are at high risk of fragility fractures, administration of teriparatide appears to be the most rational drug choice, and romosozumab, abaloparatide, and SERMs have also been suggested as alternatives to teriparatide (Fig. 5)[49]. When using teriparatide for promotion of fracture healing, 3 to 6 months of use is sufficient, and after two years of teriparatide use, antiresorptive agents are required for maintenance of bone mass gain and strength. Denosumab can improve BMD and reduce the risk of fracture for up to 10 years.

CONCLUSION

The incidence of osteoporotic fractures has shown a rapid increase in Korea owing to the aging population. Orthopedic surgeons should not focus solely on surgical treatment for bone union but should consider administering osteoporosis drugs at the earliest in order to prevent future fractures. Most medications for treatment of osteoporosis do not delay fracture healing and the positive effect of teriparatide on fracture healing has been confirmed. In cases where an osteoporotic fracture is diagnosed, selection of very high-risk patients should be made through risk assessment in order to prevent subsequent fractures, and administration of anabolic agents is recommended. In cases where an AFF occurs or is suspected, evaluation of prodromal symptoms and radiographic images must be performed and antiresorptive agents should be discontinued. If one side undergoes an operation and there are symptoms on the other side, teriparatide is considered a safe option, and prophylactic fixation may be considered in cases involving severe pain. Bilateral performance of surgical fixation can enable maintenance and use of antiresorptive agents. Our study has limitations. Among various factors that affect the healing of osteoporotic fractures, in this review of the literature, the focus is on the effect of medication; therefore, evaluation of other factors should be included in the next study.

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CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

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