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CONSENSUS STATEMENT

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Introduction

Osteoporosis is a preventable and treatable chronic metabolic disease characterized by a decreased bone strength leading to an increased fracture risk as a consequence of low bone mineral density [BMD], microarchitectural disruption and several other risk factors [1]. Post-menopausal women are by far the most commonly subjects affected by osteoporosis, as the onset of menopause overlaps with the accelerated bone loss [1]. The physiologic decline of estrogens is blamed as the key factor of increased osteoporosis risk associated to menopause. Indeed, estrogen is a major regulator of bone growth, modulating the development of bone gender-difference as well as the strength and the maintenance of bone mineral homeostasis [2]. All these processes influence the acquisition of peak bone mass (PBM), a key determinant of skeletal health and the odd of osteoporosis throughout life [2]. It is generally believed that PBM is obtained by the third decade of life, but the influence of estrogen on bone continues thereafter from young adulthood forward. Essentially, it is believed that these steroid hormones exert three main effects on bone metabolism: (1) inhibit bone remodeling and counteract the development of new basic multicellular units (BMUs). In particular, estrogens exert the antiremodeling effect reducing apoptosis of osteocyte [3] and modulating osteoblasts and osteoclasts activity [4]. Further, recent studies have reported that serum levels of sclerostin, a key inhibitor of Wnt signaling produced by osteocytes, is inversely associated with estradiol levels [5, 6]. By contrast, estrogen treatment of postmenopausal women reduces circulating sclerostin levels [5, 6]. (2) Estrogens inhibit bone resorption. In particular, estrogens modulate RANK (Receptor activator of nuclear factor κB) signaling [7, 8], decrease osteoclastogenesis [4] and induce apoptosis in osteoclastic cells [9, 10]. In addition, estrogens block the formation of new osteoclasts. (3) Estrogens also organize commitment and differentiation and prevents apoptosis of osteoblastic cells also modulating these cell activity [4], therefore maintaining bone formation. (4) The anti-resorptive action of estrogens is also due to induction of gene expression and synthesis of OPG (osteoprotegerin), a determinant factor of the RANKL/RANK system [11]. (5) Estrogens improve calcium balance regulating calcium influx into the enterocyte through ERα [12].

The decline of estrogens, starting 1 or 2 years before menopause with a plateau about 2 years after the final menstrual period, exacerbates bone loss [13]. Estrogens levels can drop even more steeply in younger women whose ovaries are removed (leading to the so-called surgical menopause) or damaged by cancer treatments (iatrogenic menopause) or certain diseases. These conditions, therefore, are at increased

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hazard for the risk of osteoporosis and bone fractures. Indeed, even though an increased osteoblast numbers can be present in menopause, essentially due to the uncoupling of bone formation to bone resorption, the possible increase in bone formation is not sufficient to replace the old bone removed by osteoclasts [13].

Before the release of two landmark studies findings in 2002, hormone replacement therapy (HRT) was routinely prescribed for primary prevention of osteoporosis and other menopause comorbidities independently from the presence of menopausal symptoms. Both the Women's Health Initiative (WHI), a huge study of nearly 162,000 women [14], and the epidemiological UK-based Million Women Study [15] indicated an increased odd of breast and ovarian cancer in women taking HRT. As consequence, thousands of physicians no longer prescribed HRT and/or suggested discontinuation (Fig. 1).

But now the pendulum has to swing back the other way. Recently, the long-term findings of the WHI study has been published showing that HRT was not associated with an increased mortality [16]. Moreover, hormonal treatment in menopause has different forms, doses, ways of administration, and regimens (estrogen combined or not with progestin). Women who have not had hysterectomies use a combination therapy of estrogen plus progestin; women who have had hysterectomy use only estrogen. There has been consistent evidence that HRT and other (even hormonal) treatments at menopause improve osteoporosis and decrease the incidence of hip fractures. In general, regarding the global health profile in postmenopausal women, the benefit/risk ratio appears to be overall positive if HRT is started within 10 years after last menstrual or before 60 years of age.

This position paper, prepared with the intersociety endorsement of the Italian Society of Endocrinology (SIE), the Italian Society of Obstetrics and Gynecology (SIGO) and the Italian Society of Osteoporosis, of Mineral Metabolism and Skeletal Diseases (SIOMMMS) updates evidence on benefits and harms of HRT for the prevention and treatment of osteoporosis and discuss other hormone-like (e.g., Selective Estrogen Receptor Modulators) options for postmenopausal women who hope to reduce the risk of fractures associated with osteoporosis.

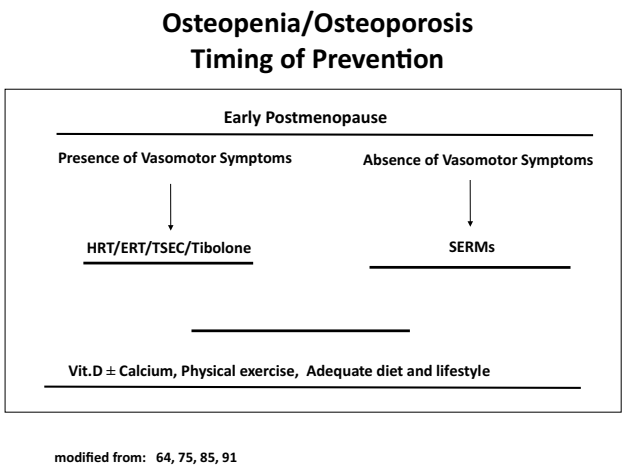

Fig. 1 Schematic diagram of pharmacological treatment to prevent osteoporotic fragility fractures

Epidemiology

In Italy, as in many developed countries, osteoporosis is becoming a major public health problem due to the ageing of population as consequence of the increased life expectancy and a progressively higher proportion of elderly people in population.

Osteoporosis is a very common disease: it is estimated that over 200 million individuals in the world are affected. In Italy it affects about 5 million people, of which over 80% are post-menopausal women. Half of Italian postmenopausal women aged 50 and older has osteoporosis [17]. It is estimated that the number of women with postmenopausal osteoporosis will increase from 3.3 to 3.7 million between 2010 and 2020 (+14.3%) and that the number of fragility fractures will increase from 285 thousand to 335.8 thousand (+17.8%) [18].

Moreover, there are almost 100 thousand hospitalizations for femur fragility fractures and data regarding other fracture sites are underestimated, as hospitalization is not always necessary. In 2010 more than 70 thousand accesses to the emergency room, due to vertebral fracture were reported, but since many are not identified, it is believed that their number is considerably greater. Fragility fractures have dramatic consequences in terms of disability and social costs [19]: mortality within a year of femur fracture is 20%, 30% of patients suffer from permanent disability and 40% of them lose their capacity to walk independently.

Thus, the economic impact of such a widespread disease is very high: it has been estimated that in Italy the cost for the treatment of osteoporosis fractures exceeds 7 billion Euro per year, of which only 360,000 for secondary drug prevention; in particular, femur fractures contribute to 60% of the costs, vertebral fractures to 4%, wrist to 1%, the remaining 35% concerns a mixed group of fractures. Furthermore, cost of drug therapies and social spending for lost work days, disability and assistance must be added.

Diagnosis

The diagnosis of osteoporosis in adults aged 50 years or older can be done in patients with a history of hip or clinical vertebral fracture due to low trauma, those with existing vertebral fractures identified on the basis of a spinal

imaging study alone (radiographic vertebral fractures), and those with a bone mineral density (BMD) evaluated by dual-energy x-ray absorptiometry (DXA), at or below the cutoff *T* score value ≥ 2.5 SDs.

Knowledge of the medical history is essential to achieve an accurate diagnosis as well as to estimate fracture risk. The anamnestic investigation should aim to determine the presence of any risk factor such a family history of osteoporosis and/or fragility fractures, previous fractures, nutritional habits and lifestyle, previous periods of amenorrhea, use of medications that affect bone metabolism, level of physical activity, and age of menopause.

Physical examination includes assessment of patient posture, to evaluate increased kyphosis of the thoracic spine, protruded abdomen, and loss of body height, which might be ascribed to the presence of one or more vertebral fragility fractures. BMD should be measured at the lumbar spine and hip (and its subregions) using DXA to make diagnosis [20]. Measurement of BMD at the hip is preferred for diagnosing osteoporosis after 70 years of age because it is a strong predictor of risk for nonvertebral fracture, including hip fracture. Of note, DXA might show and increased spine BMD with aging due to calcium deposition related to degenerative joint disease and/or abdominal aortic calcification. Recently, a software within DXA allows evaluation, in addition to density, of some geometric parameters related to bone strength, such as HSA (Hip Structural Analysis) and TBS (Trabecular Bone Score). In particular, HSA can evaluate resistance indices and geometric parameters of the proximal femur, while TBS elaborates the degree of homogeneity of vertebral densitometric scanning, providing indirect information on trabecular microarchitecture. The studies published so far show that TBS improves the ability to predict fracture risk compared to BMD measurement alone. While this app has been approved by the FDA, its usefulness in clinic is not yet well defined. Thus, it is important to remind that dorsal and lumbar xray might further help in identifying women with vertebral alteration or with fragility fractures.

Quantitative computed tomography (QCT) measures not only BMD and bone mineral content (BMC) but also true bone density expressed in g/cm3. Its main limitations are the substantially higher radiation dose delivered, its reduced accuracy, and its relatively high cost.

Bone quantitative ultrasound (QUS) analyzes the interaction between the sound signal and tissues, providing information on bone mechanical properties. It is helpful in predicting the risk of fracture using low frequencies (200 kHz–1.5 MHz) and to analyze hand phalanx bones or heel. QUS can be recommended for epidemiological investigations and as a first-level screening tool due to its low cost and the fact that it does not require ionizing radiation. QUS is a significant predictor of osteoporotic fractures but is a weaker predictor than femoral neck BMD for hip fractures. In clinical practice, it may be helpful to integrate QUS with clinical risk factors for the assessment of fracture risk.

Laboratory tests are mandatory to exclude main forms of secondary osteoporosis and for mineral metabolism assessment [20]. Biochemical markers of bone turnover and vitamin D status may provide additional information on individual fracture risk. In the absence of major trauma, any fracture in adults might suggest a diagnosis of osteoporosis, so proper clinical and imaging assessment should be undertaken.

More importantly, due to the recent knowledge it is important to determine fracture risk, more than obtain a densitometric diagnosis. Thus, new important tool has been developed in terms of prognostic algorithms (FRAX, DeFRA) which are currently used in order to decide specific therapeutic intervention [20].

Hormonal treatments

Several therapeutic hormonal agents are now available to treat postmenopausal osteoporosis and prevent fractures. The current palette includes HRT and hormone-like (e.g., Selective Estrogen Receptor Modulators) options, whose benefit and harms are discussed below.

Estrogens and progestins

Epidemiological studies and randomized clinical trials demonstrated that HRT is effective in reducing the incidence of vertebral and non-vertebral fractures [21]. This reduction was largely independent of the presence of clinical risk factors for osteoporotic fracture at the baseline [22–24]. The WHI trials were the first large-scale, double blinded, randomized, placebo-controlled, aimed to evaluate the efficacy of HRT on chronic disease prevention in predominantly healthy postmenopausal women aged 50–79 years [25–27]. WHI was conducted by using conjugated equine estrogens (CEE, 0.625 mg/day) plus medroxyprogesterone acetate (MPA; 2.5 mg/day) for women with an intact uterus and CEE alone for women with hysterectomy. Importantly, WHI trials were also the first large RCTs to demonstrate that HRT use significantly protected from fractures (including hip fractures), by enrolling women not specifically selected for known history of osteoporosis or previous fractures. In particular, in the 5.6-year trial period estrogen-progestin therapy significantly reduced incidence of hip (by 33%), lower arm/wrist (by 29%), vertebral (by 35%), and total (by 24%) fractures, as compared with placebo [28]. Data of estrogen-only arm during a 7-year trial period demonstrated similar protection (35%–39% reduction) from hip fracture as well as an improvement in BMD as compared with placebo [29, 30]. These effects were not modified after stratification

for BMI, age, or time since menopause. Recent evidences of the effect of HRT on osteoporosis risk (NCC-WCH) include studies which were very heterogeneous for several parameters including the number of enrolled women -from 36 [31] to 140,582—or for their age profile, with only one study [32] enrolling younger population of bilateral oophorectomy-induced menopause- and for the study design—among 41 included studies, 21 were comparative cohort studies and 20 were RCTs. In most of the comparative cohort studies, the type of hormone used as HRT was any estrogenic molecule, with no reference to the combination with progestogen. Among the RCTs, 50% included estrogen plus progestogen preparations [31, 33–41], 25% [42–46] included estrogen alone preparations and 5% included progestogen-only preparations [47]. The remaining 24% of RCTs were designed to compare estrogen alone vs. estrogen plus progestogen preparations, without any subanalysis by HRT preparation type.

Progesterone plays a partner role with E_2 in bone metabolism regulation, above all collaborating to the achievement of the perimenopausal peak of BMD that may reduce the risk of fracture after menopause. A recent study shows that greater bone loss occurs in patients with ovulatory disturbed cycles and a meta-analysis of randomized controlled trials (RCT) concluded that Estrogen with Progesterone therapy (EPT) caused significantly greater annual percent spinal BMD gain than the same dose of Estrogen only [48].

The large majority of prospective cohort studies (sample size ranging from 300 to 100,000 women) showed that current users of HRT were protected from any (vertebral, non-vertebral, hip and wrist) fracture, as compared with either not current users or never-users, independently from the duration of the therapy [34, 49–55]. When the effect of HRT discontinuation was analyzed, any fracture risk did not significantly differ between current HRT users or those who stopped HRT less than 5 years as compared to never-users. By analyzing RCTs a significantly lower risk of HRT users as compared to no-users was confirmed [56].

Lower doses of HRT (e.g., 0.3 mg conjugated estrogen, 25 mcg transdermal estradiol, or 0.5–1 mg of oral estradiol or estradiol valerate) are able to prevent hypoestrogenism- and menopause-related bone loss, even if there are no data as yet regarding fracture prevention [43, 56–59].

HRT may have an additional indirect skeletal action that could lead to positive protective effects on bone metabolism. Indeed, recent studies show that estrogens regulate muscle protein turnover and the lack of estrogen in postmenopausal women may reduce the muscle sensitivity to the anabolic stimuli [60]. Some recent results support the evidence of a critical and protective role for skeletal muscle of estrogen receptor (ER)α activation in the regulation of metabolic homeostasis and insulin sensitivity [61]. Therefore, estrogen hormonal replacement therapy may counteract the degenerative changes in skeletal muscle and considering the profound interaction between muscle and bone further reduce the osteoporosis risk.

In women showing premature ovarian insufficiency (POI) or early natural or induced menopause or who have had surgical menopause before age 45, and particularly before age 40, without contraindications for estrogen use, early initiation of HRT and continued use at least until the median age of menopause (51 years) is recommended to prevent osteoporosis and other conditions [62].

In women aged 50–59 years, HRT is associated with a favorable benefit/risk ratio [63]. Therefore, HRT could be considered as one of the first-line therapies for the prevention of postmenopausal osteoporosis and related fractures in postmenopausal women at increased fracture risk and younger than 60 years, or within 10 years of menopause, HRT being probably the most suitable skeleton-active treatment in women without contraindications for hormone use (Fig. 1). This is an excellent window-of-opportunity for HRT treatment due to the low risk profile. Persistent bone loss should be considered as an indication for longer duration of therapy with shared decision-making and periodic re-evaluation.

Selective estrogen receptor modulators (raloxifene e bazedoxifene)

Selective estrogen receptor modulators (SERMs) are a class of non-hormonal compounds that bind with high affinity to the ERα and β, despite not having the same chemical structure of the steroid hormones, estrogens [64–66]. The other characteristic feature of clinical pharmacology of SERMs is represented by the ability to exert estrogenic agonistic activities at the skeletal level and antagonistic actions at uterine and mammary levels [66, 67], which makes them potential ideal molecules in the post-menopausal period. Some studies had also demonstrated that raloxifene (RLX) does not increase the rate of vaginal bleeding, endometrial hyperplasia or endometrial carcinoma compared with placebo population [66, 67]. In regard to the mechanism of action at the skeletal level RLX, as also demonstrated for estradiol, can modulate the activity of both osteoclasts and osteoblasts, leading to decreased bone resorption [4] and thus leading to a positive action on the skeleton. Indeed, in a postmenopausal woman with normal or low BMD, but without vasomotor symptoms, SERMs such as RLX and bazedoxifene (BZA) could be the most appropriate pharmacological choice (Fig. 1) to prevent osteoporotic fragility fractures [68]. The outcome of several studies has, in fact, demonstrated how RLX and BZA can significantly decrease the number of patients developing osteopenia from normal BMD [69, 70].

Indeed, several studies have shown how the osteopenic status is related to a high risk to develop the first vertebral fracture [71]. The occurrence of a first fracture is already the signal of bone qualitative and quantitative changes. Several data, have demonstrated that 5 years of RLX treatment in healthy postmenopausal women preserves BMD, significantly reduces the likelihood of development of osteoporosis [67, 72]. So, in this clinical situation RLX could be considered a potential good choice as pharmacological treatment.

Moreover, RLX therapy has been shown to reduce the risk of vertebral fracture after 3 and 5 years [73, 74], respectively, and post hoc data show a significant reduction in clinical vertebral fracture risk at 1 year. However, RLX therapy has not been demonstrated as yet, to reduce the risk of hip fractures at currently approved doses.

BZA is formed from RLX molecule by a substitution of benzotiophenic structure with indole group; BZA, in a prevention study [75], appeared to protect bone mass and to decrease bone turnover in a population of women in early postmenopausal period (mean age about 58 years), with a low/normal lumbar and/or hip BMD, and clinical risk factors for osteoporosis. In a 3-year study [76] in postmenopausal women with osteoporosis (mean age ± SD: 66.4 ± 6.7; postmenopausal years: 19.5 ± 8.7), BZA reduced significantly (versus placebo) new osteoporosis-related vertebral fracture (HR 0.58; 95% CI 0.38–0.89), but not non-vertebral fracture). In a post hoc analysis on a sub-group at high-risk for fracture ($n = 1772$), with risk factors (femoral neck T-score ≤ -3.0 and/or ≥ 1 mild or severe vertebral fracture or multiple mild vertebral fractures), BZA 20 mg/day reduced non-vertebral fracture risk by 50% in comparison with placebo ($p = 0.02$; HR 0.50; 95% CI 0.28–0.90), and by 44% in comparison with RLX 60 mg/day ($p = 0.05$; HR 0.56; 95% CI 0.31–1.01); moreover BZA increased BMD at lumbar and hip level and decreased bone turnover markers significantly vs placebo ($p < 0.001$). Data from a 2-year extension (with a 5 year of total observation) have confirmed 3-year results, with a sustained anti-fracture effect of BZA on new vertebral fracture in postmenopausal women with osteoporosis and on nonvertebral fracture in the high-risk subgroup [74], while in a 7-year extension protection on new vertebral fracture was maintained with a favorable safety/tolerability profile across 7 years of administration [78].

RLX and BZA generally can induce hot flushes in postmenopausal women, even if BZA did not increase this symptom in women not suffering from this problem at the beginning of administration as compared to placebo [79].

Tibolone

Tibolone (TIB) is a pro-drug, also called Selective Tissue Estrogenic Activity Regulator (STEAR), that after oral ingestion is metabolized into three active compounds: 3α– and 3β-tibolone (with estrogenic action), and δ4-tibolone (with androgenic and progestinic properties) [80].

In ovariectomized rats, TIB significantly blocked ovariectomy-induced loss of trabecular BMD and inhibited bone resorption and bone turnover as determined by reduced Deoxypyridinoline/Creatinine ratio and osteocalcin, respectively; these effects were counteracted by the antiestrogen, but not by an antiandrogen or an antiprogestin, suggesting a major involvement of the estrogen receptor in TIB action on bone tissue [81].

TIB can be considered a suitable option, as effective as EPT, in preventing bone loss in healthy postmenopausal women. Indeed, at dose 2.5 mg/day, TIB improved bone mineral density (BMD) to a similar degree in comparison with conjugated equine estrogens (CEE) 0.625 mg/day plus medroxyprogesterone acetate (MPA) 2.5 mg/day (OPAL study) [79]. In dose-finding evaluation, TIB is active on bone at 0.625 mg/day, 1.25 mg/day and 2.5 mg/day in a 2-years study, with a significant difference versus placebo in increasing spine and total hip BMD and in decreasing bone markers levels (with a variation indicating an overall decreased rate of bone resorption) for all groups of active treatment from baseline [83].

The protective effect of TIB on bone tissue is maintained also in long-term period (10 years) [84, 85]. TIB (dosage 1.25 mg/day), in comparison with placebo, can decrease the relative hazard of osteoporosis-related vertebral and non-vertebral fractures in older postmenopausal women (mean age 68 years; age range 60–85 years; hip or spine BMD T-score of -2.5 or less or a T-score of -2.0 or less and radiologic evidence of a vertebral fracture) during a median of 34 months of treatment (LIFT study) [85]; this study was prematurely stopped due to an increase of relative hazard of stroke (2.19; 95% confidence interval 1.14–4.23; $p = 0.02$) in the TIB versus placebo group. As for HRT, TIB should be used for osteoporosis management in women before 60 years of age or 10 years after last menstrual period (Fig. 1). In addition, TIB can increase muscle strength and lean body mass [85].

Tissue selective estrogen complex (T-SEC)

The tissue-selective estrogen complex (TSEC) combines conjugated estrogens (CE) with a SERM, having the purpose of keeping the beneficial effects of estrogen [86] and avoiding its harmful effects using the antagonistic effects of the SERM component [87]. One of the goals of this mixed product was to achieve a combination that worked synergistically to preserve bone health. Currently, the novel SERM, BZA, has demonstrated its efficacy in increasing BMD and reducing bone turnover markers [88]. In particular, BZA proved to have a favorable tolerability and safety profile, regarding

Table 1 Main Studies (RCTs) about the effect of HRT/SERMs/TSEC on the prevention of osteoporosis and related factures (see references [57, 77, 82, 85, 99])

Authors	Treatment	Population	Results
Writing Group WHI (E + P arm). JAMA 2002	CEE 0.625 mg + MPA 2.5 mg/die	Postmenopausal women mean age 63.3 years	Total FXs HR: 0.76(0.69–0.83) clinical VFXs HR: 0.65 (0.46–0.92) Hip FXs HR: 0.67 (0.47–0.96)
Writing Group (E-only arm). JAMA 2004	CEE 0.625	Postmenopausal women Mean age: 63.6 years	Total FXs HR: 0.70 (0.63–0.79) Clinical VFXs: HR 0.62 (0.42–0.93) HipFXs HR: 0.61 (0.41–0.91)
Cummings SR, et al. NEJM 2008	Tibolone1,25 mg	Postmenopasual women mean age: 63.3 years	VFXs HR: 0.55 (0.41–0.74) NVFXs HR: 0.74(0.58–0.93)
Ettinger B, et al. JAMA 1999	Raloxifene 60 mg	Postmenopausal women Mean age: 67 yrs	VFXs HR: In pts w/o prev. FXs: 0.55(0.3–0.7) In pts with prev. FXs:0.7(0.6–0.9)
Silverman SL et al. JBMR 2008	Bazedoxifene 20 mg	Postmenopausal women Mean age 66.4	VFXs HR: 0.58 (0.38–0.89) NVFXs (in high-risk subgroup): 0.50 (0.28–0.90)
Lindsay R, et al. Fertil Steril 2009	TSEC (CEE 0.45 mg/BZA 20 mg)	Women > 5 years postmenopause-mean age: 58.4 Women between 1 and 5 years postmenopause—mean age: 52.1	Women > 5 years postmenopause: mean annual % vertebral BMD change 0.94 ± 0.25 ($p < 0.001$ vs PBO) Women between 1 and 5 years postmenopause: mean annual % vertebral BMD change: 1.01 ± 0.28 ($p < 0.001$ vs PBO) HIP BMD increased > placebo significantly for both subpopulation

long-term use as well. BZA did not show an increase in the incidence of breast, endometrial or ovarian cancers even if, similarly to other SERMs, it shows, as main adverse effect, a higher incidence of venous thromboembolism.

Among a few SERM/CE preparations, analyzed in terms of mechanism of action and specific effects both in vitro and in vivo, BZA showed a superior competitive inhibition of CE in breast and endometrial tissues [89]. Therefore, the CE/BZA association was designed as new comprehensive menopausal therapy. In particular, the efficacy of the CE/BZA combination as therapy for osteoporosis has been evaluated in the series of SMART trials. The SMART-1 trial [90], a 2-year international multicenter randomized double- blind placebo and active-controlled phase III trial involving 2315 women, was subdivided into two sub studies evaluating the effects of BZA/CE on osteoporosis. The Osteoporosis Prevention I sub-study examined women who were > 5 years postmenopausal while the second study enrolled those being 1–5 years post menopause. Inclusion criteria consisted of osteopenic range BMD (between − 1.0 and − 2.5) and one additional risk factor for osteoporosis. Each study included eight subgroups and six different combined doses of BZA/CE as well as raloxifene and placebo. For the current approved dose (20 mg BZA/0.45 mg CE) there was an adjusted annual increase in lumbar spine BMD of 1.01% ± 0.28%, which was significantly greater than both placebo and raloxifene. Secondary endpoints analysed bone turnover markers in the various groups. It was shown that Osteocalcin and *N*-telopeptide significantly decreased with all BZA/CE doses vs. placebo and most BZA/CE doses vs. raloxifene suggesting reduced osteoclast activity. The SMART-1 trial directly measured rates of VTEs and found no difference between treatment arms and placebo. The SMART-4 trial [91], a 1-year, multicenter, double-blind, randomized, placebo- and active-controlled, phase-3 study in non-hysterectomized, postmenopausal women ($n = 1061$) evaluated the endometrial safety of BZA/CE and the effects on BMD compared with CE/MPA and placebo. BZA 20 mg/CE 0.45 and 0.625 mg significantly improved BMD while maintaining endometrial safety and showed a favorable safety/tolerability profile over 1 year. The SMART -5 trial [92], a phase 3 study evaluating endometrial safety of BZA/CE and BMD effects vs BZA alone, hormone therapy, and placebo, showed significant increase from baseline in total hip BMD. By now, the combination of 20 mg BZA and 0.45 mg CE is the only approved drug in this class. To conclude, in Table 1 are listed the data regarding the main randomized clinical trials concerning the effects of different hormonal therapies on fragility fractures prevention.

Conclusion

This Intersociety position statement provides evidence, for clinicians caring for postmenopausal women at risk for osteoporosis, to initiate HRT (or TIB or TSEC) or hormone-like treatment based on shared decision making with the patient. A comprehensive summary of evidence, on benefits and harms, supports the concept that postmenopausal HRT should be considered as one of the first-line therapies for the prevention of osteoporosis and osteoporosis-related fractures, especially in postmenopausal women younger than 60 years, or within 10 years of menopause, due to the extremely low risk profile, and a favourable benefit/risk ratio [93–95]. Other suitable skeleton-active hormone-like (e.g., SERMs) treatments should be considered and discussed in women who are not candidate for or do not want HRT, in order to reduce the risk of fractures associated with osteoporosis. In a more holistic approach, it is also important to consider that HRT, TIB or TSEC can have further clinical benefits other than treatment of osteoporosis, with a global positive impact on quality of life of postmenopausal women (i.e., improvement of neuro-vegetative symptoms, and sexual function) [93–95].

It has also to be pointed out that following hormonal therapy, other anti-osteoporotic therapies must be considered and suggested to women with osteoporosis risk factors in order to maintain skeletal health and further prevent fragility fractures [20, 96–98].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No informed consent.

References

1. Siris E, Adler R, Bilezikian J, Bolognese M, Dawson-Hughes B, Favus MJ, Harris ST, Jan de Beur SM, Khosla S, Lane NE, Lindsay R, Nana AD, Orwoll ES, Saag K, Silverman S, Watts NB (2014) The clinical diagnosis of osteoporosis: a position statement from the national bone health alliance working group. Osteoporos Int 25(5):1439–1443
2. Berger C, Goltzman D, Langsetmo L, Joseph L, Jackson S, Kreiger N, Tenenhouse A, Davison KS, Josse RG, Prior JC, Hanley DA (2010) CaMos Research Group. Peak bone mass from longitudinal data: implications for the prevalence, pathophysiology, and diagnosis of osteoporosis. J Bone Miner Res 25(9):1948–1957
3. Tomkinson A, Reeve J, Shaw RW, Noble BS (1997) The death of osteocytes via apoptosis accompanies estrogen withdrawal in human bone. J Clin Endocrinol Metab 82:3128–3135
4. Taranta A, Brama M, Teti A, Luca V, Scandurra R, Spera G, Agnusdei D, Termine JD, Migliaccio S (2002) The selective estrogen receptor modulator raloxifene regulates osteoclast and osteoblast activity in vitro. Bone 30(2):368–376
5. Mirza FS, Padhi ID, Raisz LG, Lorenzo JA (2010) Serum sclerostin levels negatively correlate with parathyroid hormone levels and free estrogen index in postmenopausal women. J Clin Endocrinol Metab 95:1991–1997
6. Modder UIL, Clowes JA, Hoey K, Peterson JM, McCready L, Oursler MJ, Riggs BL, Khosla S (2011) Regulation of circulating sclerostin levels by sex steroids in women and men. J Bone Miner Res 26:27–34
7. Srivastava S, Weitzmann MN, Cenci S, Ross FP, Adler S, Pacifici R (1999) Estrogen decreases TNF gene expression by blocking JNK activity and the resulting production of c-Jun and Jun-D. J Clin Invest 104:503–513
8. Shevde NK, Bendixen AC, Dienger KM, Pike JW (2000) Estrogens suppress RANK ligand-induced osteoclast differentiation via a stromal cell independent mechanism involving c-Jun repression. Proc Natl Acad Sci USA 97:7829–7834
9. Nakamura T, Imai Y, Matsumoto T et al (2007) Estrogen prevents bone loss via estrogen receptor alpha and induction of fas ligand in osteoclasts. Cell 130:811–823
10. Martin-Millan M, Almeida M, Ambrogini E et al (2010) The estrogen receptor-alpha in osteoclasts mediates the protective effects of estrogens on cancellous but not cortical bone. Mol Endocrinol 24:323–334
11. Manolagas SC, O'Brien CA, Almeida M (2013) The role of estrogen and androgen receptors in bone health and disease. Nat Rev Endocrinol 9(12):699–712
12. Christakos S, Dhawan P, Porta A, Mady LJ, Seth T, Milhaud G (2011) Vitamin D and intestinal calcium absorption. Mol Cell Endocrinol 347(1–2):25–29
13. Christiansen C, Gallagher C, Reeve J, Seeman E, Chesnut C, Parfitt A (1983) Pathogenesis and treatment of postmenopausal osteoporosis. Calcif Tissue Int 35(6):708–711
14. Pradhan AD, Manson JE, Rossouw JE, Siscovick DS, Mouton CP, Rifai N, Wallace RB, Jackson RD, Pettinger MB, Ridker PM (2002) Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the women's health initiative observational study. JAMA 288(8):980–987
15. Beral V (2003) Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the million women study. Lancet 362(9382):419–427
16. Shufelt C, Bairey Merz CN, Pettinger MB, Choi L, Chlebowski R, Crandall CJ, Liu S, Lane D, Prentice R, Manson JE (2018) Women's health initiative investigators. Estrogen-alone therapy and invasive breast cancer incidence by dose, formulation, and route of delivery: findings from the WHI observational study. Menopause May:7
17. Cipriani C, Pepe J, Bertoldo F, Bianchi G, Cantatore FP, Corrado A, Di Stefano M, Frediani B, Gatti D, Giustina A, Porcelli T, Isaia G, Rossini M, Nieddu L, Minisola S, Girasole G, Pedrazzoni M (2018) The epidemiology of osteoporosis in Italian postmenopausal women according to the national bone health alliance (NBHA) diagnostic criteria: a multicenter cohort study. J Endocrinol Invest 41(4):431–438

18. Piscitelli P, Brandi M, Cawston H, Gauthier A, Kanis JA, Compston J, Borgström F, Cooper C, McCloskey E (2014) Epidemiological burden of postmenopausal osteoporosis in Italy from 2010 to 2020: estimations from a disease model. Calcif Tissue Int 95(5):419–427
19. Svedbom A, Hernlund E, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jönsson B, Kanis JA (2013) EU review panel of IOF. Osteoporosis in the European union: a compendium of country-specific reports. Arch Osteoporos 8:137–142
20. Nuti R, Brandi ML, Checchia G, Di Munno O, Dominguez L, Falaschi P, Fiore CE, Iolascon G, Maggi S, Michieli R, Migliaccio S, Minisola S, Rossini M, Sessa G, Tarantino U, Toselli A, Isaia GC (2018) Guidelines for the management of osteoporosis & fragility fractures. Int Emerg Medic 2018:1–18. https://doi.org/10.1007/s11739-018-1874-2
21. Torgerson DJ, Bell-Syer SEM (2001) Hormone replacement therapy and prevention of non-vertebral fractures. A meta-analysis of randomized trials. JAMA 285:2891–2897
22. Writing Group for the Women's Health Initiative Investigators (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. JAMA 288:321–333
23. Rossouw JE, Anderson GL, Prentice RL et al (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. JAMA 288:321–333
24. de Villiers TJ, Pines A, Panay N et al (2013) International menopause society. Updated 2013 International menopause society recommendations on menopausal hormone therapy and preventive strategies for midlife health. Climacteric 16:316–337
25. The Women's Health Initiative Study Group (1998) Design of the women's health initiative clinical trial and observational study. Control Clin Trials 19(1):61–109
26. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J (2002) Writing group for the women's health initiative investigators. Writing group for the women's health initiative investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. JAMA 288(3):321–333
27. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smoller S (2004) Women's health initiative steering committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the women's health Initiative randomized controlled trial. JAMA 291(14):1701–1712
28. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, LeBoff M, Lewis CE, McGowan J, Neuner J, Pettinger M, Stefanick ML, Wactawski-Wende J, Watts NB (2003) Women's health initiative investigators. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the women's health initiative randomized trial. JAMA 290(13):1729–1738
29. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smoller S (2004) Women's health initiative steering committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the women's health initiative randomized controlled trial. JAMA. 291(14):1701–1712
30. Jackson RD, Wactawski-Wende J, LaCroix AZ, Pettinger M, Yood RA, Watts NB, Robbins JA, Lewis CE, Beresford SA, Ko MG, Naughton MJ, Satterfield S, Bassford T (2006) Women's Health Initiative Investigators. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. J Bone Miner Res 21(6):817–828
31. Wimalawansa SJA (1998) Four-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with postmenopausal osteoporosis. Am J Med 104(3):219–226
32. Melton LJ 3rd, Crowson CS, Malkasian GD (1996) O'Fallon WM fracture risk following bilateral oophorectomy. J Clin Epidemiol 49(10):1111–1115
33. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J (2000) Committee of scientific advisors of the international osteoporosis foundation]. The use of biochemical markers of bone turnover in osteoporosis. Committee of scientific advisors of the international osteoporosis foundation. Osteoporos Int 11(S6):S2–S17
34. Hosking DJ, Ross PD, Thompson DE, Wasnich RD, McClung M, Bjarnason NH, Ravn P, Cizza G, Daley M, Yates AJ (1998) Evidence that increased calcium intake does not prevent early postmenopausal bone loss. Clin Ther 20(5):933–944
35. Komulainen MH, Kröger H, Tuppurainen MT, Heikkinen AM, Alhava E, Honkanen R, Saarikoski S (1998) HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women; a 5 year randomized trial. Maturitas 31(1):45–54
36. Lees B (2001) Stevenson JC The prevention of osteoporosis using sequential low-dose hormone replacement therapy with estradiol-17 beta and dydrogesterone. Osteoporos Int 12(4):251–258
37. Lufkin EG, Wahner HW, O'Fallon WM, Hodgson SF, Kotowicz MA, Lane AW, Judd HL, Caplan RH, Riggs BL (1992) Treatment of postmenopausal osteoporosis with transdermal estrogen. Ann Intern Med 117(1):1–9
38. Ravn P, Bidstrup M, Wasnich RD, Davis JW, McClung MR, Balske A, Coupland C, Sahota O, Kaur A, Daley M, Cizza G (1999) Alendronate and estrogen-progestin in the long-term prevention of bone loss: four-year results from the early postmenopausal intervention cohort study. A randomized, controlled trial. Ann Intern Med 131(12):935–942
39. Veerus P, Hovi SL, Fischer K, Rahu M, Hakama M, Hemminki E (2006) Results from the estonian postmenopausal hormone therapy trial [ISRCTN35338757]. Maturitas 55(2):162–173
40. Vickers MR, Martin J, Meade TW (2007) WISDOM study team. The women's international study of long-duration oestrogen after menopause (WISDOM): a randomised controlled trial. BMC Womens Health 7:2–9
41. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, Anderson G, Howard BV, Thomson CA, LaCroix AZ, Wactawski-Wende J, Jackson RD, Limacher M, Margolis KL, Wassertheil-Smoller S, Beresford SA, Cauley JA, Eaton CB, Gass M, Hsia J, Johnson KC, Kooperberg C, Kuller LH, Lewis CE, Liu S, Martin LW, Ockene JK, O'Sullivan MJ, Powell LH, Simon MS, Van Horn L, Vitolins MZ, Wallace RB (2013) Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials. JAMA 310(13):1353–1368
42. Cherry N, Gilmour K, Hannaford P, Heagerty A, Khan MA, Kitchener H, McNamee R, Elstein M, Kay C, Seif M, Buckley H (2002) ESPRIT team. Oestrogen therapy for prevention of

reinfarction in postmenopausal women: a randomised placebo controlled trial. Lancet 360(9350):2001–2008
43. Genant K, Lucas J, Weiss S, Akin M, Emkey R, McNaney-Flint H, Downs R, Mortola J, Watts N, Yang HM, Banav N, Brennan JJ, Nolan JC (1997) Low-dose esterified estrogen therapy. Effects on bone, plasma estradiol concentrations, endometrium, and lipid levels. Arch Intern Med 157:2609–2615
44. Reid IR, Eastell R, Fogelman I, Adachi JD, Rosen A, Netelenbos C, Watts NB, Seeman E, Ciaccia AV, Draper MW (2004) A comparison of the effects of raloxifene and conjugated equine estrogen on bone and lipids in healthy postmenopausal women. Arch Intern Med 164(8):871–879
45. Weiss SR, Ellman H, Dolker M (1999) A randomized controlled trial of four doses of transdermal estradiol for preventing postmenopausal bone loss. Transdermal estradiol investigator group. Obstet Gynecol 94(3):330–336
46. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, Anderson G, Howard BV, Thomson CA, LaCroix AZ, Wactawski-Wende J, Jackson RD, Limacher M, Margolis KL, Wassertheil-Smoller S, Beresford SA, Cauley JA, Eaton CB, Gass M, Hsia J, Johnson KC, Kooperberg C, Kuller LH, Lewis CE, Liu S, Martin LW, Ockene JK, O'Sullivan MJ, Powell LH, Simon MS, Van Horn L, Vitolins MZ, Wallace RB (2013) Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials. JAMA 310(13):1353–1368
47. Liu JH, Muse KN (2005) The effects of progestins on bone density and bone metabolism in postmenopausal women: a randomized controlled trial. Am J Obstet Gynecol 192(4):1316–1323
48. Prior JC (2018) Progesterone for the prevention and treatment of osteoporosis in women. Climacteric 21(4):366–374
49. Tuppurainen M, Kröger H, Saarikoski S, Honkanen R, Alhava E (1994) The effect of previous oral contraceptive use on bone mineral density in perimenopausal women. Osteoporos Int 4(2):93–98
50. Barrett-Connor E, Wehren LE, Siris ES, Miller P, Chen YT, Abbott TA 3rd, Berger ML, Santora AC, Sherwood LM (2003) Recency and duration of postmenopausal hormone therapy: effects on bone mineral density and fracture risk in the national osteoporosis risk assessment (NORA) study. Menopause 10(5):412–419
51. Banks E, Beral V, Reeves G, Balkwill A, Barnes I (2004) Million women study collaborators. Fracture incidence in relation to the pattern of use of hormone therapy in postmenopausal women. JAMA 291(18):2212–2220
52. Bagger YZ, Tankó LB, Alexandersen P, Hansen HB, Møllgaard A, Ravn P, Qvist P, Kanis JA, Christiansen C (2004) Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: the PERF study. Bone 34(4):728–735
53. Hundrup YA, Høidrup S, Ekholm O, Davidsen M, Obel EB (2004) Risk of low-energy hip, wrist, and upper arm fractures among current and previous users of hormone replacement therapy: the danish nurse cohort study. Eur J Epidemiol 19(12):1089–1095
54. Paganini-Hill A, Atchison KA, Gornbein JA, Nattiv A, Service SK, White SC (2005) Menstrual and reproductive factors and fracture risk: the leisure world cohort study. J Womens Health (Larchmt) 14(9):808–819
55. Middleton ET, Steel SA (2007) The effects of short-term hormone replacement therapy on long-term bone mineral density. Climacteric 10(3):257–263
56. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, Anderson G, Howard BV, Thomson CA, LaCroix AZ, Wactawski-Wende J, Jackson RD, Limacher M, Margolis KL, Wassertheil-Smoller S, Beresford SA, Cauley JA, Eaton CB, Gass M, Hsia J, Johnson KC, Kooperberg C, Kuller LH, Lewis CE, Liu S, Martin LW, Ockene JK, O'Sullivan MJ, Powell LH, Simon MS, Van Horn L, Vitolins MZ, Wallace RB (2013) Menopausal hormone therapy and health outcomes during the intervention and extended post-stopping phases of the WHI randomized trials. JAMA 310(13):1353–1368
57. Lindsay R, Gallagher CJ, Kleerekoper M, Pickar JH (2002) Effects of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. JAMA 287:2668–2676
58. Prestwood KM, Kenny AM, Unson C, Kulldorf M (2000) The effect of low dose micronized 17β-estradiol on bone turnover, sex hormone levels, and side effects in older women: a randomized, double blind, Placebo-Controlled Study. J Clin Endocrinol Metab 85:4462–4469
59. Weiss SR, Hellman H, Dolker M, Transdermal Estradiol Investigator Group (1999) A randomized controlled trial of four doses of transdermal estradiol for preventing postmenopausal bone loss. Obstet Gynecol 94(3):330–336
60. Laakkonen EK, Soliymani R, Karvinen S, Kaprio J, Kujala UM, Baumann M, Sipilä S, Kovanen V, Lalowski M (2017) Estrogenic regulation of skeletal muscle proteome: a study of premenopausal women and postmenopausal MZ cotwins discordant for hormonal therapy. Aging Cell 16(6):1276–1287
61. Hevener AL, Zhou Z, Moore TM, Drew BG, Ribas V (2018) The impact of ERα action on muscle metabolism and insulin sensitivity—strong enough for a man, made for a woman. Mol Metab 15:20–34
62. ACOG Committee Opinion number 698 (2017) Hormone therapy in primary ovarian insufficiency; the 2017 hormone therapy position statement of the north American menopause society. Menopause 24(7):728–753
63. The NAMS (2017) Hormone Therapy Position Statement Advisory Panel; The 2017 hormone therapy position statement of the North American Menopause Society. Menopause 24(7):728–753
64. Diez-Perez A (2006) Selective estrogen receptor modulators (SERMS). Arq Bras Endocrinol Metabol 50:720–734
65. Brzozowski AM, Pike ACW, Dauter Z et al (1997) Molecular basis of agonism and antagonism in the oestrogen receptor. Nature 389:753–758
66. Riggs BL, Hartmann LC (2003) Selective estrogen-receptor modulators. Mechanisms of action and application to clinical practice. N Engl J Med 348:618–629
67. Gandolini G, Migliaccio S, Bevilacqua M, Lello S, Malavolta N (2004) Prevent, treat and maintain: a new goal for osteoporosis management in clinical practice. Aging ClinExp Res 16S(3):37–41
68. Lello S, Brandi ML, Minisola G, Minisola S, Genazzani AR (2011) Bazedoxifene: literature data and clinical evidence. Clin Cases Miner Bone Metab 8(3):29–32
69. Jolly EE, Bjarnason NH, Neven P, Plouffe L Jr, Johnston CC Jr, Watts SD, Arnaud CD, Mason TM, Crans G, Akers R, Draper MW (2003) Prevention of osteoporosis and uterine effects in postmenopausal women taking raloxifene for 5 years. Menopause 10(4):337–344
70. Miller PD, Chines AA, Christiansen C, Hans C, Hoeck HC, Kendler DL, Michael Lewiecki EM, Woodson G, Levine AB, Constantine G, Delmas PD (2008) Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-years results of a randomized, double-blind, placebo-, and active-controlled study. J Bone Miner Res 23:525–535
71. Miller PD, Siris ES, Barrett-Connor E, Faulkner KG, Wehren LE, Abbott TA, Chen YT, Berger ML, Santora AC, Sherwood LM (2002) Prediction of fracture risk in postmenopausal white women with peripheral bone densitometry: evidence from the national osteoporosis risk assessment. J Bone Miner Res 17(12):2222–2230
72. Migliaccio S, Brama M, Spera G (2007) The differential effects of bisphosphonates, SERMS (selective estrogen receptor

modulators), and parathyroid hormone on bone remodeling in osteoporosis. Clin Interv Aging 2(1):55–64
73. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, Christiansen C, Delmas PD, Zanchetta JR, Stakkestad J, Glüer CC, Krueger K, Cohen FJ, Eckert S, Ensrud KE, Avioli LV, Lips P, Cummings SR (1999) Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of raloxifene evaluation (MORE) investigators. JAMA 282(7):637–645
74. Delmas PD, Ensrud KE, Adachi JD, Harper KD, Sarkar S, Gennari C, Reginster JY, Pols HA, Recker RR, Harris ST, Wu W, Genant HK, Black DM, Eastell R (2002) Mulitple outcomes of raloxifene evaluation Investigators. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: 4-year results from a randomized clinical trial. J Clin Endocrinol Metab 87(8):3609–3617
75. Miller PD, Chines AA, Christiansen C, Hans C, Hoeck HC, Kendler DL, Michael Lewiecki EM, Woodson G, Levine AB, Constantine G, Delmas PD (2008) Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-year Results of a Randomized, double-blind, placebo-, and active-controlled study. J Bone Miner Res 23:525–535
76. Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, de Villiers TJ, Constantine GD, Chines AA (2008) Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. J Bone Miner Res 23:1923–1934
77. Silverman S, Chines A, Kendler DL, Kung AW, Teglbjærg CS, Felsenberg D, Mairon N, Constantine GD, Adachi JD (2012) Bazedoxifene study group. Sustained efficacy of bazedoxifene in preventing fractures in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled study. Osteoporos Int 23(1):351–363
78. Palacios S, Silverman SL, de Villiers TJ, Levine AB, Goemaere S, Brown JP, De Cicco Nardone F, Williams R, Hines TL, Mirkin S, Chines AA (2015) Bazedoxifene study group. A 7-year randomized, placebo-controlled trial assessing the long-term efficacy and safety of bazedoxifene in postmenopausal women with osteoporosis: effects on bone density and fracture. Menopause 22(8):806–813
79. Bachman G, Crosby U, Feldman RA, Ronkin S, Constantine GD (2011) Effects of bazedoxifene in non-flushing postmenopausal women: a randomized phase 2 trial. Menopause 18(5):508–514
80. Reed MJ, Kloosterboer H (2004) Tibolone: a selective tissue estrogenic activity regulator (STEAR). Maturitas 48(S1):4–6
81. Ederveen AG, Kloosterboer HJ (2001) Tibolone exerts its protective effect on trabecular bone loss through the estrogen receptor. J Bone Miner Res 16:1651–1657
82. Langer RD, Landgren BM, Rymer J, Helmond FA (2003) OPAL investigators. The OPAL study. The OPAL study: BMD data from a three-year, double-blind, randomized study comparing the effects of tibolone, CEE/MPA and placebo in postmenopausal women. Menopause 10:586–591
83. Gallagher JC, Baylink DJ, Freeman R, McClung M (2001) Prevention of bone loss with tibolone in postmenopausal women; results of two-randomised, double-blind, placebo-controlled, dose finding studies. J Clin Endocrinol Metab 86:4717–4726
84. Rymer J, Robinson J, Fogelman I (2002) Ten years of treatment with tibolone 2.5 mg daily: effects on bone loss in postmenopausal women. Climacteric 5:390–398
85. Cummings SR, Ettinger B, Delmas PD, Kenemans P, Stathopoulos V, Verweij P, Mol-Arts M, Kloosterboer L, Mosca L, Christiansen C et al (2008) The effects of tibolone in older postmenopausal women. N Engl J Med 359:697–708
86. Lello S, Capozzi A, Scambia G (2017) The tissue-selective estrogen complex (bazedoxifene/conjugated estrogens) for the treatment of menopause. Int J Endocrinol 2017:5064725
87. Pazhekattu R, Lau AN, Adachi JD (2015) The tissue-selective estrogen complex: a review of current evidence. Rheumatol Ther 2(1):47–58
88. Reginster J-Y, Ferrari S, Hadji P (2014) Current challenges in the treatment of osteoporosis: an opportunity for bazedoxifene. Curr Med Res Opin 30(6):1165–1176
89. Lobo R, Pinkerton JV, Gass MLS, Dorin MH, Ronkin S, Pickar JH, Constantine G (2009) Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. Fertil Steril 92(3):1025–1038
90. Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G (2009) Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women. Fertil Steril 92(3):1045–1052
91. Mirkin S, Komm BS, Pan K, Chines AA (2013) Effects of bazedoxifene/conjugated estrogens on endometrial safety and bone in postmenopausal women. Climacteric 16(3):338–346
92. Pinkerton JV, Harvey J, Lindsay R, Pan K, Chines AA, Mirkin S, Archer DF (2014) SMART-5 investigators. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. J Clin Endocrinol Metab 99:189–198
93. Jacobsen DE, Samson MM, Kezic S, Verhaar HJ (2007) Postmenopausal HRT and tibolone in relation to muscle strength and body composition. Maturitas 58(1):7–18
94. Clayton AH, Goldstein I, Kim NN, Althof SE, Faubion SS, Faught BM, Parish SJ, Simon JA, Vignozzi L, Christiansen K, Davis SR, Freedman MA, Kingsberg SA, Kirana PS, Larkin L, McCabe M, Sadovsky R (2018) The international society for the study of women's sexual health process of care for management of hypoactive sexual desire disorder in women. Mayo Clin Proc 93(4):467–468
95. Faubion SS, Larkin LC, Stuenkel CA, Bachmann GA, Chism LA, Kagan R, Kaunitz AM, Krychman ML, Parish SJ, Partridge AH, Pinkerton JV, Rowen TS, Shapiro M, Simon JA, Goldfarb SB, Kingsberg SA (2018) Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from the north American menopause society and the international society for the study of women's sexual health. Menopause 25(6):596–608
96. Cairoli E, Palmieri S, Goggi G, Roggero L, Arosio M, Chiodini I, Eller-Vainicher C (2018) Denosumab or oral bisphosphonates in primary osteoporosis: a "real-life" study. J Endocrinol Invest 41(8):1005–1013
97. Migliaccio S, Francomano D, Romagnoli E, Marocco C, Fornari R, Resmini G, Buffa A, Di Pietro G, Corvaglia S, Gimigliano F, Moretti A, de Sire A, Malavolta N, Lenzi A, Greco EA, Iolascon G (2017) Persistence with denosumab therapy in women affected by osteoporosis with fragility fractures: a multicenter observational real practice study in Italy. J Endocrinol Invest 40(12):1321–1326
98. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, Hope S, Kanis JA, McCloskey EV, Poole KES, Reid DM, Selby P, Thompson F, Thurston A, Vine N (2017) National osteoporosis guideline group (NOGG). UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos 12(1):43
99. The Women's Health Initiative Steering Committee (2004) Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the women's health initiative randomized controlled trial. JAMA 291:1701–1712