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REVIEW ARTICLE

Recommendations for raloxifene use in daily clinical practice in the Swiss setting

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Abstract
Background/aim Raloxifene is the first selective estrogen receptor modulator that has been approved for the treatment and prevention of osteoporosis in postmenopausal women in Europe and in the US. Although raloxifene reduces the risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer, it is approved in that indication in the US but not in the EU. The aim was to characterize the clinical profiles of postmenopausal women expected to benefit most from therapy with raloxifene based on published scientific evidence to date.
Methods Key individual patient characteristics relevant to the prescription of raloxifene in daily practice were defined by a board of Swiss experts in the fields of menopause and metabolic bone diseases and linked to published scientific evidence. Consensus was reached about translating these insights into daily practice.
Results Through estrogen agonistic effects on bone, raloxifene reduces biochemical markers of bone turnover to premenopausal levels, increases bone mineral density (BMD) at the lumbar spine, proximal femur, and total body, and reduces vertebral fracture risk in women with osteopenia or osteoporosis with and without prevalent vertebral fracture. Through estrogen antagonistic effects on breast tissue, raloxifene reduces the risk of invasive estrogen-receptor positive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer. Finally, raloxifene increases the incidence of hot flushes, the risk of venous thromboembolic events, and the risk of fatal stroke in postmenopausal women at increased risk for coronary heart disease. Postmenopausal women in whom the use of raloxifene is considered can be categorized in a 2×2 matrix reflecting their bone status (osteopenic or osteoporotic based on their BMD *T*-score by dual energy X-ray

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absorptiometry) and their breast cancer risk (low or high based on the modified Gail model). Women at high risk of breast cancer should be considered for treatment with raloxifene.

Conclusion Postmenopausal women between 50 and 70 years of age without climacteric symptoms with either osteopenia or osteoporosis should be evaluated with regard to their breast cancer risk and considered for treatment with raloxifene within the framework of its contraindications and precautions.

Keywords Raloxifene · Breast cancer · Osteoporosis · Fractures

Introduction

Raloxifene, the first selective estrogen receptor modulator (SERM), induces agonistic and antagonistic estrogenic effects in tissues expressing the estrogen receptor (ER). Raloxifene is approved for the treatment and prevention of osteoporosis in postmenopausal women in the US, EU, and Switzerland. In the latter, the indication section stipulates that treatment initiation with raloxifene for the prevention of postmenopausal osteoporosis requires a *T*-score of −1 SD or less measured by dual energy X-ray absorptiometry (DXA) at either the lumbar spine or the distal forearm [1]. In 2007, raloxifene was approved for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer in the US [2]. To the best of our knowledge, such an indication has not been sought by the manufacturer neither in the EU nor in Switzerland to date.

Since marketing authorization was granted by North American and European registration agencies, four major international clinical endpoint trials with raloxifene have been completed and published: the Multiple Outcomes of Raloxifene Evaluation (MORE) trial [3], the Continuing Outcomes Relevant to Evista (CORE) trial [4], the Raloxifene Use for the Heart (RUTH) [5], and the Study of Tamoxifen and Raloxifene (STAR) [6] trials. These trials included more than 37,000 postmenopausal women with various clinical risk profiles, including long-term follow-up data up to 8 years [7, 8] so that raloxifene belongs to the best studied pharmacotherapies in this patient population.

Fully acknowledging the wealth of efficacy and safety data available for raloxifene but also recognizing that not every woman with a *T*-score below −1 SD will or can be prescribed this therapy, a clinically important challenge in the daily practice of physicians in charge of postmenopausal women care is to identify those women expected to benefit most from such an intervention. In order to assertively recommend or not the daily intake of raloxifene, the decision-making process should ideally rely on available evidence encompassing all facets of the drug's profile, including its effects on bone and invasive breast cancer risk as well as its safety and tolerability aspects.

The aim of the present review was to characterize the clinical profiles of postmenopausal women expected to benefit most from therapy with raloxifene based on published scientific evidence to date. An advisory board composed of Swiss experts in the fields of menopause and metabolic bone diseases was held in March 2011. In a first step, key individual patient characteristics relevant to the prescription of raloxifene in daily practice were identified (Table 1) and linked to published scientific evidence summarized below. Thereafter, a consensus was reached about how these insights could be translated into clinical decision-making in daily practice.

Clinical trials with raloxifene: effects on fracture risk

The World Health Organization (WHO) defined osteoporosis as "a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" [9]. The most frequent complications of the disease are the "typical" osteoporotic fractures occurring at the hip, spine, distal forearm, and proximal humerus. Furthermore, the WHO proposed an operational definition of osteoporosis as a bone mineral density (BMD) that lies 2.5 standard deviations or more below the average mean value of young healthy women (*T*-score ≤−2.5 SD) [9, 10]. Osteopenia was defined as a BMD *T*-score at or below −1.0 SD and higher than −2.5 SD [9, 10].

Table 1 Key patient characteristics underlying the decision of recommending/prescribing raloxifene or not in postmenopausal women in daily practice

Age
Presence or absence of climacteric symptoms
Fracture risk
T-score measured by DXA
FRAX®-score
Breast cancer risk
Cardiovascular risk
Risk of venous thromboembolic event (VTE)
Risk of acute coronary event (AGLA score[a])
Risk of stroke (Framingham Stroke Risk Score)

[a] The AGLA score (10-year risk for an acute coronary event) was derived from the PROCAM-score corrected for epidemiological specificities in the Swiss setting

Treatment of postmenopausal osteoporosis

The effects of raloxifene on fracture incidence and BMD in postmenopausal women with osteoporosis were examined at 3 years in a large randomized, placebo-controlled, double-blind, multinational osteoporosis treatment trial (the MORE trial [3]). The study population consisted of 7,705 postmenopausal women with osteoporosis as defined by either a BMD *T*-score ≤ -2.5 SD at the lumbar spine or the hip without vertebral fractures at baseline or by the presence of one or more vertebral fractures baseline. Women enrolled in this study had a median age of 67 years (range 31–80) and a median time since menopause of 19 years. Compared to placebo, treatment with raloxifene significantly increased BMD at the lumbar spine and the hip at all time points of measurement (12, 24, and 36 months). After 36 months, the risk of morphometric and clinical new vertebral fractures was significantly reduced by 30–50 % with raloxifene compared to placebo. In the fourth year, fracture risk reduction was similar to that in the first 3 years [11]. Furthermore, a post hoc analysis of the subgroup of patients included in MORE, who had osteopenia or osteoporosis diagnosed based on their BMD *T*-score at the hip and no prevalent vertebral fractures at baseline, and were treated with raloxifene 60 mg/day during 3 years, showed a significant reduction in clinical vertebral fracture risk in osteopenic as well as osteoporotic women [12]. Non-vertebral fractures including hip, wrist, and ankle fractures, were numerically less frequent in the raloxifene group but the difference to the placebo group did not reach statistical significance [3]. In a post hoc analysis of the MORE study at 3 years which evaluated the association between vertebral fracture severity at baseline and the risk of new vertebral and non-vertebral fractures, raloxifene 60 mg/day was shown to significantly reduce the risks of new vertebral as well as new non-vertebral fractures in patients with severe pre-existent vertebral fractures by 26 % ($p = 0.048$) and 47 % ($p = 0.046$), respectively [13]. These findings were recently corroborated by reanalyzing the anti-fracture efficacy of raloxifene as a function of individual fracture risk assessed by FRAX® (plus BMD) at baseline (see below) [14]. This analysis showed that the effectiveness of raloxifene for clinical fractures was comparable over the whole range of FRAX® probabilities [14]. While this finding is consistent with earlier observations showing the absence of interaction between baseline BMD and the magnitude of treatment efficacy with raloxifene [12] and no difference in efficacy between women with or without clinical risk factors for osteoporosis [15], they are not consistent with results obtained with the bisphosphonate clodronate [16] and with another SERM, bazedoxifene [17], where treatment efficacy was greater at higher fracture probabilities. The reasons for these discrepant findings are speculative and have been discussed earlier [12, 14]. Based on currently available evidence and consistent with the detailed indication of raloxifene in Switzerland, "treatment of osteoporosis with raloxifene results in a reduction of incident vertebral fractures. A reduction of incident non-vertebral fractures has remained so far unproven" [1].

The CORE trial examined the effect of four additional years of raloxifene therapy on the incidence of invasive breast cancer in women in MORE who agreed to continue [4, 18]. In CORE, women assigned to raloxifene in MORE ($n = 3{,}510$) were assigned to receive raloxifene 60 mg/day, while women assigned to placebo continued on placebo ($n = 1{,}703$). Concomitant use of bone active agents was permitted in the fourth year of MORE and during CORE [7]. Although raloxifene maintained the increases of lumbar spine and femoral neck BMD over 7 years after randomization in MORE, no effect on non-vertebral fracture risk was shown after 8 years [7]. However, it should be noted that the CORE trial had important limitations regarding skeletal endpoints because of its design as a breast cancer prevention study, of the predominant use of bone active substances in the placebo group, and of included patients being at lower risk of non-vertebral fractures than those included in fracture endpoint trials with bisphosphonates, such as the fracture intervention trial (FIT) with alendronate [7, 19] or the HORIZON trial with zoledronate [20].

Finally, in the RUTH trial, in which women were selected based on their increased risk for coronary events, the risk of clinical vertebral fractures (secondary endpoint) was significantly reduced by 35 % (hazard ratio 0.65, 95 % CI 0.47–0.89) with raloxifene 60 mg/day compared to placebo after a median follow-up of 5.6 years [21].

Prevention of postmenopausal osteoporosis

When leaving hormone replacement therapy out of consideration, SERMs, of which raloxifene, are the only bone active substances currently indicated and reimbursed in Switzerland for the prevention of postmenopausal osteoporosis in women with a *T*-score at or below -1.0 SD measured by DXA.

The effects of raloxifene on BMD in postmenopausal women were examined in two randomized, placebo-controlled, double blind osteoporosis prevention trials of 2 years duration: a European [22] and a North American trial [23] of similar design which enrolled 601 and 544 women, respectively. In these trials, all women received calcium supplementation (400–600 mg/day). Women enrolled had a mean age of 55 years (range 45–60 years) and a mean time since menopause of 5 years (from less than 1 up to 15 years). Mean BMD *T*-score at inclusion

ranged from −1.01 to −0.74 at the lumbar spine so that women both with normal BMD and osteopenia were included. Raloxifene 60 mg/day produced statistically significant increases in hip, spine, and total body BMD versus calcium supplementation alone already 12 months after initiation of therapy, an effect which was maintained at 24 [22], 36 [23], and 60 [24] months after initiation of therapy. Consistent findings were reported in another randomized placebo- and active-controlled trial in 619 hysterectomized postmenopausal women [25].

Raloxifene and FRAX®

Recently, the use of fracture probability assessment algorithms based on clinical risk factors has been shown to enhance the performance of BMD in the prediction of hip and osteoporotic fractures in men and women [26]. In order to identify the major clinical risk factors for osteoporotic fracture, the data from 9 prospective primary cohorts and 11 prospective validation cohorts, including more than 275,000 persons corresponding to 1.4 million person-years with more than 22,711 reported fractures were analyzed [26]. The validation analysis included the results from the Swiss SEMOF-cohort [27]. In addition to any prior fragility fracture that occurred after age 50, age, sex, and body mass index, further risk factors were considered. These included prior use of glucocorticoids, secondary osteoporosis, rheumatoid arthritis, a history of parental hip fracture, current cigarette smoking, and alcohol intake of 3 or more units/day. These factors were identified as clinical predictors of osteoporotic fracture probability [26]. Taking into account local epidemiological data, the impact of these risk factors on the 10-year absolute probability of fracture allows for country-specific prediction of individual fracture probability, based on the individual risk factor profile. This case-finding algorithm developed in collaboration with the WHO, known as FRAX® (http://www.shef.ac.uk/FRAX), has been calibrated for Swiss-specific fracture probability and life expectancy [28–30].

Recently, the skeletal effects of raloxifene versus placebo on the risk of all clinical fractures and morphometric vertebral fractures in MORE were evaluated as a function of baseline fracture risk assessed by FRAX® [14]. The 10-year probability of major osteoporotic fractures (with BMD) at baseline ranged from 0.9 to 77.2 %. Compared to placebo, treatment with raloxifene was associated with an 18 % decrease in all clinical fractures treatment ($p = 0.0063$) and a 42 % decrease in new morphometric vertebral fractures ($p < 0.001$) over the whole range of fracture risk at baseline. Furthermore, another singularity was that although vertebral fracture risk was reduced at all ages the efficacy of raloxifene on vertebral fracture risk was significantly greater in women younger than 75 years of age [14]. However, as absolute risk reduction increased with age and with the FRAX® score in all age groups, high risk women should also be targeted for treatment.

In summary, raloxifene acts as an estrogen agonist in bone. Raloxifene reduces biochemical markers of bone turnover to premenopausal levels [3, 11, 22, 23], increases BMD at the lumbar spine, proximal femur, and total body [3, 22–24, 31] and reduces vertebral fracture risk in women with osteopenia (BMD *T*-score at or below −1.0 SD and higher than −2.5 SD) or osteoporosis (BMD *T*-score ≤−2.5 SD) with and without prevalent vertebral fracture [3, 12, 21, 31]. FRAX® plus BMD might contribute to targeting intervention at younger women with clinical risk factors and to identifying women at highest risk [14].

Clinical trials with raloxifene: effects on the incidence of invasive breast cancer

At a very early stage of drug development, during MORE, it became evident that raloxifene may play an important role in reducing the incidence of invasive breast cancer in postmenopausal women. In the MORE trial, 13 cases of breast cancer were confirmed among the 5,129 women assigned to raloxifene versus 27 among the 2,576 women assigned to placebo, corresponding to a 76 % relative risk reduction ($p < 0.001$) [32]. Raloxifene decreased the risk of estrogen-receptor (ER) positive breast cancer by 90 % and had no effect on ER-negative breast cancer incidence [32]. Its effect was greater in women with detectable baseline serum estradiol levels >10 pg/ml [33].

Later, these findings were confirmed in the CORE trial, a follow-up to the MORE trial, with invasive breast cancer now the primary endpoint. During the 4 years of the CORE trial, 31 cases of breast cancer were confirmed in the 3,510 women on raloxifene versus 30 in the 1,703 women on placebo [4]. Over the 4 years of the CORE trial, the overall incidence of breast cancer, regardless of invasiveness, was reduced by 50 % ($p = 0.005$) in the raloxifene group compared with the placebo group [4]. The incidence of invasive breast cancer was significantly reduced by 59 % ($p < 0.001$) and the incidence of invasive estrogen-receptor positive breast cancer by 66 % ($p < 0.001$) [4]. Raloxifene had no effect on the incidence of non-invasive breast cancer and of ER-negative breast cancer. Similar observations were made in the full MORE and CORE cohort followed over 8 years [4]. Raloxifene therapy was associated with a reduced breast cancer risk in both women at lower and those at higher breast cancer risk [18]. Raloxifene was especially effective in women with higher estrogen levels at baseline, older than 65 years of age, and a history of breast cancer in their first-degree relatives [18].

In the RUTH trial which recruited postmenopausal women at increased risk of coronary events, raloxifene

reduced the risk of invasive breast cancer in lower risk, older women by 44 % ($p = 0.003$) [5, 34]. Similar to the findings in the MORE and CORE trials, raloxifene exclusively reduced the incidence of estrogen-receptor positive invasive breast cancer, representing the majority of all diagnosed cancers, by 55 % ($p < 0.001$) [5, 34].

Finally, the National Surgical Adjuvant Breast and Bowel Project (NSABP) conducted the prospective, double-blind, randomized, active-controlled Study of Tamoxifen and Raloxifene (STAR) [6, 35] which included 19,747 postmenopausal women (82 % of them between 50 and 69 years of age) at high risk for developing breast cancer. Based on the modified Gail model, high risk of breast cancer was defined as: at least one breast biopsy showing lobular carcinoma in situ (LCIS) or atypical hyperplasia; one or more first-degree relatives with breast cancer; or a 5-year predicted risk of breast cancer $\geq$1.66 %. Participants were randomly assigned to receive either tamoxifen at a dose of 20 mg/day or raloxifene 60 mg/day over 5 years. The primary endpoint was the incidence of invasive breast cancer. After a median of 3.2 years of therapy in the STAR trial, the incidence of invasive breast cancer was 4.3 per 1,000 versus 4.4 per 1,000 (RR = 1.02; 95 %CI, 0.82 to1.28) in the groups assigned to tamoxifen and raloxifene, respectively [6]. There were fewer cases of non-invasive breast cancer in the tamoxifen group (57 cases) than in the raloxifene group (80 cases), even if this difference did not reach statistical significance [6]. Keeping in mind that non-invasive breast cancer is not a life-threatening event, these findings are consistent with earlier results showing that tamoxifen reduces the risk of non-invasive breast cancer in women aged 35 years and older at high risk for breast cancer [36]. On the other hand, as shown in STAR, raloxifene had similar effectiveness as tamoxifen in reducing the risk of progression to invasive breast cancer for women who entered the trial with a history of either lobular carcinoma in situ or atypical hyperplasia [6].

In summary, raloxifene acts as an estrogen antagonist in breast tissue. Raloxifene reduces the risk of invasive estrogen-receptor positive breast cancer in postmenopausal women with osteoporosis [4, 32] and in postmenopausal women at high risk for invasive breast cancer [6]. Evidence regarding the effects of raloxifene in the treatment of invasive breast cancer and the reduction of risk of recurrence of breast cancer is insufficiently substantiated.

Other gynecologic effects of raloxifene

The incidence of uterine bleeding, endometrial hyperplasia, and uterine cancer was comparable to that under placebo in the MORE–CORE and RUTH trials [4, 5, 8]. In the STAR trial, the incidence of endometrial hyperplasia was significantly lower with raloxifene compared to tamoxifen (RR = 0.16, 95 %CI 0.09–0.29) [6]. Uterine cancers were numerically less with raloxifene but this difference did not reach statistical significance (annual incidence of 1.25 vs. 2.00 per 1,000 women, RR 0.62, 95 %CI 0.35–1.08) [6]. The latter non-significant trend may be explained by the significantly lower number of women undergoing hysterectomy under raloxifene vs. tamoxifen (111 vs. 244, RR 0.44, 95 %CI 0.35–0.56) [6].

In addition, the incidence of ovarian cancer was comparable to that under placebo in the MORE–CORE and RUTH trials [5, 8].

Overall, it can safely be stated that raloxifene has no detrimental effects on the endometrium.

Clinical trials with raloxifene: safety profile

Venous thromboembolic events

Venous thromboembolic events (VTE), including deep vein thrombosis, retinal vein thrombosis, and pulmonary embolism are serious albeit uncommon adverse events reported with raloxifene in all major endpoint trials. Of the 4,011 participants in MORE–CORE, after 8 years of therapy with either raloxifene (n = 2,725) or placebo (n = 1,286), VTEs were 1.7-fold more frequent with raloxifene [absolute VTE rates of 2.2 and 1.3 per 1,000 women-years ($p = 0.094$), respectively] [4]. Deep vein thrombosis and retinal vein thrombosis were numerically more frequent with raloxifene without reaching statistical significance (31 vs. 10 and 6 vs. 2 cases, respectively). However, pulmonary embolism was significantly more frequent with raloxifene (17 vs. 2 events, $p = 0.048$) [4]. Comparable increases in VTE risk were reported in the RUTH trial [5]. It was suggested that VTE risk might be greatest within the first months of initiation of therapy. However, this observation from the MORE study has neither been confirmed in subsequent analyses nor in major clinical trials [8, 37]. In STAR, the incidence of VTE was significantly lower with raloxifene than with tamoxifen [RR = 0.70 (95 %CI 0.54–0.91); 2.61 vs. 3.71 events per 1,000 women-years, respectively] [6]. Advanced age, immobilization, surgery, trauma, and cancer belong to the most important risk factors for VTE. Two-thirds of the women who presented a VTE in the MORE trial had one of these risk factors, most commonly immobilization [38]. Therefore, raloxifene should not be used in women with a history or at increased risk of VTE. It should be stopped before and during periods of immobilization such as for surgery or trauma [37].

In summary, raloxifene increases the risk of VTE and is contra-indicated in patients with present or past deep vein

thrombosis, retinal vein thrombosis, pulmonary embolism, or presenting typical risk factors for VTE.

Acute coronary events

Raloxifene lowers total and low density lipoprotein cholesterol and the ratio of apolipoprotein B to apolipoprotein A1 [22, 25, 39], all known as established risk factors for coronary heart disease. In MORE and MORE–CORE, raloxifene had no effect on the incidence of coronary events reported as safety but not primary endpoints [5, 40]. Postmenopausal women included in the RUTH trial were at increased risk for coronary events defined as either the presence of established coronary heart disease or a cardiovascular risk score of 4 points or more according to a point system taking into account the following: established CHD (4 points), arterial disease of the leg (4 points), an age of at least 70 years (2 points), diabetes mellitus (3 points), cigarette smoking (1 point), hypertension (1 point), and hyperlipidemia (1 point) [5]. Compared to placebo, raloxifene did not reduce the risk of coronary events (death from coronary causes, myocardial infarction or hospitalization with an acute coronary syndrome), the primary endpoint (hazard ratio 0.95, 95 %CI 0.84–1.07). However, in contrast to clinical endpoint trials conducted with estrogen–progestin regimens [41, 42], raloxifene did not increase coronary risk in these patients.

In summary, raloxifene does not significantly affect the risk of coronary heart disease.

Stroke

A surprising finding of the RUTH trial was that raloxifene was associated with an increased risk of fatal stroke versus placebo (59 vs. 39 events during 5.6 years of observation, hazard ratio 1.49, 95 %CI 1.00–2.24, $p = 0.05$) [5]. Such an increased incidence of fatal stroke was neither found in the MORE trial [43] nor in any other major trial [5, 8]. As in the MORE and MORE–CORE trials, the overall incidence of stroke was not significantly different between groups [5, 8, 43]. It was suggested that this inconsistent finding could be related to the heterogeneity in risk in the patient populations included in MORE–CORE and RUTH. That is, the higher prevalence of hypertension and diabetes in women included in RUTH compared to women included in MORE–CORE (31 vs. 78 % and 3 vs. 46 %, respectively) [5, 37, 40]. Furthermore, a post hoc analysis of the RUTH results showed that women with a Framingham Stroke Risk Score (FSRS) <13 showed no increase in raloxifene-associated fatal stroke risk, suggesting that even in women at high risk for coronary events, those at highest risk for stroke may be exposed to a risk of fatal stroke [44]. The FSRS estimates the risk for first stroke based on age, systolic blood pressure, presence of diabetes and non-cerebrovascular disease, cigarette smoking, atrial fibrillation and left ventricular hypertrophy [44].

In daily practice in Switzerland, the 10-year risk for an acute coronary event in postmenopausal women is calculated using the widely recommended AGLA score developed by the Working Group on Lipids and Atherosclerosis of the Swiss Society of Cardiology [45]. The AGLA score was derived from the German PROCAM score [46, 47] by adapting the algorithms to the Swiss setting. Based on the AGLA score, the 10-year probability for a coronary event can be categorized into low (<10 %), moderate (10–20 %) and high risk (>20 %) based on the following risk items: age, systolic blood pressure, presence of diabetes, history of myocardial infarction before the age of 60 years in a first grade relative, cigarette smoking, serum levels of LDL and HDL cholesterol, and serum triglycerides [45].

Therefore, while some input parameters of the FSRS and the AGLA score overlap, others do not. Special attention should be given to the latter, i.e., the presence of a personal history of cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy.

Taken together, raloxifene increased the risk of fatal stroke in postmenopausal women at increased coronary risk [5] but not in postmenopausal women with osteoporosis who were at low risk for coronary events [5, 8, 43]. In postmenopausal women at increased coronary risk, raloxifene should be used after cautious consideration of the risk–benefit balance in women at increased risk of stroke, including those with a personal history of cerebrovascular disease (stroke and transient ischemic attacks), atrial fibrillation, hypertension, and in those who smoke.

Overall mortality

A pooled analysis of mortality data was performed from large clinical trials of raloxifene (60 mg/day) versus placebo [48]. In the MORE–CORE trials, there were 45 deaths among women assigned to raloxifene 60 mg/day versus 65 among women assigned to placebo. Overall mortality was 32 % lower among participants assigned to raloxifene 60 mg/day versus placebo (1.8 vs. 2.5 %; $p = 0.04$) with a lower rate of deaths due to cancer (0.5 vs. 1.0 %; $p = 0.04$) and a non-significant difference in deaths due to cardiovascular causes (0.6 vs. 0.8 %). In the RUTH trial, overall and cardiovascular mortality did not differ between treatment groups. However, cerebrovascular mortality was significantly greater (1.2 vs. 0.8 %; $p = 0.05$) and non-cardiovascular mortality significantly lower (3.7 vs. 4.6 %; $p = 0.03$) in the raloxifene group [48].

Other patient characteristics for raloxifene treatment eligibility

Climacteric symptoms

Hot flushes were significantly more frequent in women receiving raloxifene 60 or 120 mg/day (9.7 and 11.6 %, respectively) than in women receiving placebo (6.4 %, $p < 0.001$) in the MORE trial. These findings were confirmed in the CORE trial (12.6 vs. 6.9 %, $p < 0.001$) and in the RUTH trial (8.0 vs. 4.8 %, $p < 0.001$). In osteoporosis prevention studies, i.e., in younger women with shorter time since menopause than those included in the four major endpoint trials, hot flushes were numerically but not significantly more frequent in women on raloxifene than on placebo (24.6 vs. 18.3 % [49] and 26.3 vs. 22.7 % [22], respectively). These findings are consistent with the results of a randomized controlled trial aimed at evaluating the potential of raloxifene to induce or exacerbate hot flushes: 487 postmenopausal women were randomized to either treatment for 8 months with raloxifene or placebo. At baseline, 40.4 % of all randomly assigned patients had hot flushes. Shorter time since menopause, surgical menopause, and previous estrogen-based therapy were significant predictors of hot flushes at baseline but not of incident hot flushes during treatment with raloxifene [50]. Slow-dose escalation (i.e. 60 mg of raloxifene every other day during 2 months before increasing to standard dose of 60 mg/day) was suggested to reduce the incidence of hot flushes [51]. Therefore, the ideal raloxifene patient should be a postmenopausal woman which presents without climacteric symptoms at the time of treatment initiation.

Age

Although experience with raloxifene in clinical trials covers an age range between 31 and 92 years, the vast majority of patients included in major clinical endpoint trials were postmenopausal women aged between 50 and 70 years (Table 2). Therefore, the typical raloxifene patient is a post-menopausal woman between 50 and 70 years of age. Taking into account climacteric symptoms (see below), the lower boundary of this age range may rather be 52 to 55 years.

In summary, the typical raloxifene patient is a postmenopausal woman between 50 and 70 years of age. As raloxifene increases the incidence of hot flushes, it seems appropriate to recommend treatment initiation with raloxifene in daily practice only in women not presenting with hot flushes.

Recommendations for the use of raloxifene in daily practice in the Swiss setting

Based on these considerations, the approach below was developed for identifying postmenopausal women in whom raloxifene may be prescribed on a routine basis in daily practice.

Step 1: which women should be evaluated?

All postmenopausal women between 50 and 70 years of age who do not present with climacteric symptoms.

Table 2 Synopsis of the major randomized controlled endpoint trials designs with raloxifene in postmenopausal women

	MORE [3]	CORE [4]	STAR [5]	RUTH [6]
Duration of observation	40 months	48 months	47 months	5.6 years
n randomized (*n* by treatment groups)	7,705 (5,129 raloxifene 2,576 placebo)	4,011 (2,725 raloxifene, 1,286 placebo)	19,747 (9,745 raloxifene, 9,726 tamoxifen)	10,101 (5,044 raloxifene, 5,057 placebo)
Age at inclusion (years)	Mean 66.5 SD 7.0 Range 31–80	Mean 65.8 SD 6.8	Mean 58.5 SD na Range 35–83 (72 % were between 50 and 70)	Mean 67.5 SD 6.6 Range 55–92 (39 % were ≥70)
Main inclusion criteria	Documented osteoporosis (*T* -score ≤−2.5 SD at LS or FN or low BMD and vertebral fracture)	Subset of MORE	5-year predicted breast cancer risk ≥1.66 based on the Gail model	Established coronary heart disease or at increased risk for major coronary events
Primary endpoint	Vertebral fractures LS and FN BMD	Invasive breast cancer	Invasive breast cancer	Coronary events, Invasive breast cancer

MORE Multiple Outcomes of Raloxifene Evaluation, *CORE* Continuing Outcomes Relevant to Evista, *STAR* Study Of Tamoxifen and Raloxifene, *RUTH* Raloxifene Use for the Heart

Step 2: when should raloxifene not be used?

Raloxifene is contraindicated in patients with current or past history of venous thromboembolism, including deep vein thrombosis, retinal vein thrombosis, pulmonary embolism, or presenting typical risk factors for venous thromboembolic events.

Raloxifene should be used cautiously in women at high risk for coronary events (AGLA score >20 %). In these patients, the increased risk of fatal stroke may be limited to those with Framingham Stroke risk Score ≥13.

In addition, raloxifene should be avoided in women presenting with vasomotor symptoms.

According to the Swiss prescribing information of EVISTA®, raloxifene is contra-indicated in pregnant women; in women with current or past history of venous thromboembolism, including deep vein thrombosis, retinal vein thrombosis, and pulmonary embolism; in women with hypersensitivity against raloxifene or any of the components of the tablet; in women with liver insufficiency, including cholestasis, or severe renal insufficiency; in women with uterine bleedings of unknown origin; and in women with clinical signs or symptoms of endometrial carcinoma.

Step 3: how should these women be evaluated?

Based on its currently reimbursed indication in Switzerland, raloxifene [EVISTA® (raloxifene hydrochloride)] will preferably be used for the treatment and prevention of osteoporosis with a BMD *T* -score of −1.0 SD or less or in the presence of fracture [52]. Thus, decision-making should first rely on the categorization of patients as either osteopenic or osteoporotic, based on the operational definitions proposed by the WHO [53]. Thereafter, individual breast cancer risk should be evaluated based on the modified Gail model [54, 55] used for inclusion in the STAR trial [6]. High risk for breast cancer was defined as at least one breast biopsy showing LCIS or atypical hyperplasia, one or more first-degree relatives with breast cancer, or a 5-year predicted risk of breast cancer ≥1.66 % [2].

As shown in Fig. 1, postmenopausal women in whom the use of raloxifene is considered can be categorized in a 2 × 2 matrix reflecting their bone status (osteopenic or osteoporotic based on their BMD *T*-score by DXA) and their breast cancer risk (low or high based on the modified Gail model).

In women with osteopenia and at low risk for breast cancer, the decision of using raloxifene (or not) will primarily rely on clinical judgment. This decision may be supported by increased levels of biochemical markers of bone turnover. Casually, a high FRAX® score may give some orientation, while keeping in mind that the FRAX® algorithm calculates the clinical risk factor based individual 10-year probability of either hip or major osteoporotic fracture (pooled hip, clinical spine, distal radius, and proximal humerus fractures). Thus, FRAX® does not provide an estimate of the individual 10-year probability of suffering a (morphometric or clinical) vertebral fracture, while raloxifene was consistently shown to reduce morphometric vertebral fracture risk only.

In women with a *T*-score at or below −2.5 SD with or without prevalent vertebral fractures bisphosphonates [19, 20, 56] and more recently the monoclonal antibody denosumab [57] have been shown to consistently reduce the risk of vertebral and non-vertebral fractures, including hip fractures. Even in the absence of direct comparative fracture endpoint trials between raloxifene and these substances, it seems reasonable to assume that bisphosphonates and

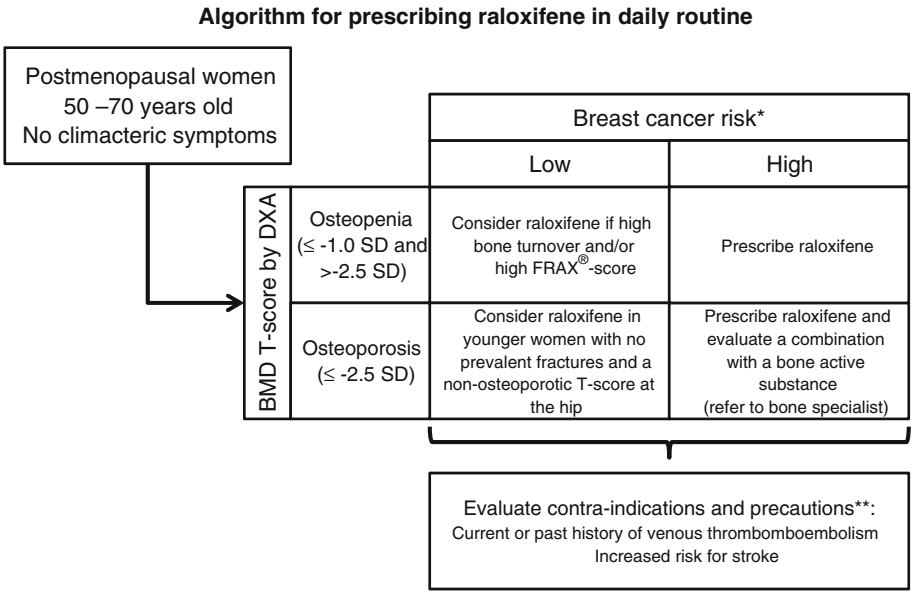

Fig. 1 Algorithm for raloxifene use in daily practice. *High risk of breast cancer defined as at least one breast biopsy showing lobular carcinoma in situ (LCIS) or atypical hyperplasia, one or more first-degree relatives with breast cancer, or a 5-year predicted risk of breast cancer ≥1.66 % (based on the modified Gail model).**Refer to text and full prescribing information for detailed contra-indications

denosumab may have a superior efficacy profile in this patient population in which the primary goal of therapy is to reduce vertebral as well as non-vertebral fracture risk. Therefore, in women with osteoporosis and at low risk for breast cancer, raloxifene can be considered for younger women without prevalent vertebral fractures and a non-osteoporotic *T*-score at the hip.

In women with osteopenia and at high risk of breast cancer, raloxifene can be broadly recommended in daily practice for the vast majority of eligible women without contra-indications. In this patient population, raloxifene preserves BMD [22, 23, 25] and reduces the risk of new vertebral fractures, including clinical fractures [3, 11] as well as the risk of incident invasive breast cancer [4–6, 32]. Interestingly, the cost-effectiveness of raloxifene was evaluated in the UK healthcare setting considering for the first time its effects on bone and on the breast [58]. Raloxifene was shown to be cost-effective in cohorts of young postmenopausal women, who do not meet the 10-year fracture risk threshold suggested by the British National Osteoporosis Foundation because cost-effectiveness was contingent on their 5-year invasive breast cancer risk. The result highlights the importance of considering a woman's full risk profile when considering anti-osteoporosis treatment [58].

Similar considerations apply to postmenopausal women with osteoporosis and a high risk of breast cancer. However, the combination of raloxifene with a bone active substance proven to reduce also non-vertebral and hip fracture risk should be considered. The combination therapy with raloxifene and alendronate was evaluated in a randomized active-controlled 12-month trial in 331 postmenopausal women with a BMD *T*-score below −2.0 SD at the femoral neck [59]. The association of raloxifene + alendronate reduced bone turnover more than either drug alone, resulting in greater BMD increment. Whether these additive effects would result in improved anti-fracture efficacy could not be shown by this trial. However, beneficial effects on bone volume resulting in improved structural properties of vertebral bone were demonstrated with the combination of alendronate + raloxifene in rats [60]. Thus, the available evidence regarding the efficacy of raloxifene combined with another bone active substance is scarce and its safety with regard to the potential risk of over-suppression of bone turnover is unknown. In daily practice, the decision to use a combination of raloxifene and a bone active substance should rely on prior advice of a bone specialist.

Conclusions

Postmenopausal women between 50 and 70 years of age without climacteric symptoms with either osteopenia or osteoporosis should be evaluated with regard to their breast cancer risk. Women at high risk of breast cancer should be considered for treatment with raloxifene within the framework of its contraindications (VTE) and precautions (stroke risk).

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