**ORIGINAL ARTICLE**

# Menopausal hormone therapy reduces the risk of fracture regardless of falls risk or baseline FRAX probability—results from the Women's Health Initiative hormone therapy trials

Mattias Lorentzon[1,2,3] · Helena Johansson[3,4] · Nicholas C. Harvey[5,6] · Enwu Liu[3] · Liesbeth Vandenput[3,7] · Carolyn J. Crandall[8] · Jane A. Cauley[9] · Meryl S. LeBoff[10,11] · Eugene V. McCloskey[12,13] · John A. Kanis[3,4]

## Abstract

*Summary* In a combined analysis of 25,389 postmenopausal women aged 50–79 years, enrolled in the two Women's Health Initiative hormone therapy trials, menopausal hormone therapy vs. placebo reduced the risk of fracture regardless of baseline FRAX fracture probability and falls history.

**Introduction** The aim of this study was to determine if the anti-fracture efficacy of menopausal hormone therapy (MHT) differed by baseline falls history or fracture risk probability as estimated by FRAX, in a combined analysis of the two Women's Health Initiative (WHI) hormone therapy trials.

**Methods** A total of 25,389 postmenopausal women aged 50–79 years were randomized to receive MHT ($n = 12,739$) or matching placebo ($n = 12,650$). At baseline, questionnaires were used to collect information on falls history, within the last 12 months, and clinical risk factors. FRAX 10-year probability of major osteoporotic fracture (MOF) was calculated without BMD. Incident clinical fractures were verified using medical records. An extension of Poisson regression was used to investigate the relationship between treatment and fractures in (1) the whole cohort; (2) those with prior falls; and (3) those without prior falls. The effect of baseline FRAX probability on efficacy was investigated in the whole cohort.

**Results** Over $4.3 \pm 2.1$ years (mean $\pm$ SD), MHT (vs. placebo) significantly reduced the risk of any clinical fracture (hazard ratio [HR] 0.72 [95% CI, 0.65–0.78]), MOF (HR 0.60 [95% CI, 0.53–0.69]), and hip fracture (0.66 [95% CI, 0.45–0.96]). Treatment was effective in reducing the risk of any clinical fracture, MOF, and hip fracture in women regardless of baseline FRAX MOF probability, with no evidence of an interaction between MHT and FRAX ($p > 0.30$). Similarly, there was no interaction ($p > 0.30$) between MHT and prior falls.

**Conclusion** In the combined WHI trials, compared to placebo, MHT reduces fracture risk regardless of FRAX probability and falls history in postmenopausal women.

## Introduction

The two parallel Women's Health Initiative (WHI) placebo-controlled, randomized, clinical trials were designed to investigate the effect of menopausal hormone therapy (MHT) on a number of chronic diseases in healthy postmenopausal women [1]. These trials investigated either the effect of conjugated equine estrogen (CEE) alone vs. placebo, or a combination of CEE and medroxyprogesterone acetate (MPA) vs. placebo. Both these treatment regimens reduced the risk of any fracture, vertebral fracture, and hip fracture [2, 3], but conversely increased the risk of stroke and deep vein thrombosis and were at the time deemed to have no overall net health benefit, resulting in the recommendation that they are not indicated for the prevention of chronic disease in postmenopausal women [1, 2, 4, 5]. Subsequent subgroup reanalyses of WHI study data revealed that the benefit-to-risk relationship for the CEE alone trial was more favorable in younger postmenopausal women and that MHT was associated with reduced overall mortality in

✉ Mattias Lorentzon
  mattias.lorentzon@medic.gu.se

Extended author information available on the last page of the article

younger women, aged 50–59 years, but had no survival benefit in older women [6]. MHT is currently recommended for the treatment of menopausal symptoms in women younger than 60 years or within 10 years of menopause onset and can be considered to treat osteoporosis in osteoporotic women who do not tolerate other osteoporosis medication [5, 7, 8].

FRAX is a computer-based algorithm used to determine fracture probability in men and women, based on several easily identifiable clinical risk factors, including prior fracture, parental hip fracture, current smoking, and oral glucocorticoid use, and can be used with or without bone mineral density (BMD). It calculates the 10-year probability of major osteoporotic fracture (MOF; clinical spine, hip, forearm, or humerus) and hip fracture alone [9].

Several medications developed to treat osteoporosis, including denosumab, clodronate, romosozumab, and bazedoxifene [10–13], have been shown to be more effective in patients with higher, rather than lower pre-treatment fracture probabilities, although no apparent interactions between fracture probability and treatment efficacy were observed for other osteoporosis medication such as teriparatide, abaloparatide, raloxifene, and strontium ranelate [14–18]. Whether or not MHT is equally effective across the range of pre-treatment fracture probability as assessed by FRAX has not yet been investigated.

Assessment of falls risk has been demonstrated to improve fracture prediction in addition to other clinical risk factors and BMD in both men and women [19, 20]. Prior falls or other indicators for fall risk are not included in the currently used FRAX model [9], although the predictive value of FRAX probability for incident falls has been demonstrated in men [21]. In the Hip Intervention Program Study, the effect of oral risedronate in reducing fracture risk was not evident in older women included due to the presence of non-skeletal risk factors, primarily high falls risk [22]. Therefore, it can be argued that treatments, such as MHT, which increase BMD, may not be effective in preventing fractures in women at high risk of fracture due to increased falls risk. Identifying postmenopausal women with high fracture risk, either by calculating FRAX or investigating falls risk, would only be meaningful if the available interventions have a beneficial effect in lowering the increased risk.

The aim of the present study was to determine if MHT was equally effective in reducing fractures in postmenopausal women included in the two combined WHI trials, across the range of falls risk or fracture probability at the time of inclusion.

## Methodsis

### Participants

The present analysis is based on women included in the two WHI randomized controlled trials investigating either the effect of 0.625 mg/d of CEE vs. placebo ($n = 10,739$) or 0.625 mg/day of CEE and MPA 2.5 mg/day vs. placebo ($n = 16,608$). Eligibility criteria and recruitment methods have been described in detail previously [23–25]. In summary, healthy postmenopausal women, 50–79 years old at the time of inclusion, were recruited at 40 centers throughout the USA, starting in 1993. The present analysis was limited to the 25,389 women (93%) with available data on FRAX probabilities and previous falls. Women were followed for the duration of treatment, until July 9th, 2002, for the CEE + MPA trial or until February, 2004, for the CEE alone trial. The average follow-up time was 6.8 and 5.2 years for the CEE alone and the CEE + MPA trials, respectively [1, 2].

### Fracture outcomes

Data regarding fractures during follow-up were collected using questionnaires administered at the semi-annual visits for all participants. All clinical fractures, other than fractures of the ribs, sternum, skull, face, fingers, toes, and cervical vertebrae, were adjudicated and verified using medical records at each participating clinical center. Hip fractures were also adjudicated centrally by trained physicians blinded to treatment allocation [1]. Major osteoporotic fracture (MOF) comprised fractures of the spine, hip, forearm, and proximal humerus [26]. For each respective fracture outcome, only the first fracture was counted.

### Risk factors for fracture and previous falls

All women completed the WHI questionnaire at baseline to collect data regarding fracture history, medications, family history of hip fracture, past medical history (rheumatoid arthritis), high alcohol consumption (3 glasses of alcohol-containing drinks per day or more), and current smoking. Oral glucocorticoid treatment was recorded as use at least 3 times per week in the month prior to the baseline assessment. Previous fracture (yes/no) at baseline was recorded for all fractures after the age of 55 years. Apart from oral glucocorticoid use and rheumatoid arthritis (both FRAX input variables), secondary causes of osteoporosis were very rare and not considered and the "Secondary Osteoporosis" input variable for FRAX probability calculations was set to no for all study participants [20]. Information regarding the number of falls during the 12 months prior to the baseline visit was collected using a self-assessment questionnaire.

### Statistical methods

This was an intention to treat (ITT) analysis. For the effects of MHT on fracture outcomes, an extension of the Poisson

regression model was used [27]. In contrast to logistic regression, the Poisson regression utilizes the length of each individual's follow-up period, and the hazard function is assumed to be exp ($\beta 0 + \beta 1 \cdot$ time from baseline $+ \beta 2 \cdot$ current age $+ \beta 3 \cdot$ current variable of interest). The observation period of each participant was divided in intervals of 1 month. One fracture per person was counted, and time to the first fracture or time at risk was censored at the time of first fracture, loss to follow-up, death, or end of follow-up. Deaths were ascertained from the National Death Index and reports from family members/physicians.

For the assessment of overall efficacy, the following regression model was used: (1) constant, (2) current time, (3) current age, (4) treatment (MHT versus placebo, where 1 = menopausal hormone therapy and 0 = placebo). The interaction between MHT and 10-year MOF probability was examined with the model: (1) constant, (2) current time, (3) current age, (4) treatment (MHT versus placebo), (5) 10-year probability, (6) treatment × 10-year probability.

Hazard ratios (HR) for treatment effect and 95% confidence intervals (95% CI) were computed as a continuous variable. For ease of presentation in tables, percent relative risk reduction (RRR = 100 − hazard ratio × 100) is shown for fracture outcomes and presented at the 10th, 25th, 50th, 75th, and 90th percentile of fracture probability for MOF. Models were adjusted for age and time since baseline and participation in the DM (Dietary Modification) trial and CAD (Calcium and Vitamin D) trial [23]. Two-sided *p* values were used for all analyses and *p* < 0.05 considered to be significant in all analyses except for analyses of interaction terms, for which *p* values < 0.10 were considered significant.

# Results

The total follow-up period for all 25,389 women included was 4.3 ± 2.1 years (mean ± SD). The 12,650 women in the placebo group and the 12,739 women in the MHT group were very similar in baseline characteristics, including age, body mass index (BMI), proportion with prevalent fracture, fall prevalence, FRAX risk factors, and FRAX fracture probabilities (Table 1).

The incidences of any fracture, major osteoporotic fracture, and hip fracture were significantly lower in women randomized to MHT than in those receiving placebo. In a Poisson regression model, adjusted for age and time since baseline, MHT reduced the risk of any fracture (Relative risk reduction (RRR) 28% [95% confidence interval (CI) 22%, 35%]), major osteoporotic fracture (RRR 40% [95% CI, 31%, 47%]), and hip fracture (RRR 34% [95% CI, 4%, 55%]). These results were not affected by additional adjustments for participation in the inclusion in the Dietary Modification trial (DM) or the Calcium and Vitamin D trial (CAD) (Table 2).

The effect of MHT on fracture risk was then investigated in those with or without a fall during the last year. Similar RRRs in women on MHT vs. those on placebo were observed for any fracture, MOF in both fallers and no fallers, although the effect was not statistically significant for hip fracture in women without falls (Table 3).

The effect of MHT on the risk of all fracture outcomes was furthermore investigated according to the number of falls during the last year, as reported at baseline. MHT was associated with lower risk of all fracture outcomes, except

**Table 1** Baseline characteristics of women randomized to menopausal hormone therapy or placebo treatment

| | Placebo | | Hormone therapy | |
|---|---|---|---|---|
| | *n* | *12,650* | *n* | *12,739* |
| Age, years (mean ± SD) | 12 650 | 63.5 (7.2) | 12 739 | 63.5 (7.2) |
| BMI, kg/m$^2$ (mean ± SD) | 12 560 | 29.1 (6.1) | 12 674 | 29.1 (6.1) |
| Prevalent fracture, *n* (%) | 10 033 | 1665 (16.6) | 10 080 | 1702 (16.9) |
| Family history of hip fracture, *n* (%) | 12 305 | 1641 (13.3) | 12 400 | 1605 (12.9) |
| Current smoking, *n* (%) | 12 497 | 1318 (10.5) | 12 609 | 1311 (10.4) |
| Oral corticosteroid use, *n* (%) | 12 650 | 6 (0.0) | 12 739 | 7 (0.0) |
| Reumatoid arthritis, *n* (%) | 12 387 | 623 (5.0) | 12 459 | 669 (5.4) |
| High alcohol intake[B], *n* (%) | 12 610 | 538 (4.3) | 12 698 | 534 (4.2) |
| FRAX MOF, % (mean ± SD) | 12 650 | 10.0 (6.8) | 12 739 | 10.0 (6.7) |
| FRAX hip fracture, % (mean ± SD) | 12 650 | 2.2 (3.6) | 12 739 | 2.2 (3.5) |
| Fall prevalence[A], *n* (%) | 12 650 | 4250 (33.6) | 12 739 | 4271 (33.5) |
| Prior falls[A], *n* (%) | | | | |
| No falls | | 8400 (66.4) | | 8468 (66.5) |
| 1 fall | | 2569 (20.3) | | 2618 (20.6) |
| 2 falls | | 1123 (8.9) | | 1073 (8.4) |
| 3 or more falls | | 558 (4.4) | | 580 (4.6) |

[A]Falls within 12 months prior to baseline. [B]3 or more glasses of alcohol-containing drinks per day

**Table 2** Effects of menopausal hormone therapy vs. placebo on fracture outcomes

| | Placebo | Menopausal hormone therapy |
|---|---|---|
| | $n = 12{,}650$ | $n = 12{,}739$ |
| Any fracture | | |
| No. (%) | 1075 (8.5) | 765 (6.0) |
| Rate per 1000 person-years | 20.8 | 14.7 |
| Time at risk, mean (SD), years | 4.1 (2.1) | 4.1 (2.2) |
| HR (95% CI) | 1 [Reference] | **0.72 [0.65, 0.78]** |
| HR (95% CI) adjusted for DM and CAD | 1 [Reference] | **0.72 [0.65, 0.78]** |
| Relative risk reduction (%) | 0 [Reference] | **28 [22, 35]** |
| Major osteoporotic fracture | | |
| No. (%) | 591 (4.7) | 350 (2.7) |
| Rate per 1000 person-years | 11.2 | 6.6 |
| Time at risk, mean (SD), years | 4.2 (2.1) | 4.2 (2.2) |
| HR (95% CI) | 1 [Reference] | **0.60 [0.53, 0.69]** |
| HR (95% CI) adjusted for DM and CAD | 1 [Reference] | **0.60 [0.53, 0.69]** |
| Relative risk reduction (%) | 0 [Reference] | **40 [31, 47]** |
| Hip fracture | | |
| No. (%) | 71 (0.6) | 44 (0.3) |
| Rate per 1000 person-years | 1.3 | 0.8 |
| Time at risk, mean (SD), years | 4.3 (2.1) | 4.2 (2.2) |
| HR (95% CI) | 1 [Reference] | **0.66 [0.45, 0.96]** |
| HR (95% CI) adjusted for DM and CAD | 1 [Reference] | **0.66 [0.45, 0.96]** |
| Relative risk reduction (%) | 0 [Reference] | **34 [4, 55]** |

Number of fractures, rate per 1000 person-years, time at risk, hazard ratios (HR), and relative risk reductions (%) with 95% confidence intervals are shown for overall treatment effect of menopausal hormone therapy (1) adjusted for age and time since baseline, and (2) adjusted for DM (Dietary Modification trial) and CAD (Calcium and Vitamin D trial). Significant ($p < 0.05$) HRs are presented in bold

hip fractures in those without falls, those with 1 prior fall, and within those with 2 prior falls (Table 4). The lower risk of hip fracture in those treated with MHT was only significant in those with 2 prior falls, but the analysis was limited by the small number of hip fractures across subgroups (Table 4). There was no interaction between MHT and prior falls for any fracture outcome ($p = 0.24$ for hip fracture and $p > 0.30$ for all other outcomes).

Treatment was effective in reducing the risk of any clinical fracture (Fig. 1 and Table 5), MOF, and hip fracture in women regardless of baseline FRAX MOF probability, with no evidence of an interaction between HT and FRAX ($p > 0.30$ for the interaction term for all fracture outcomes).

A sub-analysis was performed to investigate the effect of MHT on the risk of any fracture in women under 60 years of age. This analysis included 4031 women with MHT and 4037 women given placebo. The groups had very similar baseline characteristics (Supplemental Table 1). MHT reduced the risk of any fracture (RRR 24% [95% CI, 8%, 37%]) with no evidence of an interaction between MHT effect and FRAX MOF baseline probability ($p > 0.30$; Supplemental Table 2).

## Discussion

The present analyses indicate that MHT is effective in reducing fracture risk regardless of pre-treatment fracture probability as estimated by FRAX and history of falls in healthy postmenopausal women. No interactions between treatment efficacy and fracture probability or prior falls were observed for any fracture outcome. Thus, the observed robust fracture risk reductions amounting to 28% for any fracture and 34% for hip fracture with MHT can be anticipated across the range of baseline FRAX fracture probabilities. Our results are consistent with previous analyses of each trial alone where estrogen alone and estrogen + progesterone were shown to reduce fractures irrespective of the number of previous falls and the underlying fracture probability estimated using the Study of Osteoporotic Fractures score [3, 28]. Importantly, our findings extend these previous results by combining the 2 trials and improving statistical power to investigate any potential interaction with falls and fracture probability, having sufficient statistical power to investigate also hip fracture outcomes, and by using the well-established fracture risk algorithm, FRAX, that has been widely

**Table 3** Effect of menopausal hormone therapy vs. placebo on fracture outcomes in fallers and no fallers

|  | Within no fallers $n = 16,868$ | Within fallers $n = 8521$ |
|---|---|---|
| **Any fracture** |  |  |
| No. (%) | 1121 (6.6%) | 719 (8.4%) |
| Hazard Ratio, 95% CI | **0.70 [0.62, 0.79]** | **0.74 [0.63, 0.85]** |
| Relative risk reduction (%), 95% CI | **30 [21, 38]** | **26 [15, 37]** |
| **Major osteoporotic fracture** |  |  |
| No. (%) | 585 (3.5%) | 356 (4.2%) |
| Hazard Ratio, 95% CI | **0.62 [0.53, 0.73]** | **0.57 [0.46, 0.70]** |
| Relative risk reduction (%), 95% CI | **38 [27, 47]** | **43 [30, 54]** |
| **Hip fracture** |  |  |
| No. (%) | 65 (0.4%) | 50 (0.6%) |
| Hazard Ratio, 95% CI | 0.80 [0.49, 1.31] | **0.51 [0.28, 0.92]** |
| Relative risk reduction (%), 95% CI | 20 [-31, 51] | **49 [8, 72]** |

Hazard ratios (HR) and relative risk reductions (RRR) with 95% confidence intervals are shown for overall treatment effect of hormone therapy adjusted for DM (Dietary Modification trial) and CAD (Calcium and Vitamin D trial). Significant ($p < 0.05$) HRs and RRRs are presented in bold

incorporated and used in over 80 guidelines worldwide [29]. Thus, these findings provide additional support for MHT use in women with varying falls risk and across a wide spectrum of fracture risk, assessed with the nowadays widely used FRAX tool.

Based on that, the 10-year fracture probability of MOF in the placebo group at baseline was 10% and the observed incidence during the 4.3 years of follow-up was 4.7%, indicating that the FRAX model was well calibrated for the investigated population.

Risedronate was not effective in preventing fractures in women selected based on non-skeletal risk factors, such as high falls risk [22]. It has therefore been questioned if osteoporosis drugs should be considered in women with high

fracture risk based on non-skeletal risk factors. An analysis from the CEE + MPA WHI trial revealed that MHT was equally effective in those who reported falls and those who did not within the 12 months preceding study start, without any significant interaction [3]. These data are in agreement with the previously reported lack of interaction between falls and anti-fracture efficacy of clodronate [30]. In the CEE alone trial, there was no interaction between previous falls and MHT effect for total fracture and hip fracture, although it should be emphasized that the number of hip fractures was limited (44 and 68 in the CEE and placebo groups, respectively) and the $p$ value for interaction 0.15 [31]. The present study utilizing both WHI MHT trials confirms the lack of interaction between MHT and previous falls history on the reduction of fracture risk, a finding consistent for all fracture outcomes. Thus, also women identified to have a high risk of falls benefit in terms of fracture risk reduction with MHT.

Menopausal hormone therapy is currently primarily recommended to women younger than 60 years old or within 10 years of menopause, to relieve menopausal symptoms and improve quality of life, if the risk-to-benefit balance is favorable [5, 32]. In the herein presented analysis, we found that MHT was effective in reducing the risk of any fracture, regardless of baseline FRAX MOF probability in women under 60 years of age, further supporting this recommendation.

In a recently published position paper from the European Society for the Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Osteoporosis Foundation (IOF), a strategy on how to stratify treatment according to efficacy, costs and adverse events risk, in relation to fracture risk was proposed. It was suggested that in postmenopausal women with *very* high fracture risk, including, e.g., older women with a vertebral fracture, an anabolic agent should be considered prior to an antiresorptive, such as a bisphosphonate or denosumab. In women with a high fracture risk, an antiresorptive should be considered as first-line of choice [33]. It was furthermore proposed

**Table 4** Effect of menopausal hormone therapy vs. placebo on fracture outcomes according to number of falls

|  | Effect of hormone therapy | | | |
|---|---|---|---|---|
|  | Within no fallers $N = 16,868$ | Within those with 1 fall $N = 5187$ | Within those with 2 falls $N = 2196$ | Within those with $\geq 3$ falls $N = 1138$ |
| Any fracture | **0.70 [0.62, 0.79]** | **0.81 [0.66, 0.99]** | **0.60 [0.46, 0.80]** | 0.72 [0.50, 1.04] |
| Major osteoporotic fracture | **0.62 [0.53, 0.73]** | **0.66 [0.49, 0.89]** | **0.53 [0.36, 0.80]** | **0.39 [0.22, 0.68]** |
| Hip fracture | 0.80 [0.49, 1.31] | 0.82 [0.37, 1.86] | **0.36 [0.14, 0.92]** | – |

Hazard ratios with 95% confidence intervals, adjusted for age, time since baseline, DM (Dietary Modification trial) and CAD (Calcium and Vitamin D trial) are presented. Significant ($p < 0.05$) HRs are presented in bold

**Fig. 1** Effect of menopausal hormone therapy on risk of any fracture according to baseline FRAX major osteoporotic fracture probability
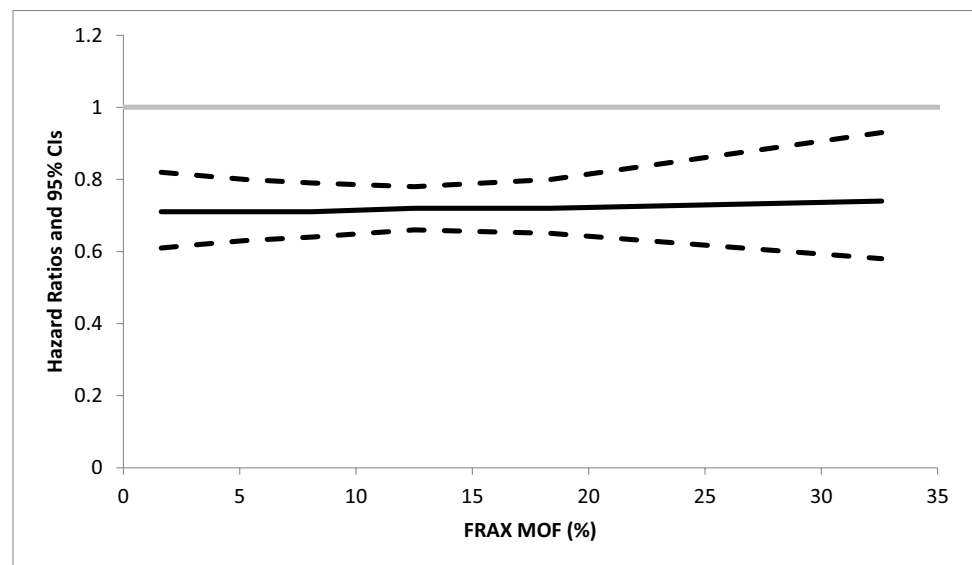


**Table 5** Effect of MHT vs. placebo on the risk of any fracture according to FRAX MOF baseline fracture probability

| Percentile of baseline FRAX score MOF | Baseline FRAX score MOF | RRR |
|---|---|---|
| 10 | 3.37 | **29% (19, 38%)** |
| 25 | 5.25 | **29% (20, 37%)** |
| 50 | 8.09 | **29% (21, 36%)** |
| 75 | 12.51 | **28% (22, 34%)** |
| 90 | 18.37 | **28% (20, 35%)** |

Relative risk reductions (RRR, %) with 95% confidence intervals are shown for overall treatment effect of menopausal hormone therapy (1) adjusted for age and time since baseline. *p* value for the interaction term > 0.30

that younger postmenopausal women with a low fracture risk could still have a high lifetime probability of fracture and would therefore be candidates for MHT, thus delaying or preventing their transition to a higher risk group, as a result of aging and declining BMD [34]. Our present analysis, demonstrating that MHT is effective in preventing fractures also in those with low baseline fracture probability according to FRAX, supports the proposed treatment stratification.

The herein presented results are in contrast to the large clinical trials with denosumab, clodronate, or bazedoxifene, in which treatment efficacy was greater in postmenopausal women with higher as opposed to those with lower fracture risk [10–12]. Important differences between these studies and the WHI trials include a higher baseline fracture probability in the former trials because they were limited to women with osteoporosis as defined by a prevalent vertebral fracture or low BMD (bazedoxifene and denosumab trials). In the WHI trials, MHT reduced fracture risk in women unselected for low BMD, refuting the need for a BMD assessment prior to MHT start in treatment candidates. Both the clodronate and WHI trials recruited postmenopausal women without requirement for risk factors for osteoporosis and fracture, but women were generally older and had higher FRAX fracture probability in the clodronate trial than in the WHI studies, which could also have contributed to the discrepancies regarding observed interactions between fracture probability and treatment efficacy.

Estrogen deficiency leads to increased bone loss, due to increased bone resorption via osteoclast recruitment and activity, and conversely MHT results in increased BMD in postmenopausal women who have low estrogen levels [3, 35]. It has recently been shown that changes in BMD can explain a considerable proportion of the anti-fracture efficacy seen with osteoporosis medications, including MHT [36], but other factors such as effects on bone turnover, may also contribute[35]. A subgroup analysis from the WHI intervention studies has failed to observe a positive effect of MHT on lean mass, measured with dual x-ray absorptiometry (DXA), and on fall risk [37]. Combined, these data indicate that the anti-fracture efficacy of MHT observed here, is primarily due to an effect on BMD and not on fall risk.

The current study has several limitations. The analyses of MHT efficacy on fracture risk according to pre-treatment history of falls and fracture probability were not prespecified. Furthermore, subgroup analysis limits the statistical power which could give rise to false results, driven by multiple comparisons and chance. However, all trial participants were included in the analysis of the interaction between MHT efficacy and fracture probability, and the subgroups of fallers and no fallers were quite large (with over 8500 women in the smallest group), and with the exception of hip fracture, many fracture outcomes were available in each group. It should though be noted that

the analysis within fallers, divided according to the number of falls, was based on much smaller groups with fewer outcomes implying that the results should be interpreted with caution. Although combining the two WHI trials resulted in a very large study cohort and increased the statistical power, combining trials of slightly different treatment regimens in one analysis could have resulted in heterogeneity in results. Even though it is unlikely to affect the interaction analysis with FRAX, it should be acknowledged that FRAX estimates fracture probability over 10 years but the observation time in the current trial was only 4.3 years on average. In addition, the FRAX variable secondary osteoporosis, which is not a major contributing variable, was not considered, which affected the calculated FRAX probabilities, probably only to a small degree, supported by the agreement found between the observed incidence and FRAX probabilities for major osteoporotic fracture. Lastly, although fractures often occur in association with falls, a history of falls was assessed at baseline. The very large combined study cohort and the treatment efficacy being evaluated in a randomized controlled setting constitute substantial strengths of the current study. It is also the first study investigating if the effect of MHT on fracture risk is dependent on fracture probability according to FRAX at the time of MHT initiation.

In conclusion, using the combined WHI trials, MHT reduces fracture risk compared to placebo, regardless of baseline FRAX probability and falls history in postmenopausal women.

## Declarations

## References

1. 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
2. Anderson GL, Limacher M, Assaf AR et al (2004) Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 291:1701–1712
3. Cauley JA, Robbins J, Chen Z et al (2003) Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 290:1729–1738
4. Force USPST, Grossman DC, Curry SJ et al (2017) Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: US Preventive Services Task Force Recommendation Statement. JAMA 318:2224–2233
5. Rozenberg S, Al-Daghri N, Aubertin-Leheudre M et al (2020) Is there a role for menopausal hormone therapy in the management of postmenopausal osteoporosis? Osteoporos Int 31:2271–2286
6. Manson JE, Aragaki AK, Rossouw JE et al (2017) Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the Women's Health Initiative randomized trials. JAMA 318:927–938
7. Palacios S, Stevenson JC, Schaudig K, Lukasiewicz M, Graziottin A (2019) Hormone therapy for first-line management of menopausal symptoms: practical recommendations. Womens Health (Lond) 15:1745506519864009
8. Kanis JA, Cooper C, Rizzoli R, Reginster JY, Scientific Advisory Board of the European Society for C, Economic Aspects of O, the Committees of Scientific A, National Societies of the International Osteoporosis F (2019) European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 30:3-44
9. Kanis JA, Oden A, Johnell O et al (2007) The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. Osteoporos Int 18:1033–1046
10. Kanis JA, Johansson H, Oden A, McCloskey EV (2009) Bazedoxifene reduces vertebral and clinical fractures in postmenopausal women at high risk assessed with FRAX. Bone 44:1049–1054
11. McCloskey EV, Johansson H, Oden A, Vasireddy S, Kayan K, Pande K, Jalava T, Kanis JA (2009) Ten-year fracture probability identifies women who will benefit from clodronate therapy–additional results from a double-blind, placebo-controlled randomised study. Osteoporos Int 20:811–817
12. McCloskey EV, Johansson H, Oden A, Austin M, Siris E, Wang A, Lewiecki EM, Lorenc R, Libanati C, Kanis JA (2012) Denosumab reduces the risk of osteoporotic fractures in postmenopausal women, particularly in those with moderate to high fracture risk as assessed with FRAX. J Bone Miner Res 27:1480–1486
13. McCloskey E, Johansson H, Lorentzon M, Harvey NC, Rojeski M, Shi Y, Kanis J (2019) A post hoc analysis of romosozumab efficacy and baseline fracture risk - greater reductions in fracture outcomes in patients at higher risk 2019 ASBMR annual meeting. American Society for Bone and Mineral Research, Orlando, Florida, US
14. Kanis JA, Johansson H, Oden A, McCloskey EV (2010) A meta-analysis of the efficacy of raloxifene on all clinical and vertebral fractures and its dependency on FRAX. Bone 47:729–735
15. Kanis JA, Johansson H, Oden A, McCloskey EV (2011) A meta-analysis of the effect of strontium ranelate on the risk of vertebral and non-vertebral fracture in postmenopausal osteoporosis and the interaction with FRAX((R)). Osteoporos Int 22:2347–2355
16. Harvey NC, Kanis JA, Oden A, Burge RT, Mitlak BH, Johansson H, McCloskey EV (2015) FRAX and the effect of teriparatide on vertebral and non-vertebral fracture. Osteoporos Int 26:2677–2684
17. Harvey NC, Kanis JA, Oden A, Nakamura T, Shiraki M, Sugimoto T, Kuroda T, Johansson H, McCloskey EV (2015) Efficacy of weekly teriparatide does not vary by baseline fracture probability calculated using FRAX. Osteoporos Int 26:2347–2353
18. McCloskey EV, Johansson H, Oden A, Harvey NC, Jiang H, Modin S, Fitzpatrick L, Kanis JA (2017) The effect of abaloparatide-SC on fracture risk is independent of baseline FRAX fracture probability: a post hoc analysis of the ACTIVE study. J Bone Miner Res 32:1625–1631
19. Leslie WD, Morin SN, Lix LM, Martineau P, Bryanton M, McCloskey EV, Johansson H, Harvey NC, Kanis JA (2019) Fracture prediction from self-reported falls in routine clinical practice: a registry-based cohort study. Osteoporos Int 30:2195–2203
20. Harvey NC, Oden A, Orwoll E et al (2018) Falls predict fractures independently of FRAX Probability: a meta-analysis of the osteoporotic fractures in men (MrOS) study. J Bone Miner Res 33:510–516
21. Harvey NC, Johansson H, Oden A et al (2016) FRAX predicts incident falls in elderly men: findings from MrOs Sweden. Osteoporos Int 27:267–274
22. McClung MR, Geusens P, Miller PD et al (2001) Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 344:333–340
23. Jackson RD, LaCroix AZ, Cauley JA, McGowan J (2003) The Women's Health Initiative calcium-vitamin D trial: overview and baseline characteristics of participants. Ann Epidemiol 13:S98-106
24. Design of the Women's Health Initiative clinical trial and observational study (1998 ) The Women's Health Initiative study group. Control Clin Trials 19(1):61–109
25. Hays J, Hunt JR, Hubbell FA, Anderson GL, Limacher M, Allen C, Rossouw JE (2003) The Women's Health Initiative recruitment methods and results. Ann Epidemiol 13:S18-77

26. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A (2001) The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int 12:417–427

27. Breslow NE, Day NE (1987) Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. IARC Sci Publ (82):1–406.

28. Black DM, Steinbuch M, Palermo L, Dargent-Molina P, Lindsay R, Hoseyni MS, Johnell O (2001) An assessment tool for predicting fracture risk in postmenopausal women. Osteoporos Int 12:519–528

29. Kanis JA, Harvey NC, Cooper C, Johansson H, Odén A, McCloskey EV (2016) A systematic review of intervention thresholds based on FRAX: a report prepared for the National Osteoporosis Guideline Group and the International Osteoporosis Foundation. Arch Osteoporos 11:25

30. Kayan K, Johansson H, Oden A, Vasireddy S, Pande K, Orgee J, Kanis JA, McCloskey EV (2009) Can fall risk be incorporated into fracture risk assessment algorithms: a pilot study of responsiveness to clodronate. Osteoporos Int 20:2055–2061

31. Jackson RD, Wactawski-Wende J, LaCroix AZ et al (2006) 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 21:817–828

32. Tremollieres F (2019) Assessment and hormonal management of osteoporosis. Climacteric 22:122–126

33. Kanis JA, Harvey NC, McCloskey E et al (2020) Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. Osteoporos Int 31:1–12

34. Kanis JA, Johnell O, Oden A, Sembo I, Redlund-Johnell I, Dawson A, De Laet C, Jonsson B (2000) Long-term risk of osteoporotic fracture in Malmo. Osteoporos Int 11:669–674

35. Gosset A, Pouillès JM, Trémollieres F (2021) Menopausal hormone therapy for the management of osteoporosis. Best Pract Res Clin Endocrinol Metab 35:101551

36. Black DM, Bauer DC, Vittinghoff E et al (2020) Treatment-related changes in bone mineral density as a surrogate biomarker for fracture risk reduction: meta-regression analyses of individual patient data from multiple randomised controlled trials. Lancet Diabetes Endocrinol 8:672–682

37. Bea JW, Zhao Q, Cauley JA, LaCroix AZ, Bassford T, Lewis CE, Jackson RD, Tylavsky FA, Chen Z (2011) Effect of hormone therapy on lean body mass, falls, and fractures: 6-year results from the Women's Health Initiative hormone trials. Menopause 18:44–52

## Authors and Affiliations

Mattias Lorentzon[1,2,3] · Helena Johansson[3,4] · Nicholas C. Harvey[5,6] · Enwu Liu[3] · Liesbeth Vandenput[3,7] · Carolyn J. Crandall[8] · Jane A. Cauley[9] · Meryl S. LeBoff[10,11] · Eugene V. McCloskey[12,13] · John A. Kanis[3,4]

1 Sahlgrenska Osteoporosis Centre, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

2 Geriatric Medicine, Sahlgrenska University Hospital Mölndal, 43180 Mölndal, Sweden

3 Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia

4 Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, UK

5 MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK

6 NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

7 Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

8 Department of Medicine, David Geffen School of Medicine at the University of California, Los Angeles, USA

9 Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

10 Division of Endocrinology, Diabetes and Hypertension, Department of Medicine, Brigham and Women's Hospital Boston, Boston, MA 02115, USA

11 Harvard Medical School, Boston, MA 02115, USA

12 Mellanby Centre for Bone Research, Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK

13 Centre for Integrated Research in Musculoskeletal Ageing (CIMA), Mellanby Centre for Bone Research, University of Sheffield, Sheffield, UK