Menopausal Hormone Therapy and Mortality: A Systematic Review and Meta-Analysis


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Objectives: The objective was to assess the effect of menopausal hormonal therapy (MHT) on all-cause and cause-specific mortality.

Methods: We conducted a comprehensive search of several databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, and Scopus) from inception until August 2013. We included randomized controlled trials (RCTs) of more than 6 months of duration comparing MHT with no treatment. Pairs of independent reviewers selected trials, assessed risk of bias and extracted data. We estimated risk ratios (RRs) and 95% confidence intervals (CIs) using the random-effects model.

Results: We included 43 RCTs at moderate risk of bias. Meta-analysis showed no effect on mortality (RR 0.99 [95% CI, 0.94–1.05]), regardless of MHT type or history of preexisting heart disease. No association was found between MHT and cardiac death (RR 1.04 [95% CI 0.87–1.23]) or stroke (RR 1.49 [95% CI 0.95–2.31]). Estrogen plus progesterone use was associated with a likely increase in breast cancer mortality (RR 1.96 [95% CI 0.98–3.94]), whereas estrogen use was not. MHT use was not associated with mortality of other types of cancer. In 5 trials, MHT was likely started at a younger age: 2 RCTs with mean age less than 60 and 3 RCTs with MHT started less than 10 years after menopause. Meta-analysis of these 5 RCTs showed a reduction of mortality with MHT (RR 0.70 [95% CI 0.52–0.95]).

Conclusion: The current evidence suggests that MHT does not affect the risk of death from all causes, cardiac death and death from stroke or cancer. These data may be used to support clinical and policy deliberations about the role of MHT in the care of symptomatic postmenopausal women. (J Clin Endocrinol Metab 100: 4021–4028, 2015)
moderately severe vasomotor symptoms for 10 years or more, and most of these women are untreated (5, 6). These undertreated menopausal symptoms are associated with significant burden on the healthcare system in terms of outpatient visits and both indirect and direct costs (7, 8).

The history of MHT prescribing reflects the seemingly conflicting evidence regarding the balance of risks and benefits of MHT for women. After the publication of numerous observational studies, including the Nurses’ Health Study, disease prevention and cardiac risk reduction were proposed as primary reasons to consider the use of MHT (9–11). However, subsequent randomized controlled trials (RCTs) did not confirm these findings and called into question the use of MHT for prevention of coronary heart disease (CHD), albeit the demographics of the trial participants did not mirror those of the observational studies (12–14). The results of the WHI trial, and data from years of follow-up and reanalysis, have provided valuable insight regarding the importance of factors such as age, time since menopause, and the specific MHT regimen used (oral conjugated equine estrogens [CEEs] therapy vs CEE plus medroxyprogesterone acetate) in the assessment of the risk to benefit balance of MHT for postmenopausal women (15).

For the purposes of this paper, we will distinguish between different estrogens (estradiol vs CEE) and between different progestogens (medroxyprogesterone acetate vs micronized progesterone vs other progestogens) when possible. If this information is not available or a combination of therapies was used, we will indicate that the type of estrogen or progestogen is undetermined and will refer to MHT containing estrogen alone as ET and therapy containing a combination of estrogen and progestogen as EPT.

In an effort to further clarify risks and benefits of MHT, studies have assessed all-cause mortality with inconsistent results (4–10). To support the development of clinical practice guidelines by The Endocrine Society, we conducted this systematic review and meta-analysis to evaluate the effect of MHT on all-cause and cause-specific mortality.

Materials and Methods

This systematic review follows a protocol that was developed by experts from The Endocrine Society and methodologists with expertise in evidence synthesis. This report follows the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (16).

Eligibility criteria

We included RCTs that enrolled postmenopausal women and compared MHT users with nonusers. Only trials with follow-up period of at least 6 months were included. Trials that did not report the outcomes of interest (all-cause mortality and specific-cause mortality due to cardiac events, stroke or cancer) were excluded. We also excluded publications without original data (clinical reviews and editorials). No study was excluded based on language or geographical location.

Data sources and search strategy

We conducted a comprehensive search of several databases from the inception of each database’s to August 2013. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced Mayo Clinic librarian with input from the principal investigator. Controlled vocabulary supplemented with keywords was used to search for comparative studies of postmenopausal women using MHT and associated mortality. The detailed search strategy is included in Supplemental Table 1.

Study selection and data extraction

Pairs of reviewers independently assessed each abstract for eligibility. Disagreement yielded an automatic inclusion. Included trials were retrieved as full texts and screened in duplicate. Disagreement at this level was resolved by discussion between 3 reviewers. Data extraction was also performed independently by 2 reviewers. A third reviewer resolved any conflicts or inconsistencies by referring to the full text article.

Reviewers independently extracted study details from the full text articles using a predesigned electronic form after piloting the form on a sample of the studies. The next data were abstracted: study design, country, patient characteristics (sex, age, body mass index, medical comorbidities), underlying disease if available, number of deaths in treated and control groups and the effect size with the confidence interval (CI) at the longest duration of complete follow-up.

Assessment of risk of bias

We assessed the risk of bias using the Cochrane risk of bias assessment tool (determined the randomization method, blinding, allocation concealment, lost to follow-up, and source of funding) (17).

Statistical analysis

The outcome of interest was death due to any cause as well as death due to cardiac events, stroke and cancer. An adjusted relative association measure (odds ratio, risk ratio [RR], hazard ratio) was extracted from the trials. If an effect size was not available, number of deaths in each group was obtained, and a 2 × 2 table was constructed to generate an unadjusted effect size. The 95% CIs were estimated using binomial distribution. We then pooled the log transformed RRs using the DerSimonian and Laird random-effect model with the heterogeneity estimated using the Mantel-Haenszel method. We planned a priori subgroup analyses based on the age at initiation of MHT (or years since menopause), the presence of preexisting heart disease, and MHT regimen (ET vs EPT).

We used the I² statistics to measure heterogeneity across the studies. Statistical analyses were conducted using Comprehensive Meta-Analysis (Biostat).

Results

Description of included studies

The initial search identified 2244 citations, of which 43 RCTs met the inclusion criteria (Figure 1).
Collectively, the trials enrolled 52,068 women. Description of the included trials is summarized in Supplemental Table 2. The mean age was 62 years (range, 49–70 y); the mean follow-up period was 4.6 years (range, 1.16–18.66 y).

Risk of bias
Supplemental Table 3 summarizes risk of bias indicators. The risk of bias was moderate to high overall because randomization methods were unclear or not reported in 12 trials, 25 trials did not report allocation concealment, and blinding was not reported in 16 trials. The proportion of patients lost to follow-up ranged from 0% to 25% and averaged 8.4%.

All-cause mortality
Meta-analysis demonstrated no association between all-cause mortality and MHT (RR 0.99 [95% CI 0.94–1.05], I² = 0%; P = .98) (Figure 2). The quality of evidence is moderate to low due to increased risk of bias and imprecision.

In subgroup analysis, there was no significant interaction based on MHT regimen (ET vs EPT) (Supplemental Figure 1) or the presence of preexisting heart disease (P > .05 for each) (Supplemental Figure 2).

Sensitivity analysis was performed to exclude the one trial that used tibolone and revealed the same conclusions (RR 0.99 [95% CI 0.94–1.05]). After excluding the tibolone trial, there was no difference in the effect of MHT on mortality based on MHT regimen (ET vs EPT) (P = .64) or the presence of preexisting heart disease (P = .49).

Subgroup analysis based on MHT timing (women’s age)
In 5 trials, MHT was likely started at a younger age: 2 RCTs with mean age less than 60 and 3 RCTs with MHT started less than 10 years after menopause. However, the designation of these trials as such was based on the mean age of participants (with the exception of WHI 2002 and WHI 2004, in which the outcome was reported exclusively for women in this age strata). Each one of these trials individually did not find a statistically significant effect: Danish Osteoporosis Prevention Study 2012 (RR 0.58 [95% CI 0.93–1.08]) (18–23), Estonian Postmenopausal Hormone Therapy 2006 (RR 0.92 [95% CI 0.06–14.71]) (24–26), Estrogen Replacement Therapy II 1979 (RR 0.43 [95% CI 0.11–1.60]) (27), WHI I2002 (RR 0.83 [95% CI 0.54–1.26]) (28), and WHI I2004 (RR 0.66 [95% CI 0.34–1.29]) (29). If the RRs for the 5 trials were pooled, results would show a decrease in mortality (RR 0.70 [95% CI 0.52–0.95]) in the younger population (30).

In a recent report of 13 year follow-up of WHI (15), stratification by age during the intervention phase suggested reduced mortality in women in the age strata of 50–59 that was not significant. A trend for increasing hazard ratio for all-cause mortality as age increases across the 3 age strata (50–59, 60–69, and 70–79). This trend was only statistically significant in the estrogen vs placebo part of the trial (not the combined EPT trial).

Cause-specific mortality
Cardiac death
No association was found between MHT use and cardiac mortality (RR 1.04 [95% CI 0.87–1.23], I² = 0%) (Figure 3).
No significant interaction was found based on MHT regimen (ET, RR 0.8 [95% CI 0.57–1.13] vs EPT, RR 1.1 [95% CI 0.9–1.35]; \( P = .11 \)) (Supplemental Figure 3).

**Mortality due to stroke**

No significant association was found between MHT use and stroke mortality (RR 1.49 [95% CI 0.95–2.31] \( I^2 = 0\% \)). No significant interaction was found when comparing MHT regimens (ET vs EPT, \( P = .61 \)) (Supplemental Figure 4). Subgroup analysis based on the type of prevention (primary vs secondary) showed no significant difference between the 2 groups (\( P = .27 \)) (Supplemental Figure 5).

**Mortality due to cancer**

**All cancer mortality**

Only 2 trials reported all cancer mortality, no association was found between MHT and cancer mortality with RR 1.03 (95% CI 0.93–1.14) \( I^2 = 0\% \) (Table 1).

**Breast cancer mortality**

Three trials reported death due to breast cancer (Table 1). There was no association between ET use and breast cancer mortality (RR 0.59 [95% CI 0.25–1.41] \( I^2 = 0\% \)) (Supplemental Figure 6). Only 1 trial used EPT and reported death due to breast cancer (RR 1.96 [95% CI 0.98–3.94]) (Supplemental Figure 6).
Lung cancer mortality
In 2 trials, there was no association between MHT use and lung cancer mortality (RR 1.38 [95% CI 0.88–2.19]) (Supplemental Figure 7).

Ovarian cancer mortality
In 1 trial, there was no association between MHT use and ovarian cancer mortality (RR 2.7 [95% CI 0.73–9.99]) (Table 1).

Colorectal cancer mortality
In 1 trial, there was no association between MHT use and colorectal cancer mortality (RR 1.29 [95% CI 0.78–2.12]) (Table 1).

Discussion
Main findings
This systematic review and meta-analysis of RCTs demonstrates no association between MHT and all-
caused and cardiac mortality, or mortality due to stroke or cancer.

Limitations and strengths

The quality of evidence presented in this systematic review for all outcomes (i.e., certainty in the estimates) is low (Supplemental Table 4), limited by increased risk of bias and imprecision (CI fails to exclude important benefit and important harm of MHT). The strengths of this systematic review are derived from following an a priori established protocol, the comprehensive literature search, collaboration with experts from The Endocrine Society, the reproducible evaluation of the quality of primary studies, and application of bias protection measures in the study selection and data extraction.

Comparison with other studies

Most observational studies associated the use of MHT with reduced risk of CHD, although this has not been supported by most RCTs (31). Early RCTs which enrolled older postmenopausal women with existing CHD (the Heart and Estrogen-progestin Replacement Study, Estrogen Replacement and Atherosclerosis trial, and Women’s Estrogen/Progestin and Lipid Lowering Hormone Atherosclerosis Regression Trial), failed to demonstrate the expected benefit of MHT on cardiac outcomes, including reduction in risk of CHD-related death (13, 32, 33). The WHI trial findings regarding total mortality with MHT are consistent with observational studies and suggested reduced mortality when initiated in women under the age of 60 years. WHI data showed nonsignificant reductions in mortality in women who initiated ET or EPT in their fifties during the intervention phase of the trial (15). In addition, results from the ET arm of the WHI trial suggest reduced CHD risk (coronary revascularization, MI and coronary death) when ET was initiated in women closer to the time of menopause (34, 35).

With regard to stroke-related mortality, the Nurses’ Health Study showed an increased risk of stroke in current users of ET and EPT compared with never users and no clear difference in risk depending on age at initiation of therapy. The risk of death related to stroke was not significantly different in current MHT users vs nonusers (36). The WHI also showed an increased risk of ischemic stroke in both the ET and EPT arms of the trial; no differences in stroke-related mortality were noted between either the ET or EPT arms and placebo (37). In Heart and Estrogen-progestin Replacement Study and Women’s Estrogen for Stroke Trial, the use of MHT in women with existing coronary artery disease and history of transient ischemic attack or ischemic stroke respectively was not associated with fatal or nonfatal stroke (38, 39).

Observational studies have shown no significant association between MHT (mixed regimens) use and breast cancer mortality (40, 41). The WHI showed that breast cancer mortality increased with EPT use and decreased with the use of ET (42, 43). The effect of ET on breast cancer mortality in our meta-analysis did not reach statistical significance due to pooling results from WHI and another trial. It is clear that the association between MHT and breast cancer mortality differs based on the type of MHT with possible harmful effect when using a combined regimen.

There are several factors that may help explain the differing results regarding the risk to benefit balance of MHT between observational and RCTs. There were differences in the biological and demographic characteristics of the women participating in these trials that influence cardiac risk and outcomes, including a healthy user effect (44, 45). Another important factor influencing risk is the timing of initiation of MHT with regard to age and time since menopause. The participants in observational studies regarding CHD risk and MHT were generally younger and closer to menopause than those participating in RCTs (46) In this study, the mean age of trial participants was 62 years, and data were insufficient to stratify analysis by age.

Other systematic reviews (41, 47, 48) suggested that MHT reduced mortality in younger women closer to the menopausal transition. Such conclusion could be true, or could be explained by ecological bias, in that a patient-level characteristic (age) is used in aggregate (mean age) to categorize studies before pooling. Recent observational studies suggest possible reduction in mortality with MHT, particularly in younger women (49, 50). Testing the effect of age (a characteristic of a patient, not a study) requires performing individual patient data subgroup meta-analysis.

Clinical implications

The body of evidence summarized here and elsewhere on the effect of MHT on important clinical outcomes provides some reassurance for clinicians caring for women with bothersome menopausal symptoms. Although it has not been established that MHT confers any mortality benefit, it has not been shown to increase mortality when used in women who are closer to the menopausal transition, and MHT is indisputably the most effective treatment for menopausal symptoms. The overall risk to benefit balance of MHT must be assessed on an individual basis, taking into account a woman’s symptoms, past medical history, family history, and personal preferences.

Data from the present analysis cannot confirm or reject the hypothesis that younger women could experience a mortality benefit with MHT as has been previously re-
ported, but, to date, the evidence for such a subgroup effect remains unreliable. Similarly, more data are needed regarding the safety of MHT in other subgroups of women, such as those with a personal history of coronary artery disease or some types of cancer. The lack of effect of MHT on all-cause and cause-specific mortality identified in this study was based on trials with a mean length of follow of 4.6 years. Any extrapolation beyond this time frame further reduces our confidence in the estimates presented here, particularly in relation to cause-specific mortality.

Conclusions

The current evidence suggests that MHT does not affect the risk of death from all causes, cardiac death, stroke, or most cancers. MHT was used for a mean duration of 4.6 years, and extrapolation beyond this time frame is limited. Further research is necessary to establish whether a mortality benefit with the use of MHT exists among younger menopausal women, with the use of ET as compared with EPT, and whether an effect on mortality (deleterious or beneficial) exists in women with cancer. There is a need for better reporting of trial specific demographic and other data (eg, information on dose, formulation, and route of administration of MHT regimen) used for meta-analysis that will reduce bias and improve the evidence on which clinical treatment guidelines can be based.

Acknowledgments

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References


