

The Role of Menopausal Hormone Therapy in Reducing All-cause Mortality in Postmenopausal Women Younger than 60 Years: An Adaptive Meta-analysis

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Introduction

Menopausal hormone therapy (MHT) is typically initiated to control climacteric symptoms during early postmenopause. MHT improves quality of life and prevents osteoporotic fracture.¹ However, concerns about risks, including cancers and cardiovascular disease, are still highly prevalent. All-cause mortality (ACM) would be one definite endpoint to use in assessing a complex balance of benefits and risks with MHT. A Cochrane Database of Systematic Reviews (CDSR) study conducted by Boardman et al.² in 2015 concluded that administering MHT at an age less than 10 years after menopause onset had a reduction of ACM (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.52–0.95) through a systematic review of 5 trials: the Danish Osteoporosis Prevention Study (DOPS; 2012),³ Estonian Postmenopausal Hormone Therapy (EPHT; 2006),⁴ Estrogen Replacement Therapy (ERT) II (1979),⁵ Women's Health Initiative (WHI) I (2002),⁶ and WHI II (2004).⁷

The U.S. Preventive Services Task Force (USPSTF)⁸ reported in 2017 that the HR of ACM with estrogen therapy (ET) during the intervention phase was 0.70 (95% CI, 0.46–1.09) among women aged 50 to 59 years but cited only 1

article from the WHI trials.⁹ In addition, ACM with estrogen plus progestogen therapy (EPT) declined similarly without statistical significance (HR, 0.67; 95% CI, 0.43–1.04). However, the USPSTF recommends against MHT in early postmenopausal women.¹⁰

The purpose of this study was to propose a scientific and valid position for the conflicting recommendations of the CDSR (2015)² and the USPSTF (2017),¹⁰ to rearrange and update the selected articles to include newer publications, and to conduct subgroup analyses by MHT regimen.

Methods and Results

As though adapting an old clinical practice guideline, an adaptive meta-analysis was performed in order to add current evidences and then conduct additional meta-analysis.¹¹ Using citation discovery tools provided by PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>), lists of recent articles 'citing' the articles selected by previous meta-analyses were made. Accordingly, lists of the cited sources in 6 articles by the CDSR² and the USPSTF¹⁰ were created and appraised. As a consequence, the WHI (2012)¹² was used to update the

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WHI I (2002),⁶ WHI II (2004),⁷ and WHI (2008).⁹ In addition, 2 trials conducted in women with a concurrent medical disorder were added to the sensitivity analyses: EStrogen in the Prevention of ReInfarction Trial (ESPRIT; 2014)¹³ in patients who survived a first myocardial infarction and ERT II (1979)⁵ in patients hospitalized for chronic disease. During appraisal of the citation lists, articles related to Heart and Estrogen/progestin Replacement Study (HERS) I (1998),¹⁴ HERS II (2002),^{15,16} and EPHT (2006)⁴ were removed because they did not contain results for women less than 60 years old.

From the final selection of 4 trials,^{3,5,12,13} the authors extracted the HRs and their 95% CIs based on the MHT medi-

cation prescribed for postmenopausal women less than 60 years old. After calculating the standard error of log HR,¹⁷ we used the Stata/SE Version 14 statistical program (Stata-Corp, College Station, TX, USA) to estimate the summary HR (sHR) and to generate the forest plots.¹⁸

Figure 1 displays a forest plot for the 4 trials with all types of MHT. For the 2 trials conducted in healthy women,^{3,12} the sHR calculated using a random effect model was 0.87 (95% CI, 0.78–0.98) with no heterogeneity (I-squared, 27.3%). Even after including 2 trials of women with certain health conditions,^{5,13} the protective effects remained statistically significant (sHR, 0.87; 95% CI, 0.78–0.98).

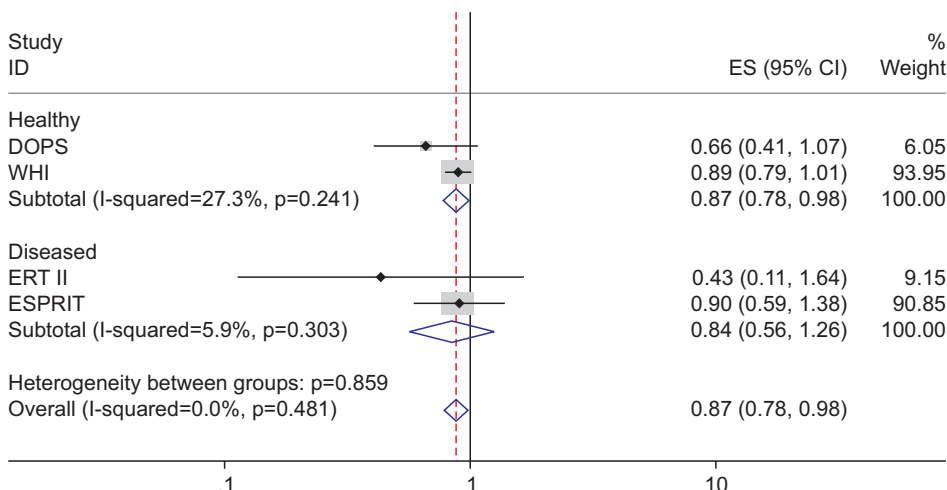


Fig. 1. Forest plot of the 4 selected trials. ID: identification, ES: effect size, CI: confidence interval, DOPS: Danish Osteoporosis Prevention Study, WHI: Women’s Health Initiative, ERT: estrogen replacement therapy, ESPRIT: EStrogen in the Prevention of ReInfarction Trial.

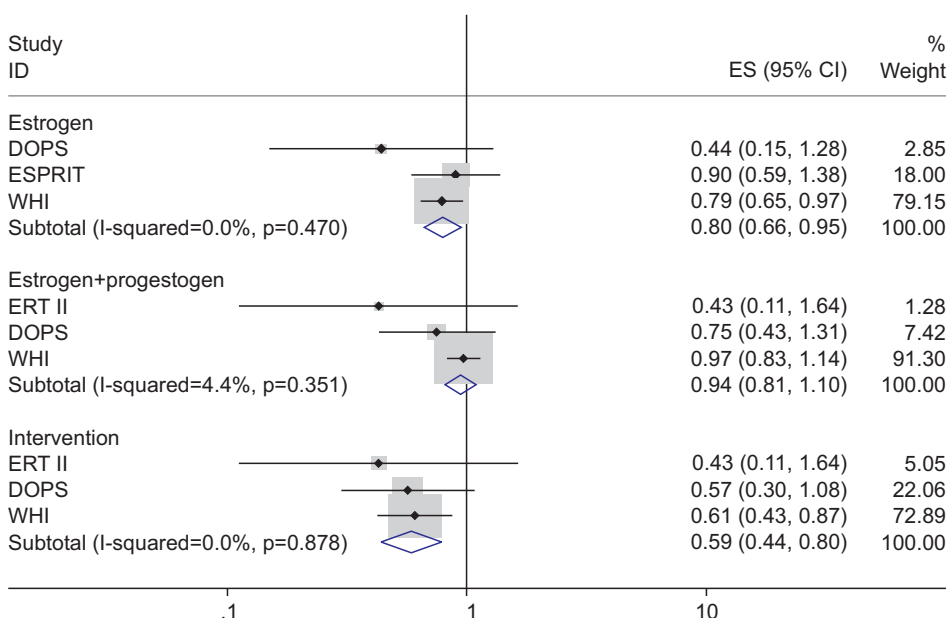


Fig. 2. A forest plot generated from subgroup analyses by menopausal hormone therapy regimen and also during the intervention period. ID: identification, ES: effect size, CI: confidence interval, DOPS: Danish Osteoporosis Prevention Study, ESPRIT: EStrogen in the Prevention of ReInfarction Trial, WHI: Women’s Health Initiative, ERT: estrogen replacement therapy.

Figure 2 shows the results of the subgroup analyses. The sHRs were 0.80 (95% CI, 0.66–0.95) and 0.94 (95% CI, 0.81–1.10) in ET and EPT, respectively. In the follow-up results of the intervention periods, the sHR was 0.59 (95% CI, 0.44–0.80).

Discussion

Based on these results, MHT may reduce the ACM for postmenopausal women younger than 60 years. In our analysis, we first analyzed pooled data of the MHT combining ET and EPT, while the USPSTF showed separate results. A recent WHI analysis¹² regarding long-term ACM showed no heterogeneity between ET and EPT and reported the pooled results of 2 trials (HR, 0.69; 95% CI, 0.51–0.94). Further, cumulative data, when available, were used, including intervention and post-intervention follow-ups in DOPS, WHI, and ESPRIT, which could provide more robust evidence. The USPSTF used WHI data during the intervention phase only. Interestingly, the protective effect of MHT seemed to be stronger during intervention periods.

ET decreased the ACM significantly in postmenopausal women younger than 60 years. However, EPT did not show statistical significance, even though sHR showed a protective tendency. In the EPT subgroup, the weight of the WHI trial was very high (91.3%). Medroxyprogesterone acetate was used in the WHI trial, and the reduction in ACM seemed to be quite attenuated in the cumulative follow-up compared with the intervention phase.¹² Of note, the norethindrone acetate used in the DOPS trial showed a similar HR during both the intervention phase and in the cumulative data.³ Further research is warranted to determine better progestogen to produce a less adverse impact on estrogen in a cumulative follow-up study.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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