Review: hormone therapy may reduce the risk of death in younger but not older postmenopausal women

Salpeter SR, Walsh JM, Greyber E, *et al.* Mortality associated with hormone replacement therapy in younger and older women: a meta-analysis. *J Gen Intern Med* 2004;**19**:791–804.

Clinical impact ratings GP/FP/Primary care ★★★★★★★ IM/Ambulatory care ★★★★☆☆

Q **Does hormone therapy (HT) affect the risk of death differently in younger and older postmenopausal women?**

METHODS

Data sources: Medline, EMBASE/Excerpta Medica, CINAHL, and Cochrane library (1966 to September 2002); journal hand searches through April 2003; and bibliographies.

Study selection and assessment: randomised controlled trials (RCTs) that compared HT with a control intervention (placebo, no treatment, or calcium supplementation), were >6 months in duration, and reported ≥1 death. Study quality was assessed for method of randomisation, allocation concealment, blinding, description of withdrawals and dropouts, and intention to treat analysis. Studies received a quality criteria score of A (all criteria met), B (≥1 criteria met), or C (0 criteria met).

Outcomes: total death, cardiovascular (CV) death, cancer death, and death from other causes. Trials were divided into those with mean age at baseline <60 or >60 years.

MAIN RESULTS

30 RCTs (n = 26 708, age range 36–87 y) met the inclusion criteria. The quality scores were A, 13 RCTs; B, 10 RCTs; and C, 7 RCTs. The interventions studied were transdermal or oral oestrogens alone or in combination with a progestogen. Using a random effects model, meta-analysis of the 30 RCTs that included all age groups indicated that HT and control groups did not differ for total mortality (table), CV death (odds ratio [OR] 1.10, 95% CI 0.90 to 1.34), or cancer death (OR 1.03, CI 0.23 to 1.29). HT reduced deaths from other causes (OR 0.67, CI 0.51 to 0.88). Of the 17 RCTs that included the younger age group (mean age 54 y), fewer patients who received HT died than did those who received control (table). These groups did not differ for CV death (OR 0.68, CI 0.22 to 2.15), cancer death (OR 0.69, CI 0.59 to 1.08), or death from other causes (OR 0.44, CI 0.17 to 1.13). Of the 13 RCTs that included the older age group (mean age 66 y), HT and control groups did not differ for total mortality (table), CV death (OR 1.11, CI 0.91 to 1.36), or cancer death (OR 1.07, CI 0.84 to 1.37). HT in this age group reduced death from other causes (OR 0.68, CI 0.56 to 0.91).

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CONCLUSIONS

Hormone therapy (HT) may reduce the risk of mortality in younger, but not in older, postmenopausal women. For all age groups combined, HT does not reduce the risk of total mortality, CV death, and cancer death, but reduces death from other causes.

Abstract and commentary also appear in ACP Journal Club.

Commentary

Believers in HT had their hopes raised by the meta-analysis by Salpeter *et al* claiming that HT reduced total mortality in women <60 years of age. However, a critical appraisal of this review dims these hopes. Firstly, the definition of young was fuzzy: The actual age of individual women at entry into a trial was not used—age was instead based on the mean age of all participants in a given trial. A number of younger women were >60 years of age, and a number of older women were <60 years of age. Age was also related to the type of patient included in the trial. For example, those women who had ovarian cancer were in the <60 years age group. Their trial level approach to the analysis cannot separate the effects of age from the effects of other entry criteria.

A closer look at the mortality data raises additional questions. If HT really reduces total mortality in younger women, what is the mechanism of action? The odds ratios for CV, cancer, and other deaths were 0.68, 0.69 and 0.44, respectively, which suggests an implausible global mortality benefit—one that was inexplicably pronounced for non-CV and non-cancer deaths. Moreover, the number of CV deaths was only 6. A global benefit is also difficult to reconcile biologically with a 39% benefit only in women <60 years of age but a lack of benefit in women >60 years of age. Finally, a benefit for a specific cause of death ought to be accompanied by a benefit, or at least a trend, for cause specific morbidity. The literature offers no such support. The most likely explanation for this difference by age is a chance subgroup finding in a meta-analysis with low power.

In conclusion, the meta-analysis by Salpeter *et al* has not provided any plausible evidence that should influence the current guidelines for use of HT. The current indication is symptomatic relief only, at the lowest effective dose for the shortest time possible.

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Outcome at mean 4.5 years	Number of trials (n)	Weighted event rates	Odds Ratio (95% CI)	RRR (CI)	NNT (CI)
Total mortality					
All ages	30 (26 708)	4.0% v 4.0%	0.98 (0.87 to 1.12)	2% (−10 to 13)	Not significant
Mean age <60 years	17 (4141)	2.7% v 4.3%	0.61 (0.39 to 0.95)	38% (5 to 60)	61 (39 to 481)†
				RRI (CI)	**NNH**
Mean age >60 years	13 (22 567)	4.0% v 3.9%	1.03 (0.9 to 1.18)	3% (−9 to 17)	Not significant

*Abbreviations defined in glossary; weighted event rates, RRR, RRI, NNT, NNH, and CI calculated from data in article using a random effects model. †Calculated from data in article using odds ratios.

Hormone therapy (HT) v control (placebo, no HT, or calcium supplements) for postmenopausal women*