THERAPEUTICS

Review: Hormone replacement therapy may reduce the risk for death in younger but not older postmenopausal women

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

QUESTION

Does hormone replacement therapy (HRT) affect the risk for death differently in younger and older postmenopausal women?

METHODS

Data sources: Searching MEDLINE, EMBASE/Excerpta Medica, CINAHL, and Cochrane databases (1966 to September 2002); scanning selected journals through April 2003; and reviewing bibliographies of identified studies.

Study selection and assessment: Randomized controlled trials (RCTs) that compared HRT 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 randomization, 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 to 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 estrogens alone or in combination with a progestin. Through use of a random-effects model, meta-analysis of the 30 RCTs that included all age groups indicated that HRT 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). HRT 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 HRT 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), HRT 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). HRT in this age group reduced death from other causes (OR 0.68, CI 0.56 to 0.91).

CONCLUSIONS

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

Hormone replacement therapy (HRT) vs control (placebo, no HRT, or calcium supplements) for total mortality in postmenopausal women at mean 4.5 years*

Age group	Number of trials (*n*)	Weighted event rates		Odds Ratio (95% CI)	RRR (CI)	NNT (CI)
		HRT	Control			
All ages	30 (26 708)	4.0%	4.0%	0.98 (0.87 to 1.12)	2% (−10 to 13)	Not significant
Younger	17 (4141)	2.7%	4.3%	0.61 (0.39 to 0.95)	38% (5 to 60)	61 (39 to 481)†
					RRI (CI)	NNH
Older	13 (22 567)	4.0%	3.9%	1.03 (0.9 to 1.18)	3% (−9 to 17)	Not significant

*Younger = mean age < 60 years; older = mean age > 60 years. 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.

COMMENTARY

Believers in HRT had their hopes raised by the meta-analysis by Salpeter and colleagues claiming that HRT reduced total mortality in women < 60 years of age. However, a critical appraisal of this review dims these hopes. First, 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, women who had ovarian cancer were in the < 60 year-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 HRT 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 and colleagues has not provided any plausible evidence that should influence the current guidelines for use of HRT. The current indication is symptomatic relief only, at the lowest effective dose for the shortest time possible.

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