Mortality Associated with Hormone Replacement Therapy in Younger and Older Women

A Meta-analysis

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OBJECTIVE: **To assess mortality associated with hormone replacement in younger and older postmenopausal women.**

DESIGN: **A comprehensive search of MEDLINE, CINAHL, and EMBASE databases was performed to identify randomized controlled trials of hormone replacement therapy from 1966 to September 2002. The search was augmented by scanning selected journals through April 2003 and references of identified articles. Randomized trials of greater than 6 months' duration were included if they compared hormone replacement with placebo or no treatment, and reported at least 1 death.**

MEASUREMENTS: **Outcomes measured were total deaths and deaths due to cardiovascular disease, cancer, or other causes. Odds ratios (OR) for total and cause-specific mortality were reported separately for trials with mean age of participants less than and greater than 60 years at baseline.**

MAIN RESULTS: **Pooled data from 30 trials with 26,708 participants showed that the OR for total mortality associated with hormone replacement was 0.98 (95% confidence interval [CI], 0.87 to 1.12). Hormone replacement reduced mortality in the younger age group (OR, 0.61; CI, 0.39 to 0.95), but not in the older age group (OR, 1.03; CI, 0.90 to 1.18). For all ages combined, treatment did not significantly affect the risk for cardiovascular or cancer mortality, but reduced mortality from other causes (OR, 0.67; CI, 0.51 to 0.88).**

CONCLUSIONS: **Hormone replacement therapy reduced total mortality in trials with mean age of participants under 60 years. No change in mortality was seen in trials with mean age over 60 years.**

KEY WORDS: **hormone replacement therapy; postmenopause; mortality; age factors; meta-analysis.**
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In the assessment of risks and benefits of hormone replacement therapy (HRT), observational studies and clinical trials have yielded apparently conflicting results. Large prospective cohort studies have shown that women who used HRT, most of whom started treatment shortly after menopause, had significant reductions in total and cardiovascular mortality compared to nonusers.[1–8] The results remained significant after adjusting for cardiovascular risk factors such as age, smoking, and blood pressure. The largest randomized trial of HRT, the Women's Health Initiative (WHI), evaluated women with mean age 63 years and found that HRT increased the risk of cardiovascular events, without changing total or cardiovascular mortality.[9]

It is possible that the mortality reduction seen in observational studies was due to a confounding variable that was not adequately adjusted for, such as general health status or access to health care.[10–12] Another explanation is that when HRT is started in younger women, a true mortality benefit is seen. Mortality is a relatively rare outcome, even in large trials. For example, the WHI had approximately 5 deaths per 1,000 patient-years.[9] A more precise estimate of the impact of HRT on mortality can be made by pooling the results of many trials. The objective of this study was to assess the effect of age on total and cause-specific mortality associated with HRT by performing a meta-analysis of randomized controlled trials.

METHODS

Search Strategy

The MEDLINE, EMBASE, CINAHL, and Cochrane databases were searched comprehensively to identify randomized controlled trials published between 1966 and September 2002 that evaluated hormone replacement in postmenopausal women. Terms used in the search were *climacter*,* *menopause*,* *perimenopaus** or *peri-menopaus**, *postmenopaus** or *post-menopaus**, and *estrogen**, *estrogen replacement therapy*, *hormone replacement therapy*, *hormone substitution*, *progesterone*, *progestogen*, *progestin*, or *gestagen*. Trials were not excluded on the basis of language. The search was augmented by scanning selected journals through April 2003, and references of identified articles.

Trial Selection

Two investigators independently evaluated studies for inclusion, and the observed interrater agreement was measured using the κ statistic.[13] Trials were included if they 1) were randomized controlled trials of postmenopausal women that compared HRT to placebo or no hormone therapy, 2) were of longer than 6 months' duration, and 3) reported at least 1 death. Attempts were made to contact the investigators of all trials longer than 6 months, to obtain information concerning deaths during the trial.

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For studies with multiple publications from the same group of participants, one publication containing the most information was chosen for inclusion. Interventions in the trials included transdermal or oral estrogens alone or in combination with a progestin. Control groups received placebo, no treatment, or calcium supplementation.

Data Extraction

Two independent reviewers extracted data from the selected articles, reconciling differences by consensus. The outcomes measured were total deaths and deaths due to cardiovascular events, cancer, and all other causes. For patients who withdrew from the study because of adverse events, deaths that were reported after withdrawal from the trial were included in the analysis.

For crossover trials, only data from the end of the first phase were used because of the potential carryover effect of HRT. For randomized trials with nonrandomized open-label extensions, only data from the randomized trial were included. For trials that provided data on other interventions, such as raloxifine, only data from the hormone and control groups were included.

Assessment of Validity

The methodological quality of each trial was assessed according to the following factors: 1) was the randomization procedure and allocation concealment adequate? 2) Were the patients and providers blinded to the intervention? 3) Were withdrawals and dropouts described, and the analysis performed as intention-to-treat? Trials received an A score when all quality criteria were met, a B score when one or more criteria were partially met, and a C score when one or more criteria were not met.[14,15] Two reviewers independently assessed quality scores and the interrater agreement was calculated using the κ statistic. The quality assessment was used for a sensitivity analysis.

Data Synthesis

For each trial, the ratio of deaths to surviving patients was calculated for both the treatment and control groups, to obtain the odds of death. The net result for mortality was expressed as an odds ratio (OR), by dividing the treatment odds by the control odds. The results were pooled to obtain a summary odds ratio using the random-effects model for dichotomous outcomes, with confidence intervals (CI) set at 95% significance.[16] The random-effects method was chosen as it accounts for the potential of interstudy heterogeneity. The analysis was performed using Meta View 4.1 (Update Software, Oxford, UK). Only trials that reported at least 1 death could be used in the estimation of odds ratio. To test for interstudy heterogeneity, the χ^2 value and the Q-value were calculated for the assumption of homogeneity.

In order to evaluate the effect of age on mortality, trials were divided into those with mean age of participants at baseline less than or greater than 60 years. The cutoff of 60 years was arbitrarily chosen, *a priori*, to divide the participants into a younger and older age group. The cutoff was thought to be appropriate because the rate of cardiovascular events in women accelerates after this age, suggesting that a primary protective effect of HRT might be lost or diminished after this time.[17,18] The results of the analysis were reported separately for all ages and for the younger and older age groups. The results of the two age groups were compared to each other using the logarithm of the odds ratio (log OR). A sensitivity analysis was performed to evaluate the effect of using different age cutoffs. Linear regression analysis was performed to evaluate mortality OR as a linear function of age.

A subgroup analysis compared the use of unopposed estrogen and combined treatment with estrogen and progestin. For trials that provided information on both unopposed and combined treatment, the data for each type of treatment were analyzed separately.

RESULTS

Search Results

The electronic database search identified 4,993 articles, of which 358 were potentially relevant trials on HRT in postmenopausal women. After scanning journals and references from selected articles, an additional 12 trials were identified. Of these 370 studies, 30 met inclusion criteria (Table 1).[9,19–47] The κ score for interrater agreement in trial selection was 0.91 (95% CI, 0.82 to 1.00). Studies were excluded for the following reasons: 98 did not report any deaths, 110 provided data on patients already included in the analysis, 79 were of 6 months' duration or less, 26 did not provide a control group, and 27 were not randomized.

Trial Characteristics

The analysis included 30 trials, with a total of 26,708 participants followed for 119,118 patient-years. The mean trial duration was 4.46 years (range 0.7 to 10 years), with a mean study size of 890 participants (range 52 to 16,608). The mean age of participants at baseline was 62.2 ± 8.9 years in the treatment group and 63.4 ± 9.1 years in the placebo group, with an age range of 36 to 87 years. The mean dropout rate was estimated to be 11.5% in the treatment group and 10.6% in the placebo group. The κ score for interrater agreement on methodological quality scores was 0.95 (95% CI, 0.6 to 1.0). Of the trials studied, 13 received a score of A, 10 received a score of B, and 7 received a score of C.

Total and Cause-specific Mortality

For all ages combined, there were 518 deaths reported in 14,147 participants in the treatment group and 501 deaths in 12,561 participants in the control group (Table 2).

Table 1. Characteristics of Included Studies

Study (Reference #)	Design, Duration	Inclusion and Exclusion Criteria	Participants (*n*) in HRT Placebo	Dropout Rate in HRT Placebo, %	Mean Age in HRT Placebo	Active Comparison Intervention	Outcomes	Comments
Angerer, 2000[20]	Double blind, 1 year	Inclusion: Postmenopausal women aged 40 to 70 years with more than 1 mm intima media thickness in at least one segment of the carotid arteries	215	28	59.0	Estradiol 1 mg/day plus gestodone 0.25 mg/day vs placebo	Carotid artery dispensability	
		Exclusion: Myocardial infarction within 6 months, angina or any contraindication to hormone use	66	29	59.5			
Arrenbrecht, 2002[21]	Double blind, 2 years	Inclusion: Healthy postmenopausal women with hysterectomy	108	24	50.5	Transdermal estradiol 50 or 100 mcg/day vs placebo	Bone mineral density, bone turnover	
		Exclusion: Medication that affects bone metabolism, smoking, or osteoporosis	53	combined	combined			
Binder, 2001[22]	Double blind, 9 months	Inclusion: Postmenopausal women over the age of 75 years	41	22	82.0	CEE 0.625 mg/day plus MPA 5 mg/day vs placebo	Lipid profiles	
		Exclusion: Recent hormone use, breast, or gynecological malignancy, current treatment for thromboembolism, cardiovascular disease, or unstable thyroid disease	22	9.1	83.0			
Cherry, 2002[23]	Double blind, 2 years	Inclusion: Women aged 50 to 69 with recent myocardial infarction	513	57.3	62.3	Estradiol valerate, 2 mg/day vs placebo	Reinfarction, cardiac death, all-cause mortality	
		Exclusion: Recent use of hormones or vaginal bleeding, gynecological malignancy, liver or renal disease, history of venous thromboembolism	504	36.5	62.9			
Gallagher, 2001[24]	Double blind, 3 years	Inclusion: Elderly postmenopausal women	121	16.5	72.0	CEE 0.625 mg/day plus MPA 2.5 mg/day vs placebo	Bone mineral density	Calcitriol with and without hormones were also studied
		Exclusion: Severe chronic illness or medications that affect bone metabolism	123	8.9	71.0			

(Continued)

Table 1. (Continued)

Study (Reference #)	Design, Duration	Inclusion and Exclusion Criteria	Participants (*n*) in HRT Placebo	Dropout Rate in HRT Placebo, %	Mean Age in HRT Placebo	Active Comparison Intervention	Outcomes	Comments
Giske, 2002[25]	Double blind, 2 years	Inclusion: Healthy postmenopausal women with hysterectomy Exclusion: Medications that affect bone metabolism	123 43	11.4 30.2	49.1 49.6	Estradiol 0.5 mg, 1 mg or 2 mg/day vs placebo	Bone mineral density	
Guidozzi, 1999[26]	Open label, 4 years	Inclusion: Postmenopausal women with ovarian cancer Exclusion: Previous hormone replacement or ovarian malignancy of low malignant potential	62 68	4 combined	51 combined	CEE 0.625 mg/day plus MPA 2.5 mg/day vs placebo	Disease-free survival and overall survival	
Hall, 1994[27]	Open label, 2 years	Inclusion: Postmenopausal women with rheumatoid arthritis Exclusion: Contraindications to hormone replacement, breast or gynecological malignancy, or thromboembolism	100 100	37 16	55.8 56.1	Transdermal estradiol 50 mcg/day vs placebo	Bone mineral density	
Hall, 1998[28]	Single blind, 1 year	Inclusion: Postmenopausal women with coronary heart disease Exclusion: None listed	40 20	20 30	58.6 61.3	Transdermal estradiol 50 mcg/day and MPA 5 mg/day vs placebo	Angina	
Herrington, 2000[29]	Double blind, 3.2 years	Inclusion: Postmenopausal women with coronary disease Exclusion: Breast or gynecological malignancy, planned coronary artery surgery, thromboembolism, symptomatic gallstones, renal or liver dysfunction, uncontrolled diabetes, hypertension, or hypertryiglyceridemia	204 105	20 combined	65.9 65.6	CEE 0.625 mg/day plus MPA 2.5 mg/day vs placebo	Angiographic changes and lipid profiles	
Hodis, 2001[30]	Double blind, 2 years	Inclusion: Postmenopausal women at least 45 years old with elevated cholesterol Exclusion: Breast or gynecological malignancy, recent or long-term hormone use, severe hot flushes, severe hypertension, or severe illness	111 111	25.2 25.2	60.9 62.1	Estradiol 1 mg/day vs placebo	Change in intimal thickness	

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Table 1. (Continued)

Study (Reference #)	Design, Duration	Inclusion and Exclusion Criteria	Participants (*n*) in HRT Placebo	Dropout Rate in HRT Placebo, %	Mean Age in HRT Placebo	Active Comparison Intervention	Outcomes	Comments
Hulley, 2002[31]	Double blind, 4.1 years	Inclusion: Postmenopausal women under the age of 80 years with coronary heart disease	1380	11.5	67	CEE 0.625 mg/day plus MPA 2.5 mg/day vs placebo	Coronary heart disease events or deaths	
		Exclusion: Thromboembolism, breast or gynecological malignancy, recent hormone use and serious disease	1383	11.2	67			
Komulainen, 1999[32]	Open label, 5 years	Inclusion: Early postmenopausal women	115	5.2	52.9	Estradiol 2 mg/day plus cyproterone acetate 1 mg/day vs placebo	Bone mineral density	Vitamin D with or without hormones was also studied
		Exclusion: Breast or gynecological malignancy, thromboembolism, or medication-resistant hypertension	115	5.2	52.6			
Kyllonen, 1998[33]	Double blind, 2 years	Inclusion: Healthy early postmenopausal women age 49 to 55 years	52	22	52.6	Estradiol 2 mg/day plus MPA 10 mg/day for 10 days vs placebo	Lumbar spine mobility and low-back symptoms	
		Exclusion: None listed	26	combined	combined			
Lindsay, 1976[34]	Double blind, 5 years	Inclusion: Postmenopausal women with oophorectomy	63	6.3	44 to 50	Mestranol 28.4 mg/day vs placebo	Bone mineral content	
		Exclusion: Prior estrogen use	57	5.3				
MacDonald, 1994[35]	Double blind, 1 year	Inclusion: Postmenopausal women with rheumatoid arthritis	40	22.5	53	Transdermal estradiol 50 mcg/day with or without norethisterone 1 mg/day for 10 days vs placebo	Bone mineral density and rheumatoid arthritis disease activity	
		Exclusion: Significant menopausal symptoms	22	40.9	55			
Mijatovic, 1998[36]	Double blind, 2 years	Inclusion: Healthy postmenopausal women with hysterectomy	13	5	55.7	CEE 0.625 mg/day vs placebo	Homocysteine levels	Raloxifine also studied
		Exclusion: Hepatic, renal, endocrinologic, gastrointestinal, or cardiovascular disease or breast or gynecological malignancies	13	6.7	54.9			
Mosekilde, 2002[37]	Open label, 5 years	Inclusion: Postmenopausal women	502	9.6	49.5	Estradiol 2 mg/day plus norethisterone 1 mg/day for 10 days vs placebo	Bone mineral density	
		Exclusion: Metabolic bone disease, recent estrogen or corticosteroid use, steroids, malignancy, chronic disease, or alcohol abuse	504	9.1	50.0			

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Table 1. (Continued)

Study (Reference #)	Design, Duration	Inclusion and Exclusion Criteria	Participants (*n*) in HRT Placebo	Dropout Rate in HRT Placebo, %	Mean Age in HRT Placebo	Active Comparison Intervention	Outcomes	Comments
Mulnard, 2000[38]	Double blind, 1 year	Inclusion: Postmenopausal women with hysterectomies and mild to moderate Alzheimer's disease Exclusion: Recent myocardial infarction, thromboembolism, hypercoagulable state, hyperlipidemia, or use of antipsychotics, anticonvulsants, anticoagulants, beta-blockers, narcotics, methyldopa, clonidine, or cognitive-enhancing or anti-Parkinson medications	81 39	19.8 17.9	75.6 74.1	CEE 0.615 or 1.25 mg/day vs placebo	Global measures of cognition, mood, motor function, and activities of daily living	
Nachtigall, 1979[39]	Double blind, 10 years	Inclusion: Postmenopausal women hospitalized for chronic diseases Exclusion: Hypertension, hysterectomy, coronary heart disease, or previous hormone use	84 84	3.6 8.3	55.3 54.9	CEE 2.5 mg/day plus MPA 2.5 mg/day vs placebo	Clinical outcomes such as medical illness or death	
Os, 2000[40]	Open label, 1 year	Inclusion: Postmenopausal women with documented coronary artery disease Exclusion: Previous hormone use, previous myocardial infarction or coronary artery bypass surgery, thromboembolism, breast or gynecological malignancy, alcoholism, or psychiatric disorder	60 58	10.2 15.3	63 66	Transdermal estradiol 50 mcg/day plus MPA 5 mg/day for 14 days vs placebo	Lipid profiles	
PEPI trial Writing Group, 1995[41]	Double blind, 3 years	Inclusion: Healthy postmenopausal women Exclusion: Severe menopausal symptoms, unstable thyroid disease, serious illness, or contraindications to hormone use	701 174	16 32.8	56.1 combined	CEE 0.625 mg/day plus MPA 2.5 mg/day or MPA 10 mg/day for 10 days or micronized progesterone 200 mg/day for 12 days vs placebo	Lipid profiles, fibrinogen, blood pressure, and insulin	

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Table 1. (Continued)

Study (Reference #)	Design, Duration	Inclusion and Exclusion Criteria	Participants (*n*) in HRT Placebo	Dropout Rate in HRT Placebo, %	Mean Age in HRT Placebo	Active Comparison Intervention	Outcomes	Comments
Perez-Jaraiz, 1996[42]	Open-label, 1 year	Inclusion: Early postmenopausal with rapid bone loss Exclusion: None listed	26 52	5.8 5.8	48 50	Transdermal estradiol transdermal 50 mcg/day plus MPA 10 mg for 12 days vs calcium supplementation	Bone mineral density	Calcitonin also studied
Ravn, 1999[43]	Open label, 4 years	Inclusion: Healthy early postmenopausal women age 49 to 55 years Exclusion: Hormone use	110 109	25.2 26.7	55 55	CEE 0.625 mg/day plus MPA 5 mg/day or estradiol 1 to 2 mg/day plus noresisterone 1 mg/day on days 13 to 22 vs placebo	Bone mineral density and bone turnover	Alendronate also studied
Raz, 1993[44]	Double blind, 8 months	Inclusion: Postmenopausal women with 3 or more confirmed urinary tract infections during previous year Exclusion: Thromboembolism disorders, liver disease, estrogen-dependent tumors, anatomical lesions in urogenital area, indwelling urinary catheter, long-term use of antimicrobial agents, or oral estrogen therapy	50 43	28 20.9	64.7 65.4	Intravaginal estradiol cream 0.5 mg/day vs placebo vaginal cream	Incidence of urinary tract infections, and vaginal pH and cultures	
Recker, 1999[45]	Double blind, 3.5 years	Inclusion: Healthy women over the age of 65 years with low bone mass Exclusion: Previous hip fracture, use of estrogen, calcitonin, or corticosteroids in the past 6 months, any use of bisphosphonates or fluoride, endometrial thickness more than 6 mm, breast cancer, and smoking	64 64	28.1 18.8	73.2 74.0	CEE 0.3 mg/day with MPA 2.5 mg/day vs placebo	Bone mineral density, serum total alkaline phosphatase and osteocalcin levels, and urinary creatinine and hydoxyproline	

(Continued)

Table 1. (Continued)

Study (Reference #)	Design, Duration	Inclusion and Exclusion Criteria	Participants (*n*) in HRT Placebo	Dropout Rate in HRT Placebo, %	Mean Age in HRT Placebo	Active Comparison Intervention	Outcomes	Comments
Viscoli, 2001[46]	Double Blind, 2.8 years	Inclusion: Postmenopausal women with recent stroke, cerebrovascular disease	337	34.4	72	Estradiol 1 mg/day vs placebo	Death and stroke incidence	
		Exclusion: Coexisting condition that limits life expectancy, breast or gynecological malignancy, thromboembolism while on estrogen therapy, or neurological or psychiatric disease	327	24.2	71			
Waters, 2002[47]	Double blind, 2.8 years	Inclusion: Postmenopausal women with coronary stenosis documented on angiogram	108	21.3	65	CEE 0.625 mg/day with medroxyproge sterone acetate 2.5 mg/day vs placebo	Annualized mean change in minimum lumen diameter on angiogram, myocardial infarction, death	Antioxidant vitamins also studied
		Exclusion: Hormone use in previous 3 months, concurrent use of vitamin C or E, gynecological or breast cancer, uncontrolled diabetes or hypertension, myocardial infarction with 1 month, renal insufficiency, gallstones, congestive heart failure, hemorrhagic stroke, thromboembolism, or untreated osteoporosis	103	36.2	66			
Watts, 2000[48]	Double Blind, 2 years	Inclusion: Early postmenopausal women	303	10	51.8	CEE 0.3, 0.625 or 1.25 mg/day vs placebo	Bone mineral density	
		Exclusion: Recent hormone use, osteoporosis, smoking, or medications that affect mineral metabolism	103	combined	51.3			
Women's Health Initiative Writing Group, 2002[49]	Double Blind, 5.2 years	Inclusion: Postmenopausal women aged 50 to 79 years	8506	6.3	63.2	CEE 0.625 mg/day plus MPA 2.5 mg/day vs placebo	Coronary heart disease events, breast cancer, and a global index for risks and benefits	
		Exclusion: Serious illness, cancer, anemia, alcohol abuse, or dementia	8102	6.1	63.3			

HRT, hormone replacement therapy.

Table 2. Odds Ratio for Total, Cardiovascular, Cancer, and Other Mortality in Younger and Older Women Associated with Hormone Replacement Therapy

		HRT Deaths	*N*	Control Deaths	*N*	OR (95% CI)
All ages	Total death	518	14,147	501	12,561	0.98 (0.87 to 1.18)
	CV death	215		187		1.10 (0.90 to 1.34)
	Cancer death	184		171		1.03 (0.23 to 1.29)
	Other death	91		126		0.67 (0.51 to 0.88)*
Mean age, y < 60	Total death	53	2,576	68	1,565	0.61 (0.39 to 0.95)*
	CV death	3		3		0.68 (0.22 to 2.15)
	Cancer death	45		54		0.69 (0.59 to 1.08)
	Other death	5		12		0.44 (0.17 to 1.13)
Mean age, y > 60	Total death	465	11,571	433	10,996	1.03 (0.90 to 1.18)
	CV death	212		184		1.11 (0.91 to 1.36)
	Cancer death	137		123		1.07 (0.84 to 1.37)
	Other death	86		116		0.68 (0.56 to 0.91)*

* *Statistical significance.*
OR, odds ratio; CV, cardiovascular; HRT, hormone replacement therapy.

The summary OR for total mortality associated with HRT was 0.98 (95% CI, 0.87 to 1.18). The OR for cardiovascular mortality was 1.10 (95% CI, 0.90 to 1.34), and for cancer deaths was 1.03 (95% CI, 0.82 to 1.29). Of note, there was no increase in breast cancer deaths in those trials that reported cancer-specific mortality (OR, 1.03; 95% CI, 0.29 to 3.67). HRT was associated with a 33% reduction in deaths from causes other than cardiovascular disease or cancer (OR, 0.67; 95% CI, 0.51 to 0.88; Table 2). The specific causes of death in this category included infectious diseases, sepsis, accidents, renal failure, respiratory failure, pulmonary embolism, liver failure, gastrointestinal bleeds, and rheumatologic diseases.

There were 17 trials in the younger age group, with 4,141 participants followed for a mean trial duration of 3.66 years. The mean age in the treatment group was 53.9 ± 3.5 years and in the control group was 53.7 ± 3.4 years. The OR for total mortality in the younger group was 0.61 (95% CI, 0.39 to 0.95), indicating a 39% reduction in mortality for those receiving HRT (Table 2; Fig. 1). The OR for cardiovascular mortality was 0.68 (95% CI, 0.22 to 2.15), for cancer mortality was 0.69 (95% CI, 0.59 to 1.08), and for other mortality was 0.44 (95% CI, 0.17 to 1.13).

There were 13 trials in the older age group, with 22,567 participants followed for a mean trial duration of 4.66 years. The mean age in the treatment group was 64.6 ± 7.2 and in the control group was 66.8 ± 7.0. The OR for total mortality associated with HRT in the older group was 1.03 (95% CI, 0.9 to 1.18; Table 2; Fig. 2). For this group, HRT did not significantly affect cardiovascular mortality (1.11; 95% CI, 0.91 to 1.36) or cancer mortality (1.07; 95% CI, 0.84 to 1.37), but was associated with a reduction in mortality from other causes (0.68; 95% CI, 0.56 to 0.91).

When the results of the two age groups were compared to each other, HRT was associated with significantly lower mortality in the younger group as compared to the older group ($P = .03$). A sensitivity analysis showed that HRT was still associated with significant reductions in mortality in the younger group using an age cutoff in the range from 56 to 63 years. In a linear regression analysis the results for OR were assessed for 3 age groups, less than 56 years (0.62; 95% CI, 0.39 to 1.00), 56 to 63 years (0.74; 95% CI, 0.47 to 1.16), and greater than 63 years (1.05; 95% CI, 0.92 to 1.21). A significant trend was found for mortality OR as a function of age, with the OR increasing by 0.024 (95% CI, 0.003 to 0.038) per year (correlation coefficient 0.98).

In a subgroup analysis, there was no significant difference in total mortality for all ages combined when unopposed estrogen (OR, 0.96; 95% CI, 0.73 to 1.27) was compared to combined treatment (OR, 1.00; 95% CI, 0.86 to 1.15). There was no significant difference in results for the two types of intervention in the younger age group or in the older age group ($P > .5$).

A sensitivity analysis was performed to evaluate the effect of including those trials with the lowest scores for methodological quality. When trials with a C score were excluded, the OR for total mortality changed by less than 0.1 points ($P > .9$) for all ages and for the two age groups. No evidence for significant interstudy variance was found in any of the analyses ($P > .7$). The Q value was calculated and found to be compatible with homogeneity between studies.

Discussion

Pooled data from 30 trials, with 26,708 postmenopausal women followed for a mean duration of 4.5 years, indicate that hormone replacement does not increase total mortality. In the younger group, with mean age 54 years at baseline, HRT was associated with a reduction in total mortality of 39%. In the older group, with mean age 66 years, HRT was not associated with a change in total mortality. A cutoff of 60 years for mean age was chosen, although the results were still robust for cutoffs in the range from 56 to 63 years. Given that there is not one single cutoff but rather a linear relationship between young and old, linear regression analysis was performed that demonstrated

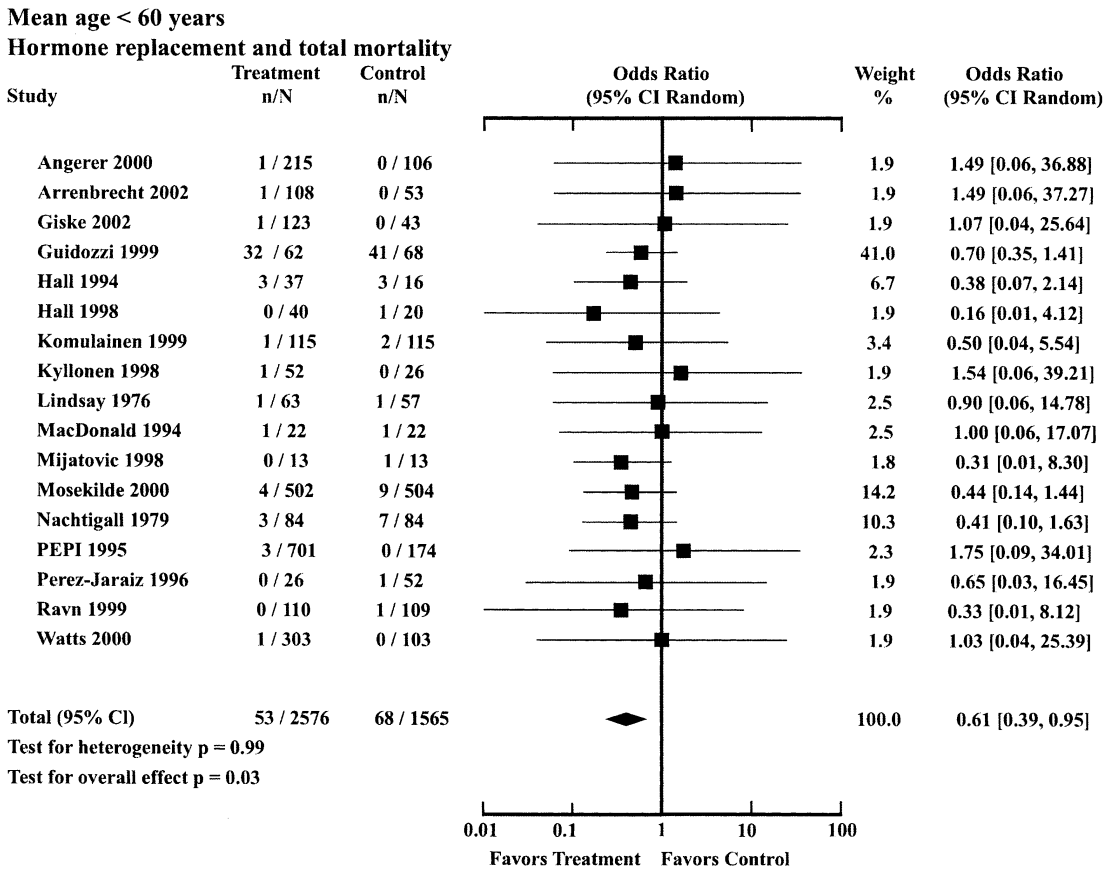

FIGURE 1. Odds ratios for total mortality associated with hormone replacement therapy: trials with mean age of participants less than 60 years.

a significant trend between increasing mortality OR and increasing age, with a correlation coefficient of 0.98.

These results may help to explain the discrepancies that have been seen between observational studies and randomized trials. The Nurses' Health Study was a 20-year prospective cohort study of 120,000 women under the age of 55 years, and the WHI was a 5-year trial of 16,000 women with mean age 63 years.[2,9] In both studies, HRT was associated with similar increases in breast cancer, stroke, and pulmonary embolism, and similar reductions in colorectal cancer and hip fracture.[48] However, the WHI found an increase in cardiac events without a change in cardiovascular or total mortality, while the Nurses' Health Study found significant reductions in cardiac events as well as cardiovascular and total mortality.

The Nurses' Health Study, after adjusting for potential confounding variables, found that current hormone users, 80% of whom had started treatment within 2 years of menopause, had a total mortality risk of 0.63 (95% CI, 0.56 to 0.70) that of nonusers.[2] This meta-analysis found similar results for total mortality in the younger group (OR, 0.61; 95% CI, 0.39 to 0.95), providing evidence that the mortality benefit seen in the observational studies may be a true effect of HRT when treatment is started shortly after menopause. Beneficial effects of HRT include increases in high-density lipoproteins and reductions in low-density lipoproteins, Lp(a) lipoproteins, homocysteine, fibrinogen, plasminogen activator inhibitor antigen, intrinsic coagulation factors, glucose, weight, insulin levels, and the incidence of new-onset diabetes mellitus, compared to placebo.[29,40,49–58] In women with diabetes mellitus, HRT reduces central adiposity and improves glycemic control and physical functioning.[59,60] HRT also causes sustained increases in nitric oxide levels and reductions in plasma norepinephrine, plasma renin activity, and endothelin.[61–64] These endothelial changes have been associated with vasodilation, reduced blood pressure, increased blood flow, and improved cardiac performance.[65–69] It is thought that estrogen has protective properties against cardiovascular disease in premenopausal women, and that the risk for atherosclerosis begins to rise after menopause.[70,71] It is possible that if HRT is started in women in the early postmenopausal period, well before the development of atherosclerosis, primary prevention could be achieved through these improvements in metabolism, hemostasis, and endothelial function. In fact, there is some evidence from clinical trials and animal studies that HRT can halt the progression of atherosclerosis if treatment is started early in the course of the disease.[29,72–76]

No mortality benefit from HRT was seen for women in the WHI trial, most of whom had not taken hormones

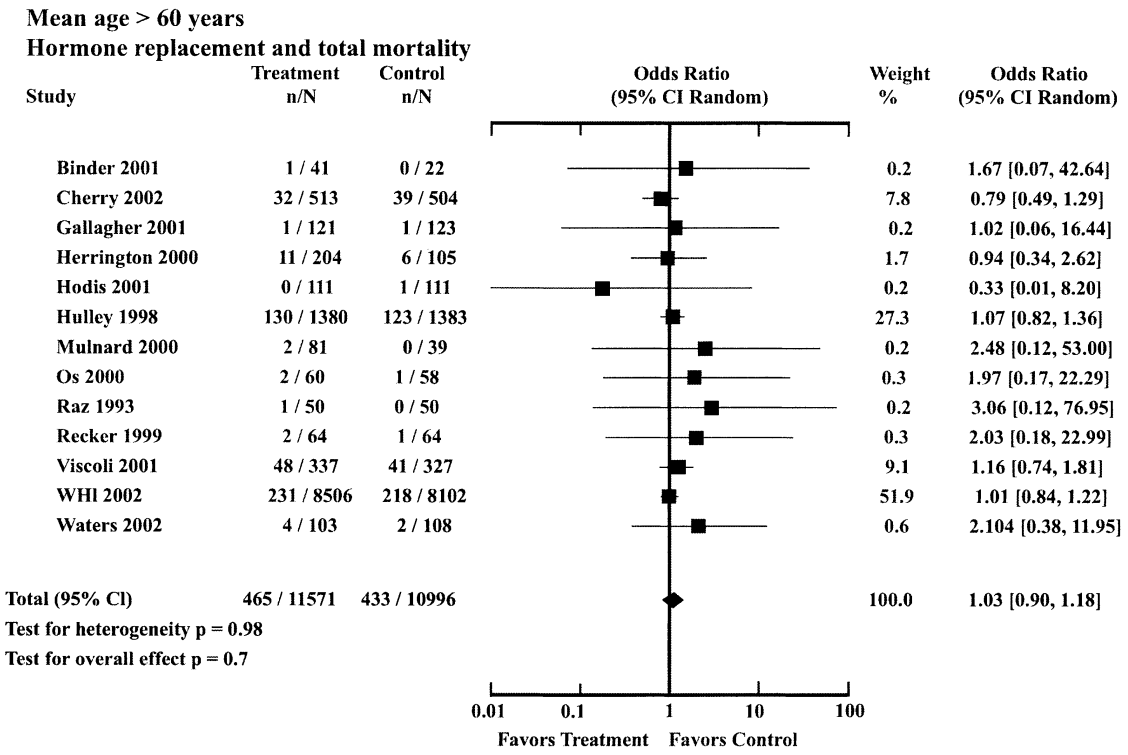

FIGURE 2. Odds ratios for total mortality associated with hormone replacement therapy: trials with mean age of participants greater than 60 years.

since the start of menopause at least 10 years earlier.[9] The WHI included women who were under the age of 60 years, but the investigators declined to provide mortality data for those women separately. Of note, a subgroup analysis of cardiac events in the trial found a hazard ratio of 0.89 for those women within 10 years of menopause, 1.22 for those 10 to 15 years from menopause, and 1.71 for those greater than 20 years from menopause.[49] The results demonstrate a nonsignificant, but suggestive, trend toward decreased events in those who initiated treatment shortly after menopause and increased events for those who started treatment many years after menopause. This meta-analysis pooled the results of 13 trials in older women and found no change in total mortality (OR, 1.03; 95% CI, 0.9 to 1.18). Of note, a *post-hoc* subgroup analysis showed that trials of women with known cardiovascular disease had the same OR for cardiovascular mortality (1.10; 95% CI, 0.86 to 1.41) as those trials of older women without known cardiovascular disease (1.12; 95% CI, 0.79 to 1.58). This indicates that there may be significant progression of atherosclerosis in healthy older women who have been without hormone replacement for many years, so that primary prevention of cardiac disease may not be possible at this stage. The accumulated evidence indicates that once atherosclerosis has already developed, HRT has no effect at reversing the process.[28,46,76,77]

When HRT is started in older women a significant time trend is seen, with increased cardiovascular events in the first year and then decreasing events over the next few years.[9,78] This is thought to be due to a prothrombotic effect of HRT that is greatest within the first year of treatment.[12,79] Estrogen treatment has been shown to increase levels of C-reactive protein and von Willebrand factor antigen, and may promote arterial thrombosis or plaque destabilization in women with established atherosclerosis.[80–82] Few trials have followed patients beyond 5 years, so it is not possible say whether long-term treatment is associated with a net cardiovascular benefit or harm in older women.

Hormone replacement has also been shown to affect cancer risk, but its effect on cancer deaths is less clear. In the WHI trial, HRT increased breast cancer incidence by 26% and reduced colon cancers by 27%, without changing the risk for death from each disease.[9,83] This meta-analysis found no change in breast cancer deaths or total cancer deaths. Observational studies have found HRT to be associated with increased mortality for breast cancer and reduced mortality for colon cancer.[84,85]

Hormone replacement has beneficial effects in conditions other than cancer and cardiovascular disease, such as a 35% reduction in the incidence of hip fractures and new-onset diabetes mellitus, and a 60% reduction in recurrent urinary tract infections.[9,30,50,86] In this meta-analysis, hormone replacement decreased the risk of deaths from causes other than cardiovascular disease or cancer. It is possible that this is due, in part, to a reduction in the complications from hip fracture, diabetes mellitus, and sepsis.

This analysis has several limitations, some that are common to most meta-analyses.[87] Standard meta-analytic

results are uncertain when the numbers of events per study are small, as is the case with mortality. There was marked heterogeneity in the trials, although no heterogeneity was seen in the results. There was a wide range in study size, medication used, and method of administration. The results for the older group were mainly from a few large high-quality trials, with a majority of the data coming from one trial.[9] The results for the younger group were from many smaller trials, and approximately one half of the deaths were from one trial in ovarian cancer survivors.[25] However, when this trial was excluded from the analysis, there still was a significant reduction in mortality (OR, 0.56; 95% CI, 0.31 to 0.99).

Another limitation of the study is that the age groups were defined according to the mean age of participants in each trial and not based on individual patient's characteristics, allowing for some overlap of ages in the two groups. Most trials did not include mortality as a primary outcome, so it is not clear how ascertainment of deaths was made in each trial. However, all trials reported adverse outcomes that included deaths, and investigators were contacted to get more information about mortality. It is unlikely that the reporting of deaths would be different for the two age groups. It was not possible to assess the absolute mortality rates in this study, as only those trials with at least 1 death could be included in the analysis. The search revealed another 98 trials that were excluded because no deaths were reported. This analysis was based only on published literature and therefore is subject to publication bias. However, funnel plots of effect size versus standard error for the trials in this analysis showed no evidence of bias. Few trials provided data on treatment for longer than 5 years, so it is not possible to assess mortality risk with long-term treatment. Despite these limitations, we believe that this meta-analysis provides valuable evidence concerning the mortality risk associated with HRT in younger and older women.

Treatment decisions concerning hormone replacement must be made on an individual basis, taking into account the age of the woman, the degree of bothersome postmenopausal symptoms, and any associated disease risk factors. The results of this analysis indicate that the benefits of HRT may outweigh the risks if treatment is given to younger women, but the risks may outweigh benefits if treatment is started at a later age. This study could not assess the optimal age at initiation of treatment or the duration of treatment needed in order to maximize benefits while minimizing risks. More large randomized trials of long duration, studying younger women near the start of menopause, would be needed to adequately address these issues.

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