

# The Women's Health Initiative could not have detected cardioprotective effects of starting hormone therapy during the menopausal transition

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The Women's Health Initiative (WHI) randomized controlled trial failed to show cardioprotection by estrogen plus progestin treatment of postmenopausal women. But by design, the WHI population was 10-fold underpowered to show cardioprotection of women starting hormone treatment during the menopausal transition. Thus, observational studies that showed cardioprotection in such women remain the only applicable clinical guide to this issue. Randomized controlled trials are urgently needed to test cardioprotection in women starting treatment during the menopausal transition. (*Fertil Steril*® 2004;81:1498–501. ©2004 by American Society for Reproductive Medicine.)

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The decision of whether to begin hormone therapy (HT) and for how long was, until recently, relatively easy for the symptomatic, healthy, newly postmenopausal woman and her caregivers. In addition to relief from symptoms of estrogen withdrawal, data from large observational studies demonstrated that women who choose to take estrogen therapy (ET) or HT (estrogen [E] or estrogen plus progestin [E+P]) experience less bone loss and fewer cardiovascular events and have lower overall mortality (1). The fact that the women enrolled in these observational studies were predominantly symptomatic of recent estrogen deficit and were newly menopausal is of central relevance because estrogen appears better able to maintain healthy tissue than to repair damage associated with estrogen deprivation. For example, after years of estrogen deprivation–driven re-

sorption, estrogen treatment does not adequately restore normal bone structure or repair fractures (2).

Similar to the case with osteoporosis and fracture, cardiovascular disease has a long latency period during which atheroma formation and endothelial dysfunction precede clinical cardiovascular events by many years. Early initiation of estrogen replacement has been shown to inhibit atherosclerosis and the response to vascular injury in a series of animal models (3–5). This is not surprising in light of the presence of both estrogen receptors and estrogen synthetase in human coronary vessels (6). However, recent studies suggest that this benefit is lost if initiation of estrogen replacement is delayed until years after the menopause. This may reflect estrogen's ability to

prevent lesion formation but not to prevent progression of already-established lesions (5). Therefore, it should not be surprising that salutary effects of estrogen on cardiovascular disease may require early administration and a long observation period before the better-maintained cardiovascular health of the treated women becomes apparent. These observations suggest that the appropriate study group for postmenopausal cardioprotection is newly menopausal women who receive estrogen for some years, as was the case in the observational studies (7, 8).

Recently, the Women's Health Initiative (WHI) investigated the effect of E+P on postmenopausal women, who ranged in age from 50 to 79 years at enrollment (8, 9). The published results 5.2 years into the trial have been interpreted as showing that there were no cardioprotective effects of E+P, as judged by comparing the number of adverse cardiovascular events in the E+P group with that in the placebo group (9). However, it must be noted that the majority of women enrolled in the WHI were in their 60s and 70s; the average age at enrollment was 63.3 years. In fact, two thirds of the women enrolled in the trial were more than 60 years old. Moreover, the 50- to 60-year-old women were required to be at least 1 year without menses and were discouraged from enrolling if they had menopausal symptoms. Thus, it is likely that even the younger women in the WHI were still well beyond menopause, which could preclude the evaluation of the cardioprotective effects of HT.

As an initial step toward addressing the impact of the duration from menopause to initiation of HT on prevention of cardiovascular disease, the WHI investigators released an unpublished report of the 50- to 59-year-old E+P and placebo groups' cardiovascular outcomes at the 5-year milestone. This was reported to show the same lack of cardioprotection in the 50- to 59-year-old E+P group as was found in the placebo group, and among the younger group as among the 60- to 79-year-olds (8). However, no detail was furnished on the composition of the 50–59 year-old group; specifically, whether the group had a homogenous distribution of subject ages from 50–59 years or was skewed toward older subjects. The same was true of the recent report of the “final results” of the cardiovascular studies reported by Manson et al., in the *New England Journal of Medicine* (10).

Randomized controlled trials are very powerful investigative tools that are, by design, limited in their interpretation to populations covered by the randomized controlled trial. Therefore, to assess the power of the WHI trial to resolve such questions, it is necessary to know the number of subjects being observed, the homogeneity of each trial group, and whether there should be subgrouping analysis because of skewed distribution of subjects that could obscure age-related occurrence of cardiovascular events within the larger group of subjects. Despite having published the “final results with regard to estrogen plus progestin and [coronary heart disease] from the [WHI],” (10) without details on the sub-

**TABLE 1**

Characteristics of the subjects making up the 50 to 59-year-old WHI estrogen + progestin and placebo groups.

Parameter	E+P	Placebo
Age 50–59 y (% of total group)	2,839 (33.4)	2,868 (33.1)
Menopausal age (y) <sup>a</sup>		
<5	1,315 (17.1)	1,224 (16.3)
5 to <10	1,467 (19.1)	1,488 (19.8)
10 to <15	1,611 (21.0)	1,566 (20.9)
≥15	3,286 (42.8)	3,231 (43.0)

Note: From Hays et al. (1). Reprinted by permission of the publisher.

<sup>a</sup> Average, 12.0 y; see text.

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jects in the 50- to 59-year-old group, there would not be a chance to evaluate the purported lack of cardioprotective effects in women randomized to E+P. This question would best be resolved by knowing the number of subjects and results by treatment in women in the WHI who started treatment between ages 50 and 54 years. More important, the chronological age is probably less informative than the years since the menopause (“menopausal age”). Hence, it would also be useful to know whether the women were sufficiently close to the menopause to still have symptoms such as hot flashes and poor sleep patterns.

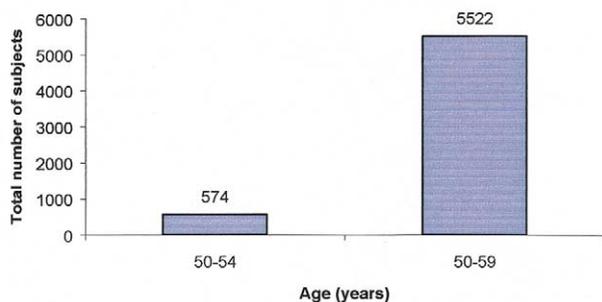
Fortunately, this important information was furnished in an unrelated report by WHI investigators, in which Hays et al. (11) furnished information that allows evaluation of the power of the WHI to determine whether symptomatic 50- to 54-year-old perimenopausal and postmenopausal women starting hormone or placebo treatment demonstrate a significant difference in cardiovascular events during the WHI study. Table 1 contains some of the relevant data published in the Hays et al. (11) article, including the following.

As indicated, in the WHI trial, the average time since menopause in the complete E+P and placebo groups is 12 years if one uses 2.5, 7.5, 12.5, and 17.5 years after menopause as the denominator for each subgroup in Table 1. This is 13 years, on average, since the last period. Perhaps of greatest importance is the information that although there were ~2,000 moderate to severely symptomatic women in the aggregate E+P and placebo subjects, only a total of 574 women in both groups were 50–54 years old and moderately to severely symptomatic (11) (Fig. 1).

Detecting differences in the occurrence of infrequent events is problematic in small sample sizes such as those were present in the 50 to 54 year-old symptomatic women in the WHI. For example, age-specific data from the Nurses Health Study indicates that the incidence of cardiac events in the 50 to 54 year-old population in 1992–1994 is 53/100,000 per year (12). This translates to 0.73 expected events in 275 women over a 5-year period. Even if there was a severalfold

**FIGURE 1**

Total number of 50- to 54-year-old moderate to severely symptomatic subjects in the E+P and placebo groups compared with the total number of subjects in the 50- to 59-year-old groups.



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difference in the number of events between the E+P and placebo groups, the small sample size would make it very unlikely that a statistically significant difference could be detected: a power analysis indicates that assuming 0 events in the placebo group and twice the number of expected events in the E+P group, it would require >4,000 women in each arm of the study to detect such a difference with statistical significance. Moreover, given that there was a 42% dropout rate, as reported by the WHI (9), the number of subjects needed per group rises to almost 9,000. Stated another way, using the number of symptomatic, newly menopausal women present in the WHI, it would require at least a ninefold increase in the number of events in the trial arm to achieve statistical significance. The excess events for the entire trial, including women 55–80 years of age, was less than onefold (10).

Thus, the WHI was more than 10-fold underpowered to detect a change in clinical cardiovascular events in the patient population most likely to be capable of receiving benefit. With ~284 (574/2) subjects per group, the WHI could not reasonably be expected to provide useful information regarding the cardioprotective effects of E+P in moderately to severely symptomatic women who were 50–54 years old at the start of the trial. Furthermore, Manson et al. (10) reported a nonstatistically significant decreased relative risk of cardiovascular events in hormone therapy users who were <10 years from the onset of menopause. Had the study been sufficiently powered, this decreased relative risk might have achieved statistical significance. Had the investigators segregated those closer to the menopausal transition or had the study included newly menopausal women, we might well have seen a further decrease in relative risk.

The results of the WHI trial may be applicable to women who are remote from the menopausal transition (13). However, in the absence of an adequately powered study group in

the menopausal transition it is not appropriate to define either clinical management of symptomatic 50- to 54-year-old women or to mandate discontinuation of appropriately initiated hormone therapy on the basis of the available data from the WHI.

Estrogen's role in clinical cardioprotection remains an open question. All who can should continue to seek resolution of this critical personal and public health issue through the performance of appropriately timed—and powered clinical trials. We hope that, in the interim, knowledge of the limitations of available RCTs will encourage caregivers, regulators, media personnel and women to consider or reconsider the issue of the potential cardioprotective effects of estrogen treatment during the climacteric. With many observational trials indicating a cardioprotective effect of early estrogen treatment and the absence of a prospective, randomized clinical trial powered to reveal cardioprotection starting during the menopausal transition it seems prudent not to dismiss such an effect (14).

*Note added in proof:* During the processing of this article the results of the estrogen-only group of the WHI were published (WHI Steering Committee. Effects of conjugated equino-estrogen in postmenopausal women with hysterectomy. *JAMA* 2004;291:1701–12). Despite some minor differences in cardioprotective effects as measured by events in the estrogen-only group versus placebo, there was nothing in the report that conflicts with our analysis of the lack of power for either hormonal arm of the WHI to have revealed cardioprotective effects in women who began the trial during the menopausal transition.

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