Letters to the Editor


We appreciate the effort by Prentice et al. (1) to elucidate the basis for differences in the relation of postmenopausal hormone therapy to risk of coronary heart disease in observational studies and in the Women’s Health Initiative (WHI) trial. Three findings from this and earlier WHI reports (2–4) are key.

First, the duration of time since starting hormone therapy differed greatly between the types of studies, in part because the observational studies enrolled a cross-section of postmenopausal women that included many who had already been using hormone therapy for years.

Second, differences in time since menopause at hormone therapy initiation were also extreme because women were randomized up to the age of 79 years in the WHI trial, whereas in usual practice hormone therapy is started near menopause, when the risk of coronary heart disease is low. As a result, in the WHI trial, fewer than one third of the women were randomized to hormone therapy within 10 years after menopause (3, 4), whereas in the Nurses’ Health Study and most observational studies, more than 80 percent of the women initiated use within 10 years of menopause (5, 6). Taken together, these observations explain why, in the observational studies enrolled a cross-section of postmenopausal women that included many who had already been using hormone therapy for years.

Third, the elevation in coronary heart disease risk from hormone therapy in the WHI trial was limited to the short interval soon after initiation of hormone therapy: For estrogen plus progestin, the relative risks were 1.68 for less than 2 years, 1.25 for 2–5 years, and 0.66 for 5 or more years. A transient elevation in risk with hormone therapy followed by reduction in risk was also seen in the estrogen-only arm of the WHI trial (4) and in the Heart Estrogen/Progestin Replacement Study (HERS) trial (7). As shown by Prentice et al. (1), when stratified by year from initiation of hormone therapy, the findings for coronary heart disease from the WHI observational and trial components did not differ appreciably.

Prentice et al. (1) suggest that in the Nurses’ Health Study an elevation in risk of coronary heart disease shortly after the initiation of hormone therapy might have been missed because women’s hormone status was determined at the start of each 2-year follow-up interval. This was done to maintain a strictly prospective analysis but will result in some misclassification of exposure. We recently examined this issue (6) by identifying women who reported both starting hormone therapy and experiencing a myocardial infarction during the same 2-year interval and, thus, could be misclassified cases. During 24 years of follow-up, there were only 17 such cases out of a total of 1,342 cases of coronary heart disease; none of these potentially misclassified cases occurred among women who started hormone therapy use within 10 years of menopause. In a simulation, we made the extreme assumptions that all of these women initiated hormone therapy before their coronary heart disease event and that their relative risk was 1.8, as seen in the first year in the WHI estrogen plus progestin trial (3). This had no effect on the relative risk for women initiating hormone therapy within 10 years of menopause and changed the overall relative risk for current use of hormone therapy from 0.71 to 0.76. The main reason our simulation findings differed from the simulation conducted by Prentice et al. in the WHI trial (in which simulated misclassification of exposure during the first 2 years of the trial could obscure an elevation in risk) is that during the first 2 years after menopause the incidence of coronary heart disease is very low.

Differences in age at initiation and duration of hormone therapy use are sufficient to explain the ostensibly discordant findings for hormone therapy use and coronary heart disease between the WHI trial and observational studies; hence, there is no basis for debate about which type of study found the right answer. These studies addressed very different ways of using hormone therapy. As the WHI has shown, when combined estrogen plus progestin is started many years after menopause, the risk of coronary heart disease increases transiently, but the cumulative incidence converges by about 8 years (2); for estrogen alone, the overall relative risk was 0.91 (4). On the other hand, the WHI trial could not address the usual practice of starting hormone therapy near menopause. Any modest, transient elevation in the risk of coronary heart disease with initiation of hormone therapy at this age would be challenging to detect because of the low absolute risk among these women, and animal models and angiographic studies suggest that there may be no adverse effects among women with healthy coronary arteries (5). Although a randomized trial in recently menopausal women is addressing hormone therapy’s effect on atherosclerotic progression by noninvasive imaging (8), trials with clinical coronary heart disease events would require an enormous sample size (many times larger than the WHI). The WHI findings, taking into account the age at initiation and duration of hormone therapy use, support the validity of findings from observational studies relating hormone therapy use to reduced coronary heart disease risk.

ACKNOWLEDGMENTS
Conflict of interest: none declared.
REFERENCES


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DOI: 10.1093/aje/kwj156; Advance Access publication April 26, 2006