Author's Response, Part II

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We encourage new ways of evaluating data, and for this reason the analysis led by Hernan et al of estrogen plus progestin menopausal hormone therapy[1] was a useful exercise. At the same time, we agree, however, with the comments of Stampfer[2] and Prentice[3] regarding the simulated "intention to treat" analysis of epidemiologic data. In this application, and perhaps others, this methodology does not seem to provide insights that cannot be obtained with existing approaches, and it can add great obscurity and complexity; therefore, we do not recommend its routine use.

Regarding other comments by Prentice[3] and Hoover,[4] the inclusion by Hernan et al of cases of coronary heart disease (CHD) occurring between the onset of hormone use and the first follow-up questionnaire, which were not included in the previous, traditional strictly prospective analysis, had only a very small effect on the overall association between hormone use and CHD. We had included these cases in an earlier sensitivity analysis,[5] and the CHD risk reduction among recently menopausal women who used hormones remained strong and statistically significant. More important, to simulate the WHI trial in the analysis by Hernan et al, the majority of CHD cases occurring within 10 years of menopause (in which hormone use was inversely related to risk of CHD) was eliminated. This gave more weight to hormone use starting more than 10 years after menopause (where hormone use was not associated with lower risk of CHD), which does not represent actual practice or the previous results from the NHS.

From these and other analyses comparing the results for CHD from the randomized trial and observational studies, it is apparent that the differences are primarily due to different distributions in time since menopause before starting hormones. Thus, as emphasized by Hoover[4] and Mendelsohn and Karas,[6] the overall Women's Health Initiative results for CHD should not be generalized to the majority of women who start hormone therapy near the time of menopause, and correspondingly the overall results of the NHS and other observational results should not be generalized to women starting hormone use many years after menopause. As noted by Hoover, we have learned much about the complexities surrounding time of initiating hormone use, which will need to be considered in future studies of various formulations, doses, and durations.

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ISSN: 1044-3983/08/1906-0793
DOI: 10.1097/EDE.0b013e318188e84e