The meta-analysis by Salpeter et al. (1) is ineligible to support the validity of the “timing hypothesis” discussed by Manson and Bassuk in a recent Journal article (2), because this work suffers from methodological shortcomings. The objective to disentangle associations between coronary heart disease and use of menopausal hormone therapies was obscured by including not only trials with defined coronary heart disease events, monitored and analyzed as primary or secondary outcomes, but also trials reporting adverse events. Eight of 12 included studies of women younger than age 60 years (3–10) report adverse events, not primary or secondary endpoints [(1), figure 1]. Likewise, five of 13 trials of women older than age 60 years also provide only adverse events [(11–15); (1), figure 2]. The authors (1) included studies that had zero coronary heart disease events in one group and one event in the other group, a situation not enabling relative risks to be calculated. It would also have been more suitable to report woman-years instead of numbers of women when calculating relative risks. Data on safety outcomes including adverse events are subject to bias due to selective reporting (16). Therefore, it is reasonable to perform meta-analyses based on predefined outcomes intended for comparison between groups (17). Finally, the results of a test of interaction was not reported (1), useful to examine age effects (18).

Three further recent meta-analyses (19–21) address cardiovascular risk in conjunction with menopausal hormone therapies. These analyses were based on trials with coronary heart disease events as the primary or secondary trial outcomes. One Cochrane review (19) with the objective to determine the effects of menopausal hormone therapies for the prevention of cardiovascular diseases analyzed specified cardiovascular events studied as primary or secondary outcomes. The authors concluded on the basis of 10 trials that there was no evidence for a protective effect for any outcome. However, results of subgroup analyses regarding interactions of chronological age and/or age at menopause in conjunction with initiation of menopausal hormone therapies were not reported. A second Cochrane review (20), based on inclusion of 15 randomized, placebo-controlled, double-blinded trials reporting myocardial infarction or coronary death, concluded that combined continuous menopausal hormone therapies increased the risk of coronary events after use for 1, 2, 3, and 4 years, not after a mean of 5.6 years. There was no change in coronary heart disease risk for unopposed estrogen therapy. Their analyses did not indicate any difference between menopausal hormone therapies and placebo groups regarding death from any cause or death from coronary heart disease. The authors stated that no trial focused on younger women. Obviously, analyses and conclusions of both studies (19, 20) were influenced by the relative weight of the Women’s Health Initiative trials. A third meta-analysis (21) based on seven trials concluded that menopausal hormone therapies did not significantly change the risk of all-cause mortality, of coronary heart disease death, or of nonfatal acute myocardial infarction.

Manson and Bassuk (2) refer to a further meta-analysis (22) in the context of mortality reduction by menopausal hormone therapies. Unfortunately, this report also suffers from shortcomings (16–18). Additionally, we are concerned about the validity of findings because one trial, providing the relatively largest proportion of cases among younger women (32 of 53), included ovarian cancer survivors.

Finally, we wonder why the risk of stroke, apart from risks for other endpoints, was not considered when examining the appropriateness of the timing hypothesis (2). According to post-hoc analyses of Women’s Health Initiative data, reporting upon the largest number of confirmed coronary endpoints and applying a uniform coding scheme for age and years since menopause (23), the risk of stroke did not vary significantly by age or time since menopause. Thus, stroke risk is of relevance and should be part of any decision making regarding use of menopausal hormone therapies in younger and older women alike.

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REFERENCES


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