We thank Dören and Greiser (1) and Rosenberg (2) for their interest in our commentary (3). We agree with Dören and Greiser that the meta-analyses of Salpeter et al. (4, 5) have limitations, but our argument concerning the validity of the timing hypothesis would be equally compelling if we omitted mention of these meta-analyses. Our thesis is based primarily on subgroup analyses of data from the Women’s Health Initiative hormone-therapy trials (6, 7) and the large observational Nurses’ Health Study (8), which suggest that hormone therapy–associated risks of coronary heart disease and total mortality vary by age (or years since menopause) at initiation of treatment, as well as underlying biologic mechanisms and experimental studies in animals and humans showing differential effects of exogenous estrogen on atherosclerotic progression according to the initial health of the vasculature (9). We agree with Rosenberg that the results of animal studies are not always generalizable to humans and that such studies cannot, taken in isolation, confirm or refute the timing hypothesis. However, these studies add an important dimension to the totality of available evidence.

The meta-analyses cited by Dören and Greiser (1)—Gabriel-Sanchez et al. (10), Farquhar et al. (11), and Magliano et al. (12)—are not relevant for addressing the validity of the timing hypothesis and do not add new information to the evidence we reviewed in our commentary. These meta-analyses are based on trials of largely older women. Gabriel-Sanchez et al. did not include analyses stratified by age or time since menopause. Beyond briefly noting the Women’s Health Initiative results for women aged 50–59 years, Farquhar et al. also did not address the issue of timing of hormone-therapy initiation. Magliano et al. did conduct a stratified analysis that categorized trials by mean baseline age of participants (utilizing a crude classification of <65 vs. ≥65 years). Because the mean ages in the Women’s Health Initiative estrogen-progestin and estrogen-alone trials were 63 and 64 years, respectively, the Women’s Health Initiative data in their entirety were placed in the “young” stratum. Thus, this analysis, which found little difference in hormone therapy–associated risks between the two age strata, is clearly suboptimal for examining the timing hypothesis.

It was not our intention to review exhaustively every individual endpoint vis-à-vis the timing hypothesis, and thus we did not address stroke outcomes in this regard. Whether timing of hormone therapy initiation affects stroke risk remains uncertain. In the Women’s Health Initiative, the increase in stroke risk associated with hormone therapy was minimal or nonexistent among women aged 50–59 years at trial entry—the relative risks were 0.89 (95 percent confidence interval: 0.47, 1.69) for estrogen alone and 1.13 (95 percent CI: 0.73, 1.76) in analyses that combined the estrogen-alone and estrogen-progestin data—but was much higher in the joint analyses among women who were within 10 years of menopause (relative risk = 1.77, 95 percent confidence interval: 1.05, 2.98), which included some women over age 60 years at entry (6). Regardless of whether stroke risk varies according to timing of treatment initiation, it is clear that absolute rates of stroke are much lower in younger or recently menopausal women than in older women or those more distant from menopause onset. We certainly agree that consideration of stroke risk is a key component of clinical decision making. Indeed, we noted this point in our commentary: “A younger, recently menopausal woman . . . at low baseline risk of CHD [coronary heart disease], stroke, or venous thromboembolism is a reasonable candidate for short-term hormone therapy. Conversely, an older woman many years past menopause, who is at higher risk of these cardiovascular conditions, is not” (3, p. 516; emphasis added). We refer readers seeking guidance on assessment of stroke risk and other aspects of hormone-therapy decision making to our book (13).

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THE AUTHORS REPLY

We thank Dören and Greiser (1) and Rosenberg (2) for their interest in our commentary (3). We agree with Dören and Greiser that the meta-analyses of Salpeter et al. (4, 5) have limitations, but our argument concerning the validity of the timing hypothesis would be equally compelling if we omitted mention of these meta-analyses. Our thesis is based primarily on subgroup analyses of data from the Women’s Health Initiative hormone-therapy trials (6, 7) and the large observational Nurses’ Health Study (8), which suggest that hormone therapy–associated risks of coronary heart disease and total mortality vary by age (or years since menopause) at initiation of treatment, as well as underlying biologic mechanisms and experimental studies in animals and humans showing differential effects of exogenous estrogen on atherosclerotic progression according to the initial health
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