Lower Doses of Estrogen Replacement Therapy and the Risk of Cardiovascular Disease

To the Editor:

In their interesting study, Koh et al demonstrated that lower dosage of oral conjugated equine estrogen (CEE) eliminated the adverse effects of conventional dosage of CEE on markers of vascular inflammation and coagulation, in addition to preserving the favorable effects of estrogen on endothelial function.1 Similar to their report, our previous findings demonstrated that CEE at a dosage of 0.625 mg increased inflammatory markers such as C-reactive protein, serum amyloid protein A, and interleukin-6, whereas CEE at a dosage of 0.3125 mg did not elevate these markers. Additionally, low-dose CEE has an effect comparable to high-dose CEE on endothelium,2 and low-dose CEE has benefits of plasma triglyceride and the size of low-density lipoprotein (LDL). High-dose CEE increases plasma concentrations of triglyceride, and this estrogen-induced increase in plasma triglyceride reduces the size of LDL particles that are more susceptible to oxidation. In contrast, plasma triglyceride concentrations and the size of LDL particles are unaffected and the oxidative susceptibility of LDL is inhibited by low-dose CEE administration.3

The Heart and Estrogen/Progestin Replacement Study and the Women’s Health Initiative reported that hormone therapy increased the risk of coronary heart disease (CHD) in postmenopausal women. In contrast, Grodstein et al demonstrated that CEE at a daily dosage of ≥0.625 mg increases the risk for stroke, whereas 0.3 mg of CEE daily is associated with a reduction in the risk for stroke.4 In addition, Ferrara et al also demonstrated that low dosage but not medium or high dosage estrogen decreased the risk of myocardial infarction (MI) in diabetic women without a recent MI.5 Thus, low dosage estrogen administration can ameliorate the adverse effects of conventional dosage of estrogen and could have a different effect on clinical outcome. Studies are needed to investigate whether low dosage estrogen therapy is protective against the risk of CHD in postmenopausal women.

Akihiko Wakatsuki
Department of Obstetrics and Gynecology,
Kochi Medical School
Kochi, Japan

References

In response:

We appreciate Dr. Wakatsu very much for the concern regarding our article.1

We and others2–5 have demonstrated that low dosages of hormone therapy (HT) ameliorated the adverse effects of conventional HT, which was used in randomized clinical trials, and we have suggested that HT could have a differential effect on clinical outcome. Indeed, recent epidemiological studies have demonstrated that low dosages of estrogen reduced the risk of stroke or myocardial infarction, compared with conventional or high dosages of estrogen.6,7 In summary, recent epidemiological and mechanistic studies have provided a strong rationale to perform a randomized clinical trial to investigate whether low dosages of HT protect the risk of coronary heart disease in postmenopausal women. However, we cannot be confident in this intriguing hypothesis until randomized prospective clinical trials have shown evidence. Thus, we agree with Dr. Wakatsuki that now is the time to show the money.

Kwang Kon Koh
Eak Kyun Shin
Cardiology, Gil Hospital
Gachon Medical School
Incheon, Korea

Ichiro Sakuma
Department of Cardiovascular Medicine
Hokkaido University Graduate School of Medicine
Sapporo, Japan

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Akihiko Wakatsuki

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