Should Progestins Be Blamed for the Failure of Hormone Replacement Therapy to Reduce Cardiovascular Events in Randomized Controlled Trials?

Kwang Kon Koh, Ichiro Sakuma

Abstract—Many observational studies and experimental and animal studies have demonstrated that estrogen replacement therapy (ERT) or hormone replacement therapy (HRT) (estrogen plus progestin) significantly reduces the risk of coronary heart disease. Nonetheless, recent randomized controlled trials demonstrated some trends toward an increased risk of cardiovascular events rather than a reduction of risk. Recently, both the HRT and ERT arms of the Women’s Health Initiative (WHI) study were terminated early because of an increased/no incidence of invasive breast cancer, increased incidence of stroke, and increased trend/no protective effects of cardiovascular disease. We discuss the controversial effects of HRT and ERT on cardiovascular system and provide a hypothesis that the failure of HRT and ERT in reducing the risk of cardiovascular events in postmenopausal women might be because of the stage of their atherosclerosis at the time of initiation of HRT or ERT. (Arterioscler Thromb Vasc Biol. 2004;24:1-10.)

Key Words: PLEASE ■ SUPPLY ■ KEY ■ WORDS ■ XXXX

Generally, postmenopausal women who choose to use hormone replacement therapy (HRT) use a progestin combined with estrogen to prevent uterine hyperplasia and malignancy. In the United States, ~90% of postmenopausal women have not undergone hysterectomy. Many observational studies and experimental and animal studies have demonstrated that estrogen replacement therapy (ERT) or HRT (estrogen plus progestin) significantly reduces the risk of coronary heart disease. Nonetheless, recent randomized controlled trials demonstrated some trends toward an increased risk of cardiovascular events rather than a reduction of risk.1,2 Recently, the HRT arm of the Women’s Health Initiative (WHI) study3 was terminated in July 2002, earlier than the original date, because of an increased incidence of invasive breast cancer and trends toward worse cardiovascular outcomes. In contrast, the parallel ERT arm of the WHI had been allowed to continue; however, very recently, this study was also terminated on March 2, 2004, earlier than the original date, because ERT did not increase or decrease the risk of coronary heart disease and increased the risk of stroke similar to HRT arm of the WHI study.4 This had caused many people to suggest that the inclusion of the progestin in the HRT portion of this study is responsible for the adverse cardiovascular outcomes observed. Discussion of this issue is the focus of this review article.

Biological Effects of ERT and HRT
The vascular endothelium plays a pivotal role in the pathogenesis of atherosclerosis, which contributes to the development of coronary heart disease. We review studies to compare the effects of ERT and HRT on endothelial function.

Effects on Lipoprotein
Orally administered estrogens lower serum levels of low-density lipoprotein (LDL) cholesterol and raise levels of high-density lipoprotein (HDL) cholesterol, each by ~15%, and raise levels of triglyceride by ~20% to 25% in postmenopausal women.5 The route of administration of estrogen influences its effects on serum lipids. Transdermally administered 17β-estradiol (E2) has less of an effect on serum lipid concentrations than do orally administered estrogens. Co-administration of a progestin can blunt the changes in serum lipids caused by estrogen.6–7 The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial reported that medroxyprogesterone acetate (MPA) attenuated the effects of conjugated equine estrogen (CEE) in increasing HDL cholesterol levels.8 We observed that CEE 0.625 mg alone or in combination with MPA 2.5 mg changed total cholesterol and LDL cholesterol levels to a similar extent; however, HRT did not increase triglyceride levels and increased HDL cholesterol levels less than did ERT, which was consistent with PEPI Trial.6 ERT and HRT have also been shown to reduce serum levels of lipoprotein(a) [Lp(a)] to a similar extent.9–10

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Effects on LDL Oxidation

Wilcox et al\textsuperscript{11} found significant inhibition in vivo of LDL oxidation by CEE in postmenopausal women. Both CEE alone and MPA combined with CEE significantly inhibited LDL oxidation in postmenopausal women.\textsuperscript{12,13} However, we observed that MPA combined with CEE or E\textsubscript{2} did not inhibit the effects of CEE or E\textsubscript{2} on LDL oxidation.\textsuperscript{6} CEE may conceivably lack an antioxidant effect, because it primarily comprises equine estrogens (EEs): the 1 human-like estrogen contained in this preparation (estrone) is a weaker antioxidant than E\textsubscript{2}.\textsuperscript{14} Interestingly, oral CEE significantly increased plasma triglyceride and decreased LDL particle size, which counteracted antioxidant effect of estrogen.\textsuperscript{15,16} MPA neither increased plasma triglyceride nor attenuated antioxidant effect of estrogen.\textsuperscript{16}

Effects on Vasomotion

We found that CEE 0.625 mg administered to 28 hypercholesterolemic postmenopausal women improved flow-mediated dilation comparable to the effect of simvastatin 10 mg daily, despite greater reduction in LDL cholesterol levels with simvastatin.\textsuperscript{8} Lieberman et al\textsuperscript{17} reported that oral E\textsubscript{2} resulted in significant improvement in flow-mediated brachial artery dilation compared with placebo. Of interest, Vehkavaara et al\textsuperscript{18} reported that oral E\textsubscript{2}-induced increase in endothelium-dependent vasodilation could be explained not by acute estradiol effects but by several antiatherogenic changes in lipoproteins, in contrast to transdermal estradiol showing no effects on both endothelium-dependent vasodilation and lipoproteins.

With regard to the effects of progestin, there have been inconsistent observations, with some groups demonstrating adverse effects of MPA\textsuperscript{19} and others\textsuperscript{20–22} reporting no adverse effects of MPA. Gerhard et al\textsuperscript{23} observed that intravaginal micronized progesterone (MP) added to E\textsubscript{2} did not significantly attenuate the improvement in flow-mediated dilation that was observed with E\textsubscript{2} alone. In contrast, Sorensen et al\textsuperscript{24} reported that cyclical E\textsubscript{2} and norethisterone did not improve endothelial function. This study has several problems. First, this study was an open-labeled design. Second, the fact that HRT users had significantly higher total cholesterol levels and similar HDL cholesterol levels than nonusers gives suspicion regarding compliance of participants. Investigators did not measure serum estradiol concentration. Third, HRT users and nonusers had very low flow-mediated dilation (2.5\% and 2.2\%, respectively) compared with others’ reports, despite healthy postmenopausal women. Under these conditions, it is very difficult to observe differences after any therapy. Fourth, because there were no ERT users and baseline vascular study as controls, we do not know whether HRT impaired or did not change flow-mediated dilation. Recently, 2 articles demonstrated that MPA inhibited the beneficial effects of E\textsubscript{2} or CEE\textsuperscript{12,25} on endothelium-dependent vasodilation. However, we and others observed that MPA 2.5 mg combined with CEE 0.625 mg significantly improved flow-mediated brachial artery dilator response to hyperemia in postmenopausal women.\textsuperscript{20,21}

There are some technical issues related to ultrasound imaging using high-frequency linear transducer that may limit the interpretation of the studies noted. For example, this technique can be greatly affected by operator’s skill. At this point, 1 study using cardiovascular magnetic resonance demonstrated that contraceptive depot MPA-impaired endothelium-dependent vasodilation and hypoestrogenism may be the mechanism of action.\textsuperscript{19} There are some problems in this study. First, the serum estradiol concentration 64.6 pmol/L in MPA users is much lower than \textasciitilde250 pmol/L in postmenopausal women using conventional HRT,\textsuperscript{6} and postmenopausal women who reached this concentration with HRT improved endothelium-dependent vasodilation, as reported by us and others.\textsuperscript{20–22} Furthermore, in the same estradiol concentration, 57.6 pmol/L and 65.3 pmol/L, respectively, CEE and CEE plus MPA both reduced coronary atherosclerosis by \textasciitilde62\% in postmenopausal cynomolgus monkeys.\textsuperscript{26} Second, MPA users had significantly lower HDL cholesterol levels than controls, which can affect endothelium-dependent vasodilation. Third, the number of subjects, 12, was too small, as authors declared in the limitation. Indeed, a recent study using radioisotope (objective measurement) demonstrated that MPA did not affect the effects of estrogen.\textsuperscript{27}

Effects on Inflammation

Cell Adhesion Molecules

The selectin family of cell adhesion molecules (CAM), which includes L-selectin and E-selectin, binds to carbohydrate ligands on leukocytes and promotes “rolling” of these cells—the first step in adhesion—on activated endothelium before the firm adherence of intercellular CAM-1 (ICAM-1) and vascular CAM-1 (VCAM-1), with subsequent incorporation into the vessel wall. The pathophysiological relevance of CAM in humans has been suggested by its localization in atherosclerotic plaques. Serum concentrations of VCAM-1, ICAM-1, and L-selectin have been reported to be higher in patients with coronary artery disease than in healthy controls.\textsuperscript{28,29}

Koh et al\textsuperscript{30} first reported that either transdermal E\textsubscript{2} or transdermal E\textsubscript{2} and oral MPA lowered inflammatory CAM expression in postmenopausal women. In this study, we observed MPA did not negate the effects of estrogen on reducing soluble CAM levels. In a randomized, double-blind, crossover study, 6 or 8 weeks of treatment with CEE alone or combined with MP or MPA significantly diminished E-selectin, ICAM-1, and VCAM-1 expression as compared with baseline (Figure 1).\textsuperscript{8,9,20} These findings have since been confirmed by others.\textsuperscript{31} The PEPI trial confirmed the reduction of E-selectin by HRT.\textsuperscript{32}

Chemokine and Cytokines

There was a significant correlation between the mean maximum intimal medial thickness and monocyte chemoattractant protein (MCP)-1 levels at baseline in postmenopausal women. In this study, E\textsubscript{2} significantly reduced MCP-1 levels.\textsuperscript{33} We recently observed that CEE with MP or MPA significantly decreased MCP-1 levels from baseline values in healthy postmenopausal women (Figure 1).\textsuperscript{20,34} Tumor necrosis factor (TNF)-\alpha is a multifunctional circulating cytokine derived from endothelial and smooth muscle cells as well as macrophages associated with coronary atheroma. Further,
TNF-α enhances the rate of monocyte recruitment into developing atherosclerotic lesions. TRN-α is involved in several cardiovascular processes. We observed that CEE with MP or MPA significantly reduced TNF-α levels from the baseline in hypertensive or overweight postmenopausal women, and, furthermore, patients with the highest baseline of TNF-α levels showed the greatest extent of reductions. Our observation was consistent with the findings of Walsh et al. The effects of ERT or HRT on soluble IL-6 levels in postmenopausal women are inconsistent. Some studies observed the increase of IL-6 levels, whereas we in our study and studies of others observed no significant changes.

C-Reactive Protein
C-reactive protein (CRP) may induce the synthesis of cytokines, CAMs, tissue factor, and angiotensin II type I receptor in monocytes, endothelial cells, and smooth muscle cells. Tissue factor activates the extrinsic coagulation cascade, providing a link between inflammation and thrombosis. In addition, CRP may contribute to atherogenesis by facilitating uptake of LDL by macrophages and decreasing endothelial nitric oxide synthase expression and activity.

Ridker et al. reported the predictive value of CRP in determining the risk of future cardiovascular events in 122 apparently healthy participants in the Women’s Health Study who subsequently had a first cardiovascular event during a 3-year follow-up period. They found that women who had cardiovascular events had higher baseline CRP levels than control subjects. The PEPI Study showed that both ERT and HRT regimens resulted in a large sustained increase in levels of CRP with a decrease in E-selectin levels. Others have reported the same observations with oral HRT. In contrast, transdermal administration of ERT significantly lowered CRP levels or did not change CRP levels in postmenopausal women. Therefore, this paradoxical effect in the inflammatory marker CRP is caused by a first pass effect in the liver as documented by the differences in transdermal and oral administration, and this increase of CRP may be not a biologically meaningful. However, this controversy over whether there are proinflammatory effects of estrogen persists. Indeed, a recent article observed that increased CRP levels for 3 years of ERT and HRT treatment in the WHI trial did not cause cardiovascular events; however, in viewing that CRP has several important atherogenic properties as well as inflammation marker, oral estrogen-induced CRP increase over years may result in atherogenesis progression. Interestingly, MPA attenuated the increase of CRP and serum amyloid A protein concentration with oral CEE in women. Both ERT and HRT significantly decreased plasma homocysteine levels.

Estrogen Receptor Polymorphisms
Estrogen receptor polymorphisms may modify the effects of ERT and HRT on lipids levels and other outcomes related to treatment in postmenopausal women. In this regard, postmenopausal women who have the estrogen receptor polymorphisms had an augmented response of HDL cholesterol and E-selectin to HRT. However, these responses were evident in both ERT and HRT. Effects on Arterial Compliance and Stiffness
Twenty-six postmenopausal women using HRT had a significantly increased total systemic arterial compliance and lower
pulse wave velocity than those not using HRT. Of interest, 11 postmenopausal women had HRT withdrawn for 4 weeks, resulting in a significant decrease in total systemic arterial compliance and significant increase in pulse wave velocity. Other studies observed that the carotid arterial stiffness index was similar in ERT users with and without MPA or MP who had no evidence of coronary artery disease and was significantly lower than in nonusers.

**Effects on Hemostasis and Fibrinolysis**

The clinical manifestation of atherosclerotic disease hinges on thrombogenic as well as inflammatory cellular and molecular pathways. After plaque disruption, platelets and circulating factors that mediate thrombosis are exposed to the lesional lipid core, which is thrombogenic. Therefore, the effects on thrombosis, fibrinolysis, and overall coagulation status of endogenous estrogen in women of childbearing status, as well as ERT and HRT in postmenopausal women, bear directly on endothelial function.

The relationship between thrombosis, estrogen status, and endothelial dysfunction is supported by the fact that soluble thrombomodulin—a key regulator of activated thrombin—and tissue-plasminogen activator (t-PA), which promotes fibrinolysis, are considered markers of endothelial damage and were elevated in a study of prematurely menopausal women. Six weeks of HRT resulted in a significant reduction in mean soluble thrombomodulin, t-PA, and von Willebrand factor (vWF) compared with premenopausal levels, suggesting beneficial effects on endothelial injury and hemo-

Stasis. Indeed, findings on coagulation status reported in the PEPI trial may partly explain the higher risk of thromboembolism in the HERS placebo group. Among control patients in the PEPI trial, factor VIIIc and fibrinogen increased over time. The vWF antigen concentration also increased to 34% after 12 months, and then returned to baseline at month 36.

Significantly enhanced systemic fibrinolysis resulted from 1 month of treatment with oral CEE, either alone or combined with MPA, in 30 postmenopausal women in a randomized crossover trial. Both CEE and CEE/MPA decreased plasma plasminogen activator inhibitor-1 (PAI-1) levels from baseline by >50%. MPA did not negate the effects of CEE on the improvement of fibrinolysis potential. These findings are surprising because MPA stimulated PAI-1 release from bovine aortic and human umbilical endothelial cells. These effects were more pronounced in women with higher levels of PAI-1 at baseline. In addition, levels of D-dimer exhibited a significant inverse correlation with PAI-1 levels, suggesting enhanced fibrinolysis potential (Figure 2). Six months of HRT with oral cyclic E₂ combined with MP also increased global fibrinolytic capacity by 63% versus baseline and reduced both PAI-1 antigen and PAI activity in 45 healthy postmenopausal women. However, such treatment was also associated with an activation in coagulant function. This hypercoagulable state was reflected by significant increases in prothrombin fragment (F₁⁺₂) and decreased antithrombin activity among HRT users as compared with women who received no HRT.

However, because activation of coagulation pathways has been detected dose-dependently in postmenopausal women treated with CEE 0.625 and 1.25 mg., potentiation of fibrinolysis could be a consequence of activation of coagulation pathways as a primary response to estrogen administration. However, Winkler et al. speculated that small doses of estrogen/progestogen induce increases in fibrinolytic capacity via a marked reduction of PAI-1. In this regard, Koh et al. observed that the increase in fibrinolytic potential was independent of any effect on coagulation of CEE at conventional dosages. Other groups also reported no correlation between fibrinolytic potential and coagulation activation using HRT regimens. Cushman et al. found that hemostasis markers and evidence of procoagulation were not associated and fibrinolytic potential increased. However, in contrast to healthy postmenopausal women, we recently reported that HRT did not significantly decrease PAI-1 antigen levels and, rather, increased tissue factor activity and F₁⁺₂ levels from baseline in hypertensive or overweight postmenopausal women, consistent with the HERS.

Lp(a) increases in serum concentration after menopause. Although Lp(a) is usually construed as an independent risk factor for coronary artery disease, it is structurally homologous with plasminogen. Through competition with this molecule as a substrate for fibrinolytic enzymes, Lp(a) can exert prothrombotic effects. In this regard, both ERT and HRT significantly decreased Lp(a) levels. Indeed, a recent study from HERS reported that CEE plus MPA appeared to have a more favorable effect in women with high initial Lp(a) levels than in women with low levels. However, activation of coagulation after ERT or HRT may not be balanced by activation of fibrinolysis in some postmenopausal wom-
Thus, ERT or HRT should not be initiated in women with coronary artery disease or the coexistence of other risk factors for hypercoagulability.

**Experimental and Animal Studies**

Experimental studies reported that synthetic, not natural, progestins interfered with estrogen protection against vasoconstriction.\(^71,72\) MPA attenuated estrogen-mediated inhibition of neointima formation after balloon injury of the rat carotid artery\(^73\) and coronary artery atherosclerosis in female monkeys.\(^74\) Contrary to these studies, some studies demonstrated that HRT (17\textbeta\textalpha-estradiol and cyclic progesterone or norethisterone acetate, or levonorgestrel) reduced LDL or cholesterol accumulation in the coronary arteries or the aorta in surgically postmenopausal rabbits\(^75\) or monkeys.\(^76\) The latter effect of HRT was similar to the effect of unopposed 17\textbeta-estradiol. A recent article from Clarkson’s group demonstrated that CEE and CEE plus MPA significantly, and to a similar extent, reduced coronary atherosclerosis measured by coronary artery intimal area by \(-62\%\) in postmenopausal cynomolgus monkeys (Figure 3).\(^26\) This study confirms that synthetic MPA did not attenuate the effects of CEE to reduce coronary atherosclerosis.

**Clinical Studies**

Nonetheless, observational studies of HRT report no differences in risk for clinical cardiovascular events between users of unopposed estrogen and users of estrogen combined with progestins (Figure 4).\(^77-83\) The Nurses’ Health Study observed a similar reduction in risk for coronary heart disease among women using oral CEE alone (relative risk: 0.55; CI: 0.45 to 0.68) and those using HRT (relative risk: 0.64; CI: 0.49 to 0.85).\(^84\) Of interest, some observational studies observed that users of estrogen combined with progestins had less cardiovascular events than users of unopposed estrogen. The Coumadin Aspirin Reinfarction Study (CARS) investigators analyzed the data from postmenopausal women with a recent myocardial infarction.\(^85\) They reported that users of estrogen/progestin had a lower incidence of death/myocardial infarction/unstable angina during follow-up than users of estrogen only (relative risk: 0.56; CI: 0.37 to 0.85). Northern California Kaiser Permanente Diabetes Registry observed that the relative hazard for myocardial infarction associated with current estrogen plus progestin use was 0.77 (95% CI: 0.61 to 0.97); in contrast, the relative hazard for myocardial infarction associated with current unopposed estrogen use was 0.88 (95% CI: 0.73 to 1.05).\(^86\)
cells and vascular smooth muscle cells,91 and these conditions on atherosclerosis, inflammation, hemostasis, and optimization of estrogen properties may depend on maintenance of a healthy endothelium. The importance of timing of intervention on the effect of estrogens on atherogenesis has been previously observed in nonhuman primates.74,92–94 When monkeys with little or no atherosclerosis were made menopausal and ERT was immediately initiated along with an atherogenic diet, CEE for 2 years was associated with a substantial 70% reduction in atherosclerosis.74,92 However, when monkeys were allowed to have more atherosclerosis in the premenopausal period and CEE was immediately initiated along with an atherogenic diet, there was a 50% reduction in atherosclerosis.93 Interestingly, when CEE was delayed for 2 years while an atherogenic diet was administered in an estrogen-deficient state, even though CEE and a healthy diet were instituted for another 2 years, there was no effect of CEE on atherosclerotic progression.94 In this regard, recent data related to the timing of estrogen initiation were reported.95 In a rat model, E2 did not cause regression or alter progression of established lesions in the carotid arteries, aortic arch, or thoracic aorta. However, E2 prevented initiation of new lesions in the iliac, femoral, and popliteal arteries, and in the abdominal aorta. We and others observed these findings in postmenopausal women (Figure 5).20,96–98 Based on these views, the subjects enrolled in HERS may have received no benefit from HRT because of the advanced stage of their atherosclerosis at the time HRT was initiated. Similarly, although the majority of the women enrolled in the WHI had not yet had a clinically apparent cardiovascular event, based on their advanced age, high body mass index, and a relatively high prevalence of smoking, diabetes, and hyperlipidemia, they too may not have been able to manifest the atheroprotective effects of the HRT (Table). Accordingly, this may have caused the failure of CEE plus MPA to demonstrate cardioprotective effects in these randomized controlled trials. We may explain why 2 recent randomized controlled trials showed different results even though these studies were performed by the same investigators with the same medications and the same study conditions.

**Angiographic Studies**

Women’s Angiographic Vitamin and Estrogen (WAVE) Trial used quantitative angiographic end points to determine whether HRT or antioxidant supplements, alone or in combination, influenced the progression of coronary artery disease in postmenopausal women.87 Participants in WAVE were on average 65 years old and had at least 1 15% to 75% coronary stenosis at baseline coronary angiography. Participants were randomly assigned in a 2×2 factorial design to receive either 0.625 mg CEE plus 2.5 mg MPA daily or matching placebo, and 400 IU of vitamin E twice daily plus 500 mg vitamin C twice daily, or placebo. The WAVE trial demonstrated that HRT failed to slow the angiographic progression of coronary artery disease in postmenopausal women with established coronary disease, speculating the possible adverse effects of MPA in the favorable effects of estrogen. However, the Estrogen Replacement and Atherosclerosis (ERA) Trial showed the lack of difference in atherosclerosis progression between the estrogen-only arm and the combined HRT arm, suggesting that potential beneficial effects of estrogen itself were not likely reduced by the addition of MPA.4

**Clinical Implications**

The fact that ERT and HRT did not confer cardioprotective effects in the recent randomized controlled trials can be assimilated readily according to the “healthy endothelium” concept.88–90 In short, the favorable vascular effects of estrogen on atherosclerosis, inflammation, hemostasis, and coronary flow reserve are dependent on the integrity of the endothelium and estrogen receptor populations in endothelial cells and vascular smooth muscle cells,91 and these conditions were probably not met by most women in these trials because of their advanced age, multiple risk factors, and coronary atherosclerosis. Optimization of estrogen’s cardioprotective properties may depend on maintenance of a healthy endothelium. A similar degree. Standard error of the mean is identified by the bars. Reproduced with permission from Koh et al.97

**Figure 5. A, Flow-mediated dilatation before therapy (baseline) and after micronized progesterone (CEE+MP) or medroxyprogesterone acetate (CEE+MPA) combined with conjugated equine estrogen (CEE). In healthy postmenopausal women, CEE+MP or CEE+MPA significantly improved the percent flow-mediated dilator response to hyperemia relative to baseline measurements (P<0.004 by ANOVA) by a similar degree. Standard error of the mean is identified by the bars. Reproduced with permission from Koh et al.20 B, Flow-mediated dilatation after placebo and conjugated equine estrogen. In type 2 diabetic postmenopausal women, CEE improved, but not significantly, the percent flow-mediated dilator response to hyperemia compared with placebo (P=0.501). Standard error of the mean is identified by the bars. Reproduced with permission from Koh et al.97**

**Comparison of Baseline Characteristics Between Nurses’ Health Study and WHI**

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<th>NHS82,84</th>
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<tr>
<td>Mean age or age range at enrollemt (years)</td>
<td>30–55</td>
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<tr>
<td>Smokers (past and current)</td>
<td>6.9%</td>
<td>49.9%</td>
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<td>BMI (mean)</td>
<td>25.1 kg/m²</td>
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*34.1% had BMI ≥30 kg/m².
In conclusion, with biological views, that added progesterin negates the beneficial effects of estrogen to prevent coronary heart disease is correct only in the effect of HDL cholesterol levels and inconsistent in the effect of vasomotion in postmenopausal women. However, animal, clinical, and angiographic studies have demonstrated that added progesterin does not negate the beneficial effects of estrogen. The main reasons why recent randomized studies reported failure of HRT in reducing the risk of cardiovascular events may be caused by other factors, such as long postmenopause state (not healthy endothelium) or thromboembolism risk and proinflammation after ERT.

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