Menopausal hormone treatment cardiovascular disease: another look at an unresolved conundrum

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Cardiovascular disease (CVD) is the most common cause of death in women. Before the Women's Health Initiative (WHI) hormone trials, evidence favored the concept that menopausal hormone treatment (MHT) protects against CVD. WHI studies failed to demonstrate CVD benefit, with worse net outcomes for MHT versus placebo in the population studied. We review evidence regarding the relationship between MHT and CVD with consideration of mechanisms and risk factors for atherogenesis and cardiac events, results of observational case-control and cohort studies, and outcomes of randomized trials. Estrogen effects on CVD risk factors favor delay or amelioration of atherosclerotic plaque development but may increase risk of acute events when at-risk plaque is present. Long-term observational studies have shown ~40% reductions in risk of myocardial infarction and all-cause mortality. Analyses of data from randomized control trials other than the WHI show a ~30% cardioprotective effect in recently menopausal women. Review of the literature as well as WHI data suggests that younger and/or more recently menopausal women may have a better risk-benefit ratio than older or remotely menopausal women and that CVD protection may only occur after >5 years; WHI women averaged 63 years of age (12 years postmenopausal) and few were studied for >6 years. Thus, a beneficial effect of long-term MHT on CVD and mortality is still an open question and is likely to remain controversial for the foreseeable future. (Fertil Steril® 2014;101:887–97. ©2014 by American Society for Reproductive Medicine.)

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Atherosclerotic cardiovascular disease (CVD) remains the leading cause of death in women >50 years of age, accounting for ~40% of mortality versus about 5% for breast cancer (1, 2). This remains the case despite trends for improvement in CVD incidence rates and reductions in CVD death rates in the population overall and women in particular (3–5). Risk for new-onset CVD increases after menopause (6), and considerable evidence suggests that the decrease in estrogen experienced by menopausal women contributes to this increase. Nonetheless, after >50 years of research on female sex steroid hormones and atherosclerosis, the questions of whether estrogen deficiency accelerates development of CVD and whether menopausal hormone treatment (MHT) can ameliorate CVD risk remain controversial.

Because the numbers of postmenopausal women in the United States population is large and growing (7), CVD risk assessment and prevention in middle-aged and elderly women is of increasing clinical importance. In this review, we first examine reports of the effects of estrogens and progestogens on factors known or thought to influence development of atherosclerosis and risk of CVD events, then examine the epidemiologic evidence derived from a studies reporting rates of CVD events in menopausal women using and not using MHT, and finally provide a critique of results of recent clinical trials of MHT in which CVD outcomes were primary or secondary endpoints.

PATHOGENESIS OF ATHEROSCLEROSIS

As outlined in a review by Mendelsohn and Karas (8), atherogenesis is a progressive sequence of overlapping stages with characteristic factors influencing each stage. Estrogens and, to a lesser extent, progestogens have been shown to influence factors involved at every stage of the atherogenic process.

Stage 1: Endothelial Injury

The initial step in atherosclerosis involves injury to endothelial cells, most

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often at sites made vulnerable by disruption of laminar flow (e.g., branch points) or increased blood pressure. Arterial flexibility and vasodilation response may be impaired at such sites owing to reduced production and action of nitric oxide (NO). Lipids, such as oxidized low-density lipoprotein (LDL) cholesterol and lipoprotein (Lp) (a), may also cause endothelial injury.

Flow-mediated vasodilation (FMD) is a reflex relaxation of arterial smooth muscle after a period of arterial occlusion with reduced or absent blood flow. FMD is mediated by endothelial NO production. FMD can be quantified after compression of the brachial artery for several minutes with a blood pressure cuff with the use of Doppler ultrasound or detection systems that respond to blood flow in the digits. Impaired FMD is an indicator of endothelial dysfunction and is associated with increased CVD risk (9). Estrogens have been reported to improve FMD (10–13) and arterial compliance (14–16) in a number of studies, whereas progestogens may oppose this effect (17). Higher levels of endogenous E_2 are associated with better FMD response (18), and estrogen treatment increases NO synthase activity (19, 20). This may be due to a direct action of estrogens to induce endothelial NO synthase, but estrogens may also act indirectly via effects on asymmetric dimethyl arginine (ADMA), blood pressure, or Lp(a).

ADMA, an amino acid derivative produced by endothelial cell injury (21, 22), is an NO synthase inhibitor. ADMA is increased in hypertension (23) and CVD (24–26). It is an independent predictor of CVD mortality (27) and worsening of congestive heart failure (28). Estradiol inhibits endothelial cell ADMA production (21, 22, 29). Postmenopausal women have increased ADMA levels (30) and reduced FMD (31), and estrogen treatment decreases ADMA levels (18, 32). Oral estrogen may be more potent than transdermal estrogen in lowering circulating ADMA (33).

Blood pressure (BP) is a major factor in inducing endothelial injury and plays a role in arterial smooth muscle proliferation and thus arterial wall thickening. Oral MHT has been reported to increase BP in younger but not older menopausal women (34) as well as to have neutral effects or even to improve BP (35–37). In one study, transdermal MHT decreased BP in postmenopausal women without altering angiotensin II, and oral HRT increased angiotensin II but did not affect BP (38). Further studies comparing route of administration showed reduction in BP during MHT with transdermal but not with oral estrogen (39). In a longitudinal study, average systolic BP increased less in MHT users than in nonusers (40). However, data from the largest clinical trial of MHT to date show no overall effect of oral conjugated estrogens with constant low-dose medroxyprogesterone acetate on BP (41) and elevations on the order of 1 mm Hg in women on oral conjugated estrogen alone (42).

Lipoprotein(a) is a lipid fraction that contributes to CVD risk independently from LDL and high-density lipoprotein (HDL) cholesterol levels (43–46). High Lp(a) levels are associated with reduced FMD, suggesting that Lp(a) mediates endothelial injury (47). In a prospective study, Lp(a) levels were more predictive of CVD events in women than in men (48). MHT has been reported to reduce levels of Lp(a) (49), with a greater decrease with oral than with transdermal estrogen (50). Also, oral MHT appears to reduce CVD events more in women who have high initial Lp(a) levels than in those who do not (44).

Stage 2: Plaque Initiation

The second stage is plaque formation due to lipid deposition in the arterial wall. During this stage, microcrystals of cholesterol and cholesterol esters from circulating Lp particles accumulate at sites of endothelial injury and are phagocytosed by macrophages. These then form clumps of lipid-engorged foam cells in the arterial intima. Factors contributing to this stage include levels of circulating Lps and endothelial adhesion factors that recruit macrophages to transit the endothelium from the arterial lumen. Plaque progression may be reduced by HDL cholesterol via reverse transport of lipid from the arterial wall to the liver (51). As plaques enlarge, increasing numbers of inflammatory cells and fibroblasts are attracted, leading to formation of a fibrous cap over the lipid deposits.

In numerous studies, high total and LDL cholesterol and triglyceride levels and low levels of HDL cholesterol have been associated with increased CVD risk (52, 53). Agents that lower LDL cholesterol have been shown to decrease CVD events in persons with (54, 55) and without (56–59) prevalent CVD. However, secondary prevention may depend in part on non–lipid-lowering (antiinflammatory and plaque stabilizing) effects of these agents (60–63). Whether interventions that increase HDL cholesterol are also protective remains an unanswered question, because recent large-scale studies examining this issue have been either negative or equivocal (51, 64, 65).

As reviewed by Tikkanen (66), estrogens lower both total and LDL cholesterol and raise HDL cholesterol levels (67–73), although the transdermal route may have less effect on HDL cholesterol (72, 74, 75). Estrogen-induced increases in HDL appear to be due mainly to elevation of the cardioprotective HDL-2 subfraction (67, 74).

Stage 3: Inflammation

The third stage of atherogenesis is characterized by increasing inflammation. As plaques reach a critical size, necrosis of foam cells, invasion by inflammatory cells, and neovascularization with invasion and smooth muscle proliferation in the arterial media occur. The end stage of this phase is the "at risk" plaque partially occluding the arterial lumen containing a core of necrotic material and infiltrated with inflammatory cells. Investigations in the past 10 years have provided strong evidence that inflammatory processes are important contributors to atherosclerosis (76–78).

Inflammatory cells and activated platelets amplify the atherosclerotic process by releasing cytokines, including interleukin (IL) 6 and tumor necrosis factor (TNF) α, which attract and activate additional cells as well as stimulate smooth muscle hyperplasia (79). A variety of circulating cytokines, including IL-6 and C-reactive protein (CRP), have been shown to predict CVD event risk independently from lipids (80–82). High CRP predicts CVD event risk in both men

(83–90) and women (91–93). CRP was the best nonlipid biochemical predictor of CVD events in National Health Service data (92) and in the Women's Health Study (94). Some data have suggested that CRP may be a better marker for CVD event risk than for prevalent atherosclerosis (95). IL-6 is the proximate stimulus for CRP production, and in one large prospective study, IL-6, but not CRP, levels independently predicted CVD event incidence, although coronary artery calcium scores were negatively correlated with CRP concentrations (96). Thus, some evidence suggests that IL-6 rather than CRP is the true "villain" in increasing plaque inflammation. However, in another study, neither CRP nor IL-6 was associated with CVD event risk (97). In a prospective nested case-control study of women in the WHI hormone trial, median baseline levels of CRP and IL-6 were significantly higher in women experiencing CVD events (91).

Both IL-6 and CRP increase during menopause (98). In the WHI trials, MHT was associated with significant elevation of median CRP but not IL-6 levels (91). In other studies in which oral estrogen increased CRP levels, no effect was seen on IL-6 (93, 99, 100), nor were changes in IL-6 observed during continuous transdermal MHT (100, 101). Thus, neither oral nor transdermal estrogen appears to affect IL-6. Estrogen effects on CRP depend on route of administration. In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial (102), oral conjugated equine estrogens (CEE) increased CRP by 85%. In other studies comparing oral and transdermal estrogens, oral treatment increased levels of CRP, whereas transdermal estrogen did not (75, 100, 101, 103). However, in one study of oral E_2 combined with cyclic P, no CRP elevation was seen (104). Taken together, these findings suggest that the oral estrogen–induced increase in CRP is an "artifact" of hepatic first-pass effect on protein synthesis. Whether such an elevation of CRP in the absence of increased IL-6 exacerbates CVD risk is unknown.

Prothrombin activator inhibitor (PAI) 1, an acute-phase reactant involved in coagulation, also has been shown to be elevated in patients with prevalent CVD compared with healthy control subjects (105) and to be associated with increased CVD risk (106). In one study, MHT users had lower PAI-1 levels than never users (107). In prospective studies, oral estrogen caused significant decreases in PAI-1 (108, 109) but transdermal estrogen did not (108).

At sites of endothelial injury, E-selectin, ICAM-1, and other adhesion molecules attach circulating leukocytes to the vascular wall. Attached mononuclear cells then transit the endothelium to enter the vascular intima, where they phagocytose lipid particles and transform into foam cells, creating a fatty streak (110). E-Selectin, produced by vascular endothelium in response to CRP, TNF-α, IL-6, and other cytokines (111), interacts with ligands on leukocyte cell membranes (112) to recruit leukocytes to the endothelial surface at sites of inflammation or injury (113, 114). In case-control studies, patients with angiographic evidence of atherosclerosis (115, 116) or myocardial infarction (MI) (117) had significantly elevated E-selectin levels compared with control subjects, whereas in another angiographic study (118) this was not the case. In a prospective study (119), baseline E-selectin levels were higher in subjects who subsequently experienced CVD events and were independently associated with degree of atherosclerosis estimated from carotid artery intima-media thickness. E-Selectin has been reported to be increased in postmenopausal versus cycling women (120), and both oral (102, 104, 121, 122) and transdermal (101, 123) MHT reduced E-selectin levels in prospective studies.

Soluble intercellular adhesion molecule (ICAM) 1, a member of the immunoglobulin gene superfamily, also mediates vascular adhesion and migration of leukocytes. In in vitro studies, CRP and TNF-α up-regulate ICAM-1 expression in coronary endothelial cells (111, 124). In carotid endarterectomy specimens, ICAM-1 mRNA expression was higher in plaques than in normal endothelium and ICAM-1 protein was increased on the surface of high-grade versus low-grade lesions (125). Plasma ICAM-1 levels have been found to be elevated in individuals with versus without angiographic evidence of CVD (116, 126), but this finding was not replicated in another angiographic study (115). Also, higher ICAM-1 levels are found in patients with MI versus control subjects (127). In the Physicians' Health Study, men with ICAM-1 levels in the highest quartile had a risk ratio (RR) of 1.8 (95% confidence interval [CI] 1.1–2.8) for future MI (124). In the Atherosclerosis Risk in Communities (ARIC) study, ICAM-1 levels strongly predicted both MI and stroke; men and women in the highest quartile of ICAM-1 had a hazard ratio of 2.64 for CVD and 5.53 for evidence of coronary atherosclerosis by ultrasound (119). In the WHI, women in the highest quartile of ICAM-1 had an RR of 2.6 (95% CI 1.3–5.1) for CVD events (94). Both oral (93, 104, 128) and transdermal (101, 123) estrogen treatment have been reported to decrease circulating ICAM-1 levels. However, in one RCT, oral E_2 did not alter ICAM-1 levels (99).

Stage 4: Plaque Rupture and Thrombosis

In the fourth stage of atherosclerosis, enzymes from inflammatory cells contribute to lysis of the fibrous cap (129, 130), allowing necrotic and inflamed tissue to contact blood. This in turn leads to thrombosis and vascular occlusion. The balance of circulating thrombotic and thrombolytic factors also plays a critical role in this process (131).

Matrix metalloproteinase (MMP) 9 is one of a family of enzymes that break down collagen, allowing remodeling of tissues and migration of cells. In the final stages of plaque evolution, metalloproteinases, notably MMP-9, are released from inflammatory cells (132, 133). The role of MMPs in rupture of the fibrous cap is supported by observations in both experimental (134) and clinical (130, 132) atherosclerosis. High levels of local intralesional MMP expression are characteristic of advanced, but not early, plaques (130). Elevated plasma MMP-9 levels are strongly associated with prevalent symptomatic CVD (135, 136) and are predictive of CVD event risk (132, 137).

Although estrogens appear to be potent inducers of several different MMPs in a variety of cell types (138–140), MHT has been variously reported to have no effect on (101), to increase significantly (100, 141), and to decrease (93) circulating levels of MMP-9 in women. A likely source of

the wide variation in the results of these studies is that variability in plasma MMP-9 levels may reflect variations in both production by vascular inflammatory cells and release of this enzyme from platelets during sample processing (142). The theory that estrogen induction of MMP-9 in at-risk plaques promotes plaque rupture followed by thrombosis and downstream ischemic damage due to luminal obstruction is thus plausible but not fully substantiated.

Effects of oral estrogen on thrombotic, antithrombotic, and fibrinolytic factors favor thrombosis and therefore could elevate risk of a CVD event. This is likely due to first-pass actions of high concentrations of estrogen on the liver after absorption into the portal circulation. These effects are much reduced or absent when estrogen is administered by a nonoral route.

EPIDEMIOLOGIC EVIDENCE

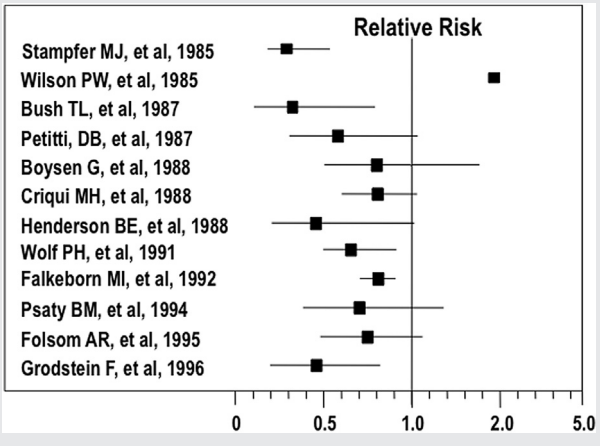
Figure 1 shows published results for HRs from 12 prospective cohort and retrospective observational studies examining risk for CVD events (143–152), stroke (153), and all-cause mortality (154). Eleven of the 12 studies show trends for reduced risk, and in five of those the reductions observed were statistically significant and averaged 40%–50%. There are observational studies not shown in Figure 1 reporting similar reductions in rates of CVD incidence (155–158) as well as additional reports of reductions in all-cause mortality (157, 159). Moreover, in one study (160) the observed decrease in mortality was significantly greater in current than in past MHT users and in women with longer duration of use, so that current users with >15 years of MHT exposure had a 40% reduction in overall mortality rates.

It is also of note that, whereas women in the Nurses Health Study starting menopausal hormone treatment at or near menopause had significantly reduced CVD event rates (HR 0.66, 95% CI 0.54–0.80, for E alone; HR 0.72, 95% CI 0.56–0.92, for E+P), those who initiated MHT ≥10 years after menopause did not (HR 0.87, 95% CI 0.69–1.10 for E alone; HR 0.90, 95% CI 0.62–1.29 for E+P) (161). This finding is consistent with the "timing hypothesis," that MHT prevents CVD only if administered during a critical window of opportunity before atherosclerosis is fully established.

Another factor, not widely considered in comparing results of RCTs of MHT, is duration of treatment. If beneficial effects of estrogen on atherogenesis risk factors occur mainly in the early to middle stages of plaque development, then it would follow that any event reductions would have to await the maturation (or lack thereof) of plaques exposed to estrogen treatment in their earlier stages. Some published results of observational studies do indicate that CVD protection may become apparent only after 5–7 years of MHT (162, 163). A case-control study of acute MI (163) found a significant risk reduction in MHT-treated women only after >60 months of treatment (163). Also consistent with a duration effect, postmenopausal women undergoing coronary angiography showed a strong inverse relationship between number of years of MHT and severity of stenosis (164).

In summary, the overwhelming evidence from observational studies comparing many thousands of women choosing versus not choosing to use MHT strongly favors the concept that prolonged use by women starting MHT early in menopause reduces CVD, CVD death, and all-cause mortality rates by ~40%.

FIGURE 1



Mean relative risk (*squares*) and 95% confidence intervals (*black lines*) for cardiovascular events in women taking versus not taking menopausal hormone treatment from results of 12 observational and cohort studies published from 1985 to 1996. Only the 1985 study by Wilson et al. shows increased risk, and in five of the 13 the 95% confidence intervals do not overlap 1.0 indicating that the decrease in risk was statistically significant the ≤.05 level.

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Bias in Epidemiological and Observational Studies

Results of nonrandomized studies need to be interpreted with caution, because a variety of factors may bias results to produce apparent significant differences between treated and untreated groups where none actually exist. These biases include (but are not limited to):

- Selection bias, in which women prescribed MHT are healthier and at lower risk at the outset than those not receiving MHT.
- Prevention bias, in which monitoring and treatment is more intensive in women prescribed MHT, leading to better outcomes in that group.
- Compliance bias, in which patients with better adherence to treatments of all kinds, including MHT, have better outcomes.
- Survivor bias, in which MHT may have been stopped owing to intervening illness and subsequently patients are classified as nonusers when outcomes are assessed.
- Prevalence-incidence bias, in which adverse events or deaths early in the period of MHT use are discounted and the user does not become part of the cohort analyzed.

Well designed RCTs have the advantage of reducing or eliminating the kinds of bias enumerated above and therefore are generally given greater credence than observational studies. However, there have been relatively few RCTs of MHT.

CLINICAL TRIALS EVIDENCE

Before 2002 there were a number of small to medium-size randomized trials of MHT reporting CVD outcomes. Twenty-three of those trials met criteria for inclusion in a meta-analysis by Salpeter et al. (165), who analyzed results according to the ages of the women studied. The authors concluded that in younger women there was significant protection from CVD events with an odds ratio (OR) of 0.68 (95% CI 0.48–0.96), whereas in older women the OR was 1.03 (95% CI 0.91–1.16), such that no effect on CVD risk was apparent. A Bayesian meta-analysis of all-cause mortality looking at randomized trials of MHT of ≥6 months' duration with mean age <60 years that reported at least one death found that in 19 randomized trials, including 16,000 women (83,000 patient-years) with a mean age of 55 years, the relative risk of mortality was 0.73 (95% CI 0.52–0.96). Thus, before 2002, the RCT data, though limited, seemed to be consistent with the data from long-term observational studies, albeit showing somewhat less protective effect, on the order of 30%, perhaps reflecting the effects of the aforementioned biases in the latter studies.

In apparent contrast to the above, results of the large randomized placebo-controlled WHI Estrogen plus Progestin (E+P) (137) and Estrogen Alone (EA) (42) trials found no evidence of CVD protection in women aged 50–79 years and showed increases in breast cancer and thromboembolic disease that, taken together, led to a conclusion that MHT produces net harm. Publication of the WHI findings led millions of menopausal women either to discontinue MHT or to avoid starting it (166, 167).

One potentially critical difference between the WHI and observational studies of MHT is that women enrolled in the WHI were an average of 63 years old, ~12 years postmenopausal (41, 42, 137, 168). In contrast, enrollees in the observational studies tended to start MHT at or near the menopause, at an average age of 51 years (169).

The idea that differences in age and/or time since menopause may account for differences in cardiovascular outcomes has become known as the "timing hypothesis" (8, 170–172). The credibility of the timing hypothesis is owed in part to the known effects of estrogen on CVD risk factors. That is, estrogens have effects on lipids, the endothelium, adhesion factors, and inflammatory factors that might be expected to retard early development of plaque. On the other hand, estrogen effects on MMP-9 secretion and, in the case of oral estrogens, thrombotic and thrombolytic factors, could promote plaque rupture and thrombosis, in women harboring mature at-risk plaques, leading to an increase in ischemia and infarction early in the course of treatment.

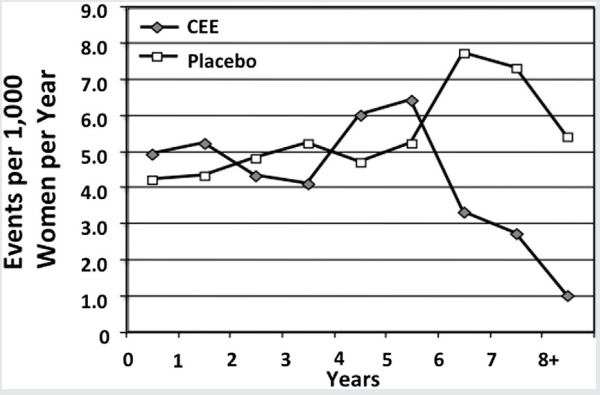
Subgroup analyses of WHI data provide support for this hypothesis. For example, in the E+P trial a nonsignificant trend toward cardiovascular protection was seen in women who were <10 years postmenopausal, whereas significant excess risk occurred in women >20 years postmenopausal (41). Similarly, in the EA trial (42, 173) there was a trend for cardiovascular protection in women 50–59 years old, but increased risk in women >70 years old. Consistent with the differential effects of estrogen on risk factors for atherogenesis versus plaque rupture and thrombosis, the excess in CVD events in the estrogen-treated groups tended to occur in the first 18–24 months, after which the rates equalized. Similar trends were seen when data from both E+P and EA trials were pooled (174). Finally, in a follow-up examination of women in the EA trial (175), at a mean of 7.4 years of treatment and 1.3 years after the trial was completed, coronary calcification was significantly less in women randomized to CEE versus placebo. This difference was magnified when only subjects compliant with study medication were compared.

A post hoc analysis of data from the WHI E+P trial (176) also supports the concept that emergence of CVD protective effects of MHT requires sufficient duration of treatment. In this analysis, compliant women initiating MHT <10 years after menopause had slightly lower CVD event–free survival rates than women on placebo during the first 5 years. However, after 6 years the placebo and treatment group curves crossed with a nonsignificant, late trend toward better event-free survival in the active MHT group. Specifically, the HR was 1.29 (95% CI 0.52–3.18), a nonsignificant increase in risk, during the first 2 years. In contrast, after 2 years the HR was 0.63 (95% CI 0.27–1.52), suggesting a trend toward decrease in risk. Interestingly, the difference between the ≤2-year and the >2-year HRs was statistically significant ($P=.038$), consistent with a duration effect.

In an effort to shed further light on the effect of treatment duration, we have performed an independent analysis (177) on published data from the WHI EA trial (42), in which women were followed ~2 years longer than in the E+P trial. We calculated annual incidence rates for CVD events during years 1–8+ as well as rate ratios and 95% CIs for rates pooled from years 1–6 and >6 with the use of a regression model that accounted for person-years at risk in both groups. Our calculated annual CVD event incidence rates, shown in Figure 2, were slightly greater for CEE- versus placebo-treated women in years 1–2 and 5–6, but declined in the CEE-treated women after year 6. Comparison of the rate ratios for years 1–6 versus 7–8+ showed a statistically significant ($P=.003$) reduction in CVD risk after >6 years of use of CEE versus placebo.

Relevant data from another much smaller RCT, the Danish Osteoporosis Prevention Study (DOPS) (178), were published in 2012. That trial was designed to test long-term effects of MHT on osteoporosis in women of average age 50 years at initiation of treatment. Women with an intact uterus were randomized to triphasic E_2 and norethisterone acetate or placebo, and hysterectomized women were given 2 mg oral E_2 or placebo. Although the treatment phase was discontinued after an average of just over 10 years, data from 1,006 women after an average of 16 years of follow-up showed a reduced incidence of a composite CVD end point consisting of death from any cause, hospital admission for congestive heart failure, and confirmed MI with an HR of 0.61 (95% CI 0.39–0.94; $P=.02$). There was an apparent excess of CVD deaths (23 of 40) in the control group compared with the MHT group (6 of 27), but no statistical analysis of this difference was provided. Although no differences in estrogen-related adverse

FIGURE 2



Plot of the mean numbers of events per 1,000 women per year in the Women's Health Initiative estrogen-alone study comparing conjugated equine estrogens (CEE) with placebo (values taken from Anderson et al., Fig. 3 [42]). There is a small excess in the CEE group in years 1 and 2 and again in years 4 and 5, but values from years 1 to 5 are relatively similar, whereas after year 5, they diverge, falling in the CEE group while remaining fairly stable in the placebo group. Calculated hazard ratio for pooled CVD events (20 in the CEE group versus 51 in the placebo group during a total of 14,633 woman-years) in years 6–8+ is 0.46 (95% confidence interval 0.28–0.78).

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events (strokes, all cancers, breast cancer, pulmonary embolus, or thrombophlebitis) were observed, these events were relatively rare (on the order of $\leq$20 per group) and the study was not powered to detect differences in rare adverse events.

SUMMARY AND DISCUSSION

Well demonstrated effects of estrogens on a plethora of known and suspected CVD risk factors strongly suggest that MHT should be protective against atherosclerosis if initiated early but is potentially harmful if administered to women who already have mature at-risk plaque. The majority of long-term large observational studies and a number of small RCTs are consistent with this interpretation. Nonetheless, data remain insufficiently definitive to provide decision makers with a high degree of comfort in advising women regarding their risk-benefit ratio for use of MHT.

The present review does not evaluate known or suspected risks of MHT, which include breast cancer, thromboembolic disease, stroke, and cholelithiasis, nor does it take into account established benefits such as relief of menopausal vasomotor symptoms or dyspareunia, reduced risk of osteoporotic fractures, and protection from colon cancer and diabetes. Even taking these risks and benefits as known quantities (which is also a questionable proposition), it remains the case that any valid risk-benefit analysis for MHT depends crucially on whether MHT provides significant CVD protection and/or contributes excess risk and, if so, the magnitude and timing of these effects. An analysis published in 1997 found that when a 40% reduction in CVD event risk is assumed, MHT is likely to be beneficial overall for most women with the exception of women at highest risk for breast cancer (179). This analysis is echoed by a more recent evaluation (180), in which a CVD benefit, at least for younger women, was also assumed.

Contrary to the CVD benefit assumed in the risk-benefit calculations cited, the WHI hormone trials, which represent the largest RCT to date, have been generally interpreted as showing no CVD benefit or even an increase in CVD risk. Limitations of this interpretation include evidence that those conclusions may apply only to older, more distantly postmenopausal women and may be valid only for a relatively short duration (<6 years) of treatment. However, there is no consensus, even among WHI investigators, as to the validity or clinical value of these criticisms.

Thus, in the final analysis, the current state of knowledge regarding the clinical effects of MHT on risk of CVD events, and risk-benefit ratios, remains controversial and in flux, nor is this situation likely to change in the near future. More information is needed regarding effects on both potential risks and benefits of MHT by age and menopausal duration, for oral versus transdermal or subcutanous routes of estrogen administration, and of the various progestational agents used for protection against endometrial hyperplasia. Yet, even with better data on these issues, without a new RCT of the magnitude of the WHI, doubt and controversy will undoubtedly continue.

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