

# Prevention of Heart Disease in Women: Is Postmenopausal Estrogen Therapy Warranted?

A *Menopause Management* “Point-Counterpoint” Feature by Elaine Meilahn, DrPH, and Ian H. Thorneycroft, PhD, MD

**“Current evidence does not support the use of hormone therapy for cardioprotection.”**

—Elaine Meilahn, DrPH

Postmenopausal hormones in the form of estrogen replacement therapy (ERT) or estrogen plus progesterone (hormone replacement therapy [HRT]) is an approved and effective treatment for menopause-related symptoms, including hot flashes and vaginal dryness. Short-term (2-5 years) use of ERT/HRT for these indications is well established and is not, therefore, the focus of this article. The question of interest is whether hormone therapy is an appropriate intervention for prevention of heart disease in postmenopausal women.

In numerous observational studies, postmenopausal women taking ERT/HRT have been shown to have a 30-50% lower risk of heart disease than do non-users of hormones.<sup>1</sup> In most studies, investigators have reported on ERT use but, more recently, similar reductions in cardiovascular risk have been found for HRT, as well.<sup>2</sup> The consistency of the observational study findings regarding reduced heart disease with postmenopausal hormone therapy use,<sup>2</sup> in combination with

generally favorable effects of ERT/HRT on several cardiovascular risk factors,<sup>1,3</sup> has led to a general perception that hormone therapy reduces heart disease risk among women.

## The Case Against ERT/HRT for Cardioprotection

Because heart disease is the major cause of death and disability among women in many developed countries, the question of whether postmenopausal hormone therapy prevents heart disease is an important one; if protection is afforded, ERT/HRT use could potentially benefit millions of women. Despite the abundant evidence for cardiovascular benefit, however, it is my opinion that estrogen therapy should not currently be prescribed for the purpose of heart disease prevention, for the following reasons.

1. *No randomized clinical trials of ERT/HRT and primary prevention of heart disease have been completed.* Recommendations regarding the use of ERT/HRT for prevention of heart disease should await results of ongoing, randomized clinical trials, because results of observational studies of ERT/HRT are subject to several types of bias, all leading to an inflated estimate of the protective effect of estrogen. In addition, ERT/HRT are drugs; without results of controlled clinical trials to identify potential benefit as well as

harm, no drug should be prescribed to a large population of healthy individuals for the purpose of disease prevention, particularly when there are alternative interventions available that have been proven effective.

Several systematic biases are likely to influence findings from observational studies of hormone therapy and heart disease. For example, women who use ERT/HRT tend to engage in an array of positive health-related behaviors (e.g., physical exercise and regular physician visits for preventive care) more often than women who don't use ERT/HRT.<sup>4</sup> Such behavior patterns are associated with a more favorable cardiovascular risk profile prior to the initiation of hormone therapy, as documented by Matthews and colleagues.<sup>5</sup> These investigators reported that subjects in the Healthy Women Study had lower serum low-density lipoprotein cholesterol (LDL-C) and higher high-density lipoprotein cholesterol (HDL-C) levels than did women who opted not to take hormone therapy after menopause; these differences were seen well before hormone therapy was initiated.

In general, ERT/HRT use is associated with higher education level and social class,<sup>4</sup> both of which are strongly associated with lower risk of heart disease in men and in women.<sup>6</sup> Furthermore, ERT/HRT is prescribed less often for women with chronic diseases such as dia-

betes mellitus and heart disease than it is for healthy women.<sup>7</sup>

In addition, whereas most women for whom ERT/HRT is prescribed take the hormones for only a few months,<sup>8</sup> those who continue with therapy make up a “compliant” group. Good compliance with treatment in clinical trials of lipid lowering and treatment of hypertension has been shown to reduce the risk of heart disease by about one-half, even when that “treatment” is a placebo.<sup>2</sup> It is important to note that the extent of risk reduction associated with good compliance is equivalent to that observed with hormone therapy use in observational studies.

Another argument in support of the need for randomized clinical trial results is the possibility of adverse effects of ERT/HRT use. Although a discussion of the overall risk-benefit balance of ERT/HRT use is beyond the scope of this article, a worrisome finding of a 2- to 4-fold excess risk of vascular disease, in the form of venous thromboembolism (VTE), has been documented by observational studies with women taking ERT/HRT<sup>9-11</sup> and confirmed recently by the Heart and Estrogen/Progestin Replacement Study (HERS).<sup>12</sup> In addition, the ongoing Women’s Health Initiative, a clinical trial of HRT use in women without heart disease, recently informed trial participants of a small increase in myocardial infarctions, strokes and thromboembolism in women enrolled in the HRT arm of the trial, compared to those taking placebo. Although rare, VTE can be very serious and, unfortunately, it is not currently possible to identify in advance those women who are likely to experience VTE if they use estrogen therapy.

For these reasons, the answer to the question of whether postmenopausal hormone therapy reduces the risk of a first occurrence of clinical heart disease in healthy women awaits the results of primary prevention trials now in progress; specifically, the Women’s Health Initiative (WHI)<sup>13</sup> in the United States

and the Women’s International Study of long Duration Oestrogen after Menopause (WISDOM) trial<sup>14</sup> in Europe. Initial results from both trials will be available in about 4 years.

2. *No benefit of hormone therapy for secondary prevention of recurrent clinical events or of atherosclerosis progression among women with clinically diagnosed heart disease was shown in the two randomized clinical trials completed to date.*<sup>12,15</sup> HERS,<sup>12</sup> the first of these trials, was designed to determine whether treatment with 0.625 mg conjugated equine estrogen (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) would, as compared to placebo, reduce the incidence of recurrent clinical coronary events in 2,763 older women (mean age, 67 years) with diagnosed coronary artery disease. Although adherence to therapy was relatively good, and previous observational study results showed that long-term estrogen therapy reduced the incidence of recurrent events,<sup>16-18</sup> no cardioprotective benefit was seen with treatment.

In HERS, the total number of events (nonfatal myocardial infarction and coronary death) in the hormone-treated group was 172, versus 176 in the placebo group (RR = 1.0, 95% CI = 0.8-1.2). This absence of effect was observed despite differences in serum cholesterol characteristic of hormone therapy use (lower [-11%] LDL-C and higher [+10%] HDL-C in the treatment group than in the placebo group).

Moreover, the HERS investigators reported a significant pattern of transient, early increased risk of events among the women in the treatment group in years 1 and 2 of the trial, with a subsequent decrease in years 4 and 5. The reasons for the increase in risk soon after initiating treatment are unknown, although an increase in thromboses, inflammation, or arrhythmias among a “susceptible subgroup” of women with existing disease is possible.

The Estrogen Replacement and Ath-

erosclerosis (ERA) trial<sup>15</sup> examined whether daily doses of CEE 0.625 mg or CEE plus MPA 2.5 mg would inhibit progression of coronary atherosclerosis over 3 years (versus placebo), as measured by angiography among 309 postmenopausal women with angiographically documented coronary disease. Again, despite expected favorable changes in serum lipid/cholesterol levels among participants in both treatment arms, no difference between the treatment groups was found with respect to progression of coronary atherosclerosis. The investigators concluded that hormone therapy—estrogen alone or in combination with a progestin—showed no cardiovascular benefit (as measured by angiography) in women with established coronary disease.

How is it possible that no benefit was shown with ERT and HRT in either of these trials of women with coronary disease, when estrogen has well-documented beneficial effects on endothelial function and lipid metabolism? The trial investigators hypothesized that benefit might be restricted to women without clinical disease, citing studies of ovariectomized monkeys and rabbits without atherosclerosis, in which estrogen inhibited vessel wall cholesterol accumulation.<sup>19,20</sup> In studies of animals with atherosclerotic disease, however, estrogen had no effect on disease progression.<sup>21</sup> Thus, in ovariectomized animals fed a high-cholesterol diet, estrogen appears to prevent atherosclerosis in the presence of a healthy endothelium, but not when disease is already present. These findings suggest that, as aging is associated with atherosclerotic progression, older women or those with diagnosed heart disease might not derive cardiovascular benefit from estrogen replacement.

The HERS and ERA investigators, therefore, reported that ERT/HRT had no cardiovascular benefit for women with established heart disease. It is worth noting that no drug or drug regimen that failed to demonstrate a benefit with re-

spect to secondary prevention of heart disease has been proven beneficial in primary prevention trials.<sup>22</sup> Until the completion of WHI and WISDOM, the ongoing primary prevention trials of estrogen and heart disease, we won't know whether estrogen will prove the exception to this observation.

3. *Proven alternative therapies exist for cardiovascular risk reduction in postmenopausal women.* The major and prevalent cardiovascular risk factors for postmenopausal women are, as they are for men, cigarette smoking, hypercholesterolemia, hypertension and diabetes. While estrogen therapy favorably affects serum cholesterol levels, it has little or no effect on blood pressure, blood glucose levels<sup>3</sup> or smoking behavior.

While heart disease risk factor levels for women in the United States have, on average, improved over the past 3 decades, the prevalence of cigarette smoking, elevated serum cholesterol and hypertension among postmenopausal women remains high. In a recently completed randomized clinical trial,<sup>23</sup> lifestyle changes in the form of increased physical activity/exercise and dietary modification have been shown to result in improvements in body weight and serum cholesterol levels over 5 years, similar to those achieved with the use of hormone therapy in 535 midlife (mean age, 47) perimenopausal women.<sup>23</sup> A major advantage of positive behavioral change is the absence of adverse side effects, in contrast to the use of pharmacologic interventions, including hormone therapy. Hypertension control<sup>24</sup> and lipid lowering by means of dietary modification<sup>25</sup> have been shown to reduce heart disease risk among women.

When behavior change does not produce the required level of risk reduction, or is not feasible, other proven therapies to reduce heart disease risk are widely available and include statins, fibrates, angiotensin-converting enzyme inhibitors, and antiplatelet and antihypertensive therapy. Such therapies have been shown

to be underutilized. For example, only one-third of the women in HERS had LDL-C levels below the recommended upper limit (130 mg/dl).<sup>26</sup>

Other, less well-documented risk factors are reported to respond to estrogen therapy—favorably in the case of elevated lipoprotein(a)<sup>27</sup> and unfavorably in the case of C-reactive protein levels,<sup>28</sup> for example. These findings are recent, however, and the implications for cardiovascular risk are unknown.

Guidelines for the prevention of heart disease in women have recently been put forth in the form of the *Guide to Preventive Cardiology for Women*,<sup>29</sup> published jointly by the American Heart Association and the American College of Cardiology, and endorsed by the American College of Obstetricians and Gynecologists. The guidelines state that postmenopausal hormone therapy is not appropriate for women with clinically diagnosed heart disease; they further state that for women at high risk but without clinical heart disease, hormone therapy should not be used alone, but rather in conjunction with a treatment proven to be effective in clinical trials (e.g., statins for lipid lowering).

## Conclusions

Is the use of hormone therapy warranted for cardiovascular risk reduction among postmenopausal women? The answer to this question must, in my view, be a definite “no” for women with diagnosed heart disease. For healthy women without clinical heart disease, the answer to this question must await completion of the large, controlled clinical trials currently under way; current evidence does not support the use of hormone therapy for cardioprotection. ■

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lished disease; however, there has been absolutely no evidence indicating that HRT does not *primarily* prevent CVD. This article puts forth the reasons that I continue to maintain that ERT/HRT prevents CVD.

## HERS

Prior to publication of the HERS findings, the epidemiologic literature very clearly demonstrated that ERT/HRT prevented CVD. In the observational study conducted by Sullivan et al,<sup>3</sup> even women with existing CVD were shown to benefit from ERT, while patients without existing cardiac disease experienced little, if any, benefit.

HERS was designed as a randomized, double-blind prospective study of patients with existing CVD. Participants were randomly assigned to HRT (CEE 0.625 mg/day plus MPA 2.5 mg/day [oral Prempro 2.5]) or placebo. The relative risk of myocardial infarction (MI) at various times after initiation of the study is demonstrated in Figure 1. An excess number of infarctions was noted in the first year; that excess rapidly disappeared and, in years 2 through 5, there was a gradual decrease in MIs in the HRT group, compared to those taking placebo. The overall relative risk was neither reduced nor, equally important, *increased* in the study. Figure 2 illustrates the rates of recurrent cardio-

vascular events (i.e., nonfatal MI and coronary heart disease death) in the placebo and HRT groups. Also illustrated is the expected event rate of 5% per year. Clearly, the placebo group did much better than expected, and much better in year 1 than in subsequent years, magnifying the apparent HRT-related risk in the first year of treatment.

Because all patients were enrolled in a clinical trial and were, therefore, likely to be well aware of their health status, most HERS participants probably received the best care possible for patients with a cardiac history. Therefore, the HERS results might not be generalizable to other populations. For example, lipid-lowering agents were begun by many participants during the follow-up period. For this reason, HERS more accurately answered the question, "Does HRT add an additional benefit beyond the best-known traditional therapy for patients with prior cardiac disease?"

The HERS results have been used to imply that HRT does not provide benefit in CVD prevention, and the adverse results in year 1 have been attributed to adverse effects of MPA on the cardiovascular system. Both of these claims are examined below.

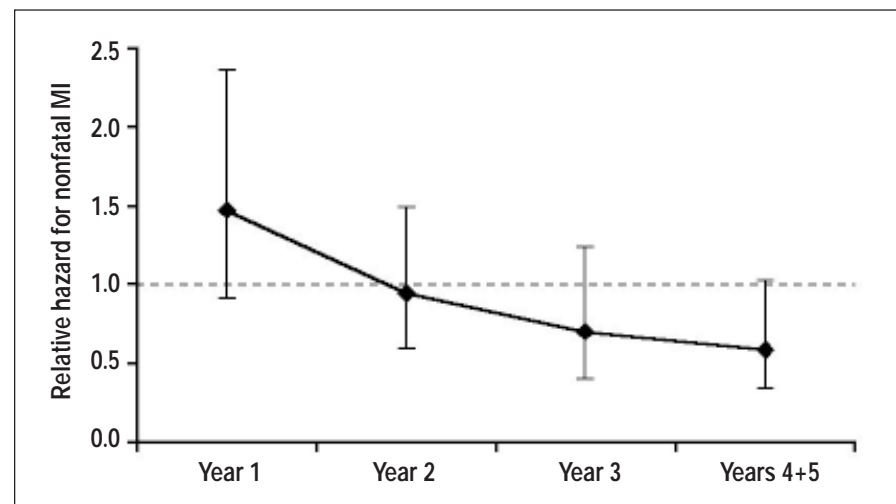
## Benefit of HRT in CVD Prevention

It is necessary to reiterate that HERS

**"The HERS trial does not confute a cardioprotective effect of hormone replacement therapy."**

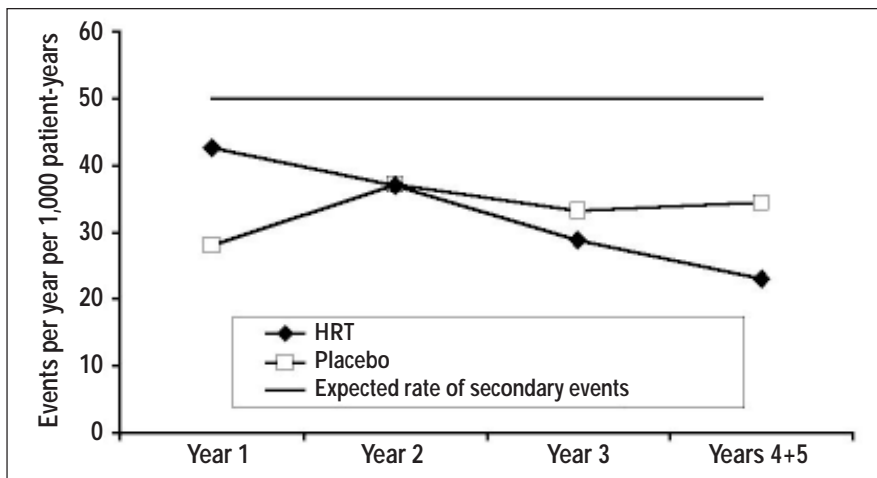
—Ian H. Thorneycroft, PhD, MD

The epidemiologic evidence that ERT or HRT prevents cardiovascular disease (CVD) is overwhelming.<sup>1</sup> Recently, with publication of the HERS findings,<sup>2</sup> this well-established, well-documented benefit has come into question, to the extent that some observers discount everything previously published in favor of this one study. HERS has raised concerns that ERT/HRT might not be beneficial for *secondary* prevention of CVD in women with estab-



**Figure 1.** Relative hazards and 95% confidence intervals for nonfatal MIs in years since randomization in HERS.

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**Figure 2.** Rates of recurrent CHD events (i.e., nonfatal MI and CHD death) in years since randomization for the HRT and placebo groups in HERS. The expected rate of events is shown for comparison.

addressed only *secondary* CVD prevention and is at odds with the epidemiologic literature on both primary *and* secondary prevention. For example, the recent ERA study, a 2-year, randomized, double-blind, placebo-controlled trial of the effect of estrogen—and estrogen plus progestin—on plaque progression, did not demonstrate a higher rate of recurrent CVD events in year 1 and, therefore, did not confirm the effect seen in HERS.<sup>4</sup> Nor did the ERA study demonstrate any benefit of either HRT or ERT over placebo with respect to cardiac events or plaque progression, while HERS demonstrated an increasing benefit of HRT with increasing duration of use. The two available randomized studies are, therefore, inconsistent. The HERS findings show that there is no justification for taking a patient off HRT, when that patient has existing cardiac disease and has been taking hormones for longer than 1 year.

A primary reason for the difference between the epidemiologic studies and this randomized prospective study (HERS) is that they examined different populations. Epidemiologic studies generally look at a wide range of individuals, in contrast to the narrowly restricted groups selected in randomized, prospective studies; therefore, epidemiologic studies are more generalizable to the

population. As mentioned above, HERS participants probably received better care than do women in the general population. One cannot, therefore, generalize the HERS findings to patients undergoing routine follow-up in a normal primary care practice (i.e., the population examined in many of the epidemiologic studies). In addition, whereas HERS was weighted very heavily toward the early years of treatment, when there was little benefit, epidemiologic studies are weighted more toward the later years, when there is a benefit.

The WHI,<sup>5</sup> which will be completed in 2006, should have sufficient power to determine a year-1 effect; it will also analyze the cardiovascular benefits and/or risks of short- and long-term HRT. It is my opinion that we should reserve judgment until completion of the WHI; at the same time we should take a broad view of what is available in the literature at the present time.

Although the design of randomized, prospective studies is more scientifically valid and, therefore, the conclusions more convincing, this does not eliminate the need to consult the epidemiologic evidence. As stated previously, randomized, prospective studies tend to look at restricted portions of the general population, whereas epidemiologic studies look

at a wider range of patients. If we are to disbelieve epidemiology in favor of randomized, prospective studies, it follows that we should no longer give progestin to prevent endometrial carcinoma in menopausal patients, since there have been no randomized, placebo-controlled trials examining whether estrogen increases endometrial carcinoma risk.

Likewise, we rely solely on the epidemiologic literature in the case of smoking. There is no randomized, prospective, blinded study to demonstrate that cigarette smoking increases lung cancer and CVD risk; nevertheless, the Surgeon General has determined that cigarette smoking causes lung cancer. In both cases the epidemiologic data are very one-sided and consistent. It is also important to remember that, in the words of Dr. Trudy Bush, “No one study has a monopoly on the truth.”

#### Effects of MPA on the Cardiovascular System

There are several reasons that the year-1 effect in HERS cannot be attributed to the use of a progestin. Most important, HERS did not include a treatment arm for estrogen alone; thus, there is no basis for the conclusion that the progestin component (MPA) of Prempro was responsible for the year-1 effect. Second, in the ERA study—which did include placebo, estrogen alone and estrogen-plus-progestin arms—investigators reported no differences between the estrogen and the estrogen-plus-progestin arms.<sup>4</sup> Third, the investigators for the Nurses’ Health Study<sup>6</sup> recently published their latest updated data and again affirmed that both ERT *and* HRT reduced CVD; once again, there were no differences between ERT and HRT.

The investigators also reanalyzed their data for women with established CVD, using criteria similar to those used in HERS;<sup>7</sup> in an abstract they reported an increased MI rate in year 1 with both ERT and HRT. Several other studies<sup>8-10</sup> also failed to demonstrate any difference between ERT and HRT in the reduction

of CVD risk or CVD mortality, regardless of the type of preparations used. It is, therefore, totally invalid to suggest that the progestin component was responsible for the HERS results.

The criticism generally made of epidemiologic studies, and particularly of ERT/HRT studies, is that they are conducted with select, healthy-user populations and are therefore not generalizable to the general population. As pointed out previously, randomized, prospective studies are also conducted with select populations of individuals who are generally healthier than those in the average population. In contrast, HERS studied patients who had existing cardiac disease, i.e., an exceptional population. The significance of this lies in the fact that patients who would normally be considered candidates for ERT/HRT in clinical practice probably more closely resemble the population studied in observational epidemiologic studies.

### Epidemiologic Study Assessment

#### Criteria: Surgeon General/Bradford Hill

In 1964 the U.S. Surgeon General published a report<sup>11</sup> examining the epidemiologic literature on the relationship between smoking and health outcomes such as lung cancer. The report outlined criteria for judging whether the studies were sufficiently substantial to support medical decisions and conclusions. These criteria were later formalized by Bradford Hill.<sup>12</sup> Below, each of these criteria is applied to the literature on ERT/HRT and heart disease.

**Biologic plausibility.** The table lists the beneficial effects of estrogen on various systems, which should result in prevention of CVD.<sup>13,14</sup> The biologic plausibility that estrogens can prevent CVD is very strong. Also strongly arguing in favor of biologic plausibility are the facts that premature menopause also increases the risk of CVD and that women have less CVD than do men.

**Consistency of results.** There are very few, if any, articles that show either no

decrease or an increase in CVD with ERT/HRT. Virtually all such articles show a benefit with either ERT or HRT, as do the meta-analyses.<sup>15</sup> There is a consistent decrease in the risk of MI.

**Dose response.** Many years ago experience indicated that high doses of estrogen might actually be harmful. Recently, the Nurses' Health Study findings<sup>6</sup> indicated that high doses of CEE (e.g., 1.25 mg) might not have a beneficial effect on CVD, but that lower doses do. In fact, some have suggested that the estrogen dose used in HERS might explain the results, noting that estrogen metabolism is decreased in the elderly, 80-year-old population and that the dose was too high for this population of individuals.

**Length of use.** In general, the longer a treatment that demonstrates a benefit is used, the greater the benefit. While this was clearly the case in HERS (Figures 1 and 2), not all of the studies have shown clear support for this trend. Indeed, the recent publication from the Nurses' Health Study<sup>6</sup> indicated that duration of use had little influence on the beneficial effects of ERT/HRT on coronary heart disease (CHD) risk. In contrast, the secondary prevention study conducted by Sullivan et al<sup>3</sup> (Figure 3) showed an increased benefit with ERT over time, an effect confirmed by most of the literature.

**Magnitude of the fact.** Generally, epidemiologists look for a doubling of risk (i.e., RR of 2.0) or a decrease of 50% (RR of 0.5) to be assured that what is being observed is not a product of chance. If one looks at the meta-analyses of the benefit of HRT on CVD,<sup>16</sup> along with the latest report from the Nurses' Health Study,<sup>6</sup> the reduction in relative risk is approximately 40%. The amount of re-

**Table.**  
**Beneficial Cardiovascular Effects of Estrogen on Various Lipid-Dependent and Lipid-Independent Mechanistic Pathways\***

System	Increase/Decrease
<b>Plasma lipid-independent mechanisms</b>	
Endothelial cell growth	↑
Vascular smooth-muscle cells	↓
Insulin sensitivity	↑
Vascular dilatation	↑
Fibrinogen concentrations	↓
Coagulation factors	↓
Coronary artery LDL uptake	↓
<b>Plasma lipid-dependent mechanisms</b>	
HDL-C	↑
LDL-C	↓
Lp (a)	↓
LDL oxidation	↓

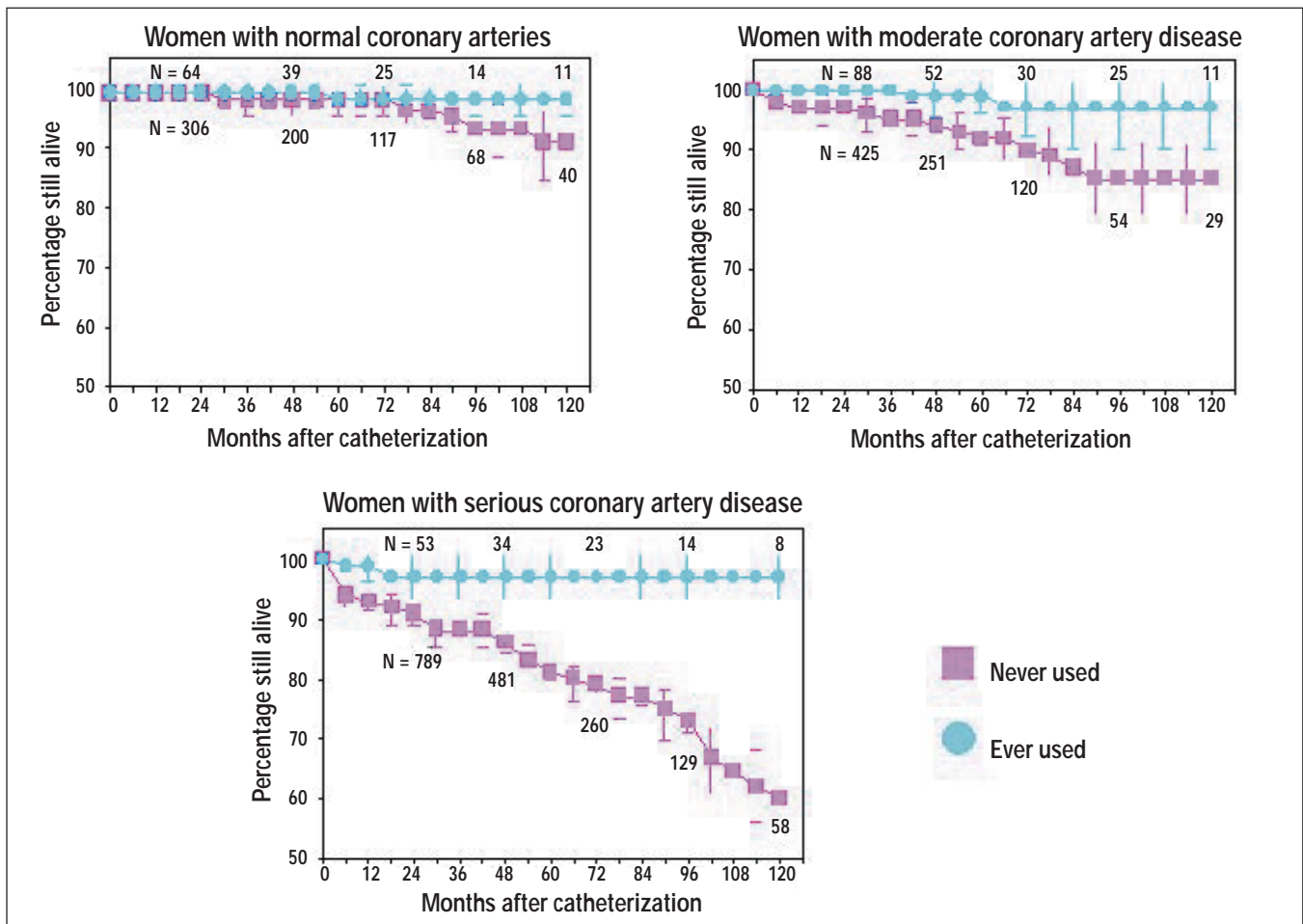
\*Adapted from Mendelsohn et al<sup>13</sup> and Clarkson et al.<sup>14</sup>

duction is, therefore, significant.

**Additional considerations.** Another important characteristic of the HERS population is that 70% of the participants were on aspirin. In the general population 70-80% of patients who have had a previous MI are not taking aspirin. One of the mechanisms whereby ERT/HRT decreases plaque formation is through a decrease in the adhesiveness of platelets to the arterial wall, and in the ensuing inflammatory responses.<sup>13</sup> It is, therefore, possible that the high percentage of HERS participants on aspirin neutralized the benefit of estrogen in this area.

### Progestin Modulation of the Cardiovascular Benefits of Estrogen

There have been many concerns over the years that, because progestins attenuate various cardiovascular protective factors that are increased by estrogen, the addition of progestin would reduce the benefit of ERT with respect to MIs. ERT increases HDL-C, reduces LDL-C and

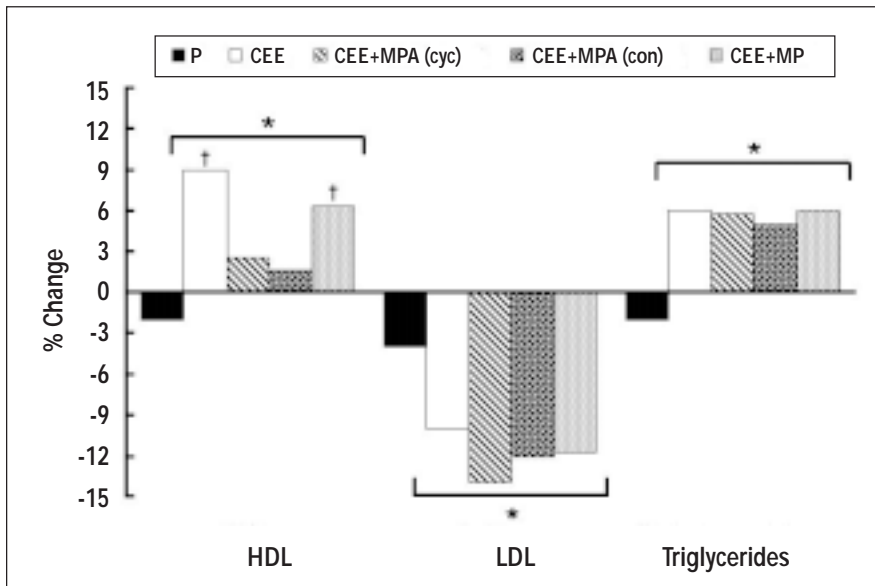


**Figure 3.** Mortality rates for never-users of ERT and for current/past users. As demonstrated by the three graphs, the beneficial effects of ERT on mortality rates increased with the severity of coronary artery disease. *Reprinted with permission from Sullivan et al. Arch Intern Med 1990;150:2557-62.<sup>3</sup> Copyright 1990, American Medical Association.*

lipoprotein(a), and increases triglycerides. The triglycerides that estrogen increases are not considered to be atherogenic. In the PEPI study<sup>17</sup> CEE alone demonstrated its typical response, increasing HDL-C, decreasing LDL-C and increasing triglycerides, as illustrated in Figure 4. The addition of micronized progesterone had little, if any, effect on HDL-C and no effect on LDL-C and triglycerides. The addition of MPA attenuated, but did not eliminate, the increase in HDL-C and had no effect on LDL-C or triglycerides. A study by Davidson et al,<sup>18</sup> involving marketed doses of estradiol plus norethindrone acetate (NETA), showed only slight increases in HDL-C; also, there was a nonsignificant trend toward enhanced LDL-C reduction, along with reductions

in triglycerides. In the Continuous Hormones as Replacement Therapy (CHART) study, Speroff and colleagues<sup>19</sup> found a significant mean reduction in LDL-C with the same formulation, a benefit that stands in contrast to a significant mean reduction in HDL-C and a significant increase in triglycerides (all compared to baseline). The triglyceride increase was less than that seen with most other HRT preparations. Raloxifene also does not significantly increase HDL-C but does decrease LDL-C and has little, if any, effect on triglycerides.<sup>20</sup> Recent studies have been used to argue that progestins have a detrimental effect on C-reactive protein,<sup>21</sup> which theoretically promotes myocardial protection. A difficulty with this concept is that the Nurses' Health

Study<sup>6</sup> and two other studies<sup>8,9</sup> failed to show any difference in the cardiovascular protection provided by HRT and ERT; therefore, any purported differences between progestins are probably inconsequential. In addition, C-reactive protein is just one of many inflammatory proteins that are affected by various agents. Clinicians should resist the temptation to fasten onto a single surrogate marker as the key one in predicting a benefit from a particular agent. The important finding is that estrogens generally decrease inflammatory lesions, whether through an effect on C-reactive protein or on other inflammatory proteins. Interestingly, tamoxifen confers, at most, an 8-19% reduction in CVD.<sup>22</sup> If tamoxifen has the same effect on C-reactive protein as does raloxifene, it



**Figure 4.** Effects of HRT on lipids in the PEPI Trial.

\*Significant compared to placebo ( $p < 0.001$ ); †significant compared to other active treatments; P = placebo; CEE = conjugated equine estrogens; MPA = medroxy-progesterone acetate; MP = micronized progestin; cyc = cyclic regimen (CEE 0.625 mg daily/MPA 10 mg daily for first 12 days of 28-day cycle); con = continuous regimen (CEE 0.625 mg daily/MPA 2.5 mg daily); HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol.

would appear that this marker (C-reactive protein) is not very protective, and that raloxifene will have little effect on CVD.

## Conclusions

The results of HERS do not contradict the weight of epidemiologic study findings showing a primary protective CVD effect in longer-term HRT users. Indeed, because of possible serious flaws in the study, a protective benefit of HRT for secondary CVD prevention cannot be ruled out. The HERS findings actually support the beneficial changes in lipoprotein profiles noted in the majority of studies, and they confirm the well-established benefit on CVD in long-term HRT users. Since HERS is at odds with virtually all of the previously published epidemiologic literature, and with the prospective, randomized ERA study, one wonders if the year-1 results are due to a type II error; that is, false rejection of the null hypothesis. Considering that the year-1 placebo values are different from those of subse-

quent years and are less than anticipated, a type II error should be considered. ■

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