Progesterone, Progestins, and the Heart

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All combination hormone replacement regimens contain estrogen and a progestational agent. The Women's Health Initiative trial demonstrated that taking the combination of conjugated estrogen and medroxyprogesterone resulted in a higher risk of myocardial infarction and stroke in the study population. However, not all progestational agents are alike in their cardiovascular properties. This article reviews what is known about the most commonly prescribed agents: progesterone, medroxyprogesterone, norethindrone, and norethindrone acetate. We compare data on markers of lipid metabolism, inflammation, and clotting function, and review studies that measure their direct effects on cardiac vessels.

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The publication of the initial data from the Women's Health Initiative (WHI) in 2001[1] and its attendant publicity in the lay press changed the paradigm for prescribing hormone replacement therapy (HRT) for postmenopausal women. The initial results from the arm of the study in which women took conjugated equine estrogens (CEE) and medroxyprogesterone (MPA) indicated that there was an increased risk of myocardial infarction (MI), stroke, and breast cancer with hormone replacement. Women were frightened into stopping HRT and physicians became more reluctant to prescribe it. The subsequent publication of data on the estrogen-alone arm showed no increased risk of MI or of breast cancer, although there was a continued increased risk of stroke. These data were not widely publicized in the lay press. Many gynecologists suspected that the unfavorable results with the combined preparation

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were due to the effect of MPA rather than CEE.

Despite this, the medical community appeared to treat combined hormone replacement regimens as if all progestins behaved in the same fashion and would therefore pose the same risk of cardiovascular disease (CVD) as MPA. The pharmaceutical package inserts for progesterone, norethindrone (NE), and norethindrone acetate (NEA) contain the same warnings as those for preparations of MPA and the combined CEE/MPA preparations.

However, all progestins are not alike and they differ in their cardiovascular effects from one another and from the natural form of progesterone synthesized in the ovaries. It is unlikely that we will ever have a randomized controlled trial of the magnitude of the WHI to test the various hormone replacement regimens for their cardiovascular effects and to allow differentiating between the effects of progesterone and progestins.

There are few indications for a postmenopausal woman to take an isolated progestational agent. Progestins are used alone, on a short-term basis, to treat endometrial hyperplasia. The vast majority of women who take progestational agents do so in combination with estrogen to protect themselves from an increased risk of endometrial cancer. Thus, most of the studies that have examined the cardiovascular effects of HRT used in combined preparations, and one must take into account the confounding effects of estrogen. In addition, there are very few effectiveness studies that compare different progestins in the same patient population.

This article reviews the existing data on cardiovascular markers and clinical endpoints for natural progesterone and the most commonly prescribed progestins for HRT, namely NE, NEA, and MPA. The data we examine include lipids, lipoproteins, inflammatory markers, clotting factors, and incidence of MI and stroke. Our goal is to provide the clinician with a means for deciding whether HRTs are safe and appropriate for a particular patient, and, if so, how to choose an appropriate preparation.

Progesterone and Progestins Available for HRT

Some form of progestational agent is used in all of the HRT formulations intended for postmenopausal women with an intact uterus. The most commonly prescribed preparations contain MPA, NE/NEA, and progesterone. Other less commonly used progestins are levonorgestrel (LEN) and norgestimate (NG). These are combined with various forms of estrogen, CEE, β-estradiol (E), ethinyl estradiol (EE), estradiol acetate (EA), and estradiol propionate (EP). The estrogens are available as oral tablets, transdermal patches, and intravaginal rings. Combination drugs containing both sex steroids exist in both the oral and transdermal forms. Table 1 summarizes the available preparations by brand name and ingredients.

The vast majority of women who take progestational agents do so in combination with estrogen to protect themselves from an increased risk of endometrial cancer.

Cardiovascular Properties of Natural Progesterone

Progesterone, the product of ovarian biosynthesis, would seem to be an obvious choice for HRT regimens. Its use, however, was initially limited by poor gastrointestinal absorption and only the development of an oral micronized form made it possible to achieve adequate and consistent physiologic blood levels.[2] Progesterone is available in the US Food and Drug Administration-approved oral micronized form as well as in a vaginal gel. In addition, various compounded progesterone creams are sold over the counter. Studies in laboratory animals have frequently used either subdermal progesterone implants or investigational transdermal preparations.

There are limited direct data on the effects of oral micronized progesterone on indirect markers of CVD. A review of 248 studies, published before 2000, examined serum markers in 42 estrogen replacement therapy and HRT regimens.[3] This review found that estrogens used alone, whether CEE, E, or EE, will lower total cholesterol and low-density lipoprotein (LDL) cholesterol, and will raise high-density lipoprotein (HDL) cholesterol. Oral estrogens raise triglycerides and transdermal estrogens lower them. For the purposes of this review, pooled data from all of these studies were analyzed, and the effects of progestins were inferred by looking at the quantitative differences between estrogen-alone preparations and combined preparations. Progestational agents, in general, do not appear to change the estrogen effects on LDL and total cholesterol, but they can decrease HDL and triglycerides. Of the most widely used progestational agents, progesterone has the least effect, MPA has an intermediate effect, and NE/NEA the strongest effect. Lipoprotein (a) is decreased with all HRT regimens studied.[3] None of the studies that were reviewed measured progesterone effects in isolation.

Table 1
HRT Preparations by Brand Name and Dose

Estrogens	Estrogen Replacement Therapies	Medroxyproges-terone	Norethindrone/ Norethindrone Acetate	Levonorgestrel	Norgestimate	Progesterone
		Provera (2.5 mg, 5 mg, 10 mg)	Ortho Micronor (0.35 mg)			Prometrium (100 mg, 200 mg)
			Nor-QD (0.35 mg)			Crinone (8%)
			Aygestin (5 mg)			
Conjugated estrogens	Premarin (0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg)	Prempro (0.3/1.5 mg, 0.45/1.5 mg, 0.625/2.5 mg, 0.625/5.0 mg)				
	Premarin cream (0.625 mg/g)	Premphase (0.625/5.0 mg)				
	Enjuvia (0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg)					
β-Estradiol	Estrace (0.5 mg, 1 mg, 2 mg)		Activella (0.5/0.1 mg, 1.0/0.5 mg)	Climara Pro (0.045/0.015/d)	Prefest (1.0/0.09 mg)	
	Estrace cream (0.01%) Vivelle-Dot (0.025 mg/d, 0.0375 mg/d, 0.05 mg/d, 0.075 mg/d, 0.1 mg/d) Climara (0.025 mg/d, 0.0375 mg/d, 0.05 mg/d, 0.06 mg/d, 0.075 mg/d, 0.1 mg/d) Vagifem (10 μg, 25 μg) Estring (2 mg/90 d) Femring (0.05 mg/d, 0.1 mg/d)		Combipatch (0.05/0.14/d, 0.05/0.25/d)			
Ethinyl estradiol			FemHrt (2.5 μg/0.05 mg, 5 μg/1 mg)			
Estradiol acetate	Femtrace (0.45 mg, 0.9 mg, 1.8 mg)					
Estropropi-onate	Ogen (0.75 mg, 1.5 mg, 3 mg)					

Activella® and Vagifem® are manufactured by Novo Nordisk (Princeton, NJ); Aygestin®, Prefest®, and Enjuvia™ are manufactured by Teva Pharmaceuticals (North Wales, PA); Climara® and Climara Pro® are manufactured by Bayer HealthCare Pharmaceuticals (Wayne, NJ); Combipatch® and Vivelle-Dot® are manufactured by Novogyne Pharmaceuticals, a joint venture between Novartis Pharmaceuticals (East Hanover, NJ) and Noven Pharmaceuticals (Miami, FL); Crinone® and Nor-QD® are manufactured by Watson Pharmaceuticals (Corona, CA); Estrace®, Estrace cream®, Femhrt®, Femring®, and Femtrace® are manufactured by Warner Chilcott (Rockaway, NJ); Estring®, Ogen®, Premarin®, Premarin cream®, Premphase®, Prempro®, and Provera® are manufactured by Pfizer (New York, NY); Ortho Micronor® is manufactured by Ortho-McNeil (Titusville, NJ); Prometrium® is manufactured by Abbott Laboratories (Abbott Park, IL).

Laboratory animal studies have provided significant information about the vascular effects of progesterone. Sex steroid receptors have been found in vascular endothelium as well as in vascular smooth muscle (VSM). Progesterone receptors A and B, identified in vascular endothelium and VSM, appear to play a role in VSM cell growth and gene transcription.[4] Progesterone has been found to cause relaxation in the coronary

arteries of primates, pigs, rabbits, and rats.[5-8] In one study, in ovariectomized rhesus monkeys, coronary vasospasm was induced using a combination of serotonin and a mimetic of thromboxane A_2. Monkeys treated with subdermal implants of estradiol and progesterone were protected from vasospasm, whereas monkeys treated with estradiol plus MPA were not protected.[9] In a subsequent study, progesterone-treated monkeys were compared with untreated monkeys to assess the degree of coronary vasospasm and the density of the thromboxane receptor TxA_2.[10] Subdermal progesterone, administered for 2 weeks, eliminated vasospasm and reduced the TxA_2 receptor density. Protective levels of progesterone were in the low physiologic range for rhesus monkeys (< 4 ng/mL). Prior studies[10] had demonstrated protection at 5 to 7 ng/mL. A recent follow-up study involved monkeys fed an atherogenic diet for 19 months and treated with either placebo or a transdermal progesterone cream.[11] Transdermal cream with lower (subphysiologic) levels of progesterone (0.6 ng/mL), was still sufficient to prevent induced coronary artery vasospasm, even in the presence of early atherosclerotic disease. In addition, expression of the thromboxane prostanoid receptor in both coronary arteries and aorta was attenuated in the presence of progesterone. Thus, it appears that, in primates, progesterone can protect against vasospasm at serum levels ranging from subphysiologic to luteal phase, even in the presence of early atherosclerosis.

An important human clinical study[12] looked at the time to exercise-induced ischemia in women with known coronary artery disease and known abnormal exercise stress tests. These women were treated with estradiol alone for 4 weeks. It was determined that the estrogen treatment increased the time to exercise-induced ischemia. They were then randomized to estradiol plus transvaginal progesterone versus estradiol plus MPA in a double-blind crossover study. The addition of progesterone increased the exercise time, whereas the addition of MPA had no effect. This result is consistent with the animal studies demonstrating the vasodilatory effects of progesterone.

Cardiovascular Properties of NE and NEA

NE and NEA have a long history of use in birth control pills for premenopausal women. In recent years they have been incorporated with E and EE in combined oral and transdermal preparations. The available randomized clinical trials have all included estrogen, either in the oral or transdermal forms, with the rationale that most women will be taking NE or NEA in an HRT preparation.

A comprehensive review of all trials of HRT measuring lipid parameters and conducted before 2000[3] noted that all forms of estrogen lowered total cholesterol and LDL, and raised HDL and triglycerides. Adding a progestational agent partly antagonized the estrogen effects, but in most cases not enough to reverse the favorable estrogenic lipid effects. In an analysis of pooled specimens, only NEA and levonorgestrel actually caused HDL to drop below its baseline level. These 2 progestins also caused triglycerides to decrease below baseline, a potentially favorable effect. Table 2 summarizes the results of 5 recent trials that measured markers of CVD in addition to the standard lipid panel.

Two of these trials were conducted in low-risk postmenopausal women, one with transdermal E and transdermal NEA,[13] and the other with oral E and oral NEA.[14] Three trials in women with type 2 diabetes[15-17] examined the effects of transdermal E combined with oral NE, and of oral E and oral NE. The authors looked at lipid and inflammatory markers of cardiac disease and at markers of thrombosis, although not all trials measured all parameters.

Across the board, all preparations lowered total cholesterol and either lowered or produced no change in LDL and triglycerides. HDL either decreased or remained unchanged, but one study that measured HDL subfractions showed that HDL_2, believed to be responsible for the cardioprotective effect, remained unchanged, with the decrease accounted for by HDL_3.[13] Lipoprotein (a) and apolipoprotein A1 (ApoA1) were unchanged whereas ApoA2 decreased. An increase in ApoA2 has been associated with development of vascular fatty streaks in animal studies.[13] The same study showed a decrease in the cell adhesion molecules E-selectin and vascular cell adhesion molecule and a decrease in angiotensin-converting enzyme activity. Studies in diabetic patients have demonstrated either no change or a decrease in fasting glucose and no change in HbA_{1c} or C-reactive protein (CRP).

With respect to thrombogenesis, many of the effects on clotting parameters have been observed with estrogen alone. In all trials that measured the clotting factors, Factor VII, and fibrinogen were reported to either demonstrate a decrease or no change from baseline. In summary, the combined HRT preparations, whether administered by the transdermal or oral route (containing NE or NEA), have had either a positive effect or no adverse effect on most of the important lipid, inflammatory, and thrombotic markers. Only HDL appears to be decreased. It is unclear whether the amount of HDL

Table 2
Clinical Trials of the Impact of NE and NEA on Serum Lipids and Other Biomarkers

	Transdermal Estrogen, 0.05 mg + NEA, 0.125 mg	Oral Estrogen, 1 mg + NEA, 0.25 mg and 0.5 mg	Transdermal Estrogen, 80 μg + Oral NE, 1 mg*	Oral Estrogen, 1 mg + NE, 0.5 mg*	Oral Estrogen, 1 mg + NE, 0.5 mg*
Total cholesterol	↓		↓	↓	↓
Low-density lipoprotein	↓		→		↓
High-density lipoprotein	↓		↓	→	→
Very low-density lipoprotein			→		
Triglycerides			↓	→	→
Lipoprotein (a)	→				
Apolipoprotein A-I	→				
Apolipoprotein A-II	↓				
Fasting insulin	↓				
Fasting glucose			→	↓	↓
Hemoglobin A_{1c}				→	
E-selectin	↓				
Vascular cell adhesion molecule-1	↓				
Angiotensin-converting enzyme	↓				
C-reactive protein				→	→
Antithrombin		↓	↓		
Factor VII	↓	↓	↓		↓
Plasminogen activator inhibitor-1		↓	→		
Fibrinogen	→	↓	→		→
Fibrin D dimer	↑		→		

*In patients with type 2 diabetes.
NE, norethindrone; NEA, norethindrone acetate.
Data from Stevenson JC et al.,[13] Borgfeldt C et al.,[14] Perera M et al.,[15] Kernohan AFB et al.,[16] and McKenzie J et al.[17]

decrease can translate into an increase in cardiovascular risk.

Animal studies have demonstrated that NEA has vascular effects that are different from MPA. In a study of New Zealand white rabbits,[18] 7 groups were treated for 4 weeks with MPA, NEA, CEE, E, MPA plus CEE, NEA plus E, and placebo. Sections of the posterior cerebral and basilar arteries were subjected to tension recordings in response to vasoconstrictors. Treatment with MPA increased vasoconstriction compared with NEA, but the addition of CEE or E eliminated the differences.

A group of rhesus monkeys, pretreated with an atherogenic diet, were placed on either CEE plus MPA or E plus NEA and underwent quantitative coronary angiography.[19] When given acetylcholine, the MPA-treated group demonstrated constriction of the coronary arteries, but the NEA-treated group did not. Electrocardiographic ST depression after administration of dobutamine was considerably less in the NEA-treated group than in the MPA-treated group.

There are few studies of the effects of NE/NEA on human vascular reactivity. One such study[20] evaluated brachial artery flow-mediated dilation (FMD), using ultrasound, in a double-blind crossover trial of 100 postmenopausal women placed on transdermal E, transdermal E plus NEA, and placebo. The only increase in FMD was noted in women in their 50s on the estrogen (β-estradiol) patch. When NEA was added, this response was blunted and there was no significant difference from placebo. For women in their 60s and 70s, HRT made no difference in FMD.

In contrast, a study of women with diabetes before and after treatment with transdermal E plus oral NEA demonstrated a definite relaxation response.[21] These women had gluteal biopsies before and after 6 months of HRT, and the gluteal arteries were tested in a myograph for their

response to acetylcholine, bradykinin, and sodium nitroprusside. Compared with baseline, the HRT group demonstrated significant relaxation. It is unclear whether either of these results can be extrapolated to any direct effect on human coronary arteries.

Cardiovascular Properties of MPA

Of all the progestins, the most comprehensive data are available on the effects of MPA because the widely used combination of CEE/MPA was chosen as the HRT preparation for the WHI trial. This trial examined lipid and inflammatory markers as well as outcomes data for coronary heart disease (CHD) in the patient and control populations.[22] In an attempt to find an explanation for the increase in CHD events found in the HRT trials, a nested case control study was performed with the WHI data.[22] This study compared all patients with CHD, stroke, and venous thromboembolism (VTE) occurring during the first 4 years of the study—a total of 359 patients with 820 control subjects. The groups were compared for baseline biomarkers, and after 2- and 4-year follow-up. Table 3 shows the qualitative changes with respect to baseline for the CEE/MPA group.

Not surprisingly, the patients who developed CHD differed from the control group in many baseline biomarkers, some of which were significantly associated with cardiac risk in the 2- and 4-year periods after hormone therapy was begun. These were matrix metalloproteinase (MMP)-9, fibrinogen, leukocyte count, insulin, Factor VIII, LDL, total cholesterol, HDL, triglycerides, D dimer, and von Willebrand factor. Of these biomarkers, those that changed in response to hormone therapy were MMP-9, fibrinogen, insulin, LDL, total cholesterol, HDL, and triglycerides. However, the statistical analysis failed to demonstrate any significant change in the risk of CHD as a result of hormone therapy after the first year, either as a result of the favorable lipid changes induced by HRT or the unfavorable changes in MMP-9 and triglycerides. The authors concluded that the changes in biomarkers may not be responsible for the increased risk of CHD with HRT demonstrated in the original WHI study.[1]

Another nested case control study arising from the WHI[23] compared 271 patients with CHD with 707 control subjects, comparing lipid status and high-sensitivity CRP at baseline and after treatment. The study concluded that women whose LDL/HDL ratio was $>$ 2.5 had an increased risk of CHD, whereas women whose baseline LDL/HDL ratio was $<$ 2.5 had no increased risk with CEE with or without MPA. Baseline CRP levels did not add to the utility of the lipid profile in predicting CHD risk.

With respect to the vascular properties of MPA, previously cited animal and human studies have already noted that MPA acts to vasoconstrict, rather than vasodilate, in contrast to NEA and progesterone.[6,9,12,18,19] In rhesus monkeys, the addition of MPA to estradiol was sufficient to counteract the estrogen-induced vasodilation and cause coronary vasospasm.[9] Coronary arteries in preatherogenic rhesus monkeys on CEE plus MPA will vasoconstrict in response to acetylcholine, but coronary arteries in those given E plus NEA will not.[19] In women with

Table 3
Lipid and Inflammatory Biomarkers and MPA Trials

	Oral CEE, 0.625 mg + MPA, 2.5 mg
Total cholesterol	↓
Low-density lipoprotein	↓
High-density lipoprotein	↑
Triglycerides	↑
Lipoprotein (a)	→
Insulin	↓
Glucose	↓
E-selectin	↓
C-reactive protein	↑
Plasminogen activator inhibitor-1 antigen	↓
Fibrinogen	↓
D-dimer	→
Factor VIII	→
Interleukin-6	→
Matrix metalloproteinase-9	↑
Prothrombin fragment 1,2	→
Thrombin-activable fibrinolysis inhibitor	→
Von Willebrand factor	→

CEE, conjugated equine estrogens; MPA, medroxyprogesterone.
Data from Rossouw JE et al.[22]

known coronary artery disease, the time to exercise-induced ischemia, which is increased with estradiol treatment, is not enhanced with the addition of MPA, although it is increased when progesterone is added.[12]

In the WHI trial, the average age of the participants was 63 years; most were hormone-naïve, and the mean time since menopause was 12 years. Thus, an important question was whether initiating HRT close to the time of menopause might demonstrate a cardioprotective effect. Only 10% of women assigned to CEE alone and 17% assigned to CEE/MPA were assigned within 5 years of menopause at the start of the trial and this was too small a population to answer this question with statistical accuracy. Thus, these data were combined with data from the WHI observational trial.[24] Most of the women who started hormone therapy within 5 years of menopause started before enrollment in the WHI trial and were from the observational study. For these women, although the hazard ratios (HRs) for stroke and VTE were suggestive of a slightly higher risk, the *P* values for the gap analysis did not reach statistical significance and the HRs for CHD were not elevated in either the CEE or CEE/MPA group. There was neither evidence of a cardioprotective effect for women who began HRT near the age of menopause nor was there statistically significant evidence of harm.

Two other trials are currently in progress to further assess the issue of early intervention. One is the Kronos Early Estrogen Prevention Study (KEEPS),[25] which is enrolling postmenopausal women aged 40 to 55 years and uses low-dose estrogen and vaginal progesterone. A second trial is the Early Versus Late Intervention Trial With Estradiol (ELITE),[26] which is enrolling 2 sets of women, those who are < 6 years from menopause and those who are > 10 years from menopause. This trial also uses estrogen and vaginal progesterone. Whether the choice of progesterone, rather than MPA, will demonstrate a cardioprotective effect awaits the data analysis.

A further subanalysis of the WHI data addressed the question of whether the increased risk of CHD ever disappeared with continuing treatment.[27] The study stratified the participants by time since menopause and by years since the start of the study up to 8 years. For women who started HRT 10 or more years after menopause, the HRs were 2.36 for the first 2 years and 1.69 for the first 8 years. For women who began therapy within 10 years of menopause, the HRs were 1.29 for the first 2 years and 0.64 for the first 8 years. The curves crossed at 6 years and thereafter demonstrated a protective effect for younger women.

The WHI also looked at what happened in the 3-year period after patients stopped taking CEE/MPA.[28] After HRT was discontinued, the risk of stroke, CHD, and pulmonary embolism immediately decreased to a level equal to that of the control group. The risk of breast cancer, however, remained slightly elevated over the subsequent 3-year period.

Discussion

One of the open questions arising out of the WHI study is why the increased risk of MI was observed only in the CEE/MPA group but not in the CEE-alone group. It is tempting to attribute the increased risk of CHD to an effect of MPA. Although multiple baseline lipid and inflammatory biomarkers are associated with an increased risk of CHD, the changes induced in these markers by the addition of MPA to CEE does not demonstrate a significant correlation and it appears that these changes in biomarkers do not mediate the increased risk.

MPA differs from all other progestins in that it causes vasoconstriction, whereas progesterone, NE, and NEA enhance the vasodilatory properties of estrogen. The balance between dilation and constriction on the coronary vasculature in any given HRT combination may depend upon the type of estrogen and the dose. In some cases, MPA may merely blunt the estrogen effect, whereas in other combinations, it may reverse it. One may also hypothesize that MPA, in addition to a vasoconstrictive effect on coronary arteries, might also affect the microvasculature, further contributing to the development of ischemia, and that perhaps the vasoconstrictive properties of MPA partly account for the increased incidence of MI in women who are already at risk. This raises the question of whether HRT combinations with other progestins might be safer.

MPA differs from all other progestins in that it causes vasoconstriction, whereas progesterone, NE, and NEA enhance the vasodilatory properties of estrogen.

It is now clear from the WHI studies that HRT containing MPA does not offer a cardioprotective benefit. It is hoped that trials looking at progesterone as a progestational HRT component will answer the question of whether this combination along with early intervention will be

protective. However, from a clinical perspective, women do not seek HRT because they want protection from CVD, and clinicians do not normally think of HRT as a first-line approach for reducing cardiovascular risk. Patients ask for hormone replacement to relieve a constellation of distressing symptoms including hot flushes, dyspareunia, mood swings, depression, and irritability, which affect the quality of their daily lives. The majority of women have this discussion with their gynecologists; however, cardiologists may be asked to weigh in on safety issues for those patients who are at higher risk because of hypertension, hypercholesterolemia, and metabolic syndrome. The retrospective look at baseline lipid values in those WHI participants who developed MI, stroke, and pulmonary embolism clearly demonstrated an increased hazard value for those patients whose LDL/HDL ratio exceeded 2.5.[23] It might therefore be prudent to use statins to lower this ratio and to use guideline-recommended antihypertensive strategies to control hypertension prior to starting any HRT regimen. If symptoms are severe enough to require HRT, the choice of a progestin other than MPA would be advisable.

The latest position statement of the North American Menopause Society[28] states, "[Hormone therapy] is currently not recommended as a sole or primary indication for coronary protection in women of any age. Initiation of [hormone therapy] by women ages 50 to 59 years or by those within 10 years of menopause to treat typical menopause symptoms (eg, vasomotor, vaginal) does not seem to increase the risk of CHD events. There is emerging evidence that initiation of [estrogen therapy] in early postmenopause may reduce CHD risk."

For each patient, the risk to benefit ratio of starting HRT is different. The severity of symptoms requiring relief must be weighed against the clinician's assessment of the patient's risk of developing CHD, stroke, and breast cancer. Each patient needs to be educated regarding the results of studies so that she can make an informed decision. Collaboration between primary care physicians, cardiologists, and gynecologists is essential in assuring the optimum treatment of newly postmenopausal women who may be at higher risk for cardiovascular events. ■

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Main Points

- Not all progestational agents used in hormone replacement therapy are alike. They differ in their effects on the biomarkers of cardiac disease as well as in their direct vascular effects on the coronary arteries.
- Animal studies have demonstrated that medroxyprogesterone acetate (MPA) offers no protection from coronary artery vasoconstriction.
- Changes in lipid and inflammatory biomarkers, induced by adding MPA to estrogen, are not the mechanism of action causing the increased risk of coronary heart disease (CHD) demonstrated in the original Women's Health Initiative trial.
- Women whose ratio of low-density lipoprotein cholesterol to high-density lipoprotein cholesterol is < 2.5 demonstrate no increased risk of CHD with estrogen replacement, with or without the addition of MPA.

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