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PERSONAL PERSPECTIVE

"Rise and fall" of hormone therapy in postmenopausal women with cardiovascular disease

Angela H.E.M. Maas, MD,[1] Yvonne T. van der Schouw, PhD,[2] Diederick E. Grobbee, MD, PhD,[2] and Yolanda van der Graaf, MD, PhD[2]

ABSTRACT

Whereas observational data for postmenopausal women using hormone therapy (HT) have shown a protective effect against cardiovascular disease, prospective, randomized trials have demonstrated a harmful effect on the vascular system.

This study describes the effects of HT on lipids, hemostatic parameters, inflammation, and the vascular wall. Reasons for the different results of observational and experimental studies of HT are postulated. The timing of hormonal supplementation seems crucial. Used chronically, HT has no harmful effects; however, first-time use of HT after a recent cardiovascular event results in an early increase in adverse cardiovascular events. In most observational studies, women started HT for postmenopausal symptoms, whereas in experimental studies, women started HT 10 to 20 years or longer after menopause.

Cumulative evidence supports the hypothesis that HT has more effect in maintaining vascular health than in alleviating endothelial dysfunction. HT has not proven beneficial in the long term in women at risk of a cardiovascular event. The interval between menopause and the start of HT plays a crucial role in the effectiveness of HT in the vascular system.

Key Words: Hormone therapy – Cardiovascular disease – Prevention.

Cardiovascular disease develops 10 to 15 years later in women than in men and is the major cause of death in women older than 65 years of age.[1] It is assumed that exposure to endogenous estrogen has an important role in the delayed manifestation of atherosclerotic disease in women. In the perimenopausal period, estrogen levels decline to about 20% of levels in the fertile period. Data from the Framingham Heart Study and Nurses' Health Study have indicated an increased risk of cardiovascular disease in young women after bilateral oophorectomy, a risk that did not occur in women using hormone therapy (HT) after surgery.[2,3] Other observational data support the hypothesis that longer exposure to endogenous estrogens protects against cardiovascular disease (CVD).[4-6] For each year's delay in the onset of menopause, the cardiovascular mortality risk decreases by 2%. This increased risk of cardiovascular disease with menopause at a younger age is more prominent at younger biological ages and is no longer important after the age of 80.[5] In the Nurses' Health Study, the adverse effect of early natural menopause on CVD risk was also found, although in this study the effect was restricted to women who smoked.[6]

The cardioprotective effects of estrogens in the fertile period support the use of HT for preventive strategies in the postmenopausal years. Thus far, however,

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From the [1]Department of Cardiology, Isala Klinieken, Zwolle, the Netherlands; and the [2]Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands.

Address correspondence to: A.H.E.M. Maas, cardiologist, Isala Klinieken, Department of Cardiology, Dr. van Heesweg 2, 8025 AB Zwolle, The Netherlands. E-mail: a.maas@diagram-zwolle.nl.

only observational data on postmenopausal use of HT have shown a beneficial effect against the occurrence of cardiovascular disease. In contrast, prospective, randomized trials with HT have demonstrated a harmful effect on the vascular system. These conflicting results complicate the understanding of postmenopausal HT use.

Metabolic changes during menopause and metabolic effects of HT

Many physiological changes occur in the years around menopause (mean age 51 years), most importantly atherogenic metabolic changes affecting the lipid profile: total cholesterol levels rise 10%, low-density lipoprotein (LDL) cholesterol levels rise 14%, and lipoprotein(a) levels increase 4% to 8%, whereas high-density lipoprotein (HDL) cholesterol levels remain unchanged.[7] Hemostatic parameters move to a more thrombogenic state, with higher levels of fibrinogen, factor VII, and plasminogen-activator inhibitor-1.[8] Homocysteine levels also increase after menopause.[9] A direct association between blood pressure, body weight, and menopause has not been demonstrated.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, involving 875 healthy postmenopausal women, showed that estrogen alone or in combination with a progestin caused lipoprotein levels to revert to those of the premenopausal state.[10] Depending on the type of progestin used, changes in lipoprotein levels were slightly different: medroxyprogesterone acetate (MPA) attenuated the beneficial effects of estrogen on the lipoprotein levels, whereas micronized progestin did not but had no detrimental effect. No significant changes in blood pressure, insulin levels, or fibrinogen levels were found among the different treatment groups. A possible negative effect of oral estrogens is an increase in the levels of triglycerides and very low-density lipoprotein (VLDL) cholesterol, the clinical significance of which is less clear.[11] The beneficial effects of estrogens on cholesterol metabolism are also related to the inhibition of LDL cholesterol oxidation and penetration in the vessel wall. Transdermal application of estrogens has been shown to be less beneficial to the lipid parameters than oral estrogens.[12]

Several studies have demonstrated a more than two-fold rise in C-reactive protein (CRP) levels after initiation of oral HT, but the clinical significance of this finding is not yet clear.[13] As more data emerge showing that HT use by high-risk women causes an increase in cardiovascular events, it is assumed that the increase in CRP levels promotes vascular inflammation and plaque instability.[14] Transdermal HT does not increase CRP levels.

VASCULAR EFFECTS OF HT

Vasodilation

Alterations in serum lipids are considered to account for one third of the assumed clinical benefits of estrogen, but direct effects on the arterial wall may be at least as important. Estrogen causes vasodilatation by a rapid (5-20 min) activation of nitric oxide synthesis in endothelial cells.[15] In small experimental studies, intravenous administration of estradiol caused direct vasodilatation in healthy women as well as in women with atherosclerotic disease.[16,17] Recent data from 1,636 women participating in the Cardiovascular Health Study, a longitudinal study of cardiovascular risk factors in men and women older than 65 years of age, only showed a significant association between HT and flow-mediated response in healthy postmenopausal women.[18] HT had no effect on brachial artery blood flow in older women (> 80 years), in women with documented cardiovascular disease, or in women with a combination of cardiovascular risk factors. These data suggest that healthy endothelium is sensitive to estrogens, whereas endothelium damaged by atherosclerotic disease is not.

Atherosclerosis

The protective effects of estrogens against atherosclerosis occur over a period of hours or days and are mediated by estrogen-α and estrogen-β receptors in the vascular wall.[15,19] In monkeys, estrogen inhibits the development of atherosclerotic plaque formation when given directly after ovariectomy.[20] When estrogens were started 2 years after ovariectomy, there was no inhibition of coronary atherosclerosis. In rats with carotid intima damage, estrogens inhibited intima hyperplasia and smooth muscle cell proliferation only when given in the early stages of vascular damage.[21] Administration of estrogens after 3 days did not have a beneficial effect on the vascular wall. In pigs, stents coated with 17β-estradiol inhibited neointima proliferation with a reduction in restenosis after percutaneous coronary interventions.[22] These findings of animal studies support the hypothesis that estrogen has beneficial effects, especially in the early stages of atherosclerotic disease and in the early stages of vascular wall repair.

Cardiac hypertrophy

An increasing amount of data from animal studies show protective effects of estrogen against the devel-

opment of cardiac hypertrophy.[23,24] The lack of estrogen in postmenopausal women may be responsible for the increase in ventricular hypertrophy seen in women in older age.[25]

HT and cardiovascular events

Extensive data from observational studies suggest that HT has a beneficial effect on the occurrence of cardiovascular disease in postmenopausal women, with a risk reduction of 35% to 50%.[26,27] The most pronounced risk reduction was reported for current HT users, but in past users a protective effect could still be found.[28] Most studies included healthy postmenopausal women without a history of cardiovascular disease and who had a relatively healthy lifestyle. The hormonal therapy was mostly started in the direct perimenopausal or postmenopausal period for the relief of menopausal symptoms. It is difficult to compare these studies because different types of HT preparations were used for different lengths of time.

More recent observational studies have yielded data showing that women are at increased risk of cardiovascular disease: in a retrospective subanalysis of 2,489 women from the Nurses' Health study, with a previous myocardial infarction (MI) or documented atherosclerosis, the risk reduction for a recurrent event was still 35% (95% CI, 0.45-0.95) among current HT users compared with never users, with up to 20 years of follow-up.[29] Short-term HT use (< 1 year), however, was associated with a 25% increase in the rate of cardiovascular events. Observational data from the National Registry of Myocardial Infarction-3 for 114,724 women older than 55 years with confirmed MI also found a mortality risk reduction of 35% in current HT users compared with nonusers (HR 0.65, 95% CI 0.59-0.72).[30] Most of these women had started HT in the postmenopausal period for menopausal complaints or for the prevention of osteoporosis.

The Estrogen and Prevention of Atherosclerosis Trial investigated 199 postmenopausal women older than 45 years (mean 60 years), with LDL-cholesterol levels higher than 3.37 mmol/L and no clinical evidence of coronary artery disease.[31] During 2 years of treatment, carotid intima-media thickness increased at a slower rate in women receiving 1 mg 17β-estradiol than in those on placebo. Although the changes in carotid intima-media thickness were reduced equally by estrogens and statins, there was no additive effect of the two treatments. This suggests that, in healthy endothelium, estrogen can inhibit atherosclerosis, and that when HT is started in the direct postmenopausal period, the vascular endothelium remains sensitive to the vasoprotective effects of estrogens.

Recently, the first data from the Women's Health Initiative (WHI) were published. This trial, started in 1993, investigates the effects of various HT regimens on the occurrence of heart disease, breast cancer, osteoporotic fractures, and colorectal cancer in healthy postmenopausal women, 50-79 years of age.[32,33] A total of 16,608 women were randomized to treatment with a combination of 0.625 mg conjugated estrogens and 2.5 mg MPA (n = 8,506) or placebo (n = 8,102). After a mean follow-up of 5.2 years, the study was stopped prematurely because overall health risks exceeded the benefits, primarily because of an increase in invasive breast cancer (26%, 166 cases), cardiovascular events (29%, 164 cases), and stroke (41%, 127 cases) in the treatment group. The excess cardiovascular events (164 in the treatment group compared with 122 on placebo) were mostly due to nonfatal MI; no significant differences in coronary heart disease (CHD) deaths or revascularization procedures were seen. As expected, a twofold (151 compared with 67) increase in the incidence of thromboembolic events was seen in women on HT. All-cause mortality was not different between both treatment arms (HR 0.98. 95% CI 0.82-1.18). Although the study was designed as a primary prevention trial, 67% of the included women were older than 60 years and had many risk factors. This confirms that early intervention with HT is important in the progression of subclinical atherosclerosis and endothelial dysfunction.

HT in cardiovascular patients

Observational data in 337 women show that current users of HT have fewer cardiovascular events (12% v 35%) and better survival (93% v 75%) after elective, percutaneous, transluminal, coronary angioplasty (PTCA) compared with nonusers.[34] Others have confirmed the better outcome after elective PTCA and coronary stenting in current users of HT.[35,36] Among women undergoing coronary artery bypass surgery, chronic HT use was associated with a significantly improved, 5-year survival.[37] However, initiation of HT after a recent MI caused a significantly higher (44%) risk of unstable angina pectoris, death, and reinfarction compared with the risk in chronic HT users and never-users.[38] This early increase in adverse cardiovascular events is attributed to proinflammatory and thrombogenic effects of HT. In a recent randomized, placebo-controlled trial of 1,017 women, aged 50-69 years, who had experienced a first MI, unopposed 17β-estradiol was neither harmful nor beneficial in terms of fre-

quency of reinfarction or cardiac death after 2 years of treatment.[39] Importantly, noncompliance to treatment was extremely high (> 50%) after 1 year in the active treatment group, which weakened the power of this study.

Despite the benefits of HT in observational studies, the first prospective randomized trial of 2,763 postmenopausal women (mean age 67 years) with documented coronary heart disease, the Heart and Estrogen/progestin Replacement Study (HERS), revealed no benefits of a combined HT regimen with 0.625 mg conjugated equine estrogen and 2.5 mg MPA in the prevention of CHD compared with placebo after 4.1 years of treatment.[40] In the first year of treatment, however, coronary events increased by more than 50% in the treated group. This excess in events was not seen in women who were on statin therapy.[41] It is assumed that initiation of HT destabilizes coronary plaques, whereas statins are postulated to have a stabilizing effect on atherosclerotic plaques. The combined therapy seems to attenuate the detrimental effect of HT on plaque stability. Others have confirmed that combined therapy with a statin reduces the rise in CRP levels caused by estrogen monotherapy.[42] After the first year of treatment, there was a nonsignificant trend to a reduction in cardiovascular events in treated women, but this trend never reached significance. Prolongation of the follow-up to 6.7 years (HERS II) did not show any benefit of HT on the CHD event rate.[43] An extensive post-hoc analysis of 86 subgroups in the HERS did not identify a specific subgroup in which postmenopausal HT was beneficial or harmful.[44] Genetic markers in HERS are still under investigation.

The Estrogen Replacement and Atherosclerosis (ERA) trial prospectively evaluated the angiographic progression of present coronary atherosclerosis in 309 women, assigned to 0.625 mg conjugated estrogens alone or in combination with 2.5 mg MPA or placebo.[45] After an average follow-up of 3.2 years, no differences were found in coronary vessel diameter and clinical outcomes. As in HERS, the women included in ERA were 66 years old and had been postmenopausal on average 20 years. As the aging endothelium becomes less sensitive to estrogens, one could argue that it is not appropriate to start HT in this age group.[46] Further genetic analysis revealed that HDL levels increased significantly more with HT use in women with the C/C genotype of the estrogen-α receptor than in women with other genotypes.[47] This might be the first step to a better identification of women who might benefit the most from HT. Recent data from two more randomized angiographic studies, the WAVE and WELLHART, have provided further information about the lack of beneficial effects of HT on the progression of coronary atherosclerotic lesions in older women with documented coronary artery disease.[48,49]

The Women's Estrogen for Stroke Trial (WEST) was the first randomized study to use the more natural 17β-estradiol in 664 postmenopausal women who recently had experienced a transient ischemic attack or stroke.[50] Estrogen was not found to have a beneficial effect compared with placebo on recurrent stroke or mortality after a mean follow-up of 2.8 years. In the first six months of treatment, there was a significant increase in mortality or recurrent stroke in the women treated with estrogen (HR 2.3, 95% CI 1.1-5.0), reflecting early deleterious effects in high-risk women. As in the HERS and ERA trials, women in this trial were relatively old (71 years).

In the Postmenopausal Hormone Replacement Against Atherosclerosis trial, 321 postmenopausal women at risk for a first cardiovascular event were investigated for adverse changes in carotid intima-media thickness after 48 weeks of treatment with 17β-estradiol, a combined regimen with a progestin, or placebo. In neither active treatment group was the progressive increase in carotid intima-media thickness slowed, although both active treatments decreased LDL levels and fibrinogen levels.[51] The duration of this study was too short to draw further conclusions.

In summary, in chronic HT users, hormonal therapy is not harmful during coronary interventions, whereas starting HT after a recent cardiovascular event causes an early increase in adverse cardiovascular events and has no beneficial effects in secondary prevention in the long term. The concomitant activation of the thrombotic system by HT and the vulnerability of existing coronary plaques play an important role in the negative effects of HT on the vascular system. These data support the hypothesis that the vascular endothelium is susceptible to the beneficial effects of estrogens when started early after menopause but is no longer susceptible with later administration.

Failure of HT or failure of clinical trials?

Despite the consistent benefit of HT on cardiovascular events in past and more recent observational studies, randomized trials thus far have failed to show any benefit (Table 1). On the contrary, more reports of early negative effects of initiating HT in women at risk for cardiovascular disease are emerging.[29,52] The discrepancy between the proven beneficial effects of estrogens on the cardiovascular system and the lack of positive effects in clinical practice is as yet unsolved. Recent

TABLE 1. *Randomized controlled prevention studies with HT*

Study	Published	Population	Type prevention	Medication and follow-up	Results (*n*)
HERS	1998	2,763 women with documented CAD >55 y	Secondary	CEE+ MPA or placebo, follow-up 4.1 y	No benefit HT (179 HT, 182 placebo)
WEST	2001	644 women >55 y after stroke/TIA	Secondary	E or placebo, follow-up 2.8 y	No benefit HT (99 E, 93 placebo)
ESPRIT	2002	1,017 women 50-69 y after first MI	Secondary	E_2 or placebo, follow-up 2 y	No benefit HT (83 E_2, 91 placebo)
PHOREA	2001	321 women >55 y with atherosclerosis (IMT-carotis)	Secondary	E, or E+G, or placebo; follow-up 48 wk	No benefit HT
ERA	2000	309 women with ≥1 stenosis coronary artery ≥30% (QCA)	Secondary	CEE, or CEE+MPA, or placebo; follow-up 3.2 y	No benefit HT
WAVE	2002	423 women with ≥1 stenosis coronary artery 15%-75% (QCA)	Secondary	CEE or CEE+MPA and/or Vit. E, C, or placebo; follow-up 2.8 y	No benefit HT, no benefit Vit. C, E
WELLHART	2002	226 women with ≥1 stenosis coronary artery ≥50% (QCA)	Secondary	CEE, or CEE+MPA, or placebo; follow-up 3 y	No benefit HT
EPAT	2001	199 healthy postmenopausal women >45 y with LDL-C >3.37 mmol/L (IMT-carotis)	Primary	E or placebo, with statin if LDL-C > 4.15 mmol/L; follow-up 2 y	Benefit HT equal to statin
WHI	2002	16,608 healthy postmenopausal women 50-79 y	Primary	CEE+MPA or placebo, follow-up 5.2 y	No benefit HT (694 HT, 546 placebo)

HERS, Heart and Estrogen/progestin Replacement Study;[40] West, Women's Estrogen for Stroke Trial;[50] ESPRIT, OEStrogen in the Prevention ReInfarction Trial;[39] PHOREA, Postmenopausal HormOne REplacement against Atherosclerosis;[51] ERA, Estrogen Replacement and Atherosclerosis;[45] WAVE, Women's Angiographic Vitamin and Estrogen trial;[48] WELLHART, Women's Lipid Lowering Heart Atherosclerosis Trial;[49] EPAT, Estrogen in the Prevention of Atherosclerosis;[31] WHI, Women's Health Initiative.[32]
CEE, 0.625 mg conjugated estrogens; MPA, 2.5 mg medroxyprogesterone acetate; E_2, 2 mg estradiol valerate; E, 1 mg 17 β-estradiol; G, 0.025 mg gestodene; CAD, coronary artery disease; TIA, transient ischemic attack; MI, myocardial infarction; IMT, intima-media thickness; *n*, CVD event rate; CVD, cardiovascular disease; QCA, quantitative angiography.

meta-analyses of observational HT trials have shown no benefit of HT on the cardiovascular disease event rate in postmenopausal women and emphasize the healthy user bias of most observational studies.[53,54]

One important aspect in comparing observational data and randomized studies is the age of the participants and the time since menopause. Nearly all observational data are derived from women who started HT for postmenopausal symptoms, and thus therapy was started in the early postmenopausal period. In the randomized HT trials, however, the indication for inclusion was age 50 to 79 years, without clinical signs of atherosclerotic disease (WHI) or with clinically manifest cardiovascular disease in the secondary prevention trials. In all these studies, the women no longer suffered from perimenopausal complaints and started HT 10 to 20 years or even longer after menopause.[55-57] The time when HT is started relative to menopause seems to be crucial in the effectiveness of HT in the vascular system.

The authors of the WHI stated that the study was done in "apparently" healthy, postmenopausal women.[32] As endothelial function declines with aging, long before clinical symptoms of atherosclerotic disease become manifest, one can argue whether the women included in the WHI were as healthy as they were assumed to be. Two-thirds (67%) of the women in the WHI were older than 60 years, and many had risk factors for coronary heart disease. Recent data from the Cardiovascular Health Study support the hypothesis that estrogens might be more important in maintaining vascular health than in treating subclinical endothelial dysfunction.[18] Therefore, the first data from the WHI, although it was intended to be a primary prevention trial, might indicate again that HT does not work in "secondary" prevention.[58]

The proinflammatory and thrombogenic effects of HT are still under investigation and are probably more complex than initially thought. In a nested case-control study of 304 participants within the still-ongoing observational study of the Women's Health Initiative (WHI-OS), it was found that HT was associated with significantly elevated levels of CRP but not with other inflammatory markers such as interleukin 6.[59] Total levels of these inflammatory biomarkers seem to be even more important in predicting coronary risk than

the use or nonuse of HT per se. This suggests that more factors than HT are involved in creating a systemic inflammatory state that causes the early risk of cardiovascular events in healthy, postmenopausal women.

Many have attributed the failure of HT in secondary prevention trials to the rapidly growing use of statins. Although women were less well represented in the large statin trials, most studies showed a comparable or even higher risk reduction in CHD events in women than in men.[60,61] Statin users in HERS had a lower CHD event rate than nonusers (HR 0.79, 95% CI 0.63-0.99) and a mean 30% lower rate of mortality from all causes compared with nonusers.[41] Concomitant statin and HT use diminished the early risk of cardiovascular events seen with HT in the first year of treatment but did not have an additional benefit of HT throughout the study. An interesting finding was that the use of a statin with or without HT resulted in a much lower incidence of venous thromboembolic events (RH 0.40, 95% CI 0.18-0.91).

Will alternatives to HT fulfill the promise?

The recent negative results of the WHI and secondary prevention trials indicate that postmenopausal therapy with estrogen and progestin results in increased risks of disease, does not make asymptomatic women feel better, and does not improve cognition. There seems to be no role for HT in the treatment of women without menopausal symptoms. Women with vasomotor symptoms must weigh the risks associated with treatment against the benefit of symptom relief.[62-64]

Selective estrogen receptor modulators such as raloxifene are not suited for the treatment of perimenopausal symptoms but are effective in the treatment of osteoporosis and are likely to reduce the incidence of invasive breast cancer.[65] Raloxifene decreases levels of LDL-cholesterol, but levels of HDL-cholesterol and triglycerides remain unchanged.[66] Other changes in biochemical markers are a reduction in lipoprotein(a), fibrinogen, and homocysteine with no change in plasma activator inhibitor-1. Thrombogenic side effects are comparable to those of HT. An important difference with HT is that raloxifene does not increase CRP levels.[67]

Although in experimental animals the cardioprotective effect of raloxifene on endothelial function is less well documented than that of HT, the first clinical data in women are promising. In a secondary, retrospective, subgroup analysis of 1,035 women with increased cardiovascular risk included in the Multiple Outcomes of Raloxifene Evaluation trial, a large osteoporosis study, no early increase in adverse cardiovascular events was noted in the first year of treatment, whereas there was a significant reduction in cardiovascular events of 40% (RR 0.60, 95% CI, 0.38-0.95) after 4 years of treatment with raloxifene.[68] The effects of raloxifene are currently being investigated in the Raloxifene Use for the Heart randomized trial involving 10,101 postmenopausal women older than 55 years at risk of a cardiovascular event. Primary end points of the study are invasive breast cancer, acute coronary syndromes, and cardiovascular mortality.[69] As in the other secondary prevention trials, the mean age of the participants in the study is relatively high at 68 years.[70]

CONCLUSION

Cumulative evidence supports the hypothesis that HT has more effect in maintaining vascular health than in restoring endothelial function. The initiation of HT in women at risk of a cardiovascular event results in more cardiovascular complications and has not been proven beneficial in the long term. The time when HT is started relative to menopause plays a crucial role in the effectiveness of the hormones in the vascular system. It is still not known whether starting HT shortly after menopause can delay clinical signs of atherosclerotic disease.

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