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REVIEW ARTICLE

Postmenopausal hormone therapy and coronary heart disease in early postmenopausal women

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In women, cardiovascular disease (CVD) accounts for about half of all deaths in Western countries. It is generally accepted that endogenous estrogen protects premenopausal women from CVD. However, whether postmenopausal hormone therapy (HT) confers cardiovascular benefit or harm remains controversial. One of the most pronounced factors modifying the cardiovascular effects of HT is age or time since menopause at the initiation of HT. Recently also the impact of hot flushes on CVD risk and the outcomes of HT has gained attention. This review summarizes the newest data regarding HT and CVD in recently postmenopausal women aged 50–59 years in light of the results from older HT trials. The aim is to help clinicians counsel their patients regarding the individual risks and benefits associated with HT use in this age group, where HT use is most prevalent.

Key words: Coronary heart disease, estrogen, menopause

Key messages

- In healthy, recently postmenopausal women aged 50–59 years hormone therapy use seems to be associated with benefit in terms of reduced CHD.
- Cardiovascular benefits associated with hormone therapy use may be more pronounced or even concentrated to women who have vasomotor symptoms.
- In these women postmenopausal hormone therapy may give several health benefits and a modest rise in risks, which may be modified with choice of treatment.

Introduction

Coronary heart disease (CHD) is the leading killer of women worldwide (1,2). Yet, heart disease is still under-detected in women (3,4). Acute myocardial infarction (MI) in women also often presents with atypical signs, which makes diagnosis more difficult, and women also have a higher in-hospital mortality for CHD than men of the same age (5). It has been estimated that a 50-year-old woman has a 39% lifetime risk of dying of cardiovascular disease (CVD), mainly CHD or stroke (6). However, this risk is greatly increased by advancing age and the presence of risk factors for CVD, such as smoking, hypertension, hypercholesterolemia, and diabetes (7). Management of risk factors and improved treatments have shown a tendency to decrease female CVD mortality (8,9). However, there are also data that imply that the risk of CHD in women seems to increase, whereas for men it is decreasing (10). This could in part be due to the increasing obesity epidemic, which is effectively negating the beneficial trend of decreasing mortality. Overall, women are more obese than men, especially in developing countries (11). This is further complicated by the fact that obesity confers a greater risk of CHD for women than for men (12). Therefore, increasing awareness of CHD and its risk factors in women is of utmost importance.

Due to the fact that CHD is rare in young women as compared to age-matched men, it is generally thought that women are protected from CHD during their premenopausal years by endogenous estrogen (13,14). A substantial body of experimental and observational data (15–17) also indicates a protective effect of postmenopausal hormone therapy (HT) against CHD. However, placebo-controlled trials (18–20) have failed to demonstrate any cardiovascular benefit with postmenopausal HT. There are, however, many caveats in interpreting these data. This review summarizes the current knowledge regarding cardiovascular risks and benefits with postmenopausal HT focusing on recently postmenopausal women aged 50–59 years, who are the main patient group initiating and using HT.

Results from observational studies

Postmenopausal HT has been used for approximately 80 years, and thus abundant clinical data on its effects on CVD have accumulated. Approximately 40 observational or case-controlled studies show a 30%–50% lower risk of coronary heart disease (CHD) and also a decreased risk of stroke in HT users (see e.g. 15–17,21). The results from the largest observational studies that

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Table I. Outcomes of observational studies (number of participants ≥ 5000 or follow-up ≥ 5 years) in which the effects of long-term hormone therapy have been assessed.

	Population; follow-up	Main outcome measure	Results
Leisure World (47,48)	$n = 8841$; 5.7 years	Cardiac death $n = 149$	ET: RR 0.59, $P = 0.002$
		Death due to stroke $n = 63$	ET: RR 0.53 (95% CI 0.31–0.91)
Sourander et al. (49)	$n = 7944$; 8 years	Cardiac death $n = 258$	HT: RR 0.21 (95% CI 0.08–0.59)
		Death due to stroke $n = 51$	HT: RR 0.16 (95% CI 0.02–1.18)
Swedish cohort (81)	$n = 9236$; 8 years	Myocardial infarction $n = 213$	ET: RR 0.75 (95% CI 0.56–0.99); EPT: RR 0.69 (95% CI 0.45–0.90)
		Stroke $n = 289$	ET: RR 0.91 (95% CI 0.71–1.17); EPT: RR 0.81 (95% CI 0.61–1.10)
Nurses' Health Study (17)	$n = 70,533$; 20 years	Coronary heart disease $n = 1253$	ET: RR 0.55 (95% CI 0.45–0.68); EPT: RR 0.64 (95% CI 0.49–0.85)
		Stroke $n = 767$	ET: RR 1.18 (95% CI 0.95–1.46); EPT: RR 1.45 (95% CI 1.10–1.92)
WHI Observational Study (82)	$n = 53,054$; 5.5 years	Coronary heart disease $n = 158$	EPT: HR 0.87 (95% CI 0.72–1.05)
		Stroke $n = 123$	EPT: HR 0.86 (95% CI 0.70–1.07)
OSTPRE (83)	$n = 11,667$; 6.7 years	Cardiac death $n = 58$	HT ≤ 5 years: RR 0.79 (95% CI 0.36–1.73) HT > 5 years: RR 2.16 (95% CI 0.93–4.98)
California Teachers Cohort Study (51)	$n = 71,237$; 5.7 years	Cardiac death $n = 1391$	HT: HR 0.84, 95% CI (0.74–0.95)

assess the cardiovascular effects of HT in healthy postmenopausal women are summed up in Table I.

The most comprehensive and still ongoing observational study is the Nurses' Health Study (22). In this study, initiated in 1976, 121,700 healthy women aged 30–55 years completed a mailed questionnaire on their medical history and HT use. By 2000, data comprising follow-up on 70,533 women showed that postmenopausal HT decreased the risk of CHD by 45% in women using estrogen-only therapy (ET) and by 36% in users of estrogen and progestin therapy (EPT) (17). However, the risk of stroke (mainly ischemic) was increased by up to 45% in current users of EPT, and by up to 63% in ET users.

The protective effect of HT against CHD seen in observational studies has in part been attributed to the 'healthy woman effect', i.e. women who chose to use HT were in general healthier than women who did not take HT. Observational studies can also fail to carefully record early clinical events. Many early observational studies also comprise data only on unopposed estrogen. Importantly, women in observational studies were fairly young when they chose to use HT, likely to control their vasomotor symptoms. Whether HT would also protect older women well past menopausal age and with cardiovascular risk factors had not been investigated in a randomized and placebo-controlled setting. Moreover, the increased risk of stroke associated with HT use demanded more investigation (13,23). Therefore, randomized, placebo-controlled trials, such as the HERS (18) and the Women's Health Initiative (WHI) (19), were commenced.

Results from randomized trials

Secondary prevention trials

The first HT trials in secondary prevention of CHD were mainly conducted with women who were several years past menopause. In the HERS trial the use of conjugated equine estrogen (CEE) 0.625 mg/d and 2.5 mg/d of medroxyprogesterone acetate (MPA) in older women ($n = 2763$, mean age 68) with established CHD was associated with significantly more CHD events (nonfatal MIs and CHD deaths) already after 4 months of treatment compared to placebo use (18). Interestingly, this harmful effect of HT was negated by concomitant statin use, known to stabilize vulnerable atherosclerotic plaques (24). Furthermore, the increase in CHD events did not persist after 6.8 years of treatment (25). In the ESPRIT trial 2 years of oral estradiol 2 mg/d did not prevent recurrent coronary events in women with previous MI ($n = 1017$, mean age 63) (26). However, neither was any significant harm compared with placebo use demonstrated. There are also several other secondary prevention trials, all of which show a null effect. Results from the largest of these are listed in Table II. Thus, the secondary prevention of CVD with HT in older women failed. Next, a primary prevention trial—the Women's Health Initiative (WHI)—was undertaken.

Primary prevention trial—the Women's Health Initiative

The WHI was initiated in 1992 and planned to continue until 2007 with a median follow-up of 9 years (23). Participants were enrolled to both a randomized clinical trial (RCT) and an observational study (WHI-OS) with goals to assess the overall benefit-risk ratio of HT (CEE and MPA (WHI-EP), or CEE only for hysterectomized women (WHI-E)) on the risk of CVD and fractures. The trial aimed at 45% of the participants being 60–69 years old. This was rationalized with the lower CHD and higher breast cancer incidences in younger women that could affect the study's power or distort the benefit-to-risk profile (23). Despite the primary prevention nature of the trial, women with a previous CVD incident, such as acute MI, stroke, or transient ischemic attack, were not excluded from the trial, as long the incident had occurred over 6 months before screening. Moreover, women with severe menopausal symptoms were excluded due to the anticipated unwillingness to adhere to a possible placebo treatment (23). These choices may have had profound impact on the outcomes of the WHI, as is reviewed later on in this paper.

In 2002, after an average follow-up of 5.2 years, the data and safety monitoring board discontinued the WHI-EP arm, because the global index summarizing the risks and benefits indicated overall harm associated with active treatment (Table III) (19). The risk of coronary events was particularly high in the first year after initiation and in women with high baseline LDL-cholesterol (27)—results resembling the HERS data (18). In these analyses, no significant interactions between CHD, HT use, age or time since menopause, or the presence of vasomotor symptoms were detected (27). In 2004, after an average follow-up of 6.8 years the WHI-E was also terminated 1 year earlier than planned. Although the increased risk of coronary events seen in the WHI-EP was not detected in the WHI-E, the increased risks for stroke and deep vein thrombosis were also

Table II. Secondary prevention trials on hormone therapy with number of participants ≥ 100 or follow-up ≥ 1 year.

Secondary prevention trials	Population	Treatment	Main outcome	Results
HERS 1998, 2002 (18,25)	n = 2763–2321; mean age: 68; established CHD	4.1 to 6.8 years; CEE 0.625 mg + MPA 2.5 mg	MI or death	No benefit or harm
ERA 2000 (84)	n = 309; mean age: 66; established CHD	3.2 years; CEE 0.625 mg ± MPA 2.5 mg	Angiography: change in coronary lumen diameter	No benefit or harm
PHOREA 2001 (85)	n = 321; mean age: 59; CIMT ≥ 1 mm	11 months; oral estradiol 1 mg ± gestodene 0.025 mg	Ultrasound: change in CIMT	No benefit or harm
PHASE 2002 (86)	n = 255; mean age: 66; established CHD	30.8 months transdermal estradiol 2 mg ± 4 mg cyclic NETA	Unstable angina, proven MI, or cardiac death	No benefit or harm
WAVE 2002 (87)	n = 423; mean age: 65; established CHD	2.8 years; CEE 0.625 mg ± MPA 2.5 mg, and/or vitamin C or E	Angiography: change in coronary lumen diameter	No benefit or harm
ESPRIT 2002 (26)	n = 1017; mean age: 62; previous MI	2 years oral estradiol 2 mg	MI or death	No benefit or harm
WELL-HART 2003 (88)	n = 226; mean age: 64; established CHD	3.3 years oral estradiol 1 mg ± MPA 2.5 mg	Angiography: change in coronary stenosis	No benefit or harm
WHISP 2006 (89)	n = 100; mean age: 69; acute coronary event < 28 days	1 year oral estradiol 1 mg ± NETA 0.5 mg	Death, MI, stroke, CVD admissions	Non-significant reduction in CVD events

CEE = conjugated equine estrogens; CHD = coronary heart disease; CIMT = carotid intima-media thickness; CVD = cardiovascular disease; MI = myocardial infarction; MPA = medroxyprogesterone acetate; NETA = norethindrone acetate; ± with or without; + with.

detected for ET (Table III) (28). Looking at the results according to 10-year age groups, in women aged 50–59 years ET was associated with a 44% non-significantly decreased risk of CHD and no increased risk of stroke (28). This was confirmed by the final adjudicated results from the WHI-E (29) and coronary artery calcification substudy (n = 1064) (30), which showed that there was no increased risk for MI or coronary death associated with ET use in women aged 50–59 years. Moreover, these women also had a 45% lower risk of coronary revascularization and a 42% lower coronary artery calcification score.

The combined results of the WHI-EP and the WHI-E study arms stratified either by age or time since menopause came in 2007 (31). This report shows that in women aged 50–59 years at HT initiation there was a statistically non-significant 37% protective effect of ET against coronary events, whereas the use of CEE and MPA was associated with a non-significant 29% increase in coronary events. Similar non-significant results were also seen for stroke and for women less than 10 years from menopause. Instead, all the CVD risks accumulated in older women (31). Later on, several reports from the WHI have been published. In a recent article the WHI researchers themselves conclude that the risk of CHD tends to be reduced in recently postmenopausal women and the absolute risks of stroke and venous thromboembolism are small (32). However, whether the cardiovascular benefit achieved with HT persists into older ages is not established. Moreover, other factors, such as vasomotor symptoms, proved to have an influence on the WHI results (32). The possible impact of this is reviewed in the following section.

Table III. Hazard ratios (95% CI) for major outcomes in the HERS (18) and WHI-trials (19,28) associated with HT use. Statistically significant results are in italics.

	HERS 1998 (18)	WHI-EP 2002 (19)	WHI-E 2004 (28)
CHD events	1.30 (0.77–2.19)	*1.29 (1.02–1.63)*	0.91 (0.75–1.12)
Stroke	1.23 (0.89–1.70)	*1.41 (1.07–1.85)*	*1.39 (1.10–1.77)*
Pulmonary embolism	2.79 (0.89–8.75)	*2.31 (1.39–3.25)*	1.34 (0.87–2.06)
Deep vein thrombosis	*3.18 (1.43–7.04)*	*2.07 (1.49–2.87)*	*1.47 (1.04–2.08)*
Breast cancer	1.30 (0.77–2.19)	*1.26 (1.00–1.59)*	0.77 (0.59–1.01)
Death	1.08 (0.84–1.38)	0.98 (0.82–1.18)	1.04 (0.88–1.22)
Hip fracture	1.10 (0.49–2.50)	*0.66 (0.45–0.98)*	*0.61 (0.41–0.91)*
Colorectal cancer	0.69 (0.32–1.49)	*0.63 (0.43–0.92)*	1.08 (0.75–1.55)

Commentary on the WHI results and beyond—factors possibly modifying the effect of HT

The results from the RCTs showing cardiovascular harm associated with HT use are in contrast to the findings from experimental data and observational studies. Consequently, the first WHI results led to major changes in clinical practice when millions of women around the world discontinued the use of HT in fear of breast cancer and heart disease (33). Although the WHI was considered the first primary prevention trial, it has received much criticism (34,35). For instance, the mean age of the participants in the EPT arm was 63 years, and hypertension (36%), smoking (10.5%), hypercholesterolemia (13%), and diabetes (4.4%) were common among the study subjects. Thus, the primary prevention nature of the WHI trial may well be disputed (34,36).

The timing hypothesis—effect of age and time since menopause

Already before the publication of the WHI results stratified by age group, a consensus had started to emerge that a woman's age or time since menopause is likely to influence the outcomes of HT (13,37,38).

This was based on the 'timing hypothesis', which suggests that the cardiovascular effects of HT are dependent on the individual's vascular health (13). Hormone therapy, mainly estrogen, has many effects on the cardiovascular system, including effects on lipids, inflammatory and procoagulatory factors, and vasomotion (39). These effects are mediated by estrogen receptors α and β. The loss of these receptors in the arterial wall with progressing atherosclerosis is an important mechanism, which diminishes the atheroprotective effect of HT. Conversely, in women with pre-existing vascular lesions HT initiation causes pro-inflammatory changes and production of matrix metalloproteinases, which lead to plaque instability and subsequent CVD events (40–42). Thus, the effects of HT may be deleterious in diseased blood vessels even though they are beneficial in healthy blood vessels. Therefore, there may be a window (age and time since menopause) for the opportunity to prevent CHD by HT; early initiation of HT may be protective, whereas late initiation may be detrimental (13,42,43). This theory is supported by an abundance of animal data (42). Moreover, in line with the timing hypothesis is the fact that premature menopause before the age of 40 years and bilateral oophorectomy, both causing

hypoestrogenism, are associated with an increased incidence of CVD, which can be reversed with estrogen therapy (44–46).

In the WHI, for women who were 50–59 years of age or less than 10 years postmenopausal when initiating HT, none of the outcomes analysed (coronary events, stroke, total mortality, global index) showed any significant increased risk. Instead, the risks accumulated in women who were between the ages 70 and 79 years, or over 20 years postmenopausal, at the time of HT initiation. Hence, analysing the WHI data with regard to a woman's age or time since menopause yields results similar to the Nurses' Health Study and the HERS—the cardiovascular risks with HT, in accordance with the timing hypothesis, accumulate in older women. Interestingly, these same features, presence of CVD risk factors and advancing age, which at first were regarded by the WHI investigators as having no impact on the risk of CHD associated with HT use (23), had now been proven to be those most importantly modifying the outcomes of HT (31).

Is timing everything? Results from recent studies

The timing hypothesis, however, does not fully explain why HT has also shown protective effects in older women (47–49), and other explanations have been sought. For instance, the length of follow-up has been criticized; in observational studies this has been up to 10–20 years, whereas in RCTs it has been only 5–7 years. Thus, due to shorter follow-up RCTs cannot record clinical events occurring decade(s) later, and CVD may take years to develop. On the other hand, observational studies can be criticized as regards failure to record early clinical events (13,36,50). These potential biases may to some degree affect the results of the different studies.

Indeed, contradicting the impact of age or time since menopause on the outcomes of HT are data from a recent case-control study (cases, $n = 22{,}225$; controls, $n = 144{,}085$) (51). The study reports that the protective effect of HT was more pronounced if the treatment was started at an older age. In women aged 55–64 years the risk of MI was decreased by 33%, and by 50% in the age group 65–74 years. Of note, women aged 65 and older comprised 78% of the population, and only 0.4% had used HT. Moreover, only 2.4% of the participants were current users of HT; in the age groups of 45 to 64 years, where HT use is most common, only 10.3% were current HT users. Thus, the data may not be representative of a general menopausal population, and this may have affected the results.

Another study (52) shows results both opposing and compatible with the timing hypothesis and the WHI. The researchers combined register data on HT use, hospitalizations, and causes of death comprising data on almost 3 million woman-years with 4947 incident MIs (52). Interestingly, in younger women (51–54 years) with current HT use the risk of MI was elevated by 24% as compared with non-users, whereas in older age groups up to 69 years no significant effect of HT was detected. However, in older women (60–69 years) with previous HT use the risk of MI was decreased by up to 26%. This finding of elevated MI risk in young women using HT is in disagreement with the timing hypothesis, but to a degree in line with the WHI results, since the increase in the risk of MI was detected for continuous EPT regimen, whereas no risk increase was associated with the use of ET. With regard to the progestin component the risk was highest for continuous norethisterone acetate (NETA) when compared with cyclic progestins. Of note, use of other continuously used progestins, such as MPA, was not evaluated. Moreover, no data were available as regards smoking, weight, or body fat. These aspects may have resulted in residual confounding and can have affected the results.

The most recent RCT data are from an open-label trial on the effects of estradiol and NETA on CVD (53). These data are particularly interesting because of the use of estradiol, not CEE. In this trial 1006 healthy, recently postmenopausal women aged 45–58 were randomized to receive a cyclic treatment with 1–2 mg/d of estradiol combined with NETA 1 mg/d for 10 days (continuous estradiol 2 mg/d for hysterectomized women), or no treatment. The primary end-point of this trial was a composite outcome combining death or hospitalization due to heart failure or myocardial infarction. Following the publication of the WHI results in 2002 the trial was prematurely terminated after approximately 11 years, and follow-up of the participants continued for a total of 16 years. The results also show an effect of age on the outcomes of HT, which is similar to the WHI results. The use of HT was associated with a 65% decreased risk of the composite outcome in women aged ≤ 50 years, but not in women aged over 50. However, the study was initially designed as an osteoporosis prevention study, and cardiovascular mortality was not a prespecified secondary outcome, and these aspects may have affected the results. This trial is nevertheless the largest RCT on estradiol with a long intervention time and follow-up. These data further confirm the effect of age on the outcomes of HT, also with regard to estradiol use.

Thus, in addition to the timing hypothesis, other features, such as type of HT, or factors possibly yet unidentified, may have an important role as modifiers of the cardiovascular effects of HT. For instance, estrogen receptor polymorphisms have been suggested to make some women genetically more vulnerable to the effects of HT (39). The presence of menopausal hot flushes has also emerged as an independent factor possibly modifying both cardiovascular health and the outcomes of HT (54,55).

Effect of vasomotor symptoms on the cardiovascular outcomes of hormone therapy

A menopausal hot flush is a powerful reaction of the blood vessels originating from the central nervous system (56), and it has been speculated that vasomotor symptoms could also have implications on vascular health (54,57). Hot flushes have also been presented as one additional explanation for the divergent results between observational studies and randomized trials (54,58,59). Indeed, participants in observational studies were younger and, thus, recently postmenopausal or perimenopausal women who had mostly initiated HT to alleviate their vasomotor symptoms. Hot flushes were, in turn, absent or mild in the majority of the WHI participants, who also were on average older than participants e.g. in the Nurses' Health Study.

The timing of hot flushes per se may be of significance, especially if vasomotor symptoms occur much later than at the usual menopausal age of approximately 51 years. In the WHI-OS women with vasomotor symptoms at menopause, but not any more at WHI-OS enrolment, had 17% lower risk of stroke, 11% lower risk of total CVD, and 8% lower risk of mortality of all causes compared with women with no hot flushes (60). Instead, the risks were concentrated in women with vasomotor symptoms beginning as late as at WHI-OS enrolment (mean age of participants 63 years) and not at physiological menopause. The risks for CHD, total CVD, and all-cause mortality were increased by 23% to 32% in these women.

Does the absence or presence of hot flushes at treatment initiation predict the outcomes of HT? There is only one trial so far specifically designed to assess the potential impact of hot flushes on the cardiovascular outcomes of HT. This study showed that in mostly asymptomatic women 6 months of oral ET reduced vascular reactivity up to 13%, whereas transdermal ET improved vascular reactivity by up to 11% (61). In these women oral

ET also led to increases in 24-hour systolic and diastolic blood pressures (up to 3.7 mmHg and 1.8 mmHg, respectively) (62), whereas lipids and other biomarkers for CVD were unaffected by hot flushes (63). Importantly, no unbeneficial effect of HT was seen in flushing women (61–63). These data are in accordance with the hypothesis regarding healthy blood vessels in flushing women that react beneficially to HT, if supplied soon after menopause. In contrast, asymptomatic women (and thus not in need of HT) have less reactive blood vessels in which possible deleterious vascular processes may begin during prolonged HT treatment. These data suggest an effect of hot flushes on the cardiovascular outcomes of HT, but these findings need to be confirmed in larger trials.

Data from cohort studies and randomized studies have also been analysed with regard to hot flushes and HT use. The report combining both the WHI-EP and WHI-E data (31) shows that in women aged 50–59 years, with moderate to severe hot flushes at baseline, HT use did not increase the risk of either CHD, stroke, or total mortality, or cause a rise in the global index of disease. Instead, in flushing women aged 70–79 years, those receiving HT had a five-fold increase in CHD risk compared to those receiving placebo. The risk of stroke was also increased almost fourfold. In a pooled cohort study ($n = 8865$, mean age 53.8 years, mean follow-up 10.3 years) the researchers captured CHD events from registries, whereas HT use and vasomotor symptoms were determined via questionnaires. The results did not quite reach statistical significance, but in women without intense vasomotor symptoms there was a tendency towards increased risk for CHD as compared with women with intense hot flushes (64). Re-analyses of data from older HT trials (65,66) show conflicting results as regards cardiovascular outcomes of HT in older women with vasomotor symptoms. For instance, data from the HERS trial show that hot flushes were associated with a ninefold increased risk for CHD during the first year of HT use (65), whereas in another study women with vasomotor symptoms had 28% lower all-cause mortality independent of HT use (66).

It appears that not only age, but also vasomotor symptoms, are indicative of the cardiovascular effects of HT. Hot flushes occurring at the time of menopause may signal more reactive blood vessels, which may predict a positive impact on the cardiovascular outcomes of HT, whereas hot flushes starting at an older age may be indicative of a vulnerability to the thromboembolic complications of HT.

Future research

Due to the possible cardiovascular harm associated with HT use, treatment is usually stopped if a woman experiences a thromboembolic event, such as stroke or MI. Interestingly, a Danish register-based cohort study (67) showed that discontinuation of overall HT after an MI within 30–90 days after discharge was associated with an almost two-fold increased risk of cardiovascular mortality. The risk was even greater for discontinuation of systemic estrogen treatment. These data warrant further attention since a relevant problem in the clinical setting is how to manage vasomotor symptoms in a woman with established CVD.

According to the timing hypothesis and supporting findings from the RCTs, the effect of HT in diseased blood vessels may be detrimental. However, there may be biological differences between individuals and their sensitivities to estrogen, depending on whether they acquire CVD during HT use or without simultaneous estrogen treatment. For instance, atherosclerosis progression in women using HT has been shown to differ according to the woman's estrogen receptor status (68). Moreover, in postmenopausal women with medically treated CVD risk factors, such as hypertension and hypercholesterolemia, HT use was associated with a maintained endothelium-dependent coronary function, whereas in postmenopausal women without HT it deteriorated during follow-up (69). Data from the HERS trial also show that in older women with established CHD the use of HT in combination with a statin was associated with lower rates of MI and CHD death compared with no statin use concomitant with HT. The early harm associated with HT use was also concentrated in women without statin use (24).

Thus, the current praxis to recommend discontinuation of HT after a CVD event may not be needed for every patient (70,71). The observational nature of the Danish study (67) has its limitations, but if these findings were repeated in a randomized setting, they would give much-needed information on the safety of HT in controlling hot flushes in a woman with established CVD.

For now, it remains unestablished what the cardiovascular effects of HT are with lower oral doses or with transdermal route of delivery, or with different estrogens and progestins (72). A detailed review of the current knowledge of the impact of different routes of administration and different substances is beyond the scope of this paper. Although the results from the WHI possibly irreversibly revoked the use of HT for prevention of CVD, research on the topic is still ongoing (73). Randomized, placebo-controlled trials of the same magnitude as the WHI will probably not be initiated in the future, but smaller randomized trials with indirect outcome measures, such as the Kronos Early Estrogen Prevention Study (KEEPS) (74) and the Early Versus Late Intervention Trial with Estradiol (ELITE) (75), will provide new data regarding the differences between regimens and early or late initiation of HT. Preliminary results from the KEEPS show that 48 months of oral CEE 0.45 mg/d or transdermal estradiol 50 μg/day, both with cyclic micronized progesterone, did not differ from placebo with regard to atherosclerosis progression (76). Results from the ELITE trial are not yet available. It will be interesting to see whether the timing hypothesis will be proven true also in a RCT setting.

Future research will hopefully give more information regarding the effects of different routes of administration and different estrogens and progestins. In addition to transdermal estrogen and micronized progesterone, attention has been directed towards developing a tissue-selective estrogen complex (TSEC), containing both estrogen and a selective estrogen receptor modulator. An ideal TSEC would effectively alleviate hot flushes and prevent bone loss whilst lacking harmful effects on the cardiovascular system as well as breast and endometrial tissues (77). A TSEC containing 0.45 mg CEE and 20 mg bazedoxifene is the first product in clinical development, and phase 3 data have shown efficacy on reducing hot flushes and preventing osteoporosis. This TSEC is currently under registration in the EU (78). Clinical data with long-term safety data with outcomes such as MI or breast cancer will need longer studies with more participants. Nevertheless, since both cardiovascular harm and the risk of breast cancer may be associated with combined HT, a product without progestin may provide an interesting alternative in the future treatment of menopausal women.

As reviewed earlier, menopausal hot flushes may have an impact of cardiovascular health and the outcomes of HT. Vasomotor symptoms may also affect bone mineral density, and all these factors may be interrelated (79). Interestingly, in a recent population-based case-control study increasing intensity of hot flushes was associated with a linearly decreased risk of invasive breast cancer (80). Importantly, since hot flushes show complex physiological effects, they should be included as a confounding factor in all future studies investigating the health of menopausal women.

Conclusion

In healthy, recently postmenopausal women HT use may be associated with benefits in terms of reduced risk of CHD. Possible cardiovascular benefits associated with HT use may be pronounced or even concentrated to women who have vasomotor symptoms, and who, according to current guidelines, are those who may be treated with HT. However, HT should not be used to prevent CHD, but to control hot flushes, and thus asymptomatic women should not receive HT. Moreover, HT should not be prescribed to women with cardiovascular risk factors or women over 10 years from menopause at HT initiation.

It is ultimately up to the woman herself to decide whether she uses HT to control her hot flushes. It seems, however, that in women aged 50–59 years—the most common age group to suffer from hot flushes—HT may give several health benefits and only a modest rise in risks, which may be modified with choice of treatment.

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