Review Article

Menopause and Hormone Therapy: From Vascular Endothelial Function to Cardiovascular Disease

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Cardiovascular diseases (CVD), including coronary artery, cerebrovascular and peripheral vascular disease, are the major causes of morbidity and mortality in both men and women, although female sex has long been considered to be a "protective factor" against CVD. Indeed, the incidence of CVD is low in premenopausal women but increases with age, especially after menopause; women develop CVD about a decade later than men.[1-3] This has been attributed to the cardioprotective effects of endogenous oestrogen, whose levels decline after menopause.

Hormone therapy (HT), i.e. oestrogen only or oestrogen/progestogen treatment, still remains the most important means for treating menopausal symptoms. Until about a decade ago, it was thought that HT could contribute to the prevention of cardiovascular (CV) events in post-menopausal women, as observational studies had shown that women who used HT had a 35-50% lower risk of coronary artery disease (CAD) than nonusers,[4-6] while numerous basic research, animal and human studies had also demonstrated that oestrogen exerts protective effects on the CV system.[7-11] Surprisingly, more recent randomised trials have shown no clinical benefit of HT in primary or secondary CVD prevention,[12-18] thus creating great confusion about the effects of HT on CVD.[19]

Atherosclerosis is the pathology underlying the majority of CV events. Endothelial dysfunction is considered to be the first step in the process of atherosclerosis and can be detected noninvasively, long before structural changes in the vascular wall are evident.[20-22] Endothelial dysfunction has been associated with most established CV risk factors,[20,23-25] while its magnitude has been shown to predict future CV events.[26-28] Menopause has also been associated with endothelial dysfunction, which seems to be reversed by HT mostly in healthy postmenopausal women; however, this beneficial effect has not been demonstrated in older women, women with CVD or multiple CV risk factors.[29, 30]

The present review summarises the current evidence regarding the effects of menopause and HT on vascular endothelial function and CVD in women and presents a unifying point of view regarding the complex effects of HT on the CV system.

Menopause and increased cardiovascular risk

Menopause is the permanent cessation of menses following the loss of ovarian function and is defined retrospectively after 12 months of amenorrhoea. Menopausal transition is the period of time when the endocrinological, biological, and clinical features of the approaching menopause com-

mence.[31] Menopausal transition usually begins approximately 4 years prior to menopause and is characterised by menstrual cycle irregularity caused by increased frequency of anovulatory cycles. Natural menopause occurs at a median age of 51 years, with the average life span of a woman in post-menopausal status extending up to 30-35 years.

Women commonly report a variety of symptoms associated with menopausal transition, including more frequent vasomotor symptoms (hot flushes and night sweats), vaginal symptoms and trouble sleeping.[32] Major hormonal changes that occur in menopause are a decrease in estradiol levels with concomitant increases in follicular stimulating and luteinising hormone levels. Significant increases in triglycerides, total and low-density lipoprotein (LDL) cholesterol occur within 3-5 years of natural menopause, while in ovariectomised women an increase in total cholesterol, triglycerides and lipoprotein a [Lp(a)] occurs within the first 6 weeks after ovariectomy.[33-37] Menopause is associated with an androidal body shape and deposition of abdominal fat, a body "profile" that is associated with an increased risk for CAD in women.[38,39] More women than men develop hypertension at an older age, particularly after menopause.[39]

CVD-related morbidity and mortality are low in women of reproductive age, but increase to a significant level in older women, especially after menopause;[1-3, 40] this increase in CVD risk has been attributed to the loss of oestrogen at menopause. However, it is difficult to distinguish the effect of age from that of menopause on CVD, as age and menopause are strongly related and the increase in CVD risk with menopause may be simply due to ageing. The overall epidemiological evidence on the relationship between menopause, rather than age, and CVD remains controversial.[41] Most epidemiological studies suggest that post-menopausal compared to pre-menopausal women are at higher risk of CVD.[1,41,42] A recent meta-analysis of eighteen observational studies revealed no relationship between natural menopausal transition and CVD occurrence after controlling for study design, age and smoking status. However, a significant modest effect of early age at menopause and a more pronounced effect of bilateral ovariectomy on CVD were reported.[43] Several other studies have suggested that a younger age at menopause may be associated with increased risk of CV mortality.[44-46] Furthermore, the Nurses' Health Study demonstrated that, besides a younger age at natural menopause, bilateral ovariectomy is associated with a higher risk of CVD in women who have never used HT.[47]

Vascular endothelial function: effects of menopause and hormone therapy

Endothelium, the innermost cell layer in the vascular wall, is a very important regulator of vascular homeostasis, maintaining the balance between vasodilation and vasoconstriction, inhibition and stimulation of vascular smooth muscle cell proliferation and migration, thrombogenesis and fibrinolysis.[22,23] Endothelium regulates vascular tone by releasing vasodilators, such as nitric oxide (NO), prostacyclin and bradykinin, and vasoconstrictors, such as endothelin and angiotensin II, in response to physical and chemical stimuli. Endothelium-derived NO is the principal mediator of all vasoprotective effects; apart from being the most potent vasodilator, NO also has anti-inflammatory, antiproliferative, and antithrombotic properties.[20,22,48] Reduced NO bio-availability, due to reduced production and/or increased inactivation of NO by reactive oxygen species, leads to endothelial dysfunction, initiating a series of processes that promote atherosclerosis. Endothelial dysfunction is present in the pre-clinical stages of atherosclerosis and can be detected long before structural changes in vessel wall are evident on angiography or intravascular ultrasound; its assessment could therefore serve as an integrating index of CV risk factor burden.[21]

Endothelial function can be assessed noninvasively using high-resolution ultrasound in the brachial artery to monitor changes in arterial diameter in response to increased blood flow, an important physiological stimulus for endothelial NO production.[24,49,50] This endothelium-dependent, NO-mediated process is known as flow-mediated dilation (FMD).

Endothelial dysfunction, demonstrated as reduced FMD, has been associated with most of the established CV risk factors (dyslipidaemia, hypertension, smoking, diabetes mellitus, family history of premature CAD, elevated plasma homocysteine)[20,23,24] and has been shown to be a reversible process.[21,49] Recently, its prognostic importance has also been reported; FMD has been reported to predict long-term CV events in patients with CV diseases[26,51] and in healthy subjects.[28, 52] However, the relation of endothelial dysfunction with clinical outcome has not been established in large prospective clinical trials and only limited data so far suggest that improvement of impaired FMD with treatment may also lead to an amelioration of CV prognosis.[27]

Natural menopause has been associated with vascular endothelial dysfunction. Several studies have demon-

strated impaired endothelium-dependent vasodilation in healthy post-menopausal women (aged between 53 and 58 years) compared to younger pre-menopausal women (aged 30-35 years).[53-55] FMD of the brachial artery has also been shown to provide additional prognostic information about the CV risk of post-menopausal women.[56] However, since no direct comparison between age-matched post-menopausal and pre-menopausal women has been performed, it is not clear yet whether the observed endothelial dysfunction at menopause is due to the oestrogen loss at menopause or merely ageing. Indeed, age has been identified, along with vessel diameter, as an independent predictor of impaired endothelium-dependent vasodilation in post-menopausal women.[54] In another study, time since menopause has been shown to predict impaired FMD in these women.[57]

A large amount of evidence has recently emerged to strengthen the role of oestrogen loss in the endothelial dysfunction observed at menopause. Acute oestrogen deprivation following ovariectomy is related to endothelial dysfunction,[58,59] which occurs within as little as 1 week after surgery.[60] Even in young women with normal menses, endothelial function assessed using FMD has been found to vary cyclically during the menstrual cycle in relation to endogenous oestrogen levels; low levels are associated with a relative decrease in FMD.[61,62] This observation has attracted much clinical attention, as an increased vulnerability to acute coronary events during and immediately after menses, when the levels of endogenous oestrogen are low, was demonstrated.[63] Finally, endothelial dysfunction has been demonstrated in several groups of young women with low levels of endogenous oestrogen. Young women with premature ovarian failure, who are known to be at increased risk for CVD,[64] present significant vascular endothelial dysfunction compared to age-matched women with normal ovarian function.[65] Other groups of young women with low levels of endogenous oestrogen, such as women with hypothalamic hypogonadism[66] and athletic amenorrhoea,[67] also demonstrate impaired endothelial function. In these studies, endothelial dysfunction was attributed to low oestrogen levels, while androgens did not seem to play an important role.[67]

The effect of HT on peripheral vascular endothelial function, assessed by FMD, in post-menopausal women has been extensively studied (Tables 1 and 2). Most of these studies have shown a beneficial effect of HT that seems to be preserved with various formulations (per os or transdermal, oestrogen alone or combined therapy) or dosages, both in healthy post-menopausal women[68-78] and women with few CV risk factors (Table 1).[53,79-81] Young women with premature ovarian failure have also been shown to benefit; HT for 6 months completely reversed significant endothelial dysfunction in this group of women.[65] However, there have been some studies that showed no or partial improvement of endothelial dysfunction with HT administration in several groups of women (Table 2), including some healthy post-menopausal women.[54,82] Oestrogen use in women with diabetes mellitus has been shown to be less effective in ameliorating endothelial function[30] and arterial stiffness indices.[83] Furthermore, elderly women with many CV risk factors, with or without established CVD,[29,84] have been reported to be non-responsive to HT. Time since menopause has recently been demonstrated as a predictor of FMD improvement with HT; the improvement in endothelial function following oestrogen administration was greater in women within 5 years from menopause compared to those with more than 5 years in menopause.[57] It has to be noted that, apart from endothelial function, which is the focus of the current review, arterial stiffness has also been studied in relation to menopause and HT. Increased arterial stiffness has been demonstrated in post-menopausal women,[85] while the effect of HT on arterial stiffness does not appear to be very clear, with various studies reporting conflicting results.[83,86-88]

The differences in the effect of HT on endothelial function in different groups of women presented above are also reflected in the divergent results of clinical studies and have thus led to interesting discussions about the underlying potential pathophysiological mechanisms involved in the effects of HT. Several recent reports indicate that the effects of HT on vascular pathophysiology are very complex; the effects of oestrogen on the evolution of the atherosclerotic process appear to depend largely on the state of vascular pathology.[89-91] Oestrogen appears to have beneficial effects in vessels with no atherosclerotic or early atherosclerotic lesions and harmful effects in vessels with advanced atherosclerotic lesions (Table 3).

In animal studies, oestrogen administration has been shown to decrease the incidence of newly formed lesions and the size of new plaques in vessels that are healthy or have early atherosclerotic lesions.[92-94] Oestrogen decreases LDL accumulation[10] and oxidation,[95,96] and the formation of foam cells[97] and fatty streaks[98] in the vascular wall, leading to reduced progression of atherosclerosis. Oestrogen also down-regulates the expression of various proinflammatory molecules,[99-102] thus attenuating monocyte adhesion/migration[103] and vascular smooth muscle cell activation/mi-

Table 1. Studies of hormone therapy (HT) and peripheral vascular endothelial function (flow-mediated dilation) in post-menopausal women (PMW) that showed beneficial effects.

Population	N	Age (years)	Formulation	Effect
Studies in healthy PMW showing mostly a beneficial effect				
Healthy PMW[68]	13	55 (44-69)	placebo vs. per os estradiol	(+)
Healthy PMW[69]	95	57-58	HT users (oestrogen alone or oestrogen + progesterone) vs. non users	(+)
Healthy PMW[70]	28	57 ± 7	CEE vs. vitamin E vs. combined therapy	(+) for all
Healthy PMW[71]	27	55 ± 1	placebo vs. per os estradiol vs. TTS estradiol	per os (+) TTS (-)
Healthy PMW[72]	20	55 ± 8	CEE+MPA vs. CEE+MP	(+) for both
Healthy PMW[73]	14	53 (45-65)	per os oestrogen vs.	(+)
	31		per os oestrogen + MPA	(-)
Healthy PMW[74]	70	59 ± 4	placebo vs. CEE + MPA	(+)
Healthy PMW[75]	61	55	placebo vs. per os estradiol + NETA	(+)
Healthy early PMW[76]	51	54 (47-57)	no HT vs. standard dose CEE + MPA vs. low dose CEE + MPA	(+) for both
Healthy PMW[77]	45	54 ± 6	no HT vs. standard dose CEE vs. low dose CEE	(+) for both
Healthy PMW[78]	60	56 ± 6	no HT vs. TTS estradiol + MPA	(+)
Studies in PMW with cardiovascular risk factors showing a beneficial effect				
PMW with mild hypercholesterolaemia[79]	17	60 (48-75)	placebo vs. TTS estradiol vs. TTS estradiol + vaginal MP	(+) for both
PMW with few risk factors[53]	18	56 (41-73)	oestrogen+MPA or oestrogen alone	(+)
PMW with >1 risk factors for CVD[80]	20	64 ± 6	per os estradiol vs. per os estradiol valerate + cyproterone	(+) for both
PMW with mild hypercholesterolaemia[81]	24	53	TTS estradiol vs. per os CEE	(+) for both
PMW with few risk factors[57]	134	62 ± 6	sublingual estradiol and per os estradiol	(+) for both

CEE – conjugated equine oestrogen; CVD – cardiovascular disease; MP – micronised progesterone; MPA – medroxyprogesterone acetate; NETA – norethisterone acetate; TTS – transdermal.
(+) marks beneficial effect for the active treatment(s) and (-) neutral effect

Table 2. Studies of hormone therapy (HT) and peripheral vascular endothelial function (flow-mediated dilation) in post-menopausal women (PMW) that showed neutral effects.

Population	N	Age (years)	Formulation	Effect
Healthy PMW[54]	100	53 ± 3	no HT vs. per os estradiol + NETA	(-)
Healthy PMW[82]	59	60	placebo vs. per os estradiol + NETA	(-)
Elderly PMW	1636	>65	291 HT users (76% unopposed oestrogen) vs. 1345 non users	(-)
Subgroup with no CVD or risk factors[29]	32			(+)
PMW with type 2 diabetes mellitus[30]	20	59 ± 7	placebo vs. CEE 0.625 mg	(-)
PMW healthy or with known CVD[84]				
≥60 years old	81	69 ± 3	TTS estradiol vs. TTS estradiol + NETA vs. TTS placebo	(-)
<60 years old	19	55 ± 3		(+) for TTS estradiol

Abbreviations and notes as in Table 1.

Table 3. Effects of oestrogen therapy depending on vascular wall pathology.

Beneficial effects in healthy vessels (more probable in peri-menopausal & early menopausal women)	Harmful effects in vessels with established atherosclerosis (more probable in late menopausal women)
favourable changes in lipoproteins[109]	↓ expression of oestrogen receptors[127, 128] (↓ actions of oestrogen)
↑ fibrinolytic / ↓ thrombotic activity[110-112]	↓ oestrogen receptor-mediated actions of oestrogen secondary to endothelial inflammation[129, 130]
↑ nitric oxide bio-availability[104-106] (improvement in endothelial function)	↑ production of matrix metalloproteinases[125] (plaque destabilisation)
↓ endothelial inflammation[99-102]	
↓ monocyte migration/adhesion[103]	With oral treatment only
↓ vascular smooth muscle cell proliferation/migration[104]	↑ production of C-reactive protein[118-122]
↓ low density lipoprotein accumulation in vessel wall[10]	↑ small dense low density lipoprotein particles[117] (more atherogenic)
↓ oxidative modulation of low density lipoproteins[95, 96]	
↓ foam cell/fatty streak formation[97, 98]	
↑ production of matrix metalloproteinases[126, 166] (positive remodelling of the vessel)	

gration.[104] Increased NO bioavailability[105,106] and preservation of the integrity of endothelial cells[107,108] lead to improvement of endothelial function. Besides the direct vascular effects, 30% of the anti-atherogenic action of oestrogen reflects its beneficial influence on lipids[109] and other known CV risk factors.[110-112]

On the other hand, there is evidence to suggest that oestrogen exerts proinflammatory and pro-atherogenic effects in vessels with established atherosclerosis, possibly leading to plaque destabilisation and acute CV events.[90,113] Animal and human studies show that oestrogen does not inhibit the progression of atherosclerosis in the presence of advanced atherosclerotic lesions.[114-116] Oral oestrogen administration increases triglycerides and small dense LDL particles, which are known to be more atherogenic,[117] and is associated with increased expression of C-reactive protein,[118-122] a well established marker of inflammation and a molecule with several possible proinflammatory and pro-atherogenic actions.[123,124] Another potential harmful effect of oestrogen is the induction of matrix metalloproteinases,[125] enzymes that may weaken fibrous cap and lead to plaque destabilisation and rupture.[126] Besides, advanced atherosclerosis and vascular inflammation lead to diminished expression[127,128] and function of oestrogen receptors[129,130] that mediate most of the beneficial vascular effects of estrogen.[91]

Hormone therapy and cardiovascular disease

Several prospective cohort studies have suggested that HT results in an approximately 30-50% decrease in the risk of CAD in relatively young and healthy post-menopausal women.[4-6] The Nurses' Health Study, the largest and most important prospective observational study, which included over 70,000 women aged 30-55 years, showed that post-menopausal women who used HT had a 40% risk reduction in major coronary events after 20 years of follow up, and a 35% increase in the risk for stroke;[5,131] increased incidence of stroke was mainly observed in women who used higher doses and combined HT. A meta-analysis that included observational studies conducted until 2000 has also shown a benefit of current HT use in terms of CVD mortality (relative risk, RR=0.75) and CAD incidence (RR=0.74); however, this benefit was not so clear after adjustment for socio-economic and major CAD risk factors (RR=1.07).[132]

Surprisingly, more recent randomised controlled trials investigating the effects of HT in primary and secondary CV prevention have shown results different to those of observational studies (Table 4). The Women's Health Initiative (WHI) study was designed to assess the impact of HT in apparently healthy post-menopausal women (mean age 63 years) on primary CVD

Table 4. Randomised controlled trials of hormone therapy for prevention of cardiovascular disease in post-menopausal women (PMW).

Trial	Population of PMW	Mean age (years)	Medications tested	Results
		Primary CVD prevention		
Women's Health Initiative (WHI) trial[133]	10739 OVX women	64	Oral CEE	no benefit for CAD trend of ↓ risk by year since randomisation ↑ risk for stroke
Women's Health Initiative (WHI) trial[18]	16608 non OVX women	67	Oral CEE + MPA	no benefit for CAD overall ↑ risk in 1st year trend of ↓ risk by year since randomisation ↑ risk for stroke
Women's Health Initiative (WHI-CACS)[134]	1064 OVX women	55	Oral CEE	↓ of coronary artery calcification
Estrogen in the Prevention of Atherosclerosis (EPAT) trial[116]	222	61	Oral 17β estradiol	↓ of subclinical carotid atherosclerosis
Postmenopausal Hormone Replacement against Atherosclerosis (PHOREA) trial144	321	60	Oral 17β estradiol	no effect on subclinical atherosclerosis
		Secondary CVD prevention		
Heart and Estrogen/progestin Replacement Study (HERS)[12]	2763	68	Oral CEE + MPA	no benefit for CAD overall ↑ risk in first year trend of ↓ risk by year since randomisation
Estrogen for the Prevention of Reinfarction (ESPRIT) trial[16]	1017	63	Oral estradiol	no benefit for CAD
Hormone therapy in postmenopausal women with CAD[148]	226	64	Oral 17β estradiol or oral 17β estradiol + MPA	no effect on angiographic progression of coronary atherosclerosis
Estrogen Replacement and Atherosclerosis (ERA) trial[13]	309	66	Oral CEE or Oral CEE + MPA	no effect on angiographic progression of coronary atherosclerosis
Women's Angiographic Vitamins and Estrogen (WAVE) trial[147]	423	65	Oral CEE + MPA	no cardiovascular benefit

CAD – coronary artery disease; CEE – conjugated equine oestrogen; CVD – cardiovascular disease; MPA – medroxyprogesterone acetate; OVX – ovariectomised.

prevention. Combined HT was associated with an increased risk of CAD (hazard ratio, HR=1.24, 95% confidence interval, CI 1.00-1.54) after 5.2 years' follow up, with the elevated risk being most apparent in the first year (HR=1.81, 95% CI 1.09-3.01), despite the favourable effects of HT on most metabolic factors (decrease in total and LDL cholesterol, glucose and insulin, increase in high density lipoprotein [HDL] cholesterol but also in triglycerides).[18] The oestrogen-only arm of WHI showed no significant effect of HT on CAD risk,[133] while both HT regimens had significant unfavourable effects on the rates of stroke and deep vein thrombosis.[18,133] However, a subgroup of women in WHI, who were younger (aged 50-59 years) or within only 10 years of menopause and who received oestrogen only, did not appear to be at increased CV risk[18] and were also shown to have a lower burden of coronary artery calcification compared to women taking placebo.[134] In addition, a recent WHI analysis[135,136] showed a significant CV benefit in this group of young menopausal women who initiated HT closer to menopause; a greater reduction in CAD-related events and deaths from all causes was observed in these women compared to women in whom HT was initiated late in menopause (>10 years since menopause). Nevertheless, it has been recently suggested that the true CV benefit, even in this specific population, is small; it was calculated that 1000 women would need to be treated to prevent one CVD event.[41]

Another recent study showed that post-menopausal women who received HT early after menopause (mean age 52 years) for a short time (2-3 years) presented with lower rates of overall and CV mortality (mean follow up 9.8 years), as well as decreased severity of aortic atherosclerosis, compared to women who either never used HT or used it at an older age (mean age 61 years).[137] Finally, a recent meta-analysis of 22 small randomised trials of HT and WHI revealed a 30-40% decrease in CV risk in young post-menopausal women.[138]

Two large cohorts revealed a low incidence of CV events within the first year of HT use in healthy young post-menopausal women with menopausal complaints.[139] Vasomotor menopausal complaints have been suggested as a marker of susceptibility to beneficial CV effects of HT in post-menopausal women.[140] Hot flushes in post-menopausal women have been associated with increased oxidative stress, which was improved with HT.[141] More recently, vasomotor complaints have been related to a less favourable CV risk profile; women with flushes and night sweats had higher cholesterol levels, body mass index, systolic and diastolic blood pressure.[142]

Randomised studies of surrogate markers of atherosclerosis have also shown a beneficial effect of HT in primary prevention. The progression of sub-clinical carotid atherosclerosis was attenuated in healthy post-menopausal women (mean age 61 years) receiving 17β-estradiol for 2 years in the EPAT trial.[116] This was confirmed in an observational study that associated HT use in post-menopausal women (mean age 64 years) with lower carotid intima-media thickness and a lower prevalence of carotid atherosclerosis compared to non-users.[143] In contrast, the Post-menopausal Hormone Replacement against Atherosclerosis (PHOREA) trial in post-menopausal women at increased risk for atherosclerosis showed that 17β-estradiol was not effective in slowing the progression of subclinical atherosclerosis.[144]

Randomised controlled trials investigating HT use in post-menopausal women with a history of CVD demonstrated neutral effects on secondary CVD prevention. The Heart and Estrogen/progestin Replacement Study (HERS) found no effect of continuous-combined HT in post-menopausal women (mean age 67 years), despite an 11% decrease in LDL and a 10% increase in HDL cholesterol.[12] Again, there was a trend for more CAD events during the first year and a significant 2-3 fold increase in thromboembolic events throughout the study.[145] Further analysis of 86 subgroups of the HERS study revealed Lp(a) as a possible modifier of the HT effect on CAD events during 5 years of follow up.[146] In the ESPRIT Trial, estradiol treatment in post-menopausal women (mean age 63 years) with a history of prior myocardial infarction did not reduce the incidence of re-infarction or cardiac death.[16] More recent trials demonstrated that the progression of angiographically verified CAD was not affected by HT use.[13,147,148]

Based on all these trials, the most recent guidelines recommend HT administration for the relief of menopausal symptoms and the prevention of osteoporosis,[149-151] while HT is clearly not recommended for the prevention (primary or secondary) of CVD.[3, 151]

However, the conflicting results between observational studies and randomised clinical trials with HT may be explained: 1) most observational and prospective cohort studies with HT showing a beneficial effect on CVD involved relatively young post-menopausal women (aged ~30-55 years), whereas most randomised studies indicating that HT has a neutral or even harmful effect on CV events involved mainly women well over 50 years of age (mean age 65 years), the majority of whom were 10 years or more beyond

menopause; 2) The effects of oestrogen on the evolution of the atherosclerotic process appear to depend largely on the state of vascular wall pathology as described in Table 3. In relatively healthy vessels (i.e. with no or early signs of atherosclerosis), oestrogen appears to prevent the development and progression of atherosclerotic lesions.[89,90,116] In contrast, in the presence of established atherosclerotic lesions, oestrogen fails to inhibit the progression of atherosclerosis or may even trigger CV events.[152, 153] Furthermore, the direct anti-atherogenic effect of oestrogen has been shown to vary depending on the state of the arterial endothelium; the vascular benefits of menopausal HT are less apparent in conditions of endothelial dysfunction.[154] Indeed, at the average age of menopause (~51 years), about 50% of women have asymptomatic atherosclerotic vascular lesions, predominantly at an early phase of the atherosclerotic process. In contrast to the relative healthy profile of women entering menopause (i.e. aged <50 years), women around the age of 65 years, even without overt CVD, present with a greater prevalence of CV risk factors and complicated atherosclerotic lesions.[153] For example, the population studied in the WHI trial, even though it was a primary prevention study, showed a high prevalence of CV risk factors such as hypertension, smoking and obesity.[18]

Given the above, the conclusions drawn from randomised clinical trials with HT should perhaps not be generalised to younger, early post-menopausal women (including peri-menopausal women). As explained previously, increasing evidence from clinical studies suggests that this group of women may have a CV benefit from HT administration.[18,134,137] Experimental studies in primates support this hypothesis: the beneficial anti-atherogenic action of oestrogen is lost when HT is administered many years after the menopausal transition.[11] Furthermore, these results should not be extended to women who suffer from premature ovarian failure, since these women are at a greater risk of CVD and therefore may have great need of early initiation and longer use of HT.

The divergence in results of HT clinical studies may also be attributed to the combination with progestogens, as well as the complexity of the effects of HT on the coagulation system and insulin resistance. Indeed, some of the beneficial CV effects of oestrogen may be counteracted by the addition of progestogens, which have been shown to attenuate oestrogen's effects on lipid profile, Lp(a), fibrinogen, plasminogen activator inhibitor-1 (PAI-1) and endothelial function.[110,118,155,156] Medroxy-progesterone acetate, the progestogen used in most large randomised clinical studies of HT, has been shown to antagonise the inhibitory effects of oestrogen on atherosclerosis in monkey models.[92] On the other hand, micronised progesterone added to oestrogen does not appear to have such harmful effects; it does not attenuate the favourable effect of oestrogen on endothelial function,[79] cellular adhesion molecules and LDL accumulation in the arterial wall.[10,157] Oestrogen administration has been shown to reduce homocysteine,[111] Lp(a)[110] and other prothrombotic factors such as PAI-1,[112] thus contributing to increased fibrinolytic activity, while oral oestrogen increases prothrombotic factors[158] and decreases antithrombin levels,[159] thus promoting thrombogenesis. Finally, the effect of oestrogen on insulin resistance does not appear to be very clear, with studies reporting contradictory results.[160-163]

Further research is required to assess the long-term effects of HT on cardiovascular prognosis when used early in menopause in relatively young women (~50-55 years of age) without evidence of atherosclerosis, as well as in women who become menopausal at a young age. Two ongoing clinical studies (KEEPS, Kronos Early Estrogen Prevention Study and ELITE, Early versus Late Intervention Trial with Estradiol) that aim to examine the effects of HT on the progression of subclinical atherosclerosis in early post-menopausal women will help in clinical decision making.[164,165]

It has to be emphasised that the current review focuses on HT, i.e. oestrogen only or oestrogen/progestogen administration, on vascular endothelial function and CVD. Other treatments used in post-menopausal women, such as selective oestrogen receptor modulators (e.g. raloxifene for osteoporosis and tamoxifene for breast cancer treatment), or tibolone and phytoestrogens used for relief of menopausal symptoms, which have various important effects on the CV system, different to those of HT, are not within the scope of the current review.

Conclusions

Menopause is associated with several important hormonal, metabolic and vascular changes that appear to increase the risk for CVD in women. Loss of endogenous oestrogen results in overt endothelial dysfunction, which is an independent predictor for future CV events. HT is an effective means to decrease the severity and frequency of menopausal symptoms and improve women's quality of life. Despite the disappointing results of randomised clinical trials with HT use

for CV prevention, clinicians should not consider HT as harmful and left aside. However, it remains unclear which women can safely receive HT and which are at increased risk from HT. It is likely that the timing of HT administration as well as the status of vascular health may determine the effects of oestrogen on the CV system. The initiation of HT in young healthy women with vasomotor complaints, close to menopausal transition, reverses endothelial dysfunction and probably decelerates the progression of atherosclerosis in its early stages. Further research is needed to assess whether an initial evaluation of CV risk factors and clinical atherosclerosis with non-invasive tests (such as increased carotid intima-media thickness or coronary artery calcification with computed tomography) could reveal a subgroup of women at high risk for CV complications with HT.

HT should probably not be considered harmful if it is to be used in post-menopausal women aged 50-59 years, early after menopause for the relief of symptoms, and may potentially even reduce the risk of CAD in those women. The CV benefit/risk ratio in recently menopausal women needs to be evaluated in further studies. However, it should be stressed that HT should not be used for CVD prevention; there are many preventive strategies that remain underused in women, such as healthy diet, regular physical exercise, smoking cessation, medications to treat hypertension, dyslipidaemia or diabetes.

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