

REVIEW

The Impact of Hormone Replacement Therapy on the Pathophysiology of Peripheral Arterial Disease

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Background. Hormone replacement therapy (HRT) is recommended to post-menopausal women to control menopausal symptoms and prevent osteoporosis. The management of women with peripheral arterial disease (PAD) and who are taking HRT is controversial.

Aim. To summarise what is known about HRT and its effect on the natural progression of PAD and its subsequent treatment.

Methods. A MEDLINE (1966–2004) and Cochrane library search for articles relating to HRT and PAD was undertaken. **Results.** The potential benefits of unopposed estrogen therapy on atherosclerotic progression and limb microcirculation are outweighed by the increased risk of endometrial dysplasia and thrombotic complications. Only one major study (Rotterdam) specifically assessed the impact of HRT on the clinical course of PAD. The findings suggested a decreased risk of PAD among healthy post-menopausal women taking HRT which contrasts with the sub-group analyses of other major studies (HERS/HERS II). HRT appears to reduce the primary success rates of both endovascular and open surgical revascularisation in patients with PAD.

Conclusions. Further studies are required to investigate the effects of HRT on the progression of PAD and its management.

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Introduction

The effect of hormone replacement therapy (HRT) on the prevention and outcome of cardiovascular disease has been the subject of a number of clinical trials. Very few studies, however, have directly addressed the effect of HRT on peripheral arterial disease (PAD).¹ Three important clinical dilemmas exist when managing PAD in postmenopausal women:

1. Should patients with PAD be advised to start, continue or discontinue taking HRT and how does this advice impact upon disease progression?
2. Does HRT impact on the benefits of best medical therapy (BMT) in patients with PAD?

3. Does HRT influence the short and long-term outcomes of vascular and endovascular intervention for the treatment of PAD?

Methods

We performed a MEDLINE (1966–2004) and Cochrane library search looking for articles relating to HRT, its effect on arterial physiology and the influence this has on the management of PAD. The terms hormone therapy, HRT, menopause, estrogens and progestogens were included amongst others. These were linked with terms such as cardiovascular disease, peripheral vascular disease and peripheral arterial disease. Further articles were identified by following MEDLINE links, by cross-referencing from the reference lists of major articles and by following citations for these studies. The studies were then graded and prioritised according to the level of the evidence presented.

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Results

Studies examining the effect of HRT on cardiovascular disease progression and outcomes are summarised in Table 1.

The effect of HRT on the arterial wall and atherosclerosis

Several studies^{2–5} have examined the effects of HRT in relation to coronary events, but few have examined its impact on the progression of atherosclerosis in the peripheral arterial system. Change in carotid intima-media thickness correlates well with the sub-clinical progression of generalized atherosclerosis.⁶ Various studies, including one large randomised, double-blind, placebo-controlled trial (the Estrogen in the Prevention of Atherosclerosis (EPAT) study)⁷ measured carotid intima-media thickness and demonstrated that unopposed estrogen therapy slows or halts the progression of atherosclerosis.⁸ By contrast, other studies such as the Atherosclerosis Risk in Communities (ARIC) study,⁹ and the more recent Healthy Women's Study¹⁰ reported no beneficial effect of HRT on carotid intimal thickening. The different findings of these studies may be due to the different types of estrogen used (17beta-estradiol *vs* conjugated equine estrogen) and the fact that by studying different age groups, different stages of disease were targeted. This is particularly relevant since patients seen by vascular specialists are more likely to be older with more advanced atherosclerosis and may not enjoy the full benefits seen in healthy postmenopausal women without pre-existing cardiovascular disease.⁷ The differences in the effect that estrogen has on different stages of atherosclerosis may be secondary to its effects on the endothelium which becomes dysfunctional early in the development of atherosclerosis;¹¹ this said there is evidence that estrogen promotes endothelial function and augments endothelium-dependent vasodilatation at the micro- and macrovascular levels. Conjugated equine estrogen has been shown to reduce the accumulation of collagen and attenuate the fall of elastin content in monkey aortas.¹² In this way, HRT may also have a beneficial effect on arterial wall stiffness.

HRT and the coagulation cascade

Clinical trials² and experimental evidence indicates that the overall effect of HRT is to stimulate coagulation, inhibit anticoagulation and stimulate fibrinolysis.^{13–15} This effect is by no means certain, however,

as both the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial¹⁵ and other experimental studies have demonstrated a reduction in plasma fibrinogen levels in those on combined HRT (cHRT). It is, as yet, unclear to what extent the addition of progesterone attenuates the oestrogenic prothrombotic tendency.¹⁶ Subgroup analysis of data from the Heart and Estrogen/Progestin Replacement (HERS) study² demonstrated that estrogen increases the risk of early acute cardiovascular events in those women genetically predisposed to arterial thrombosis.^{17,18} In this study, an early increased risk of venous thromboembolism (VTE) was also identified and this has been reinforced by findings in other prospective and case-control studies.¹⁴ HRT is now contraindicated in patients with a history of myocardial infarction or VTE.¹⁹ The prothrombotic properties of HRT may account for the increased risk of thrombotic cardiovascular events in the first year after starting cHRT, as demonstrated in the HERS and Rotterdam studies, and this risk may be attenuated beyond the first year by the beneficial effect on lipid profile. Patients with PAD starting HRT may be at increased immediate risk of thromboembolic events that extends for weeks following cessation of drug administration. While oral HRT at least doubles the risk of VTE,^{2,20} the Estrogen and Thromboembolism Risk Study Group (ESTHER)²¹ found transdermal HRT does not appear to have the same effect. It would not be unreasonable to stop oral HRT 4–6 weeks prior to endovascular or surgical revascularisation particularly in those patients with PAD who have additional risk factors for VTE.

The impact of different types of HRT on arterial structure and physiology

The dose and types of estrogen and progesterone used in major studies of post-menopausal HRT are shown in Table 2. In the UK, there are a range of combined treatments available but the most widely used contain 1–2 mg of estradiol (*Climesse*®, *Climagest*®, *Elleste-Duet*®, *Femoston*®, *Nouvelle*® etc.) or 0.625 mg conjugated equine estrogen (*Prempak C*®). The type and dose of progestin is more variable but most treatments in common use include a dose of 1 mg norethisterone acetate for 10–14 days (*Climesse*®, *Climagest*®, *Elleste-Duet*®, *Evorell*®) or 75 mg of levonorgestrel (*Prempak C*®, *Nouvelle*®).¹⁴ The significance, if any, of these variations is unclear. Acute administration of oestrogen is known to improve endothelium-dependent flow in the microcirculation in healthy postmenopausal women,²² and many studies in both animals and human subjects have suggested a

Table 1. Studies examining the effect of HRT on cardiovascular disease progression and outcome

Trial	Author	Type	Patient no.	Mean follow-up	HRT		Summary	RR (95%CI)
					Type	Route		
HERS	Hulley <i>et al.</i> ²	RCT	2763	4.1 years	(conjugated equine) Oestrogen + Progestin	oral	no overall reduction in CHD events in women with established coronary disease. Higher risk of CHD in first year	0.99 (0.8–1.22)
HERS II	Grady <i>et al.</i> ³	RCT	2763	6.8 years	(conjugated equine) Oestrogen + Progestin	oral	Hormone therapy did not reduce risk of cardiovascular events in women with CHD	1.0 (0.77–1.29)
WHI	Writing group ⁵	RCT	16608	5.2 years	Oestrogen + Progestin	oral	no benefit for primary CHD prevention	1.29 (1.02–1.63)
ERA	Herrington <i>et al.</i> ⁴	RCT	309	3.2 years	(conjugated equine) Oestrogen	oral	No alteration in progression of coronary atherosclerosis in women with established disease	N/A
WEST	Viscoli <i>et al.</i> ⁵⁷	RCT	664	2.8 years	(conjugated equine) Oestrogen + Progestin Oestrogen	oral	In PNP women with recent CVA HRT did not reduce risk of any cardiac event	N/A
EPAT	Hodis <i>et al.</i> ⁷	RCT	222	2 years	Oestradiol	oral	Average rate of progression of subclinical atherosclerosis was slower in healthy PMP women taking Oestradiol	N/A
PEPI	Writing group ¹⁵	RCT	875	3 years	conjugated equine oestrogen	oral	estrogen alone or in combination with	N/A
					conjugated equine oestrogen + Progesterone	oral	progesterone improves lipoproteins and lowers fibrinogen levels in PMP women	N/A
	Schulman <i>et al.</i> ⁵⁸	RCT	293	6 months	iv oestrogen → oral oestrogen	iv/oral	acute hormone therapy did not reduce ischaemia in PMP women with unstable angina	N/A
					iv oestrogen → oral oestrogen + progestin	iv/oral	May not be CVS beneficial in PMP women	N/A
	Teede <i>et al.</i> ²⁷	RCT	59	2 years	Oestradiol + Norethisterone	oral	Cardiovascular protective	0.69 (0.54–0.86)
Falkeborn <i>et al.</i> ⁵⁹	Prospective cohort study	23174	5.8 years	Conjugated Oestrogen/ oestradiol	oral	No Cardiovascular protection	0.9 (0.74–1.08)	
				Other oestrogen Oestradiol + Lenonogesterola	oral	Cardiovascular protective	0.53 (0.3–0.87)	

Table 2. The dose and types of oestrogen and progesterone used in major studies of post-menopausal HRT

Trial	Route	Oestrogen		Progesterone	
		Type	Dose	Type	Dose
HERS ²	oral	conjugate equine	0.625 mg	medroxyprogesterone acetate	2.5 mg
HERS II ³	oral	conjugate equine	0.625 mg	medroxyprogesterone acetate	2.5 mg
WHI ⁵	oral	conjugate equine	0.625 mg	medroxyprogesterone acetate	2.5 mg
ERA ⁴	oral	conjugate equine	0.625 mg	medroxyprogesterone acetate	2.5 mg
WEST ⁵⁷	oral	17 β -estradiol	1 mg	NA	NA
EPAT ⁷	oral	miconized 17 β -estradiol	1 mg	NA	NA
PEPI ¹⁵	oral	conjugate equine	0.625 mg	cyclical medroxyprogesterone acetate cyclic micronized progesterone	10 mg/2.5 mg 200 mg

relationship between estrogen and increased production of nitric oxide (NO), a potent vasodilator. One study showed that administration of estrogen increased levels of cGMP and presumably therefore NO in postmenopausal women.²³ This effect did not occur when progesterone was also administered and interestingly the effect was only seen in smokers. Indeed, when vascular bed reactivity and the levels of NO in the circulation were examined in patients on oestrogen therapy compared with subjects on cHRT, the beneficial effects of long-term estrogen therapy appeared to be abolished by the addition of a Progestin.^{24,25} One study demonstrated improved skin vasodilatation in response to vasodilators in postmenopausal women taking estrogen replacement therapy.¹¹ Progestins, possibly by increasing plasma renin activity, have a potential pressor effect which may antagonise the effect of estrogen on vascular tone.²⁶ Animal studies have also shown that medroxyprogesterone acetate may inhibit the beneficial effect estrogen has on connective tissue metabolism.¹² These findings may explain why continuous cHRT has been shown to have no effect on systemic arterial compliance, pulse wave velocity and endothelial function in healthy postmenopausal women.²⁷

The impact of HRT on the clinical course of PAD

The Rotterdam study,¹ a population-based prospective, longitudinal, observational study of 2196 women aged 55 to 80 years, suggested that HRT given for a year or more was associated with a decreased risk of PAD among postmenopausal women. However an important study limitation was the fact that 91% of the participants were taking unopposed estrogen. The findings of this study, however, appear to contradict several controlled trials²⁻⁵ examining the effects of HRT on the coronary and cerebral vasculature. Analysis of data from a group of patients with known coronary heart disease (CHD) in the HERS study^{2,3,28} showed that HRT did not significantly lower the number of peripheral arterial events in this group of patients.

HRT and cardiovascular risk factor management

The recent Womens Health Initiative (WHI)⁵ and the HERS II trials³ have shown no cardioprotective properties associated with HRT in postmenopausal women and this has also been demonstrated in a meta-analysis.^{29,30} Women with pre-existing cardiovascular disease were found to be at increased risk of cardiovascular events in the first year after commencing HRT² while longer term use may actually protect against development of PAD.¹

The HERS and HERS II trials did not demonstrate any significant difference in coronary events between women taking HRT and aspirin, and women taking HRT without aspirin (RR: 0.96(95%CI, 0.7–1.31) HRT + Aspirin vs. 1.01(95%CI, 0.83–1.22) HRT alone).^{2,3}

Estrogen therapy has consistently been shown to reduce levels of circulating low density lipoproteins (LDL) and increase levels of high density lipoproteins (HDL),^{2,15,31,32} and this may prevent progression of atherosclerosis.³³⁻³⁵ This does not, however, mean that the routine use of cHRT results in direct clinical benefit via this mechanism. Indeed, one of the most important randomised controlled trials (HERS) failed to show an overall cardiovascular benefit despite significant changes in lipid profiles.⁴ During the HERS trial, a 14% decrease in LDL cholesterol occurred by the end of the first year of treatment compared with 3% in the placebo group. Despite this there appeared to be an increase in primary CHD events during this year (but a decrease in subsequent years). This may be related to the use of progesterone. It was shown in the PEPI trial that progesterone lessens the effect of estrogen on HDL cholesterol, and it is thought that progesterone attenuates the beneficial effect of oestrogen.^{15,36,37} However, two other trials using combined hormones have shown conflicting results.^{20,38,39}

Statins (HMG-CoA reductase inhibitors) have been shown to reduce mortality in patients with coronary artery disease and elevated low-density lipoprotein (LDL) levels.^{40,41} However, the absence of reductions in mortality by any other lipid lowering

pharmacotherapy, despite significant LDL lowering, suggests that non-lipid effects may be important in mediating these benefits.⁴² Statins inhibit GTPase activation and preserve vascular function independently of their lipid lowering properties. Specifically, statins increase the bioavailability of endothelium-derived nitric oxide (NO) -a potent vasodilator-through the up regulation of endothelial nitric oxide synthetase (eNOS).⁴³ Both human and animal models indicate that estrogen also has potent stimulatory effects on eNOS expression and activity.⁴⁴ The clinical beneficial of this effect is doubtful, however, in light of the lack of mortality benefits reported by the HERS trial. An alternative hypothesis is that estrogen is associated with an early prothrombotic effect which acts in conflict with a more gradual beneficial effect on prevention of progression of atherosclerosis.¹³ Further comparison of the actions of statins and estrogen would appear to offer some support to this hypothesis: statins also appear to have an anticoagulation effect and this may account for some of their short term mortality benefits.

Although simvastatin is better at lowering LDL cholesterol than oestrogen, one study did show that oestrogen replacement therapy was better at raising HDL cholesterol. It concluded that there was a modest additional benefit of adding oestrogen to a statin in relation to lipid profile outcome.⁴⁹ Statins may also protect against some of the apparent negative effects of HRT seen in the immediate treatment period. An analysis of the HERS trial found that the increased cardiovascular mortality risk found for HRT users in the first year was attenuated by statins.⁴⁵ A further beneficial effect of unopposed estrogen was shown in the Asymptomatic Carotid Artery Progression Study where changes in carotid intima-media thickness were reduced in women taking unopposed estrogen and no additional effect was identified in women receiving lovastatin.⁴⁶ In addition to the beneficial effects on lipid profiles and vascular beds, unopposed estrogen therapy seems to have a favourable effect on glucose metabolism in patients with diabetes mellitus.⁴⁷

There is a lack of consensus about the effects of HRT on blood pressure (BP). Cross-sectional studies have generally reported HRT as having no effect on BP.^{37,48,49} The PEPI trial¹⁵ did not show HRT (estrogen or combination estrogen and progesterone) as having any effect on BP in 875 patients followed up for 3 years. This may be related to the counter balance vasopressor effects of progestin to the vasodilator effects of oestrogen. In contrast, Scuteri *et al.* reported post-menopausal women taking both oestrogen and progestin to have a smaller increase in systolic BP

compared to those not taking HRT over a mean follow up period of 5.7 years.⁵⁰ These contradictory data suggest that national hypertension guidelines should be adhered to irrespective of the individuals HRT status.

HRT and the medical management of intermittent claudication

Although no study has examined the effect of HRT on claudication distance in patients with PAD, estrogen therapy has been shown to improve exercise capacity in postmenopausal women with CHD possibly as a result of short term improvements in endothelial-dependent and non-endothelial-dependent vasodilation.⁵¹

HRT and peripheral revascularisation

HRT has been shown to increase circulating levels of coagulation activation markers and it is well-recognised that patients with PAD have a prothrombotic haemostatic derangement.⁵² Only one study has examined the influence of HRT on the outcome of peripheral angioplasty/stenting. A longitudinal observational study of 126 iliac angioplasties and 144 stents over a 5 year period found HRT significantly reduced primary patency rates (HRT users: 49% vs. non-HRT users: 74% 5-year primary patency rate).⁵³ In another study examining the outcome of femoro-popliteal bypass grafting in women, HRT emerged as the only predictor of diminished primary graft patency⁵⁴ with the risk of graft failure increasing with use of prosthetic material. The same findings applied irrespective of whether the subjects were on estrogen alone or cHRT.

Discussion

In summary, unopposed oestrogen has an overall beneficial effect in preventing progression of atherosclerosis. There is an initial prothrombotic effect of treatment, which may lead to an increase in both arterial and venous thrombotic effects within the first year, with subsequent improvement in the rate of these events occurring possibly as a consequence of improved lipid profile. The addition of progesterone therapy (cHRT) appears to attenuate any beneficial effects from estrogen. In view of the high risk of endometrial dysplasia from unopposed estrogen¹⁵ it is inadvisable to prescribe unopposed estrogen to postmenopausal women who have not had a hysterectomy. Those who have undergone hysterectomy may derive some benefit from unopposed estrogen;

however, this group of patients has been excluded from most studies. Alternatives to 'standard' HRT, such as selective estrogen receptor modulators (e.g. raloxifene), appear to have beneficial effects on lipids without the deleterious effects on coagulation¹³ but there are no data assessing their effect on PAD.

To address the important clinical dilemmas for the vascular specialist, we recommend to our patients with PAD that they should *continue* their HRT as there appears to be no significant effect on the prevention or progression of PAD (other than perhaps improving ability to increase exercise capacity in those with concomitant CHD).⁵¹ However, unless strong clinical indications exist, we advise patients with PAD against *starting* on HRT in view of the initial increase in thrombotic cardiovascular events up to one year. This may also apply to patients with PAD who are admitted for any type of surgery.

There is currently no clear evidence supporting the routine discontinuation of HRT prior to surgery. The Royal College of Obstetricians and Gynaecologists currently advise that HRT should be viewed as a risk factor for VTE and recommend the addition of appropriate thromboembolic prophylaxis, but not the routine cessation of HRT, prior to surgery.⁵⁵ In contrast, the current advice in the British national Formulary (BNF) is to stop treatment 4–6 weeks prior to surgery.¹⁴ It is well established that PAD is associated with a resting prothrombotic state which correlates with disease severity and that patients undergoing lower limb revascularisation procedures are at a high risk of peri-operative cardiac thrombotic events.^{52,56} Furthermore, HRT may have a deleterious effect on the success of both endovascular and open surgical revascularisation.^{53,54} In view of these factors we currently advise our patients to stop HRT 6 weeks prior to surgical or endovascular intervention.

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