Commentary

Do we need clinical trials to test the ability of transdermal HRT to prevent coronary heart disease?

David Crook

Department of Cardiovascular Biochemistry, St Bartholomew's and the Royal London School of Dentistry and Medicine, London, UK

Correspondence: David Crook, e-mail: dcrook@mac.com

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Abstract

Postmenopausal hormone replacement therapy (HRT) with oral oestrogen was predicted to reduce coronary heart disease (CHD) risk by 50%. Randomized controlled trials show no such benefit, however, pointing instead to an initial increase in CHD events. Although the cardiovascular effects of transdermal HRT are largely unknown, improvements in arterial function are maintained when oestrogen is administered transdermally. Transdermal HRT also avoids the increased plasma levels of C-reactive protein (CRP) that are seen with oral HRT. However, the clinical significance of this general reduction in hepatic over-synthesis of plasma proteins is difficult to assess. Nevertheless, the available evidence on transdermal HRT appears to justify a formal clinical trial.

Keywords coronary heart disease, hormone replacement therapy, oestradiol, progestin, transdermal delivery

The claim that postmenopausal hormone replacement therapy (HRT) reduces coronary heart disease (CHD) risk by 50% has until recently been a mantra in female health care and, to a lesser extent, in preventive cardiology [1]. This belief originated in the 1960s and is based on the logic that if the menopause causes CHD (a dubious proposal at best) then oestrogen replacement should prevent the disease. Plasma lipoprotein levels were an aspect of metabolism that was at the core of cardiovascular research at that time, and the changes in response to oestrogen were encouraging [2].

A low incidence of CHD was subsequently shown in observational (nonrandomized) studies of HRT users [3]. This association was strengthened by the antiatherosclerotic effect of oestrogen demonstrated in fat-fed animals [4], which was consistent with the identification of this steroid as a powerful vasoactive agent.

Administration of HRT through skin patches has become a common treatment option in postmenopausal women [5], resonating with the late 20th century distrust of 'pills'. By providing relatively stable blood hormone levels, it was expected to reduce side effects and improve compliance. The major disadvantages, aside from cost, are that patches may fall off or induce skin reactions. These problems have been minimized by advances such as 'matrix' patches that incorporate the steroid in the adhesive layer of the patch. Transdermal HRT is as effective as oral HRT in relieving climacteric symptoms, such as hot flushes, and has comparable effects on bone metabolism and bone density. Some women prefer patches and others prefer pills, and with such a complex and multisystem condition as the menopause it was always unlikely that any one therapy would emerge as a clear favourite.

Transdermal and oral HRT differ in their impact on some CHD risk factors (Table 1). The long-standing view that oral HRT prevents CHD has been strongly challenged by recent randomized controlled trials [6]. Whereas a few years ago the question of interest was whether transdermal HRT could match the cardiovascular benefits of oral HRT, we have now entered a new phase in which the transdermal route might even be preferable.

CHD = coronary heart disease; CRP = C-reactive protein; HDL = high-density lipoprotein; HRT = hormone replacement therapy; PAI = plasminogen activator inhibitor.

Table 1

Differences in the cardiovascular risk profiles of oral and transdermal HRT

Differences that favour transdermal or oral HRT	Parameter
Transdermal	Decrease in factor VII activity, fibrinogen, and triglycerides levels
	Neutral effect on C-reactive protein
Oral	Decrease in LDL and Lp(a) levels
	Increase in HDL levels
	Decrease in PAI-1 levels

Note that coadministration of progestin may influence many of these changes. LDL, low-density lipoprotein.

Oral hormone replacement therapy and coronary heart disease

When oestrogen is given orally the liver reacts to the rapid increase or 'bolus' of hormone emerging in the hepatic portal vein by attempting to deactivate this seemingly alien material. Relatively large steroid doses are needed to overcome this 'first-pass' effect in order to ensure sustained and clinically relevant plasma hormone levels. One consequence of this overdosing is a dramatic increase in hepatic synthesis (and hence plasma levels) of many proteins, including those that are involved in haemostasis and blood pressure regulation [7].

Transdermal delivery of oestrogen was developed in part to avoid this over-synthesis, although a certain amount of hepatic stimulation may be desirable. For instance, oral oestrogen induces hepatic synthesis of apolipoprotein A-I and so increases plasma levels of high-density lipoproteins (HDLs) – a change that is often considered pivotal to the perceived cardiovascular benefit of HRT. The possibility that the transdermal route may have advantages or disadvantages over oral HRT in CHD prevention could form the basis of a clinical trial.

Transdermal hormone replacement therapy and coronary heart disease

In the first randomized controlled trial of the effects of transdermal HRT on CHD end-points, the Papworth HRT Atherosclerosis Study, 255 women with angiographically defined CHD were randomly assigned to receive placebo or transdermal HRT [8]. That study was terminated prematurely because of a higher incidence of myocardial infarction, stroke and venous thromboembolism in the transdermal HRT group – a similar pattern to that encountered in recent trials of oral therapy [6]. There are obvious concerns that this trial was underpowered, a limitation that was exacerbated by a 40% dropout rate in HRT users. Some would argue that these results are not relevant to the average HRT user, but it should be remembered that the consensus has always been that HRT is especially beneficial in CHD patients [9].

Although transdermal oestradiol was no better than placebo in preventing atherosclerosis in fat-fed rabbits [10], the possibility of clinical benefit of transdermal HRT has been raised in a case–control study conducted by a manufacturer of the skin patches [11]. The health records of 164,769 women in UK general practices were used to assemble an adjusted odds ratio for myocardial infarction of 0.75 (95% confidence interval 0.47–1.21) in women currently or recently using transdermal HRT, as compared with nonusers. The limitation of such an observational study is that women often choose HRT of their own volition, which leads to health and health care differences between HRT users and control individuals. Observational epidemiological studies cannot adjust adequately for baseline differences in socioeconomic status and other CHD risk factors. Even conventional risk factors such as hypertension and dyslipidaemia are poorly quantified in such surveys.

The coronary heart disease risk profile of transdermal hormone replacement therapy

The evidence for transdermal HRT is often inconclusive. Research is frequently contaminated by the concomitant use of different types and doses of progestins to prevent oestrogen-induced endometrial hyperplasia and cancer, with the route of progestin administration being less of an issue. Progestins can exhibit androgenic characteristics and in particular can reduce oestrogen-induced rises in plasma levels both of HDLs and of fasting triglycerides. This antagonism is, in theory, both undesirable and desirable [12]. In light of this, a logical step is to look at surrogate measures of atherosclerosis.

Plasma lipoproteins

When transdermal HRT was first introduced it appeared to be neutral in its effect on plasma lipoprotein metabolism [13], which was consistent with avoidance of hepatic first-pass metabolism. Larger and more sophisticated studies confirmed the lack of effect on HDL levels, but showed modest reductions in low-density lipoproteins and (less consistently) lipoprotein(a), as well as an intriguing fall in levels of fasting triglycerides [14]. When a progestin was coadministered with transdermal HRT, HDL levels tended to fall. Therefore, transdermal HRT theoretically has beneficial effects on low-density lipoprotein (LDL), lipoprotein(a) and triglycerides, but has little effect on HDL – a lipoprotein that was previously considered the cornerstone of the cardiovascular benefits of HRT.

Glucose and insulin homeostasis

Some studies suggest that oestrogens and progestogens can induce a mild form of insulin resistance [15]. Because insulin resistance may underlie many forms of CHD, claims for a beneficial effect of transdermal HRT in this area of

cardiovascular risk were of obvious interest [16]. At present, methodological arguments dominate this area of risk assessment, but recent studies using the classic 'euglycaemic clamp' technique fail to show any influence of transdermal HRT on insulin kinetics [17,18]. In this procedure, plasma glucose levels are continually monitored and kept stable or 'clamped' at a pre-agreed value, following intravenous infusion of insulin. In contrast to insulin resistance, an insulin-sensitive person needs more glucose to maintain this plasma glucose level, because they respond strongly to the insulin.

Coagulation and fibrinolysis

It was hoped that induction of a 'prothrombic' state linked with oral HRT could be avoided with transdermal oestradiol, because it has no effect on hepatic synthesis of coagulation factors and other proteins that are involved in haemostasis. The evidence for such a benefit is unconvincing, however. Reductions in factor VII activity and fibrinogen levels have been reported with transdermal therapy [19], which is consistent with a reduction in plasma levels of triglyceride-rich lipoproteins [20]. This potential benefit has to be balanced against the claim that only oral oestrogen reduces plasma levels of the inhibitor of fibrinolysis plasminogen activator inhibitor (PAI)-1 [21]. This in turn has been challenged by Falco *et al* [22], who claim that transdermal oestradiol reduces PAI-1 levels and improves fibrinolysis in CHD patients.

More comparative studies are needed, with an emphasis on markers of haemostatic flux such as F1.2 and D-dimer. Although transdermal HRT is often perceived to be free of the increased risk for venous thromboembolism that is seen with oral HRT, the evidence for such an assertion is weak [23].

Blood pressure

Transdermal oestradiol can reduce blood pressure [24] and, in particular, restores the night-time blood pressure 'dip' that is absent in some older individuals [25]. The clinical significance of these small changes is uncertain, but raises the possibility that transdermal HRT may be a better choice for a subset of hypertensive women with genetic susceptibility to oral oestrogen.

Vascular function

Despite claims that transdermal oestradiol has less effect on plasma markers of endothelial function in comparison with oral therapy [26], a recent study [27] found substantial reductions in soluble intercellular adhesion molecule, E-selectin and vascular cell adhesion molecule-1. The disparities between studies may reflect the use of different study populations, such as CHD patients or smokers. One critical distinction between oral and transdermal HRT may exist in the effect on plasma levels of C-reactive protein (CRP), which is considered to be a marker of the inflammatory response in atherosclerosis. Oral HRT substantially increases plasma CRP levels, but this is not seen with transdermal therapy [28,29].

de Ziegler *et al* [30] first showed that transdermal oestradiol reduced vascular resistance in uterine arteries, and this was subsequently confirmed in both coronary and carotid arteries. Transdermal oestradiol improves forearm blood flow [31] and coronary vasomotion [32], although studies of treadmill performance in CHD patients are contradictory [33,34].

Despite some negative studies, there are sufficient clear indications of a theoretical benefit with at least some transdermal therapies in certain groups of women to conclude that transdermal HRT has the potential to improve arterial function. This is consistent with our understanding of the direct actions of oestradiol on the arterial wall.

Conclusion

The severe mismatch between observed and expected results for oral HRT in randomized controlled trials of CHD end-points challenges the validity of observational epidemiology, animal studies, and traditional CHD surrogates. Transdermal HRT is considered inferior to oral HRT for CHD prevention, because of the lack of effect on HDL and PAI-1. If the apparent lack of activation of CRP by transdermal HRT can be confirmed, and if the increased CRP levels seen in oral HRT users can be linked to their adverse clinical outcomes, then an adequately powered controlled trial of transdermal HRT in the prevention of CHD would be desirable. The lesson from recent HRT trials is that such a venture should not be started in the absence of a consensus regarding the study population (healthy women or CHD patients) and regarding the use of progestin.

Competing interests

None declared.

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