Hormone Replacement Therapy (HRT) and Ischaemic Heart Disease: Getting to the Heart of the Matter

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ABSTRACT

Numerous observational studies have previously shown that estrogen therapy (ERT) or estrogen/progestin hormone replacement therapy (HRT) can significantly reduce the risk of Coronary Artery Disease (CAD) in healthy postmenopausal women by up to 50%. However, due to statistical limitations inherent in these earlier studies, several large randomised trials are now under way. The results from some of these randomised trials are expected sometime in 2005 and will certainly help confirm or refute the present perceived cardio-protective effects of ERT/HRT in healthy menopausal women.

On the other hand, the role of hormonal therapy in menopausal women with established CAD is more controversial. Although results from earlier observational trials have been encouraging, more recent randomised controlled data from the Heart and Estrogen/Progestin Replacement (HER) study and the Estrogen Replacement and Atherosclerosis (ERA) study have been more sober. In fact, both have generally reported on the failure of ERT/HRT to reduce the overall rate of ischaemic cardiovascular events or to halt the progression of coronary atherosclerosis in menopausal women with established CAD. However, these studies are not without their own limitations. As such, more future trials will be needed before the role of postmenopausal hormone therapy in the secondary prevention of CAD can be firmly established.

Keywords: Hormone replacement therapy, coronary heart disease, primary and secondary prevention

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INTRODUCTION

Women in the developed world can now expect to spend one-third of their lives in a post-menopausal state. Unfortunately, it is well recognised that the risk of cardiovascular disease, especially that of ischaemic heart disease (IHD), increases significantly after menopause[1,2]. In fact, heart disease is still the number one killer of women in many industrialised countries of the world[3]. The various post-menopausal changes in blood pressure, serum lipids, vessel dynamics, insulin resistance and blood haemostatic properties, have all been cited as possible causes of this increased cardiovascular risk[1,2,4]. It is also interesting to note that the median age of death from IHD is 74 years and that women tend to die from IHD 10 - 15 years later than men. This "delayed mortality" is again believed to be related to the loss of estrogen and its cardio-protective effects in these menopausal women[5-7].

Various possible mechanisms of estrogen mediated cardio-protection have been mooted. For example, estrogen replacement therapy has been shown to favourably reduce serum levels of total cholesterol, low-density lipo-protein (LDL) cholesterol, lipoprotein (a) and apo-lipoprotein B as well as raise protective levels of high density lipoprotein (HDL) cholesterol[8,9]. In addition, the landmark Post-menopausal Estrogen/Progestin interventions (PEPI) trial[10] has also shown that combined hormone replacement therapy (estrogen plus progestin) could still significantly increase HDL and lower LDL cholesterol levels. Although the beneficial increase in HDL levels were somewhat attenuated by the addition of a progestin; the investigators found that the use of micronised progesterone had the least detrimental effect on serum lipids.

However, it should be noted that the protective effects of HRT on lipids can probably only account for one third of the overall benefit observed. In fact, several other lipid independent protective mechanisms have been described. These have included favourable effects on vascular reactivity and blood pressure[8,11,12], reduction of insulin resistance[13], lowering of serum fibrinogen[10]; as well as favourably attenuating the progression of atherosclerosis[1,14,15].

Role of Hormone Therapy in Healthy Postmenopausal women without CAD

Various observational studies have already reported that post-menopausal estrogen replacement therapy (ERT) or estrogen/progestin hormone replacement therapy (HRT) can significantly reduce the risk of coronary heart disease (CHD) in healthy postmenopausal women by up to 35 - 50%[5,8,16-21].

Looking at the largest and most authoritative

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epidemiological study to date, in the Nurse's Health Study by Grodstein et al 1996[16], the authors reported a marked decrease in the risk of CHD among healthy women who took either estrogen alone (relative risk 0.60) or estrogen with progestin (relative risk 0.39), as compared with women who did not use hormones. Furthermore, healthy postmenopausal women but with risk factors for CHD, also enjoyed a 50% reduction in all-cause mortality compared with an 11% reduction in women without such risk factors[17].

In a subsequent follow-up analysis of the same Nurse's Health study (70,533 patients observed over 20 years) by Grodstein et al 2000[22], the investigators again found a lower risk for major coronary events among healthy users of estrogen (relative risk 0.54) and those taking estrogens and progestins (relative risk 0.61), compared with women who never used hormones. In addition, other investigators[5,18,20,23] have also demonstrated an overall cardiovascular risk reduction of up to 50% in healthy postmenopausal patients on HRT/ERT compared with those who were not on hormones.

However, there are limitations associated with these aforementioned studies. For example, postmenopausal women who use hormone replacement therapy may also be better educated and more health conscious (in terms of diet and exercise)[24]. This form of "prevention bias"[25] may very well be overlooked in observational trials and this may thus lead to findings that are biased towards a cardio-protective effect of HRT/ERT.

Furthermore, postmenopausal women who are compliant on HRT/ERT may also be more motivated to lead healthier lifestyles. This type of "compliance bias" could also possibly explain the reduction in relative risks of CHD between users and non-users of HRT/ERT[26].

In addition, not all observational data have reported lower rates of cardiovascular disease associated with HRT[27]. For example, Hemminki and McPherson[27] have reviewed pooled data from 22 placebo-controlled trials and have reported no overall reduction in cardiovascular events in women receiving HRT compared to those not on any hormones.

To help clarify the situation, several large randomised trials are now underway[28,29]. An example is the Women's Health Initiative (WHI) study[28] which is a 15-year, multi-million dollar exercise and certainly one of the largest US prevention trials of its kind. Commenced in 1991, the WHI trial will eventually recruit over 27,000 healthy postmenopausal women without heart disease and have them randomised to receive placebo, ERT or HRT (depending on their uterine status). The cardiovascular effects of therapy will then be observed over a nine-year period and these results are expected to be ready sometime around 2005. In addition, the Women's International Study of long Duration Oestrogen after Menopause (WISDOM) has also started and hopes to recruit approximately 34,000 healthy postmenopausal women without any CHD[29]. This 10-year trial will randomise some women to receive placebo and another group to receive conjugated equine oestrogen (0.625 mg) with or without medroxyprogesterone acetate 2.5 mg daily (depending on their uterine status). The effects of therapy on serious cardiovascular events will then be documented. The data from these randomised trials will certainly help confirm or refute the cardio-protective benefits of ERT/HRT in healthy menopausal women.

Role of hormonal therapy (HRT/ERT) in menopausal women with established heart disease

At present, the role of hormonal therapy in menopausal patients with established ischaemic heart disease is still controversial. In the past, observational data had generally supported the use of HRT in menopausal patients with CHD. For example in the Lipid Research Clinics Program[47], over 2000 women with and without coronary artery disease were followed for more than eight years. That study was able to show that although HRT use was generally cardio-protective, it was in fact the postmenopausal patients with baseline CHD who actually benefited more (with greater reductions in mortality) compared to women on HRT who were healthy. In addition, various other observational studies[31-33] have also reported on the use of ERT in women with established CHD; and these have generally shown a lower risk of re-infarction, CHD related deaths as well as lower risks of coronary artery re-stenosis in users of ERT. Unfortunately the euphoria generated by these earlier studies has been dampened by sobering data from more recent randomised controlled trials.

The Heart and Estrogen/Progestin Replacement Study (HERS)

The Heart and Estrogen/progestin Replacement Study (HERS) was the first prospective, randomised, double-blind, placebo-controlled trial of HRT (conjugated oestrogen and medroxyprogesterone acetate) that was carried in postmenopausal women with established coronary artery disease[34]. Involving some 2,763 postmenopausal women (average age 66.7 years) with CHD, the study subjects were randomly assigned to receive either HRT (n = 1,380) or a placebo of identical appearance (n = 1,383). Follow-up was continued for 4.1 years and both primary (non-fatal myocardial infarct or CHD death) and secondary cardiovascular outcomes (coronary revascularisation, unstable angina, congestive heart failure etc) were recorded.

Interestingly, the investigators found no significant differences between the HRT treatment and placebo groups in terms of both the primary and secondary cardio-vascular outcomes. This lack of overall effect

occurred despite a net 11% lower low-density lipo-protein (LDL) level and a 10% higher high-density lipo-protein (HDL) in the HRT group compared to the placebo group (P<0.001). Also noteworthy was the finding of a statistically significant time trend, with more CHD events occurring in the HRT group (n = 57) than in the placebo group (n = 38) in the first year of study. However, by the 4th and 5th years of the trial, this trend had reversed, with 33 events being reported in the HRT group and 49 cardio-vascular events in the placebo group.

In addition, women in the HRT group experienced three times more venous thromboembolic events and had 40% more cases of gallbladder disease as compared to the women receiving only placebo.

The investigators thus concluded that HRT did not reduce the overall rate of CHD events in postmenopausal women with established ischaemic heart disease; and as such HRT should not be given specifically for the secondary prevention of CHD. However on the other hand, given the late trend of benefit as well as the fact that the majority of cardio-vascular events occurred within the first year of treatment; it may thus be acceptable for women already receiving HRT for more than 12 months to safely continue with their hormones.

In addition, the authors also tried to account for the interesting pattern of "early harm and later benefit" of HRT seen in the trial. They reasoned that the early increase in risk for cardio-vascular events might be due to an immediate pro-thrombotic or pro-ischaemic effect of hormone therapy. However, these early deleterious effects might gradually be counterbalanced over time, by the anti-atherogenic lipo-protein profiles seen in HRT users. In fact, Rosenburg et al[35] in an earlier case-controlled trial also reported a similar pattern of relative risk of myocardial infarction in hormone users over time.

Although the HERS trial has been hailed as a landmark study, several limitations have been identified. Firstly, the HERS study involved only post-menopausal women with ischaemic heart disease, and as such these results cannot be extrapolated to healthy menopausal women for the primary prevention of CHD. Secondly, the study was conducted over a period of 4.1 years which was nearly seven months less than what was originally planned. With significantly fewer cardiovascular (CV) events occurring in the 4th and 5th years of study in the HRT group (compared to those taking placebo); a longer follow-up period might have enabled the trial to detect a significant overall protective effect of HRT over time. Thirdly, some concern has also been expressed over the fact that only 78% of the patients were on acetylsalicylic acid, 32% were on beta-blockers and only 10% were achieving the desired LDL targets for patients with CHD. In addition, significantly more women in the placebo group were started on lipid lowering drugs (statins) and this itself could have reduced the incidence of CV events in this group. Finally, most of the patients in the HERS study were also older and this late initiation of HRT in the post-menopausal period might not have been so cardio-protective. This is unlike in previous observational studies where women receiving HRT were generally started on medication in the early post-menopausal period.

The Estrogen replacement and Atherosclerosis (ERA) study

The Estrogen replacement and Atherosclerosis (ERA) trial is the first randomised, placebo-controlled, double -blind study to examine the effects of HRT/ERT on coronary atherosclerosis in postmenopausal women[36]. Involving a total of 309 postmenopausal women with angiographically verified coronary artery disease, these patients were randomised to receive either estrogen alone (0.625 mg of conjugated estrogen/day); combined hormone replacement (0.625 mg of conjugated estrogen and 2.5 mg of medroxyprogesterone acetate/day) or placebo. The subjects were then followed for a mean of 3.2 years with baseline and follow-up angiograms taken for comparison and analysis.

The authors found that although both ERT and HRT produced significant reductions and elevations of LDL and HDL respectively; neither treatment group actually managed to alter the progression of atherosclerosis. In fact, the mean minimal coronary artery diameters in the three groups were not significantly different. In addition, the analyses of several other secondary angiographic outcomes as well as rates of clinical cardio-vascular events were also similar among the three treatment groups. The investigators thus concluded that neither estrogen alone nor estrogen plus medroxyprogesterone acetate was able to affect the progression of coronary artery disease in women with established heart disease. As such, these patients should not be given ERT/HRT in anticipation of cardiovascular benefit.

However, several limitations of the study have been pointed out[37]. Firstly, the study's use of angiographic findings as an end point has been called into question. This is because based on data and experience from other trials[38], changes in angiographic lesion size may not always be predictive of subsequent ischaemic cardiovascular events. In addition, hormonal treatment was also given relatively late (on average 23 years after the menopause) in the ERA trial. This late initiation of HRT so long after the menopause may have inadvertently reduced the protective effects of hormone therapy against secondary cardiovascular events.

CONCLUSION

Numerous observational studies have previously shown that estrogen therapy (ERT) or estrogen/

progestin hormone replacement therapy (HRT) can significantly reduce the risk of Coronary Artery Disease (CAD) in healthy postmenopausal women by up to 50%. However, due to statistical limitations inherent in these earlier studies, several large randomised trials are now under way. The results from some of these randomised trials are expected sometime in 2005 and will certainly help confirm or refute the present perceived cardio-protective effects of ERT/HRT in healthy menopausal women.

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