Editorial comment

Hyperlipidaemia and cardiovascular disease

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Abbreviations

CEE	conjugated equine oestrogen
CHD	coronary heart disease
HRT	hormone replacement therapy
MPA	medroxyprogesterone acetate

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Coronary heart disease (CHD) is the leading cause of mortality in women in the west, with 92% of cases occurring in the postmenopausal age group [1]. The cardioprotective effect of hormone replacement therapy (HRT) has been attributed to favourable changes in lipoproteins, lipoprotein (a), plasminogen activator inhibitor-1, antithrombin III, homocysteine, endothelial function, and vascular reactivity [2]. A Greek group [3••] recently compared combination HRT [0.625 mg/day conjugated equine oestrogen (CEE) and 2.5 mg/day medroxyprogesterone acetate (MPA)], simvastatin (20 mg/day), or a combination of both in 16 postmenopausal women with CHD and hypercholesterolaemia in a randomized, placebo-controlled, crossover study. All three active treatments significantly reduced total and LDL cholesterol ($P<0.001$). Only HRT, alone or in combination with simvastatin, significantly reduced intercellular adhesion molecule plasma levels ($P=0.03$ and $P=0.02$, respectively), lipoprotein (a) levels ($P<0.05$) [3••] as well as plasminogen activator inhibitor-1 levels [4••]. In addition to the favourable lipid profile, the results argue for the additional benefits of combination HRT.

The recently reported Estrogen Replacement and Atherosclerosis Trial [5] contradicted the theory of the cardioprotective effect of HRT. This double-blind, placebo-controlled trial randomly assigned 309 women with angiographically verified CHD to either 0.625 g/day CEE, CEE plus 2.5 mg/day MPA or placebo. Oestrogen alone or with MPA significantly reduced LDL (9.4 and 16.5%, respectively) and increased HDL (18.8 and 14.2%, respectively). However, neither treatment altered the progression of coronary atherosclerosis progression.

This supports the findings of the Heart and Estrogen/Progestin Replacement Study [6], the first large randomized, placebo-controlled trial evaluating the relationship of oestrogen and CHD. It revealed that CHD rates did not differ between the active (CEE plus MPA) versus placebo groups, with an even higher risk of cardiovascular events during the first year in the active group.

The unexpected results of both studies have to be viewed carefully, considering the following issues. First, in both studies, HRT was initiated late after the menopause (mean age >65 years), with a short duration (4.1 and 3.2 years, respectively) of therapy. HRT may not protect against secondary events if initiated so long after the menopause. Again, a longer follow-up might have yielded a more favourable response, as supported by the observation that a longer duration of oestrogen therapy (mean 8.2 ± 7.9 years) significantly reduced the need for revascularization after intracoronary stenting in postmenopausal patients who had been on HRT before stenting [7]. Second, oestrogen might be more effective in preventing the development, rather than slowing the progression, of atherosclerosis. Animal studies have demonstrated the efficacy of oestrogen in primary, as opposed to secondary, prevention [8], as well as the necessity for a healthy endothelium for oestrogen to prevent cholesterol accumulation in the vessel wall [9]. In a landmark report [10] on 85 941 women from the Nurses' Health Study cohort who had no history of CHD and were followed for 14 years, an increased proportion of the postmenopausal use of HRT by 175% was demonstrated, explaining a 9% decline in CHD. This supports the efficacy of HRT in primary prevention.

Finally, angiography is not a valuable end-point. Discordance between changes in the size of lesions on angiography and the incidence of clinical events has been demonstrated in lipid trials [11].

Although it is difficult to question the results of the well-designed Heart and Estrogen/Progestin Replacement Study and the Estrogen Replacement and Atherosclerosis Trial, the potential beneficial role of HRT should not be totally dismissed, especially in primary prevention. Awaiting more trial data to define the efficacy of HRT in secondary prevention, the observed excess early risk will invalidate the initiation of HRT for that indication,

especially in the presence of compelling evidence as to the efficacy of statins in women with or without CHD. With confirmed efficacy [10], life-style modifications, including the cessation of smoking, exercise, weight control, diet modification, etc. should always be reinforced.

References

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3 •• Sbarouni E, Kroupis C, Kyriakides ZS, *et al.* Cell adhesion molecules in relation to simvastatin and hormone replacement therapy in coronary artery disease. Eur Heart J 2000; 21:975–980.

4 •• Sbarouni E, Melissari E, Zenon S, *et al.* Effects of simvastatin, hormone replacement therapy, or both, on fibrinogen, factor VII, and plasminogen activator inhibitor levels in postmenopausal women with proven coronary artery disease. Am J Cardiol 2000; 86:80–83.

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8 Haarbo J, Leth-Espensen P, Stender S, Christiansen C. Estrogen monotherapy and combined estrogen progestogen replacement therapy attenuate aortic accumulation of cholesterol in ovariectomised cholesterol-fed rabbits. J Clin Invest 1991; 87:1274–1279.

9 Holm P, Andersen HL, Andersen MR, *et al.* The direct antiatherogenic effect of estrogen is present, absent, or reversed, depending on the state of the endothelium: a time course study in cholesterol-clamped rabbits. Circulation 1999; 100:1727–17233.

10 Hu FB, Stampfer MJ, Manson JE, *et al.* Trends in the incidence of coronary heart disease and changes in diet and lifestyle in women. N Engl J Med 2000; 343:530–537.

11 Brown BG, Zhao XQ, Sacco DE, Albers JJ. Lipid lowering and plaque regression: new insights into prevention of plaque disruption and clinical events in coronary disease. Circulation 1993; 87:1781–1791.

Recommended reading

English KM, Mandour O, Steeds RP, *et al.* Men with coronary artery disease have
• lower levels of androgens than men with normal coronary angiograms. Eur Heart J 2000; 21:890–894.

Another support to the notion of the cardioprotective effect of natural androgens. Androgen levels were compared in 60 male subjects with positive coronary angiograms with 30 matched subjects with negative angiograms. Men with coronary artery disease had significantly lower levels of free and bioavailable testosterone as well as free androgen index. The results challenge the preconception that physiologically high androgen levels in men account for their increased relative risk of coronary artery disease.

Rosano GMC. Androgens and coronary artery disease. A sex-specific effect of
• sex hormones? Eur Heart J 2000; 21:872–873.

This editorial reviews the historical links between androgens and CHD. Animal models and human data on the metabolic effects of androgens are discussed. The concept of the antiatherogenic effect of androgens in men and oestrogen in women is presented, arguing that sex hormones play a sex-specific role in the two sexes, but with regard to cardioprotection, the likelihood is that their balance is the most important factor.

Sbarouni E, Melissari E, Zenon S, *et al.* Effects of simvastatin, hormone
•• replacement therapy, or both, on fibrinogen, factor VII, and plasminogen activator inhibitor levels in postmenopausal women with proven coronary artery disease. Am J Cardiol 2000; 86:80–83.

A well-designed study, proving the superiority of oestrogen/progestin replacement therapy over simvastatin in lowering plasminogen activator inhibitor-1 levels.

Sbarouni E, Kroupis C, Kyriakides ZS, *et al.* Cell adhesion molecules in relation to
• simvastatin and hormone replacement therapy in coronary artery disease. Eur Heart J 2000; 21:975–980.

HRT is superior to simvastatin in reducing intercellular adhesion molecule plasma levels.

van Lennep JER, Zwinderman AH, van Lennep HWOR, *et al.* Gender differences
• in diagnosis and treatment of coronary artery disease from 1981 to 1997 – no evidence for the Yentl syndrome. Eur Heart J 2000; 21:911–918.

Over a 16-year period (1981–1997), the coronary angiograms of 1894 patients (368 women) revealed no sex difference with regard to the extent and localization of lesions. Again, there was no sex difference in subsequent referrals for further management. That study questioned the presence of the Yentl syndrome (presumed discrimination of women).

Varas Lorenzo C, Garcia Rodriguez LA, Perez Gutthann S, Duque Oliart A.
• Hormone replacement therapy and incidence of acute myocardial infarction – a population-based nested case–control study. Circulation 2000; 101:2572–2578.

The cardioprotective efficacy of transdermal forms of HRT has been confirmed in this population-based nested case–control study from the UK. In a cohort of women aged 50–74 years without a history of CHD, the overall risk reduction was similar for both oral and transdermal preparations [0.63, 95% confidence interval (CI) 0.46–0.86; and 0.62, 95% CI 0.37–1.06, respectively]. The protective effect was stronger after one year of continuous use and only with medium–high doses of either preparation, but diminished 2–3 years after the cessation of HRT.