Hormone replacement therapy: where we stand in Europe

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There is overwhelming observational epidemiological evidence to indicate that ovarian hormones are cardioprotective in post-menopausal women. Age of onset of coronary heart disease is on average 10 years later in women than in men, reaching the same incidence at around the age of 75. Oestrogens have been proven to have a positive effect upon the lipid metabolism, insulin resistance, haemostasis, endothelial function and large artery compliance as well as a protective effect against the progression of coronary atherosclerosis in animals and humans.[1-6].

Three different meta-analyses of observational studies have shown that oestrogen replacement therapy is associated with a 35% to 50% lower risk of coronary heart disease and a predicted increase in life expectancy in hormone users of 3 years[3,4,6]. However, at present little is known regarding the cardiovascular effect of progestogens and how these hormones may influence the cardioprotective effects of oestrogens. The few epidemiological studies that have investigated the effect of the addition of a progestogen to oestrogen therapy on cardiovascular mortality and morbidity have suggested that this type of hormone replacement therapy may be at least as effective as oestrogen replacement alone in reducing cardiovascular events[5,7-9]. There are, however, several reasons to view the results of observational studies with caution, due to possible biases inherent in cohort and case-control studies and to the variability of dosage and duration of hormone replacement therapy. Therefore there is an urgent need for prospective randomized clinical trials.

The Heart and Estrogen/progestin Replacement Study (HERS) was the first large randomized placebo-controlled study evaluating the effect of treatment with conjugated equine oestrogens (0.625 mg) and medroxyprogesterone acetate (2.5 mg) on coronary events in 2763 north-American post-menopausal women with established coronary heart disease[10]. The results of this study showed no apparent effect on cardiovascular end-points. Overall, there were 172 myocardial infarctions in the hormone treated group and 176 in the placebo group with an increased incidence (post hoc analysis) in events in the hormone group during the first year.

There are, however, methodological problems which complicate its interpretation. The size of the trial was determined by power calculations based upon assumptions which were not verified (Table 1). The study was prematurely discontinued without any obvious explanation when there was a clear trend towards a protective effect of hormone replacement therapy. The interpretation of the reported increase in cardiovascular events during the first year in the hormone-treated group, and also of the year by year analysis, has to be viewed with great caution since these were post hoc analyses (Fig. 1). The event rate in the placebo group at year 1 was considerably lower than expected and remains unexplained. In addition, a significant proportion of cardiac events was due to venous thromboembolism and not related to an arterial event. Another important issue is the significantly greater use of statins in the placebo group after year 1 during the study which could have disguised a greater difference between the two groups in the HERS study by the end of the study. The findings of the HERS study are difficult to interpret and in any case are not applicable to the population of post-menopausal women currently being given hormone replacement therapy. Yet the results of this single trial appear to have affected views on the role of hormone replacement therapy in secondary, and even primary, prevention of coronary heart disease. Where does this leave us in Europe, where different types of hormone preparations are commonly used?

### Table 1

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<thead>
<tr>
<th></th>
<th>Calculated</th>
<th>Actual</th>
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<tbody>
<tr>
<td>Event rate in the placebo group</td>
<td>5%</td>
<td>3.3%</td>
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<tr>
<td>Average follow-up (years)</td>
<td>4.75</td>
<td>4.1</td>
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<tr>
<td>Drop out rate</td>
<td>5% in year 1</td>
<td>18% at year 1</td>
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Differences exist between oestrogens, not only according to their chemical structure but also in their route of administration. Although oral conjugated equine oestrogens are the most widely studied, other orally administered oestrogens are likely to share similar cardiovascular effects[11]. Non-orally administered oestrogens are widely used in Europe but as yet there are no data on their effect on cardiovascular events.

Progestogen administration is necessary in non-hysterectomized women. However, due to different metabolic and vascular actions, the cardiovascular effect of the progestogens may vary depending on the type of steroid and its dosage regimen[11–13]. It has been suggested that selective oestrogen receptor modulators might have a cardioprotective effect. These suggestions come from one epidemiological study conducted with tamoxifen and from data on surrogate end-points with raloxifene and droloxifene. Therefore, until proper randomized controlled trials on the cardiovascular effect of selective oestrogen receptor modulators are completed, they cannot be recommended for cardioprotection[14–15].

Epidemiological factors should be taken into account when considering hormone replacement therapy for cardiovascular protection. The frequency of coronary heart disease varies across Europe, with differences up to eightfold[16]. Acute coronary syndromes and reinfarction are more frequent in central and eastern Europe and in parts of northern Europe, whilst being very low in southern European countries. Also, the distribution and prevalence of hyperlipidaemia, arterial hypertension, diabetes and smoking vary enormously in the different European populations[17]. These differences will have a bearing on risk/benefit considerations. In the future, it will be important to evaluate the effect of hormone replacement therapy in different risk groups in order to determine which women may benefit.

Obviously, a European prevention study should be considered as the objective. The major question is to determine which population of post-menopausal women could benefit the most from hormone replace-

**Figure 1** Post hoc analysis of the reported increase in cardiovascular events during the first year in the hormone-treated group. ◆ = HRT; □ = placebo.

**References**


