The relative effects of progesterone and progestins in hormone replacement therapy

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Hormone replacement therapy (HRT) was initially given to protect women against osteoporosis and alleviate menopausal symptoms, such as hot flashes, depression, sleep disturbances, and vaginal dryness. In view of the understanding of oestrogen deficiency as a major trigger for the acceleration of cardiovascular risk after menopause, HRT may also be proposed as a substantial beneficial cardioprotective agent. Progestins, which may be added to oestrogen in combined HRT to reduce the risk of uterine malignancy, have a number of potential adverse effects on the cardiovascular system which could even attenuate the benefit of unopposed oestrogen replacement therapy in post-menopausal women.

Key words: cardiovascular system/coronary artery disease/hormone replacement therapy

Introduction

Women are protected until the menopause from the development of coronary artery disease and lag behind men in the incidence of myocardial infarction and sudden death by 20 years (Gordon et al., 1978). The reasons for this protection are largely unclear, but significant protection is given by ovarian hormones since castrated women not taking oestrogen replacement therapy show an incidence of coronary artery disease similar to that of men of similar age (Wuest et al., 1953). Furthermore, a large body of evidence (large scale case-control and cohort studies) has been accumulated to suggest that oestrogen replacement therapy after either surgical or natural menopause is associated with a 50% reduction in cardiovascular mortality and morbidity (Bush et al., 1987; Hunt et al., 1987; Paganini-Hill et al., 1989; Stampfer and Colditz, 1991; Grodstein et al., 1997). Consequently, post-menopausal oestrogen replacement therapy is becoming a legitimate component of preventive health care for women and the protection against coronary artery disease is presently considered the most significant benefit of this therapeutic strategy.
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Apart from the data available from the Nurse’s Health Study (Grodstein et al., 1996), the majority of case-control or cohort studies have been conducted using unopposed oestrogen replacement therapy which, however, is now prescribed only in women who have undergone a hysterectomy. In the remainder, progestins are prescribed in order to protect the endometrium from the hyperplastic and potentially carcinomatous effects of prolonged unopposed oestrogen replacement therapy.

There is evidence that progesterone receptors are present at the level of vasal endometrium and of smooth muscular fibrocytes in animal (Lin et al., 1986) and human arterial walls (Ingegno, 1988). Hormonal vascular effects may be mediated through these receptors as well as through a functional resetting of oestradiol receptors (Horowitz and Horowitz, 1982; Lin et al., 1982).

Progestin affects arterial function, both by inducing a state of vasomotor instability and by causing vasoconstriction of oestrogenized vessels; in this way, progestin may influence the cardioprotective effect of oestrogens. Because of the benefit of oestrogen replacement therapy on cardiovascular diseases, it is of pivotal importance to know whether or not the addition of progestin could have a negative effect on the clinical cardiovascular protection given by oestrogen.

Progestins and lipid profile

It is well known that ovarian hormones have a great effect on lipid metabolism. Unopposed oestrogen replacement therapy beneficially affects the lipid profile in menopausal women by lowering total serum cholesterol and low density lipoprotein (LDL)–cholesterol, and increasing high density lipoprotein (HDL)–cholesterol, especially the HDL₂ subfraction (Tikkanen et al., 1982; Godsland et al., 1987; Samsioe, 1990; Walsh et al., 1991; Soma et al., 1991; Srivastava et al., 1993). The effects of oestrogens upon plasma lipids are due to their reduction in hepatic triglyceride lipase, that degrades HDL, and to their stimulation of HDL–cholesterol production and synthesis of apolipoprotein (apo) A-I (Samsioe, 1990). Furthermore, oestrogen replacement therapy stimulates the removal of cholesterol from the systemic circulation resulting in an increased reverse cholesterol transport. The oestrogen-induced reduction in LDL–cholesterol seems to be dependent upon hepatic and non-hepatic effects (Tikkanen et al., 1982; Samsioe, 1990). Oestrogens enhance the synthesis and secretion of very low density lipoprotein (VLDL) but also reduce the catabolism of VLDL to LDL by enhancing the VLDL uptake by the liver. Another beneficial effect of oestrogens upon LDL–cholesterol metabolism is the increase in the rate of LDL removal from the plasma which seems to be dependent upon the up-regulation of LDL receptors both in the liver and in the peripheral tissues (Walsh et al., 1991).

In contrast to oestrogens, progestins administered alone induce hepatic lipase activity, increasing, in this way, the degradation of HDL–cholesterol; whereas, the addition of progestin to oestrogens tends to attenuate the increase in serum HDL–cholesterol and the decrease in LDL–cholesterol. These effects of progestins upon lipid profile seem to depend on their biochemical structures, doses and
regimens. Progestins with pure progestogenic effect do not alter the lipid metabolism, 19-nortestosterone derivatives reduce HDL cholesterol while 17-α-hydroxyprogesterone derivatives, e.g. medroxyprogesterone acetate (MPA), the most widely used progestin, seem to have little effect and progesterone no effect upon plasma lipids (Tikkanen, 1986; Rijpkema et al., 1990; Grady et al., 1992; PEPI Trial, 1995). Early studies showed that norethisterone acetate (NETA) or levonorgestrel had a strong detrimental effect upon lipid metabolism (20–30% reduction in HDL cholesterol) so that they were labelled as androgenic; however, the early results were, at least in part, the result of over-treatment. It must be underlined that since 19-nortestosterone derivatives are not subject to a major hepatic first-pass, their usage produces similar effects upon lipid metabolism, irrespective of oral or non-oral route of administration.

Effect of progestins on coronary atherosclerosis and vascular reactivity

The vasodilator and anti-atherogenic effects of oestrogens on normal and diseased arteries are well known. Oestrogens reduce the progression of coronary atherosclerosis in both animals and humans; in addition, when administered either acutely (20 min) or chronically (3 years), they can reverse the acetylcholine-induced vasoconstriction in animals and humans (Pick et al., 1952; Stamler et al., 1953; Williams et al., 1990; Adams et al., 1997; Geary et al., 1998). Although the mechanisms involved in this protective effect on coronary reactivity have not been clearly established, it may be supposed that oestrogens act by increasing the production of nitrous oxide and preserving it from the oxidative degradation (Niki and Nkano, 1990).

Adams et al. (1997) evaluated the effect of oestrogen replacement therapy with and without progestins in ovariectomized monkeys fed with an atherogenetic diet. Oestradiol-17β was found to reduce by 50% the degree of coronary atherosclerosis; the adjunct of progesterone did not antagonize the anti-atherogenic effect of oestradiol-17β. In another study, the same group evaluated in the same animal model the effect of the most widely prescribed compounds for hormone replacement therapy (HRT) in the USA, i.e. conjugated equine oestrogens (CEE) and MPA. CEE reduced by 70% the degree of coronary atherosclerosis while the adjunct of MPA resulted in a non-significant decrease of coronary atherosclerosis (Adams et al., 1990, 1997).

Taken together, these data suggest that while there is no significant difference in the anti-atherogenic effect of oestrogens, the adjunct of progesterone or progestins to oestrogen replacement therapy produce a different impact on the progression of coronary artery disease. Therefore, natural progesterone seems to be the drug of choice for treating patients at risk of cardiovascular disease.

Regarding the vascular activity of progestins, the effect of progesterone on rabbit coronary arteries in vitro were evaluated and demonstrated an endothelium-independent relaxation induced by progesterone (Jiang et al., 1992). In addition, Miller and Vanhoutte, (1991) assessed arterial relaxation in coronary artery strips
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Table I. Effect of sequential oestrogen–progestin treatment upon uterine artery pulsatility index in menopausal women

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment scheme</th>
<th>Pulsatility index change compared with oestrogens alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marsh et al. (1994)</td>
<td>17β-oestradiol + CEE or NETA</td>
<td>↓↓oestrogen phase</td>
</tr>
<tr>
<td>Hillard et al. (1992)</td>
<td>17β-oestradiol + NETA</td>
<td>↓↓oestrogen phase</td>
</tr>
<tr>
<td>de Ziegler et al. (1994)</td>
<td>17β-oestradiol + nomegestrol</td>
<td>↓oestrogen and combination phase</td>
</tr>
<tr>
<td>Bonilla-Musoles et al. (1995)</td>
<td>17β-oestradiol + MPA</td>
<td>↓combination phase</td>
</tr>
<tr>
<td>de Ziegler et al. (1991)</td>
<td>17β-oestradiol + vaginal progesterone</td>
<td>↓↓oestrogen and combination phase</td>
</tr>
</tbody>
</table>

CEE = conjugated equine oestrogens; MPA = medroxyprogesterone acetate; NETA = norethisterone acetate.

from ovariectomized dogs treated with oestrogen, progesterone or oestrogen plus progesterone. The relaxation response was similar in the coronary arteries of animals receiving oestrogen and in those receiving progesterone. On the contrary, it was minimally reduced in the group receiving the combined therapy. Therefore, it seems that there is little or no detrimental effect of progesterone on the cardiovascular protective effect of oestrogens. Pure progesterone, however, is not commonly used in HRT and the progestogens used have vascular and metabolic effects which are different from those of progesterone.

Synthetic progestins seem to antagonize the beneficial effect of oestrogens upon blood flow and vasodilation in normal (non-atherosclerotic) experimental animals. Williams et al. (1994) evaluated the separate and combined effects of CEE and MPA on coronary reactivity of atherosclerotic monkeys. Oestrogen increased coronary dilator responses and blood flow reserve while co-administration of MPA (Clarkson, 1994) resulted in a 50% reduction in the dilator response. This effect does not seem to be attributable only to MPA but to synthetic progestins in general. On the other hand, different progestins and therapeutic regimens have different effects upon vascular reactivity. Progestins given in a cyclical regimen are likely to produce unfavourable vascular effects. Conversely, continuous combined regimens appear to reduce the potential detrimental effects of progestins (Penotti et al., 1993; Yim et al., 1998).

Few data are currently available on the vascular effect of oestrogen–progestin therapy in menopausal females apart that from the study of uterine arteries, which may respond to hormone stimulation differently from other arteries. Some investigators have evaluated the effect of oestrogen–progestin therapy upon the pulsatility index, which is a measure of arterial stiffness (Penotti et al., 1993). A decrease in pulsatility index is indicative of a better arterial compliance. As shown in Table I, some progestins (e.g. NETA), reduced the beneficial effect of oestrogens upon pulsatility index, while progesterone had no detrimental effect upon the beneficial decrease of pulsatility index induced by transdermal oestradiol-
17β. These data underline the concept that synthetic progestins may reduce the beneficial activity of oestrogens upon vascular reactivity, whereas natural progesterone seems to preserve it. However, the effect of synthetic progestins depends not only on the type of progestin, but also on the dose and scheme of administration.

Rosano et al. have recently evaluated the effect of two different regimens of HRT upon forearm vascular resistance in 12 menopausal women (mean age 55 ± 2 years) referred to a menopause clinic for evaluation of their HRT (Rosano et al., 1998). Patients entered a double-blind single cross-over study evaluating the effect of continuous combined HRT with either CEE (0.625 mg) plus MPA (2.5 mg) or oestradiol-17β (2 mg) plus NETA (1 mg), randomly administered. Forearm vascular reactivity and blood pressure were measured at baseline and at the end of each treatment cycle by means of high-resolution, two-dimensional ultrasound images obtained by an ultrasound machine with a 7.5 MHz linear array transducer. Compared with baseline values, CEE plus MPA caused a marginal reduction of blood pressure while the association of oestradiol-17β plus norethisterone acetate increased blood pressure values. A significant difference in systolic blood pressure was noted between the two treatment phases (126 ± 12 compared with 138 ± 8 mm Hg, P < 0.01). Compared with baseline values, CEE plus MPA increased brachial artery flow-mediated dilatation by 12%, while oestradiol-17β plus NETA reduced this parameter by nearly 20% (P < 0.01, Figure 1). These changes were mainly attributable to the effect of the two hormone regimens upon forearm vascular resistance. Indeed, brachial artery
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Figure 3. Effect of oestrogen-progestin treatment upon brachial artery blood flow (percentage change to baseline).

resistance was reduced by 15% by CEE plus MPA, while oestradiol-17β plus NETA caused a 16% increase of the same \( (P < 0.01, \text{Figure 2}) \). Both oestrogen–progestin treatments induced an increase in brachial blood flow, but this increase was more pronounced following CEE plus MPA (Figure 3). Hence, the MPA behaved as a spastic element in women, confirming the result of previous clinical studies, carried out in menopausal women (Giraud et al., 1996) and in experimental studies on the vascular spasticity at the coronary territory in monkeys (Williams et al., 1994; Minshall et al., 1998).

In view of the different effects upon blood pressure and vascular reactivity produced by different oestrogen–progestin treatments, careful selection of the dose and type of progestin to be used during HRT seems to be crucial in order to preserve and possibly enhance the beneficial vascular effects of oestrogens.

The decrease in aortic compliance after menopause together with the increase in systemic vascular resistance due to ageing may contribute to the development of atherosclerosis, while increasing afterload and myocardial oxygen consumption. Oestrogen receptors have been seen in aortic tissue suggesting that the aorta might be a target organ for oestrogen actions. The calcium antagonistic effect of oestrogen may increase vessel distensibility and compliance of aorta as suggested by the changes occurring during pregnancy. The question arises as to whether oestrogen replacement therapy could increase aortic compliance therefore exerting a potential beneficial effect upon the cardiovascular system and whether the adjunct of progestins could reverse this effect. Giraud et al. (1996) evaluated the effect of oestrogen replacement therapy alone or in a continuous combined regimen (CEE plus MPA) upon aortic size and compliance in 26 menopausal women. Patients were randomized to receive either CEE (0.625 mg) alone or in combination with MPA (2.5 mg) for 3 months. The cross-sectional area of the aorta was measured by magnetic resonance imaging before and after replacement therapy. Aortic size (ascending aorta cross-sectional area) increased from 439 ± 7 to 466 ± 7 mm\(^2\) in patients receiving CEE alone while it remained unchanged in patients receiving continuous combined HRT. No difference in aortic compliance was detected by comparing the two treatments. This study suggests that unopposed oestrogen replacement therapy increases aortic cross-sectional area and that progestins may attenuate the oestrogen-induced increase in arterial distensibility during combined HRT.
Effect of oestrogen–progestin associations upon haemostasis

Changes in the haemostatic balance play an important role in the pathophysiology of cardiovascular disease. After the menopause, the haemostatic balance shifts towards a state of hypercoagulability, since fibrinogen plasma, factor VII (FVII) and plasminogen activator inhibitor type 1 (PAI-1) concentrations increase. It is well known that post-menopausal women face an increased risk of cardiovascular events and stroke in comparison with pre-menopausal subjects. As to the increase of the deep vein thrombosis after menopause, this could be a true effect or a misleading one, due to the fact that post-menopausal women are older than pre-menopausal ones (Anderson et al., 1991).

HRT reduces cardiovascular events, whereas it may increase the incidence of deep vein thrombosis (Devor et al., 1992), since cardiovascular events and deep vein thrombosis are due to different ways of activation of the coagulation cascade. The arterial clot is white, consisting mainly of platelets and fibrin and adhering to a site of endothelial damage which is a prerequisite of arterial thrombogenesis. Venous clots are red, consisting of all types of blood cells within a fibrin gel and without appreciable adhesion to the underlying endothelial surface. Thus the most striking difference between the thrombotic diseases in venous and arterial vessel is the absence of endothelial damage in venous disease and the presence of an ‘acute phase reaction’ within the arterial wall in arterial thrombosis (Sporrong et al., 1990; Gebara et al., 1995; Koh et al., 1997). The increased incidence of venous thrombosis with HRT is not attributable only to changes in the coagulation profile, but also to variations in venous tone and blood flow velocity which per se increase the risk of thrombosis. Recent evidence suggests that oestrogen replacement therapy after the menopause may lead to a decrease of fibrinogen plasma concentrations which is attenuated, but not eliminated, by the adjunct of progestins, apart from their different chemical classes. The effect of oestrogen replacement therapy on FVII is still a controversial issue: some investigators detected an increase of FVII (Boschetti et al., 1991; Kroon et al., 1994; Habiba et al., 1996; Andersen et al., 1999), but others detected a decrease (Scarabin et al., 1993, 1997; Lindoff et al., 1996). The hormonal effect on FVII may depend upon dose and method of administration. A marked decrease of PAI-1 has been found. This effect is attenuated by 19-norprogestins, but not by MPA (Koh et al., 1997).

The decrease in fibrinogen with all routes of administration and preparations is small and may not translate itself into a significant decrease in risk while the large decrease in PAI-1 activity with oral oestrogen therapy (Gebara et al., 1995) is likely to be of clinical relevance especially in women with atheromatous arterial disease. The magnitude of the changes in haemostatic balance varies according to different oestrogen and progestin preparation with transdermal oestrogens. These are much less effective than oral oestrogens in causing beneficial changes.

In conclusion, the effects of HRT upon markers of arterial risk are compatible with a reduction of cardiovascular events; these effects are present mainly with
oral therapy and are not attenuated by MPA acetate or cyproterone acetate although they are significantly reduced by 19-norprogestins.

**Effect of progestins upon chest pain and myocardial ischaemia**

In recent years, it has become evident that oestrogens do have anti-ischaemic and anti-anginal properties. Rosano et al. (1993, 1996) have demonstrated that oestradiol-17β improves exercise-induced myocardial ischaemia in menopausal patients with coronary artery disease and reduces chest pain in female patients with angina and normal coronary arteriograms. The question arises as to whether the adjunct of progestins could influence these beneficial effects of oestrogens.

It has been shown that the adjunct of NETA reverses the anti-anginal properties of oestradiol-17β in female patients with X syndrome and may even worsen symptoms in these patients (Rosano et al., 1996). Recently, Rosano et al. (1997) have reported preliminary data of a randomized double-blind cross-over study which evaluated the effect of adjunctive therapy with cyclical progesterone (45 mg/daily) or MPA (10 mg/daily) to oestradiol-17β upon exercise-induced myocardial ischaemia in 18 post-menopausal women with coronary artery disease. During the study two patients were withdrawn during the MPA phase because of the development of unstable angina. In comparison to baseline, oestradiol-17β alone increased the time to 1 mm ST depression (ischaemic threshold) (325 ± 158 versus 257 ± 143 s, \( P < 0.01 \)). In five patients in whom the exercise test was negative after oestradiol-17β plus progesterone, the test become positive during oestradiol-17β plus MPA (\( P < 0.01 \)). Compared with oestradiol-17β alone, oestradiol-17β plus MPA failed to increase both time to 1 mm ST depression and exercise time. By contrast, no difference was found between oestradiol-17β alone or in combination with natural progesterone in either time to 1 mm ST depression or exercise time. This study demonstrates that in menopausal patients with coronary artery disease, the adjunct of cyclical natural progesterone to oestrogen replacement therapy enhances the beneficial effects of oestrogen therapy upon exercise-induced myocardial ischaemia; instead, the adjunct of cyclical MPA does not have such a beneficial effect and may even precipitate acute coronary syndromes.

The effect of natural progesterone and MPA upon myocardial ischaemia may be related to the different effect of the two hormones upon coronary blood flow and peripheral vascular resistances. Progesterone, probably by an endothelium-independent mechanism, may facilitate the vasorelaxing effects of oestrogens, while MPA may partly reverse these effects. The rapid presentation of these changes lead us to suppose that these hormonal effects are not genome-mediated and that, on the contrary, progestins use alternative pathways, such as rapid changes of the intracellular calcium content and the activation of protein kinase C, as it has been recently claimed in the literature (Minshall et al., 1998).
Epidemiological studies on oestrogen and progestin efficacy in primary and secondary cardiovascular prevention

Oestrogen replacement therapy after the menopause can provide protection against heart disease and possibly stroke. The most substantial benefits, a 50% reduction in cardiovascular mortality and morbidity, are conferred on current oestrogen users (Bush and Miller, 1986; Bush et al., 1987; Grodstein and Stompfer, 1995). Because of the large cardioprotective effect of oestrogen replacement therapy it is important for a progestin therapy not to reduce this cardioprotection.

Few epidemiological studies have investigated the effect of addition of a progestogen to oestrogen therapy upon cardiovascular mortality and morbidity. Nachtigall et al. (1979) reported a 68% reduction in the risk of myocardial infarction in women given oestrogen and cyclic progestin in comparison with women receiving placebos. Falkeborn et al. (1992) found that women prescribed an oestrogen–progestin combination had a 50% reduction in the risk of myocardial infarction, when compared with women in the general population, while the risk reduction in women receiving oestrogen alone was 26%. Similarly, Psaty et al. (1994) reported a reduction in the risk of myocardial infarction in women receiving oestrogen alone (relative risk 0.69) or oestrogen–progestin combination (relative risk 0.68) as compared with non-users. Based on these results, it seems conceivable to say that the risk of major coronary events is substantially reduced by combined HRT and that progestins do not decrease the cardioprotective effect of oestrogens.

Post-menopausal oestrogen/progestin interventions (PEPI) trial

The PEPI trial aimed to examine (control versus placebo) the differences between CEE and three different oestrogen–progestin combinations using CEE plus MPA or CEE plus natural progesterone on four risk factors for coronary artery disease: (i) HDL–cholesterol; (ii) systolic blood pressure; (iii) 2 h serum insulin concentrations; and (iv) fibrinogen concentrations (PEPI Trial, 1995). All the HRT regimens used proved to be more efficient than placebos in increasing mean HDL–cholesterol with a maximal efficacy of oestrogen alone (+5.6 mg/dl). The remaining therapeutic schemes were progressively less efficacious, as follows: CEE plus progesterone (+4.1 mg/dl), CEE plus cyclic MPA (+1.6 mg/dl), and CEE plus continuous MPA (+1.2 mg/dl). On the other hand, all regimens showed similar decreases in LDL-C concentration (average −15.9 mg/dl) and an increase in mean triglyceride concentrations (average +12.7 mg/dl).

The PEPI study apparently did not show any effect of HRT upon blood pressure in menopausal women. However, the study was conducted in normotensive women in whom it would have been difficult to detect any blood pressure lowering effect. Finally, no regimen modified the mean changes in 2 h insulin concentrations, the primary outcome measure for carbohydrate metabolism, while fibrinogen
The relative effects of progesterone and progestins in HRT concentrations were significantly lower after all HRT, in comparison with placebos, with no differences being found between the treated groups.

Nurses’ Health Study

A recent 16 year follow-up report of 59,337 women included in the Nurses’ Health Study suggested that those currently taking oestrogen in combination with progestins (more commonly MPA) had a significant reduction in their risk of heart disease (Grodstein et al., 1996). During follow up, the authors documented a total of 54 non-fatal myocardial infarctions, 186 cardiac deaths and 572 strokes (285 ischaemic, 155 haemorrhagic, 132 non-specified) and 553 coronary revascularization surgical procedures. The authors found that women who took oestrogen with progestin had a 61% reduction in the risk of a major coronary event as compared with the risk among women who had never used HRT (multivariate adjusted RR 0.39; 95% confidence interval 0.19 to 0.78) and a 40% reduction as compared to those women who took oestrogen replacement therapy (RR 0.60; 95% confidence interval 0.43–0.83). Despite this protective effect upon cardiac events, oestrogen therapy alone or in combination with progestins did not show any protective effect against stroke.

Heart and oestrogen/progestin replacement study

It must be pointed out that the above studies were conducted on healthy women and that, consequently, the effect of the adjunct of a progestin to oestrogens in patients at risk for cardiovascular disease may be different because of the effect of progestins upon lipid profile and vascular functions. The results of the recently published heart and oestrogen/progestin replacement study have added some critical data on the effect of HRT for secondary prevention in women with coronary artery disease (Hulley et al., 1998).

The heart and oestrogen/progestin replacement study did not show any protective effect of CEE and MPA (2.5 mg in a continuous combined regimen) on cardiovascular end points in elderly women with coronary artery disease and suggested a possible increase in the occurrence of acute coronary events during the first year of hormone therapy. However, the study is affected by several important methodological and statistical problems which make its interpretation difficult and its conclusions useless for clinical practice.

The first problem with the study is the relatively old age of the study population (67.5 years). Women at this age are rarely considered for initiation of HRT. The major concern with the study is that, although conducted in a relatively large patient population, it does not have enough statistical power to detect significant differences between patients allocated to HRT or placebo. Indeed the sample size of the study was calculated on the basis of a yearly event rate of 5% in the placebo group, while the observed event rate in this group was 3.3%. With such
an event rate the sample size should have been at least twice of the reported study. Another important problem is the relatively short duration of the study. The ‘per protocol’ estimated duration of the trial should have been 4.75 years, while the study was interrupted without a clear explanation at 4.1 years, when there was a significant trend towards a reduction in cardiac events in the hormone treated group. If the study had continued to its planned duration it would have probably shown a significant reduction in the occurrence of coronary events in the hormone-treated patients.

Another important issue which makes the results of the study difficult to interpret is the high use of statins administered for hypercholesterolaemia in the placebo group (22%). The use of statins significantly reduces cardiovascular mortality and morbidity in patients with coronary artery disease, as shown by the Scandinavian simvastatin survival study, in which female cardiovascular mortality was seen to decrease by >35% (Miettinen, 1997). Therefore patients allocated to the placebo group were treated with drugs able to influence the results of the study. Finally, heart and oestrogen/progestin replacement study did not evaluate unopposed oestrogen replacement therapy, other combined oestrogen–progestin association or women without coronary artery disease.

Based on the above considerations, the heart and oestrogen/progestin replacement study should not be regarded as a negative, but rather as an inconclusive investigation and its findings should not be extrapolated to other hormone regimens or to healthier, younger individuals. No women should be interrupting their oestrogen replacement therapy or HRT regimens because of the heart and oestrogen/progestin replacement study.

Conclusions

The data available at present on the cardiovascular effect of progestins suggests that the adjunct of these hormones to oestrogen replacement therapy may have different effects upon the cardiovascular system and that these effects depend on type, dosage and route of administration of progestins. Some progestin therapies may antagonize the favourable cardiovascular effect of oestrogens. Furthermore, the therapeutic scheme of administration (continuous or sequential) may influence the cardiovascular effects of the hormones and it is therefore possible that similar hormones have different effects according to their schemes of administration. While in menopausal women without risk factors for coronary events any progestin can be safely administered, in menopausal patients at risk for coronary artery disease, natural progesterone seems to be the progestational agent of choice as it avoids the unwanted detrimental effect of synthetic progestins. Further randomized studies are warranted to evaluate the effect of oestrogen replacement therapy and HRT upon cardiovascular events in menopausal women. Until completion of these studies HRT should be seen by cardiologists with no early enthusiasm but also with no fear.
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