

## Menopause, Hormone Therapy and Cardiovascular and Cerebrovascular Disease

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### Abstract

**Introduction:** Cardiovascular disease is the leading cause of death and morbidity among postmenopausal women, and oestrogen deficiency may be an important factor in its development. The role of oestrogen replacement in preventing cardiovascular disease is controversial. The aim of this descriptive review is to analyse the available data and to recommend evidence-based practice guidelines pertaining to hormone therapy in the context of cardiovascular and cerebrovascular health. **Materials and Methods:** Relevant clinical trials were identified by computerised literature search. The collated data were presented to fellow gynaecologists for review, analysis of results and discussion in a series of meetings dedicated to finding the best evidence in menopause management. The evidence was used to formulate clinical practice guidelines for the management of women with significant cardiovascular risk factors. **Results:** Evidence from animal studies and observational trials supported a cardio-protective effect of postmenopausal hormone therapy. More recent randomised clinical trial data have shown no significant reduction of coronary heart disease, and have confirmed a higher incidence of stroke and venous thromboembolism. **Conclusions:** The evidence is widely divergent regarding postmenopausal hormone therapy and cardiovascular risk. More consistent data are available reporting an increased risk in the incidence of venous thromboembolism and stroke. It is important to be clear about the indications of hormone use and to utilise alternative modalities to promote cardiovascular health in the postmenopausal population.

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**Key words:** Cerebrovascular accident, Hormone replacement therapy, Stroke, Thromboembolism

### Introduction

Cardiovascular disease is a major cause of morbidity among postmenopausal women. Up to the age of 50 years, the prevalence of coronary artery disease (CAD) among women is lower than among men, but the incidence rises significantly after the menopause.<sup>1-3</sup> This suggests a causal relationship between oestrogen deficiency and cardiovascular disease. Furthermore there is a rising trend in mortality from CAD among women, despite a decrease in deaths among men.<sup>1</sup>

Although similar mechanisms operate to induce coronary disease in women and men, there are gender-related differences regarding the development, course, prognosis and survival outcome of CAD.<sup>1</sup> Sex hormones modify the course of CAD. Several physiological alterations in the menopause affect lipid metabolism, biochemical and

coagulation factors. Total cholesterol, triglycerides and low-density lipoprotein cholesterol levels rise; high-density lipoprotein cholesterol decreases slightly.<sup>4,5</sup> Low levels of high-density lipoprotein (HDL)-cholesterol and high low-density lipoprotein (LDL)-cholesterol are considered independent atherogenic risk factors. An additional change is the activation of the coagulation pathway, with an increase in fibrinogen and plasminogen activator inhibitor-1 values.<sup>6,7</sup> Endothelial dysfunction and impaired vasoreactivity of the coronary artery is more pronounced in postmenopausal women.<sup>8</sup> These menopause-associated physiological changes increase atherogenic risk and are associated with oestrogen deficiency.

Large epidemiological studies have found evidence of a heightened cardiovascular risk in women with early menopause. Data suggest that every year by which

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menopause is delayed contributes to a 2% reduction in cardiovascular mortality risk.<sup>9,10</sup> Studies found that women with premature menopause have a shorter life-expectancy compared to women who reached menopause after the age of 55.<sup>10,11</sup> These findings support the theory that increased oestrogen exposure mitigates cardiovascular risk in women.

The hypothesis that oestrogen exposure provided protection against the vascular pathology underlying cardiac and cerebrovascular disease was based on laboratory and clinical evidence, with many observational studies<sup>12-18</sup> demonstrating reduced cardiovascular disease risk in postmenopausal hormone users. However, the earlier findings are at odds with evidence provided by later randomised clinical trials that have failed to demonstrate cardiovascular and cerebrovascular benefit with hormone therapy, even on long-term follow-up, with some evidence suggesting an even higher risk of myocardial infarct and stroke among users.<sup>19-22</sup>

The aims of this review were to analyse and compare the available data pertaining to hormone therapy and cardiovascular, cerebrovascular and thromboembolic disease, and to recommend practice guidelines based on this evidence.

## Materials and Methods

The search criteria included all English-language clinical trials performed in humans published between 1960 and 2006. The evidence considered was derived from laboratory and animal experiments, observational non-randomised studies and randomised clinical trials. The relevant literature was identified and retrieved from a search of PubMed, Medline and the Cochrane Database, using terms including but not restricted to menopause, postmenopause, hormone replacement, hormone therapy, cardiovascular disease, cerebrovascular accident, stroke and thromboembolism. In addition, references from textbooks and published articles were used. After employing the search methods outlined above, the reviewers selected the trials for consideration. Data regarding patient characteristics, hormone therapy, cardiovascular risk factors, and cardiovascular, cerebrovascular and thromboembolic disease were extracted. The collated data were presented to fellow gynaecologists for analysis and discussion during a series of weekly meetings held at the Department of Obstetrics and Gynaecology, National University Hospital, Singapore. The gynaecologists attending the meetings were the clinical staff working in the department. At each meeting the individual studies were discussed, the data assessed and analysed and at the end of the series of meetings recommendations on management issues and practice guidelines were produced. The date of the last literature search was November 30, 2006.

## Results

### 1. Cardiovascular Disease and Hormone Therapy

Experimental data obtained from animal models of arterial injury have demonstrated the ability of oestrogen to accelerate re-endothelialisation<sup>23</sup> and inhibit neointimal thickening after arterial injury<sup>24</sup> and ameliorate serum lipid patterns,<sup>25</sup> factors which contribute to the anti-atherogenic effect of oestrogen. There is also evidence that oestrogen may increase inflammation or destabilise raised atherosclerotic plaques.<sup>26</sup> Combined oestrogen and progestin therapy decreased the accumulation of LDL-cholesterol in the coronary arteries of oophorectomised rabbits<sup>27</sup> and non-human primates.<sup>28</sup> Other studies in non-human primates indicate that oestrogen replacement therapy is effective in inhibiting the progression of early stage atherosclerosis (fatty streak) but less effective at reversing more advanced atherosclerosis (established plaque).<sup>29</sup>

Human clinical studies have demonstrated a mixed though largely beneficial effect of oestrogen on the individual pathophysiological components of cardiovascular disease. These components include vasodilatation, endothelial damage and plaque formation, lipid metabolism, hypercoagulability and inflammatory processes. Conjugated oestrogen administered to postmenopausal women was shown to significantly improve flow-mediated brachial artery dilatation compared with placebo, either when used alone<sup>30</sup> or with medroxyprogesterone acetate.<sup>31</sup> Hormone therapy was additionally associated with decreased carotid intima-media thickness<sup>32,33</sup> and a lower occurrence of carotid atherosclerotic plaques.<sup>34</sup>

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial<sup>35</sup> demonstrated a favourable change in the serum lipid profile with hormone therapy. Healthy postmenopausal women aged between 45 and 64 years were randomly assigned to receive placebo, conjugated equine oestrogen alone or oestrogen plus progestin, and were monitored in terms of blood pressure, serum insulin, glucose intolerance, and serum levels of fibrinogen, triglyceride, LDL and HDL-cholesterol. Oestrogen alone or in combination with cyclical or continuous progestin was associated with an increase in mean HDL-cholesterol levels ranging from 0.03 to 0.14 mmol/L ( $P < 0.001$ ), with the average increase similar among the treatment groups. There was a concurrent decrease in mean LDL-cholesterol levels (0.37 to 0.46 mmol/L,  $P < 0.001$ ) and an increase in mean triglyceride levels (0.13 to 0.15 mmol/L,  $P < 0.001$ ) compared to placebo. Mean fibrinogen levels were significantly lower over time in the active treatment groups (by 0.02 to 0.06 g/L,  $P < 0.001$ ) compared with placebo. The improvement in lipid profile among women on hormone therapy was observed without detectable changes in blood

pressure or post-challenge insulin levels.

Conjugated oestrogen alone or with progestin reduced the expression of cell adhesion molecules (ICAM-1 and VCAM-1), higher levels of which are found in patients with CAD.<sup>36</sup> Other inflammatory markers, including tumour necrosis factor (TNF) and C-reactive protein (CRP), are involved in several atherogenic processes.<sup>37,38</sup> Conjugated oestrogen was observed to decrease TNF levels from baseline in hypertensive or overweight postmenopausal women,<sup>39</sup> but higher levels of CRP were reported in women using either unopposed oestrogen or oestrogen plus progestin.<sup>35,38,40</sup>

Following surgical menopause, higher levels of procoagulant markers (soluble thrombomodulin, soluble leukocyte adhesion molecule P-selectin, plasminogen activator inhibitor, tissue plasminogen activator) have been reported.<sup>41</sup> Hormone therapy was associated with significant reductions in the levels of von Willebrand factor, soluble thrombomodulin, and tissue plasminogen activator. Significant reductions in von Willebrand factor levels have been observed following long-term use of transdermal oestrogen.<sup>42</sup>

These findings are in support of many observational studies that demonstrate the association between postmenopausal hormone therapy and a lower incidence of CAD.<sup>15,43</sup> However, this evidence of the cardioprotective benefit of postmenopausal hormone therapy derived from observational trials and from animal studies was not supported by later randomised trials.

The efficacy of oestrogen-progestin therapy in the context of primary prevention of cardiovascular disease was studied in the Women's Health Initiative trial. Women between the ages of 50 and 79 years with an intact uterus at the time of initial screening were randomly assigned to receive one daily tablet containing either 0.625 mg of conjugated equine oestrogen and 2.5 mg of medroxyprogesterone acetate or placebo.<sup>44</sup> Baseline characteristics were very similar between groups. Only 2% of subjects had previous CAD and 4.4% reported previous CAD, stroke, or transient cerebral ischaemia. Cardiac events that were outcome measures included acute myocardial infarction necessitating overnight hospitalisation, death due to CAD, or silent myocardial infarction identified on serial electrocardiography performed at 3 and 6 years. The lipid profile of participants was also assessed. The results showed no significant reduction of coronary disease. Women taking oestrogen plus progestin had greater reductions in the total cholesterol, LDL-cholesterol, glucose and insulin levels, and greater increases in the HDL-cholesterol and triglyceride levels than women in the placebo group. The adjusted hazard ratio for CAD was 1.24 among women on oestrogen plus progestin therapy (adjusted 95% confidence interval

[CI], 0.97-1.60); in other words, women on hormone therapy had a 24% higher risk of CAD than women on placebo. Hazard ratios for non-fatal myocardial infarction and cardiac death were 1.28 and 1.10, respectively. There were 39 cases of CAD per 10,000 person-years and 33 cases per 10,000 person-years for hormone therapy and placebo, respectively. No significant differences were observed with regard to coronary revascularisation, hospitalisation for angina, confirmed angina, acute coronary syndrome, or congestive heart failure. The elevated risk of CAD with hormone use was apparent after 1 year of follow-up (hazard ratio [HR], 1.81; 95% CI, 1.09-3.01). The cumulative hazard rates for CAD of treatment and placebo groups only began to converge after the 6<sup>th</sup> year of follow-up. The authors discovered that higher baseline levels of LDL-cholesterol were associated with excess coronary heart disease risk in women receiving hormone therapy ( $P = 0.01$ ); however other clinical characteristics, such as age, previous use of hormone therapy and body mass index, did not significantly modify the treatment-related risk of CAD. Even though the results from this trial did not reach statistical significance, they demonstrated that hormone therapy had no beneficial effect on primary prevention of heart disease as was once thought to be the case. Women with hysterectomy using oestrogen alone did not demonstrate a significant difference in the risk of CAD over a surveillance period of 6.8 years compared to women using placebo (HR, 0.91; adjusted 95% CI, 0.75-1.15).<sup>45</sup>

Observational studies have suggested an association between postmenopausal hormone therapy and lower rates of recurrent cardiac events, even among users with existing CAD<sup>46-49</sup> in whom there are 35% to 80% fewer recurrent cardiac events compared to non-users.<sup>50-56</sup> Because of these findings, oestrogen was purported to be a useful adjunct treatment for secondary prevention of coronary disease. However this hypothesis was not supported by the findings from randomised trials. The conflicting data from observational studies and randomised trials may be a result of basic differences in the characteristics of the study populations, including number of years since menopause and baseline risk of CAD, as well as the methodological limitations of observational studies.

In the Estrogen Replacement and Atherosclerosis (ERA) trial<sup>31</sup> a similar significant decrease in LDL-cholesterol and significant increase in HDL-cholesterol was demonstrated with oestrogen, used alone or in combination with progestins, compared to placebo. In over 300 women with established CAD, those randomly assigned to receive 0.625 mg of conjugated oestrogen alone or plus 2.5 mg of medroxyprogesterone acetate daily showed significant decreases in LDL-cholesterol (9.4% and 16% respectively vs. 1.3% with placebo,  $P < 0.05$ ) and significant increases

in HDL-cholesterol (18.8% and 14.2% respectively vs. 6.8% with placebo,  $P < 0.01$ ) over the 3-year surveillance period. However, when minimal coronary-artery diameters and other secondary angiographic outcomes were measured at follow-up it was demonstrated that neither treatment regime altered the progression of atherosclerosis compared to placebo. The rate of new coronary lesion occurrence was similar among the treatment and placebo groups.

The Heart and Estrogen/progestin Replacement Study (HERS) was the first large secondary prevention trial studying the effect of hormone therapy in 2763 women with an intact uterus and existing coronary disease.<sup>19</sup> Postmenopausal women enrolled in this trial were randomly assigned to a daily dose of 0.625 mg conjugated equine oestrogen plus 2.5 mg medroxyprogesterone acetate or placebo. The primary outcome was non-fatal myocardial infarction (MI) or death from CAD. There were no significant differences in primary outcomes between the treatment and placebo groups, either over an average surveillance period of 4.1 years in the initial trial (172 women in the hormone group vs. 176 women in the placebo group; relative hazard [RH], 0.99; 95% CI, 0.80-1.22),<sup>19</sup> or over an extended period of 2.7 additional years (in HERS II).<sup>20</sup> This was despite a significant decrease in LDL-cholesterol levels (by 11%) and increased HDL-cholesterol levels (by 10%) in the hormone group compared to the placebo group. Sub-group analysis of data showed that women on hormone therapy with concurrent statin use had a lower rate of non-fatal myocardial infarct or CAD death (RH, 0.79; 95% CI, 0.63-0.99,  $P = 0.04$ ). Women on hormone therapy without statin use showed an increased risk of 75% for primary events in the first year (RH, 1.75; 95% CI, 1.02-3.03,  $P = 0.04$ ).<sup>21</sup> Statin users also showed a lower total mortality (RH, 0.67; 95% CI, 0.51-0.87,  $P = 0.003$ ) and lower incidence of venous thromboembolism (RH, 0.45; 95% CI, 0.23-0.88,  $P = 0.02$ ). There was a significant early increase in the risk of primary events among hormone users who did not take statins (RH, 1.75; 95% CI, 1.02-3.03;  $P = 0.04$ ). However statin users tended to be healthier and better educated, with fewer comorbid conditions compared to non-users. They also were more likely to have had coronary revascularisation prior to randomisation. Despite the differences seen after the first year of observation, the risk hazards of myocardial infarct and CAD death among hormone users were very similar between statin-users and non-users after 4.1 years of follow-up (RH, 0.99 vs. RH, 0.97).

Herrington et al<sup>31</sup> studied the effect of hormone therapy on women with angiographically-confirmed coronary atherosclerosis in a randomised placebo-controlled trial over 3.2 years. Baseline characteristics, including concomitant use of nitrates, were similar between the

groups. Although the use of conjugated oestrogen or oestrogen plus progestin was associated with a significant decrease in LDL-cholesterol levels (9.4% and 16.5% respectively vs. 1.3% in controls,  $P < 0.05$ ) and a significant increase in HDL-cholesterol levels (18.8% and 14.2% respectively vs. 6.8%,  $P < 0.01$ ), neither treatment altered the progression of coronary atherosclerosis. There were no significant differences in the incidence of new lesions, minimal coronary-artery diameter, cardiac deaths or non-fatal myocardial infarcts between groups.

Following HERS and HERS II, other trials were designed to assess the impact of alternate oestrogen preparations. In the WELLHART trial, the use of 17 $\beta$ -estradiol alone or with progestins in postmenopausal women with at least one coronary artery lesion failed to slow the progression of angiographically-determined atherosclerosis after 3.3 years of follow-up.<sup>22</sup> The degree of coronary artery stenosis increased by a mean of 0.29% in the oestrogen-only arm compared to placebo, and decreased by 0.65% in the oestrogen-progestin arm compared to placebo ( $P = 0.66$ ). This observation was apparent despite the greater decrease in LDL-cholesterol in the oestrogen alone and oestrogen plus progestin groups compared to placebo (22.2% and 20.1% respectively vs. 14.9% with placebo,  $P = 0.02$ ), and the greater increases in HDL cholesterol among treatment groups (12% and 9.4% respectively vs. 5.7% with placebo,  $P = 0.002$ ).

The Estrogen therapy for Prevention of Reinfarction Trial (ESPRIT) was a placebo-controlled secondary prevention trial of postmenopausal women aged 50 to 69 years, who had survived a first myocardial infarction. These women randomly received either oestradiol valerate (2 mg) or placebo for 2 years. The frequency of reinfarction or cardiac death (rate ratio [RR], 0.99; 95% CI, 0.70-1.41;  $P = 0.97$ ) and all-cause mortality (RR, 0.79; 95% CI, 0.50-1.27;  $P = 0.34$ ) did not differ between the groups.<sup>57</sup> The use of transdermal oestrogen was also found to be associated with a higher (non-significant) incidence of myocardial infarct or cardiac death, compared to non-users, among postmenopausal women with ischaemic heart disease.<sup>58</sup>

The difference in the outcomes of animal studies, observational trials and randomised clinical trials may lie in the timing of hormone initiation and vascular endothelial integrity prior to therapy. Animal models of coronary disease have demonstrated that the ability of oestrogen therapy to prevent plaque formation depends on the underlying health of the endothelium.<sup>23-29</sup> The data imply that the timing of hormone therapy initiation is more important than the type of hormones used with regard to cardiovascular outcomes. When oophorectomised non-human primates with minimal coronary atherosclerosis were given oestrogen with an atherogenic diet, 2 years of

therapy was associated with a 70% reduction in atherosclerosis.<sup>59</sup> When oophorectomised primates were fed an atherogenic diet in a hypoestrogenic state for 2 years, with delayed oestrogen therapy, there was no beneficial effect on atherosclerotic progression, despite 2 years of therapy in combination with a non-atherogenic diet.<sup>60</sup>

Plaque progression on already damaged endothelium is not affected by oestrogen therapy. The association between ageing and impaired endothelial function may be the main reason why postmenopausal women did not enjoy the expected cardioprotective benefits while using hormones in randomised trials. On this reasoning, the absence of a cardioprotective effect for users of hormone therapy in the large HERS and WHI trials may be due to the presence of existing coronary atherosclerosis, even in subjects with no clinically documented cardiovascular disease. The women enrolled in the WHI were older (50 to 79 years) and showed a higher prevalence of smoking, diabetes, hyperlipidaemia and higher body mass index. The effect of timing of oestrogen therapy initiation can be inferred from the oestrogen-only arm of the WHI.<sup>45</sup> The hazard ratio for CHD in women aged 50 to 59 years was 0.56 (95% CI, 0.30-1.03), 0.92 in the 60 to 69 years group (95% CI, 0.69-1.23) and 1.04 in the 70 to 79 years group (95% CI, 0.75-1.44) although this trend was not statistically significant.

## 2. Cerebrovascular Disease and Hormone Replacement Therapy

The incidence of stroke is very much age-dependent. Because women tend to live longer than men, the incidence of new strokes and stroke-related deaths is greater among older females than males.<sup>61</sup> Premenopausal women have a lower incidence of strokes compared to men and postmenopausal women.

The evidence from animal and human studies of the benefits of oestrogen on vessel function, particularly with effects like vasodilation, accelerated endothelial repair and improved lipid profile, suggests a protective effect on the cerebrovascular as well as cardiovascular system. Oestrogens have demonstrated neuroprotective effects against cerebral ischaemia that include antioxidant and anti-inflammatory effects, modulation of protein synthesis, inhibition of apoptosis and trophic effects and preservation of microvascular blood flow in the ischaemic area. Oestrogens maintain the functions and promote activity of key neural structures like the hippocampus, basal forebrain and the dopaminergic, serotonergic and noradrenergic systems, thus conferring a resilience against damage from various agents<sup>62</sup> and blocking neurotoxic effects.<sup>63</sup> During menopause these systems undergo a reversible decline which appears to respond to oestrogen replacement.<sup>64</sup> Oestrogens at concentrations ranging from physiological

to pharmacological are neuroprotective in a variety of in vitro and in vivo models of cerebral ischaemia and brain trauma as well as in reducing key neuropathologies of Alzheimer's disease.<sup>62</sup> The observational studies that have addressed hormone therapy and risk of stroke tend to support a protective effect of oestrogen, although this evidence was less consistent than that for protection against coronary heart disease.<sup>65-68</sup> The main evidence is derived from 3 main clinical trials: WHI,<sup>69</sup> HERS,<sup>70</sup> and the Women's Estrogen for Stroke Trial (WEST).<sup>71</sup>

The relationship between hormone therapy and stroke was assessed in both the oestrogen plus progestin and oestrogen only arms of the WHI trial and in the HERS. In the WHI trial of oestrogen-progestin versus placebo, the hazard ratio of all strokes was 1.31 (95% CI, 1.02-1.68).<sup>69</sup> This translated into 7 additional strokes in the treatment group per 10,000 women per year. The risk of ischaemic strokes, but not haemorrhagic strokes, was significantly increased (HR 1.44; 95% CI, 1.09-1.90), with 8 additional events per 10,000 women per year. The excess risk for all strokes attributed to hormone therapy appeared to be present in all subgroups of women examined. There appeared to be no interaction between hormone therapy and other risk factors for stroke. The increase in the risk of stroke emerged after the first year and persisted through the 5 years of treatment. In the oestrogen-only arm of the WHI, the hazard ratio for stroke was 1.39 (adjusted 95% CI, 0.97-1.99), or an absolute excess of 12 additional strokes per 10,000 women per year, although it is not statistically significant by strict criteria.<sup>45</sup>

The HERS examined hormone replacement and myocardial infarction among postmenopausal women. No reduction in this primary end-point was found after a mean of 4.1 years of surveillance. When data regarding stroke incidence were analysed, conjugated oestrogen and progestin did not significantly alter the incidence of transient ischaemic attacks, non-fatal or fatal stroke events in these women.<sup>70</sup>

The WEST was conducted to determine if therapy with 17- $\beta$  oestradiol (1mg daily) reduced a woman's risk of stroke and death during menopause.<sup>71</sup> Six hundred and sixty-four women who had recently suffered an ischaemic stroke or transient ischaemic attack were recruited and randomised to receive either 17- $\beta$  oestradiol or placebo, in this double-blind placebo-controlled trial. The primary end-point was stroke and death. Secondary end-points included transient ischaemic attacks and non-fatal myocardial infarcts. During a mean follow-up period of 2.8 years, there were 99 strokes or deaths among women in the oestrogen group compared with 93 strokes or deaths in the placebo group (HR, 1.1; 95% CI, 0.8-1.4). There was evidence of increased early risk among women randomised

to oestradiol. During the first 3 months of surveillance, there were 3 fatal and 18 non-fatal strokes in the oestradiol group compared to 1 fatal and 8 non-fatal strokes in the placebo group (relative risk [RR], 2.3; 95% CI, 1.1-5.0;  $P = 0.03$ ). The evidence also suggested that fewer women randomised to 17- $\beta$  oestradiol had only mild or no neurological deficits following a stroke compared to placebo (19% vs. 33%;  $P = 0.12$ ) and were less likely to regain functional independence compared to women on placebo (44% vs. 58%;  $P = 0.16$ ), leading to the conclusion that 17- $\beta$  oestradiol is ineffective for the prevention of strokes.

The clinical trials reviewed do not demonstrate evidence of benefit from the use of conjugated oestrogen or 17- $\beta$  oestradiol with regard to primary or secondary prevention of stroke. There was in fact a deleterious effect with more strokes reported in the treatment groups compared to placebo, although numerically these differences were not significant. This finding should be reflected in the management of postmenopausal women with respect to cerebrovascular disease.

### 3. Venous Thromboembolism and Hormone Replacement Therapy

Data from observational studies and controlled trials consistently demonstrate that current oestrogen use is associated with an increase in the incidence of venous thromboembolic events.<sup>72,73</sup> Several studies found that the risk of thromboembolism appeared greatest in the first year of use. Analysis of data from the WHI trial<sup>74</sup> showed that venous thrombosis occurred in 3.5 per 1000 women-years of participants on oestrogen-plus-progestins compared to 1.7 per 1000 person-years on placebo (HR 2.06; 95% CI, 1.57-2.70). Older age and obesity further increased the risk of thromboembolism. In the follow-up to HERS, the relative hazard of venous thromboembolic events was 2.08 for 6.8 years of use (95% CI, 1.28-3.40).<sup>75</sup> A meta-analysis of available data from randomised clinical trials and observational studies calculates that current use of hormone therapy is associated with an absolute increase of 1.5 events per 10,000 women per year, or a relative risk of 2.14 (95% CI, 1.64-2.81).<sup>73</sup> The timing of thromboembolic events also suggested a higher risk during the first year of use than after the first year (RR 3.49; 95% CI, 2.33-5.59).<sup>75-80</sup>

#### Guidelines

This data have enabled certain recommendations to be made based on the available evidence. There are appropriate indications for hormone use in postmenopausal women. Given the current evidence, hormone therapy should not be initiated for the main purpose of preventing cardiovascular or cerebrovascular disease.

### 1. Recommendations on Hormone Therapy and Cardiovascular Disease

#### (A) Primary prevention (no history of cardiovascular disease)

Hormone therapy should not be initiated for the main purpose of primary prevention of CAD in postmenopausal women. The initiation and continuation of hormone therapy should be based on assessment of non-cardiovascular benefits and risks, and the patient's preference.

#### (B) Secondary prevention (history of cardiovascular disease)

Hormone therapy should not be initiated in women with established CAD for the purpose of preventing recurrent cardiac events.

The decision to continue, stop or reinstate hormone therapy in long-term users with established CAD should be based on assessment of non-cardiovascular benefits and risks, and the patient's preference. If coronary disease develops while on hormone therapy, consider discontinuing hormone therapy and initiating thromboprophylaxis where necessary.

Women at high risk of myocardial infarct or stroke will benefit from joint management with the cardiologist and the use of statins, anti-hypertensives and other medications where appropriate.

#### (C) Recommendations for cardiovascular health in postmenopausal women

Lifestyle modifications are key and include cessation of cigarette smoking, physical activity, weight reduction and healthy eating.<sup>81</sup>

Major risk factor modification would include maintaining optimal blood pressure and lipid levels through lifestyle approaches, instituting pharmacotherapy when necessary.<sup>81</sup>

### 2. Recommendations on Hormone Therapy and Cerebrovascular Disease

#### (A) Primary prevention of cerebrovascular disease

Therapy with oestrogen alone or in combination with progestin should not be initiated or continued with the aim of stroke prevention, as there is no beneficial or protective effect.

#### (B) Secondary prevention of established cerebrovascular disease

The use of hormone therapy in women with previous stroke is not associated with any significant reduction in the risk of recurrent cerebrovascular events and is not recommended.

### 3. Recommendations on Hormone Therapy and Thromboembolic Disease

#### (A) Personal history of venous thromboembolism

Women with a personal history of venous thromboembolism, with or without an underlying thrombophilia, should be referred to a haematologist. Such women should avoid using oral hormone therapy because of the relatively high risk of recurrent venous thromboembolism, unless concurrent anticoagulation therapy is employed. Transdermal therapy is preferred in a situation in which the use of hormones is deemed necessary<sup>82</sup> but specialist advice should be sought. Women over 50 years old with a personal history of venous thromboembolism within the previous year should be screened for malignancy and connective tissue disorders.<sup>83</sup>

#### (B) Family history of venous thromboembolism.

Where a thrombophilic defect has been identified, the family history of a woman without a personal history of venous thromboembolism, specialist advice for the individual is advisable. In general, women with antithrombin III defects or other clotting defects should avoid hormone therapy, unless concurrently using anticoagulation therapy. These women should be managed at specialist centres.<sup>83</sup> Hormone therapy should be avoided in the presence of multiple risk factors for venous thromboembolism.

### Conclusions

Postmenopausal hormone therapy is an important clinical tool for women requiring relief of vasomotor symptoms or other oestrogen deficiency effects. The question still remains as to why the null findings of the large randomised trials diverged widely from the findings of earlier laboratory and animal studies and from observational trials. Several methodological and biological differences may account for the discrepancies.

Observational studies examining the cardiovascular effects of hormone use may include as subjects women with a better coronary heart disease risk profile, who observe preventative care and who are more likely to opt for hormone therapy, thus introducing potential confounding factors (healthy compliant users).<sup>84</sup> On the other hand, prospective randomised trials have often included older women who would not normally be candidates for hormone therapy or those with pre-existing risk factors for coronary disease.<sup>85</sup> Thus, the cardiovascular risk associated with hormone therapy may have been underestimated in earlier studies, and the beneficial effects overestimated. Observational studies have limited ability to control for socio-economic factors that may have an important bearing on outcomes such as stroke and myocardial infarct incidence.

There are physical differences in the study populations of the observational and randomised trials that may account for the divergent results. By studying a very large cohort of postmenopausal women, Rodriguez et al<sup>86</sup> showed that the coronary benefits of hormone therapy were primarily seen women with lower body-mass indices. The mean BMI in the WHI was 28.5.

The number of years between menopause and initiation of hormone therapy is also important. Women who are older at initiation are more likely to have coronary endothelial damage and established atherosclerosis. Thus the mean age at which women begin postmenopausal hormone therapy is important. As animal data have suggested, the use of oestrogen should not be expected to prevent the progression from complicated plaques to clinical coronary events in older women with existing endothelial damage.

The most effective way of reducing the impact of cardiovascular disease on women's health is with an active approach from childhood maintained throughout life, with attention paid to nutrition, exercise, abstinence from smoking, prevention of obesity, early detection and treatment of hypertension, hyperlipidaemia, diabetes and other contributory factors.<sup>81,87</sup> Oestrogen therapy alone or with progestin should be reserved for women who have severe oestrogen-deficiency symptoms that are not relieved by other means, pharmacological or otherwise. Long-term oestrogen therapy for the purpose of promoting cardiovascular or cerebrovascular health should be avoided.

### REFERENCES

1. Stangl V, Baumann G, Stangl K. Coronary atherogenic risk factors in women. *Eur Heart J* 2002;23:1738-52.
2. Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and the risk of cardiovascular disease: the Framingham Study. *Ann Intern Med* 1976;85:447-52.
3. Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH. Menopause and the risk of coronary heart disease in women. *N Engl J Med* 1987;316:1105-10.
4. Stevenson JC, Crook D, Godsland IF. Influence of age and menopause on serum lipids and lipoproteins in healthy women. *Atherosclerosis* 1993;98:83-90.
5. Peters HW, Westendorp IC, Hak AE, Grobbee DE, Stehouwer CD, Hofman A, et al. Menopausal status and risk factors for cardiovascular disease. *J Intern Med* 1999;246:521-8.
6. Gebara OC, Mittleman MA, Sutherland P, Lipinska I, Matheny T, Xu P, et al. Association between increased estrogen status and increased fibrinolytic potential in the Framingham Offspring Study. *Circulation* 1995;91:1952-8.
7. Scarabin PY, Plu-Bureau G, Bara L, Bonithon-Kopp C, Guize L, Samama MM. Haemostatic variables in menopausal status: influence on hormone replacement therapy. *Thromb Haemost* 1993;70:584-7.
8. Taddei S, Virdis A, Ghiadoni L, Mattei P, Sudano I, Bernini G, et al. Menopause is associated with endothelial dysfunction in women. *Hypertension* 1996;28:576-82.
9. Van der Schouw YT, van der Graf Y, Steyerberg EW, Eijkemans MJC, Banga JD. Age at natural menopause as a risk factor for cardiovascular

- mortality. *Lancet* 1996;347:714-18.
10. Ossewaarde ME, Bots ML, Verbeek AL, Peeters PH, van der Graaf Y, Grobbee DE, et al. Age at menopause, cause-specific mortality and total life expectancy. *Epidemiology* 2005;16:556-62.
  11. de Kleijn MJ, van der Schouw YT, Verbeek AL, Peeters PH, Banga JD, van der Graaf Y. Endogenous estrogen exposure and cardiovascular mortality risk in postmenopausal women. *Am J Epidemiol* 2002;155:339-45.
  12. Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Willett WC, Rosner B, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996;335:453-61.
  13. Grodstein F, Stampfer MJ, Falkeborn M, Naessen T, Persson I. Postmenopausal hormone therapy and risk of cardiovascular disease and hip fracture in a cohort of Swedish women. *Epidemiology* 1999;10:476-80.
  14. Grodstein F, Manson JE, Stampfer MJ. Postmenopausal hormone use and secondary prevention of coronary events in the nurses' health study. A prospective, observational study. *Ann Intern Med* 2001;135:1-8.
  15. Grodstein F, Stampfer M. The epidemiology of coronary heart disease and estrogen replacement in postmenopausal women. *Prog Cardiovasc Dis* 1995;38:199-210.
  16. Stampfer MJ, Colditz GA, Willett WC, Manson JE, Rosner B, Speizer FE, et al. Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study. *N Engl J Med* 1991;325:756-62.
  17. Psaty BM, Heckbert SR, Atkins D, Lemaitre R, Koepsell TD, Wahl PW, et al. The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. *Arch Intern Med* 1994;154:1333-9.
  18. Nabulsi AA, Folsom AR, White A, Patsch W, Heiss G, Wu KK, et al. Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. The Atherosclerosis Risk in Communities Study Investigators. *N Engl J Med*;328:1069-75.
  19. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women: the Heart and Estrogen/progestin Replacement Study (HERS) research group. *JAMA* 1998;289:605-13.
  20. Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al. Cardiovascular disease outcomes during 6.8 years of Hormone Therapy. Heart and Estrogen/Progestin therapy follow-up (HERS II). *JAMA* 2002;288:49-57.
  21. Herrington DM, Vittinghoff E, Lin F, Fong J, Harris F, Hunninghake D, et al. Statin therapy, cardiovascular events, and total mortality in the Heart and Estrogen/Progestin Replacement Study (HERS). *Circulation* 2002;105:2962-67.
  22. Hodis HN, Mack WJ, Azen SP, Lobo RA, Shoupe D, Mahrer PR, et al. Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELLHART) Research Group: Hormone therapy and the progression of coronary atherosclerosis in post-menopausal women. *N Engl J Med* 2003;349:535-45.
  23. Krasinski K, Spyridopoulos I, Asahara T, van der Zee R, Isner JM, Losordo DW. Estradiol accelerates functional endothelial recovery after arterial injury. *Circulation* 1997;95:1768-72.
  24. Chen SJ, Li H, Durand J, Oparil S, Chen YF. Estrogen reduces myointimal proliferation after balloon injury of rat carotid artery. *Circulation* 1996;93:577-84.
  25. Kushwaha RS, Lewis DS, Carey KD, McGill HC Jr. Effects of estrogen and progesterone on plasma lipoproteins and experimental atherosclerosis in the baboon (*Papio sp.*). *Arterioscler Thromb* 1991;11:23-31.
  26. Arnal JF, Gourdy P, Elhage R, Garmy-Susini B, Delmas E, Brouchet L, et al. Estrogens and atherosclerosis. *Eur J Endocrinol* 2004;150:113-7.
  27. Haarbo J, Leth-Espensen P, Stender S, Christiansen C. Estrogen monotherapy and combined estrogen-progestogen replacement therapy attenuate aortic accumulation of cholesterol in ovariectomized cholesterol-fed rabbits. *J Clin Invest* 1991;87:1274-9.
  28. Adams MR, Kaplan JR, Manuck SB, Koritnik DR, Parks JS, Wolfe MS, et al. Inhibition of coronary artery atherosclerosis by 17-beta estradiol in ovariectomized monkeys: lack of an effect of added progesterone. *Arteriosclerosis* 1990;10:1051-7.
  29. Holm P, Andersen HL, Andersen MR, Erhardtson E, Stender S. The direct antiatherogenic effect of estrogen is present, absent, or reversed, depending on the state of the arterial endothelium: a time course study in cholesterol-clamped rabbits. *Circulation* 1999;100:1727-33.
  30. Lieberman EH, Gerhard MD, Uehata A, Walsh BW, Selwyn AP, Ganz P, et al. Estrogen improves endothelium-dependent, flow-mediated vasodilation in postmenopausal women. *Ann Intern Med* 1994;121:936-41.
  31. Herrington DM, Reboussin DM, Brosnihan KB, Sharp PC, Shumaker SA, Snyder TE, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000;343:522-9. Comment in: *N Engl J Med* 2000;343:572-4; *N Engl J Med* 2000;343:1891-2; author reply 1892-3; *N Engl J Med* 2000;343:1891; author reply 1892-3.
  32. Takahashi K, Tanaka E, Murakami M, Mori-Abe A, Kawagoe J, Takata K, et al. Long-term hormone replacement therapy delays the age related progression of carotid intima-media thickness in healthy postmenopausal women. *Maturitas* 2004;49:170-7.
  33. Sumino H, Ichikawa S, Kasama S, Kumakura H, Takayama Y, Sakamaki T, et al. Effect of transdermal hormone replacement therapy on carotid artery wall thickness and levels of vascular inflammatory markers in postmenopausal women. *Hypertens Res* 2005;28:579-84.
  34. Le Gal G, Gourlet V, Hogrel P, Plu-Bureau G, Touboul PJ, Scarabin PY. Hormone replacement therapy use is associated with a lower occurrence of carotid atherosclerotic plaques but not with intima-media thickness progression among postmenopausal women. The vascular aging (EVA) study. *Atherosclerosis* 2003;166:163-70.
  35. [No authors listed] Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA* 1995;273:199-208. Erratum in: *JAMA* 1995;274:1676. Comment in: *JAMA* 1995;274:1675-6. *JAMA* 1995;274:1675; author reply 1676. *JAMA* 1995;273:240-1.
  36. Haught WH, Mansour M, Rothlein R, Kishimoto TK, Mainolfi EA, Hendricks JB, et al. Alterations in circulating intercellular adhesion molecule-1 and L-selectin: further evidence for chronic inflammation in ischemic heart disease. *Am Heart J* 1996;132:1-8.
  37. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;342:836-43.
  38. Ridker PM, Morrow DA. C-reactive protein, inflammation, and coronary risk. *Cardiol Clin* 2003;21:315-25.
  39. Walsh BW, Cox DA, Sashegyi A, Dean RA, Tracy RP, Anderson PW. Role of tumor necrosis factor-alpha and interleukin-6 in the effects of hormone replacement therapy and raloxifene on C-reactive protein in postmenopausal women. *Am J Cardiol* 2001;88:825-8.
  40. van Baal WM, Kenemans P, van der Mooren MJ, Kessel H, Emeis JJ, Stehouwer CDA. Increased C-reactive protein levels during short-term hormone replacement therapy in healthy postmenopausal women. *Thromb Haemost* 1999;81:925-8.
  41. Lip GY, Blann AD, Jones AF, Beevers DG. Effects of hormone-replacement therapy on hemostatic factors, lipid factors, and endothelial function in women undergoing surgical menopause: implications for prevention of atherosclerosis. *Am Heart J* 1997;134:764-71.
  42. Seljeflot I, Arnesen H, Hofstad AE, Os I. Reduced expression of endothelial cell markers after long-term transdermal hormone replacement therapy in women with coronary artery disease. *Thromb Haemost* 2000;83:944-8.
  43. Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;117:1016-37.
  44. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, et al. Estrogen plus Progestin and the Risk of Coronary Heart Disease. *N Engl J Med* 2003;349:523-34. Comment in: *ACP J Club* 2004;140:46; *Evid Based Nurs* 2004;7:49; *N Engl J Med* 2003;349:519-21; *N Engl J Med* 2003;349:521-2.
  45. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. The Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701-12.
  46. Bush TL. Noncontraceptive estrogen use and risk of cardiovascular

- disease: an overview and critique of the literature. In: Korenman SG, editor. *The Menopause: Biological and Clinical Consequences of Ovarian Failure: Evolution and Management*. Norwell, Mass: Serono Symposia, 1990:211-23.
47. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991;20:47-63.
  48. Psaty BM, Heckbert SR, Atkins D, Lemaitre R, Koepsell TD, Wahl PW, et al. The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. *Arch Intern Med* 1994;154:1333-9.
  49. Sidney S, Petitti DB, Quesenberry CP Jr. Myocardial infarction and the use of estrogen and estrogen-progestogen in postmenopausal women. *Ann Intern Med* 1997;127:501-8.
  50. Bush TL, Barrett-Connor E, Cowan LD, Criqui MH, Wallace RB, Suchindran CM, et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. *Circulation* 1987;75:1102-9.
  51. Sullivan JM, Vander Zwaag R, Hughes JP, Maddock V, Kroetz FW, Ramanathan KB, et al. Estrogen replacement and coronary artery disease. *Arch Intern Med* 1990;150:2557-62.
  52. Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. *Arch Intern Med* 1991;151:75-8.
  53. O'Brien JE, Peterson ED, Keeler GP, Berdan LG, Ohman EM, Faxon DP, et al. Relation between estrogen replacement therapy and restenosis after percutaneous coronary interventions. *J Am Coll Cardiol* 1996;28:1111-8.
  54. Newton KM, LaCroix AZ, McKnight B, Knopp RH, Siscovick DS, Heckbert SR, et al. Estrogen replacement therapy and prognosis after first myocardial infarction. *Am J Epidemiol* 1997;145:269-77.
  55. Sullivan JM, El-Zeky F, Vander Zwaag R, Ramanathan KB. Effect on survival of estrogen replacement therapy after coronary artery bypass grafting. *Am J Cardiol* 1997;79:847-50.
  56. O'Keefe JH, Kim SC, Hall RR, Cochran VC, Lawhorn SL, McCallister BD. Estrogen replacement therapy after coronary angioplasty in women. *J Am Coll Cardiol* 1997;29:1-5.
  57. Cherry N, Gilmour K, Hannaford P, Heagerty A, Khan MA, Kitchener H, et al. ESPRIT team. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. *Lancet* 2002;360:2001-8.
  58. Clarke SC, Kelleher J, Lloyd-Jones H, Slack M, Schofield PM. A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: the Papworth HRT atherosclerosis study. *Br J Obstet Gynaecol* 2002;109:1056-62.
  59. Adams MR, Kaplan JR, Manuck SB, Koritnik DR, Parks JS, Wolfe MS, et al. Inhibition of coronary artery atherosclerosis by 17-beta estradiol in ovariectomized monkeys: lack of an effect of added progesterone. *Arteriosclerosis* 1990;10:1051-7.
  60. Williams JK, Shively CA, Clarkson TB. Determinants of coronary artery reactivity in premenopausal female cynomolgus monkeys with diet-induced atherosclerosis. *Circulation* 1994;90:983-7.
  61. Wolf PA, D'Agostino RB, O'Neal A, Sytkowski P, Kase CS, Belander AJ, et al. Secular trends in stroke incidence and mortality. *Stroke* 1992;23:1551-5.
  62. McEwan BS. Genome and Hormones: Gender differences in physiology. Invited review: estrogens on the brain: multiple sites and molecular mechanisms. *J Appl Physiol* 2001;91:2785-801.
  63. McEwan ES, Alves SH. Estrogen actions in the central nervous system. *Endocr Rev* 1999;20:279-307.
  64. Kimura D. Sex differences in the brain. *Sci Am* 1992;267:119-25.
  65. Paganini-Hill A, Ross RK, Henderson BE. Postmenopausal estrogen treatment and stroke: a prospective study. *BMJ* 1988;297:519-22.
  66. Hunt K, Vessey M, McPherson K. Mortality in a cohort of long-term users of hormone replacement therapy: an updated analysis. *Br J Obstet Gynaecol* 1990;97:1080-6.
  67. Finucane FF, Madans JH, Bush TL, Wolf PH, Kleinman JC. Decreased risk of stroke among postmenopausal hormone users: results from a national cohort. *Arch Intern Med* 1993;153:73-9.
  68. Falkeborn M, Persson I, Terent A, Adami HO, Lithell H, Bergstrom R. Hormone replacement therapy and the risk of stroke: follow-up of a population-based cohort in Sweden. *Arch Intern Med* 1993;153:1201-9.
  69. Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, Kooperberg C, Baird A, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: The Women's Health Initiative Memory Study: A randomized controlled trial. *JAMA* 2003;289:2673-84.
  70. Simon JA, Hsia J, Cauley JA, Richards C, Harris F, Fong J, et al. Postmenopausal Hormone Therapy and Risk of Stroke: the Heart and Estrogen/progestin Replacement Study (HERS). *Circulation* 2001;103:638-42.
  71. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A Clinical Trial of Estrogen-Replacement therapy after Ischaemic Stroke. Women's Estrogen for Stroke Trial (WEST). *N Engl J Med* 2001;345:1243-9.
  72. Daly E, Vessey MP, Hawkins MM, Carson JL, Gough P, Marsh S. Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* 1996;348:977-80.
  73. Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002;136:680-90.
  74. Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, et al. Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004;292:1573-80.
  75. Hulley S, Furberg C, Barrett-Connor E, Cauley J, Grady D, Haskell W, HERS Research Group. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 2002;288:58-66.
  76. Daly E, Vessey MP, Hawkins MM, Carson JL, Gough P, Marsh S. Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* 1996;348:977-80.
  77. Jick H, Derby LE, Myers MW, Vasilakis C, Newton KM. Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. *Lancet* 1996;348:981-3.
  78. Perez Gutthann S, Garcia Rodriguez LA, Castellsague J, Duque Oliart A. Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. *BMJ* 1997;314:796-800.
  79. Varas-Lorenzo C, Garcia-Rodriguez LA, Cattaruzzi C, Troncon MG, Agostinis L, Perez-Gutthann S. Hormone replacement therapy and the risk of hospitalization for venous thromboembolism: a population-based study in southern Europe. *Am J Epidemiol* 1998;147:387-90.
  80. Hoibraaten E, Abdelnoor M, Sandset PM. Hormone replacement therapy with estradiol and risk of venous thromboembolism – a population-based case-control study. *Thromb Haemostasis* 1999;82:1218-21.
  81. Mosca L, Appel LJ, Benjamin EJ, Berra K, Chandra-Strobos N, Fabunmi RP, et al. Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation* 2004;109:672-93.
  82. Scarabin PY, Oger E, Plu-Bureau G. The Estrogen and Thromboembolism Risk (ESTHER) study group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428-32.
  83. Royal College of Obstetricians and Gynaecologists [www.rcog.org.uk]. Hormone replacement therapy and venous thromboembolism. Guideline No. 19. Revised January 2004. Available at: <http://www.rcog.org.uk/index.asp?PageID=23>.
  84. Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prior to use of estrogen replacement therapy, are users healthier than nonusers? *Am J Epidemiol* 1996;143:971-8.
  85. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.
  86. Rodriguez C, Calle EE, Patel AV, Tatham LM, Jacobs EJ, Thun MJ. Effect of body mass on the association between estrogen replacement therapy and mortality among elderly US women. *Am J Epidemiol* 2001;153:145-52.
  87. Mosca L, Collins P, Herrington DM, Mendelsohn ME, Pasternak RC, Robertson RM, et al. Hormone therapy and cardiovascular disease: A statement for healthcare professionals from the American heart association. *Circulation* 2001;104:499-503.