

# HORMONE REPLACEMENT THERAPY AND CARDIOVASCULAR DISEASE

*This Policy Statement has been prepared and approved by:  
The Heart and Stroke Foundation of Canada  
The Society of Obstetricians and Gynaecologists of Canada  
The Canadian Cardiovascular Society*

## PRINCIPAL AUTHORS

Beth Abramson, MD, FRCPC, Toronto ON  
Christine Derzko, MD, FRCSC, Toronto ON  
André Lalonde, MD, FRCSC, Toronto ON  
Robert Reid, MD, FRCSC, Kingston ON  
Michele Turek, MD, FRCPC, Ottawa ON  
Andreas Wielgosz, MD, FRCPC, Ottawa ON

In Canada, cardiovascular diseases (CVD) are the leading cause of mortality. In 1998, CVD were responsible for 39,447 deaths among Canadian women (almost 38% of all deaths in women), which is greater than the number of deaths for women due to all cancers combined. The proportion of deaths due to CVD in women increases significantly after menopause and continues to increase with advancing age. It remains unclear, however, whether this increase in incidence of CVD in middle-aged and elderly women is caused by lower estrogen levels or is an overall manifestation of advancing age. The use of hormone replacement therapy (HRT), especially estrogen, has been advocated as a means to reduce the risk of CVD.

Menopause is associated with adverse effects on blood lipids including an increase in total cholesterol, LDL cholesterol, and triglycerides, and a decrease in HDL cholesterol. Reduced estrogen levels after menopause can also lead to adverse changes in blood pressure, obesity, body fat distribution, blood clotting factors, glucose metabolism and diabetes, all of which increase the risk of coronary heart disease.

Laboratory studies have found evidence for both beneficial and adverse effects of estrogen. Oral estrogen has been shown to lower LDL cholesterol, lipoprotein (a), and increase HDL cholesterol. There is accumulating evidence that estrogen improves endothelial function, thus enhancing vasodilatation. In addition, estrogen replacement is associated with reduced blood levels of

fibrinogen and plasminogen activator inhibitor-1, and may thus have anti-thrombotic and pro-fibrinolytic effects. However, other effects may be pro-inflammatory (increased C-reactive protein) and pro-coagulant and therefore detrimental to the overall cardiovascular risk profile.

As estrogen is usually prescribed with progestin in those women with a uterus in order to protect against endometrial cancer, some of the beneficial cardiovascular effects may be attenuated by the addition of progestin (such as a lesser effect on HDL cholesterol). Other routes of administration of estrogen may have less favourable effects on plasma lipoproteins, but may be beneficial in other ways. Selective estrogen receptor modulators (SERMs) are also being studied because these may result in direct cardiovascular effects.

The evidence for a protective effect of estrogen on coronary heart disease is based on over 30 observational epidemiologic studies conducted over the last two decades. These studies have shown a 40% reduction in the risk of coronary heart disease for current users of estrogen or estrogen and progestin compared to women who have never used these hormones. Recent updates have confirmed this conclusion, even with lower doses of estrogen, and have also found no effect of HRT on stroke. However, these types of studies are hampered by an inability to control completely for confounding factors, including the fact that women who are compliant with HRT

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tend to be healthier. Randomized controlled clinical trials are considered to provide the strongest evidence for definitive conclusions concerning HRT and CVD outcomes. To date, there are no randomized controlled trials in primary prevention that have been published, although trials such as the Women's Health Initiative (WHI) are in progress.

The Heart and Estrogen/Progestin Replacement Study (HERS) was a randomized trial of secondary prevention using HRT in women with established coronary disease. The investigators did not find an overall benefit after 4.1 years of treatment with combined estrogen and progestin. There was a significant increase in the risk of nonfatal myocardial infarction or coronary death in the first year in women on active treatment (this risk lessened over time) and an approximate three-fold increase in the risk of venous thromboembolic events. Another randomized trial using a similar regimen of HRT or estrogen alone and conducted in a similar group of women as HERS, the Estrogen Replacement and Atherosclerosis (ERA) trial, found no difference in the progression of coronary atherosclerotic disease using angiography as an endpoint. These two important, well-conducted, randomized trials have appropriately tempered enthusiasm for using HRT in the secondary prevention of heart disease in women.

Such randomized trials were conducted in only those women who already had evidence of coronary heart disease, whereas cohort observational studies such as the Nurses' Health Study include women who have no evidence of heart disease. Consequently, there is currently debate as to whether results from secondary prevention trials can be extrapolated to HRT for primary prevention and whether other doses and/or routes of administration may prove effective. Fortunately, there are ongoing randomized controlled clinical trials of primary prevention, including the WHI, which involves 27,000 women; a report is expected in 2005. However, this trial released preliminary results showing a trend toward an early increase in thrombotic events in the treatment group, as in HERS. This and other such primary prevention trials will provide important additional data about the use of HRT.

Other effects of HRT besides those on the cardiovascular system must also be considered. The evidence linking unopposed estrogen to endometrial cancer is extensive, strong, and consistent; however, the addition of progestin in women with a uterus reduces this risk. There is no clear evidence that estrogen causes breast cancer. Analysis of numerous observational studies has shown that the short-term use (less than 5 years) of estrogen does not increase the risk of breast cancer. There is uncertainty about this risk with longer-term use. There is a small excess risk of venous thromboembolic events in women who use HRT. Non-cardiovascular risks should be balanced with non-cardiovascular benefits, such as treatment of menopausal symptoms and osteoporosis.

Coronary heart disease is the leading cause of death and an

important contributor to morbidity and disability in women. It is largely preventable. Efforts should focus on reducing the risk of coronary heart disease among women in known and effective ways. Women should receive counselling about lifestyle modifications (smoking cessation, maintenance of a normal body weight, regular moderate to vigorous physical activity, and consumption of a heart-healthy diet) because of the profound beneficial effects of these strategies. In addition, pharmacotherapy of hypertension and dyslipidemias should also be utilized when indicated. For women who already have established heart disease, lifestyle modification and control of hypertension and diabetes assume heightened importance given their greater mortality associated with acute coronary events, such as myocardial infarction. Therapy with aspirin, beta blockers, ACE inhibitors and lipid-lowering medications is recommended when indicated and is amply supported by evidence of benefit.

HRT should not be initiated in women with confirmed coronary heart disease for the sole purpose of preventing future cardiovascular events. Women with cardiovascular disease who have been on HRT long-term can usually continue, particularly if they are stable and require HRT for non-cardiovascular indications. For postmenopausal women who do not have pre-existing coronary heart disease, HRT should be considered following a careful assessment of risk if this therapy is prescribed for the sole purpose of preventing future cardiovascular events. Non-cardiovascular risks and benefits, as well as patient preference, should guide any decision regarding such therapy. Until ongoing trials provide further data, a cautious approach to the use of HRT for cardiovascular protection is advisable.

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