PRACTICE

WOMEN'S HEALTH

Postmenopausal hormone replacement therapy for primary prevention of cardiovascular and cerebrovascular disease

Recommendation statement from the Canadian Task Force on Preventive Health Care

Recommendations

- The Canadian Task Force on Preventive Health Care concludes that there is fair evidence to recommend against the use of hormone replacement therapy (HRT) for the primary prevention of myocardial infarction and death from cardiovascular disease in perimenopausal women without established coronary artery disease (CAD) (grade D recommendation). There is insufficient evidence to make a recommendation on the use of HRT for the primary prevention of stroke and death from cerebrovascular disease. However, because stroke is a major cause of morbidity and death among Canadian women, other beneficial preventive measures, such as aggressive treatment of hypertension, should be used rather than HRT.
- To maintain good heart health, women should be advised to adopt other effective preventive strategies, such as lifestyle changes that include increased exercise, lower fat diets, smoking cessation, and blood pressure assessment and control.

Coronary artery disease (CAD) is a leading cause of morbidity and death among North American women.[1,2] Each year, 4 of every 10 deaths of women in Canada,[3] and up to 3.8 million days in hospital,[4] are due to heart disease and stroke. Prevention of cardiovascular disease through modification of various risk factors (e.g., lowering of lipid levels, control of hypertension) has been shown to decrease morbidity and mortality among both men and women.[5]

A unique risk factor among older women is the hypoestrogenemic, postmenopausal state. Until recently, hormone replacement therapy (HRT) was postulated to have a role in the primary prevention of cardiovascular disease in women without established CAD. Results of early observational and cohort studies showed promise for the cardioprotective role of HRT in general. This was later tempered by the results of the HERS[6] and ERA[7] trials, which showed no benefit from HRT in the reduction of death or coronary events over 4 years among women with established CAD.[6] An observational cohort study involving women at high risk of recurrent coronary events showed similar results.[8] Large randomized trials, including the Women's Health Initiative (WHI), were designed to assess the long-term effect of various HRT regimens on CAD and non-CAD outcomes among women without a history of CAD. Initially scheduled for completion in 2005, the WHI was stopped early in July 2002, and the data regarding the use of HRT for primary prevention of cardiovascular disease and other chronic diseases is now more clear.[9,10]

Manoeuvres

- Combined estrogen and progestin therapy
- Estrogen-only therapy (for women without an intact uterus)

Potential benefits

- Reduction in cardiac disease outcomes, including incidence of myocardial infarction and cardiovascular-related mortality
- Reduction in cerebrovascular disease outcomes, including stroke incidence and mortality

Potential harms

- Thromboembolic events; hypertriglyceridemia

Recommendations by others

Several groups have issued updated recommendations following the release of the WHI results. The US Preventive Services Task Force recommends against combination estrogen–progestin therapy on the basis of an overall balance of harms versus benefits for chronic disease prevention. It found inconclusive evidence to recommend for or against the use of unopposed estrogen for chronic disease prevention in women who have had a hysterectomy.[11] The Society of Obstetricians and Gynaecologists of Canada (SOGC) maintains that the best treatment for distressing menopausal symptoms is combined continuous HRT. However, it also advises that combined continuous HRT should not be recommended routinely for all post-

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menopausal women, as it does not appear to offer cardioprotection and the slightly increased risk of cardiovascular disease and breast cancer outweigh the benefits in asymptomatic women.[12] The Heart and Stroke Foundation of Canada, in collaboration with the Canadian Cardiovascular Society and the SOGC, states that HRT should not be initiated or continued in women for the sole purpose of preventing future cardiovascular events.[13]

The American College of Obstetricians and Gynecologists also states that HRT is no longer recommended to prevent heart disease in healthy women or to protect women with pre-existing heart disease. It goes further to state that women who take HRT for the management of menopausal symptoms should be encouraged to take it for as short a time as possible and to use the lowest effective dose.[14]

The North American Menopause Society, in its recent report on HRT, states that "no estrogen/progestin therapy regimen should be used for primary or secondary prevention of coronary heart disease." It also advises that the use of estrogen/progestin therapy and unopposed estrogen therapy "should be limited to the shortest duration consistent with treatment goals, benefits, and risks for the individual woman."[15]

In light of the estrogen-only arm of the WHI having recently been discontinued, these recommendations are likely to be updated in the near future.

Evidence and clinical summary

- Before the WHI, 17 studies meeting our inclusion criteria were published (1 small randomized controlled trial[16] and 16 prospective cohort studies[17–32]). Most observed lower rates of death among women using HRT than among those not using HRT, largely from a reduction in CAD. The summary relative risk of these studies has been calculated previously to be 0.5 (95% CI 0.43–0.56)[33] and 0.65 (95% CI 0.59–0.71).[34] However, the observational nature of these studies left open the question of whether certain confounding variables were at play, in particular the fact that healthier women tend to take HRT.
- Women in the WHI estrogen-plus-progestin trial[9,10] had an increased risk (6 more cases per 10 000)[10] of nonfatal myocardial infarction and death from coronary disease. This was seen early on, within the first year of treatment, and remained elevated over the ensuing years. The WHI also found an excess risk of stroke (8 more cases per 10 000), which persisted throughout the trial, and a doubling of risk of venous thromboembolism (18 more cases per 10 000). This translates into an increased relative risk of an adverse outcome from cardiovascular disease of 22% (hazard ratio 1.22; adjusted 95% CI 1.00–1.49), or 25 more events per 10 000 person-years of HRT use (157 v. 132 events per 10 000), with a risk of early harm from acute myocardial infarction and a risk of continuing harm from stroke and venous thromboembolism with the use of this combined HRT regimen.
- Additional cardiovascular risks from estrogen include a 3-fold increase in thromboembolic events (about 4 per 1000 women-years)[6] and hypertriglyceridemia.[35]

Competing Interests: None declared.

Contributors: Beth Abramson authored the original systematic evidence review, drafted the current article and made subsequent revisions. The Canadian Task Force on Preventive Health Care critically reviewed the evidence and developed the recommendations according to its methodology and consensus development process.

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