Cardiovascular Disease

Consensus is emerging from the controversy and confusion that has occupied the past decade regarding the effects of postmenopausal HT on CVD. Since the publication of the SOGC's Canadian Consensus Conference on Menopause in 2006,[1] several publications have shed additional light on this subject.

The areas of agreement can be summarized as follows.

1. Menopausal EPT is indicated for relief of symptoms, but it is not indicated for primary or secondary prevention of CVD; the evidence supports aggressive identification and modification of risk factors as the most effective means of reducing cardiovascular risk.
2. Women who initiate EPT 10 or more years after menopause are at increased risk for adverse cardiac events.
3. Women who initiate EPT shortly after menopause are, in general, at low risk for events in the subsequent few years. Studies have been reassuring regarding safety in this age group.
4. With respect to stroke, increased risk has been identified in all age groups using standard formulations of HT; however, the incidence in young women is extremely low. There is increasing evidence to suggest that lower doses of estrogen, either oral or transdermal, are associated with a lower or no increase in risk.
5. Venous thrombotic events in otherwise healthy women increase in incidence with age and obesity. HT increases the risk; events are associated more with oral than with transdermal preparations and more with EPT than with ET.
6. Women on EPT are reported to have more adverse cardiovascular events than women on ET. Progestogens may differ with respect to cardiovascular risk.
7. There is an emerging literature on the use of a SERM rather than a progestin to protect the uterus from hyperplasia. To date, these agents do not appear to be associated with cardiovascular risk.

Reduction of modifiable risk factors is the most effective strategy for prevention of CVD. The INTERHEART study, a global case–control study examining modifiable risk factors across many populations, determined that for women 94% of CVD risk could be attributed to modifiable factors.[2] Factors identified in that study included diabetes mellitus (OR 2.37), hypertension (OR 1.91), abdominal obesity (OR 1.62), current smoking (OR 2.87), and psychosocial stress (OR 2.67). Women at pre-existing risk because of elevated Framingham scores or pre-existing metabolic syndrome appear to be at elevated risk of cardiovascular events when on HT, adverse events arising in the first years of use.

Reproductive hormones do have important beneficial effects on risk markers of CVD; however, the outcomes that guide treatment decisions must be confirmed cardiovascular events. The systemic effects on lipids, hemostasis, and carbohydrate metabolism are well known.[3]

HT has no role in reducing future risks of cardiovascular events in women with established CAD. The HERS secondary prevention trial demonstrated no benefit and an increased risk of early adverse cardiac events in women with known CVD.[4] Other research has confirmed that HT fails to delay the progression of disease.[5–7]

The data on the role of HT for primary prevention of CVD have been the primary reason for the ongoing debate. Whereas data from a variety of sources (epidemiologic studies, observational studies, and clinical trials examining surrogate endpoints) suggested a possible cardioprotective role for estrogen,[8,9] the WHI cast doubt on the value of HT in this situation. The first publication from the WHI reported that EPT increased the risk of myocardial infarction and stroke.[10] The subsequently published findings showed no statistically significant overall increase in the incidence of coronary events or death among users of the combination of CEE and MPA (EPT).[11] There was a significant elevation in the incidence of cardiovascular events in EPT users compared with women receiving a placebo in the first year of therapy but not thereafter. The estrogen-only arm of the trial demonstrated no evidence of coronary artery benefit or risk (HR 0.63; 95% CI

0.36 to 1.08).[12,13] Subsequent subgroup analysis demonstrated a reduction in the total mortality rate in the age group 50 to 59 years (HR 0.70; 95% CI 0.51 to 0.96).[14]

Observational studies are at risk of confounding. Women who seek HT are better educated and of higher socioeconomic status; thus, they have greater access to other health care resources, from which they may receive treatment for other cardiovascular risk factors, such as diabetes, hypertension, and hypercholesterolemia.[15,16] Those who seek HT are more likely to adhere to other wellness advice: they tend to be leaner, to exercise more often, and to consume more alcohol, which by itself affords a degree of cardioprotection. Women who become sick with other conditions are more likely to stop HT, so that there appear to be more deaths in non-users or past users than in current users.

Because of the potential for bias in observational studies, RCT data are important to clarify the observation of cardioprotective benefits for HT when started early in postmenopausal women.

Conclusions about the role of HT for primary cardioprevention based on the WHI findings have been challenged because of the greater ages (an average of 63 years) of the participants and the time since loss of ovarian estrogen production (an average of 13 years).[17] Time since menopause has been shown to correlate with extent of subclinical atherosclerosis as determined by carotid-wall IMT in populations of women with natural and surgical menopause.[18] WHI subsamples were weighted heavily in favour of the inclusion of marginalized and disadvantaged women, and many of the modifiable risks for CVD identified in the INTERHEART study were present in such women. With close to 70% of women in the WHI over the age of 60 years at enrolment, it seems likely that a substantial proportion of the WHI population would have had subclinical CVD. The early increase in the incidence of cardiac events reported in the EPT arm of the WHI, with no overall difference in the cardiovascular mortality rate, is similar to the effect of HT started in older women in the HERS secondary prevention trial.[4] In the EPT arm of the WHI the RR for CAD was 1.68 in the first 2 years after the start of HT, 1.25 at 2 to 5 years, and 0.66 beyond 5 years.

Lobo[19] looked at data from 2 clinical trials in which all adverse events were recorded for 4065 young, healthy postmenopausal women started on HT and found no increase in the incidence of either myocardial infarction or stroke in the year after initiation of therapy. These women were not followed for long enough to determine whether there might be longer-term benefit or risk.

A "critical-window" or "critical-timing" hypothesis was advanced as a way to try to explain how the use of HT at the onset of menopause could be cardioprotective whereas later initiation could cause adverse coronary events as seen in the WHI.[20–23] This theory suggests that the prothrombotic or plaque-destabilizing effects of HT in women with established CAD may account for an initial increase in the incidence of coronary artery events in older women but that the healthy coronary arteries of younger women benefit from the anti-atherogenic effects of estrogen. Salpeter et al.[24,25] performed a meta-analysis of RCTs to assess the effect of HT for at least 6 months on the incidence of CHD events including myocardial infarction and death in younger and older postmenopausal women. They found that HT significantly reduced the incidence of CHD events when initiated in younger (OR 0.68; 95% CI 0.48 to 0.96) but not older (OR 1.03; 95% CI 0.91 to 1.16) menopausal women. The cardiac event rate for younger women seen in this meta-analysis paralleled that seen in the observational Nurses' Health Study, which followed a cohort of 120 000 women below the age of 55 years. After adjustment for potential confounding variables, such as age, cardiovascular risk factors, and socioeconomic status, HT use was found to be associated with a 40% reduction in the incidence of CHD events.[8] As with the HERS[4] and WHI[10] trials, initiation of HT in older women was associated with an increase in the incidence of adverse CHD events in the first year only.

In addition to the well-publicized RCT, the WHI included an observational arm, which reported lower rates of cardiac events in 17 503 current users of EPT (62% had used EPT for more than 5 years at enrolment) than in 35 551 age-matched control subjects (OR 0.71).[26]

Grodstein et al.[27] re-examined the observational data from the Nurses' Health Study to determine the effect of different ages at initiation of HT on the incidence of cardiac events. For women beginning HT near the onset of menopause, both ET alone (RR 0.66; 95% CI 0.54 to 0.80) and EPT (RR 0.72; 95% CI 0.56 to 0.92) were associated with a significantly reduced risk of CHD. No significant benefit was observed in women starting HT beyond age 60 or more than 10 years after menopause.

Rossouw et al.[14] performed a secondary analysis of the WHI data to determine the impact of years since menopause and age at the time of HT initiation on cardiovascular outcomes. The HR for adverse cardiovascular outcomes was 0.76 in women starting HT less than 10 years after menopause, 1.10 for women starting 10 to 20 years since menopause, and 1.28 for women starting more than 20 years after menopause (P for trend = 0.02). The HR for