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

total mortality among the women aged 50 to 59 years who were randomly assigned to HT was significantly reduced, at 0.76 (95% CI 0.51 to 0.96).

Ideally this critical-timing hypothesis would be tested in an RCT designed for that specific purpose rather than through post-hoc and subgroup analysis of the data from other trials.[28] Depypere et al.[29] estimated the numbers of women needed in any RCT designed to assess possible cardioprotective benefits of HT in newly menopausal women. To detect a 30% difference in women 50 to 54 years old approximately 35 000 women would be required, twice as many as were enrolled in the EPT trial arm. To detect a 10% difference close to 350 000 women would be required. Such a large trial would not be feasible.

The Danish Osteoporosis Study reported on 1006 women who were randomly assigned to cyclic EPT or no treatment (there was no placebo arm) early in menopause and followed for 10 years with a 6-year extension. At the time of analysis 15 of the 504 women in the treated groups had experienced cardiovascular events versus 26 of the 502 control subjects (HR 0.48; 95% CI 0.26 to 0.87, $P = 0.015$). The primary endpoint was a composite of death, admission to hospital for heart failure, and myocardial infarction. After 10 years of intervention, 16 women in the treatment group had experienced the primary composite endpoint compared with 33 in the control group (HR 0.48; 95% CI 0.26 to 0.87, $P = 0.015$). There was no increased risk of cancer in general, breast cancer in particular, or stroke.[30]

Although clinical outcomes are the preferred study endpoint, data on clinically relevant indicators are helpful when a clinical trial is not feasible. Carotid-wall IMT has been followed as an early marker of atherosclerotic disease.[9,31,32]

The Kronos Early Estrogen Prevention Study (KEEPS) is a multicentre, 5-year clinical trial to evaluate the effectiveness of 0.45 mg/d of CEE, 50 g/wk of transdermal estradiol (both in combination with cyclic oral micronized progesterone, 200 mg/d for 12 days each month), and placebo in preventing the progression of carotid-wall IMT and the accrual of coronary-artery calcium in women aged 42 to 58 years who are within 36 months of their final menstrual period.[33] The investigators have presented preliminary data (http://www.menopause.org/annual-meetings/2012-meeting/keeps-report), unpublished at the time of writing, that do not show any evidence of a difference in IMT progression between the treatment and control groups.

Calcium scores for the coronary arteries, generated by means of electron-beam computed tomography, have been shown to correlate with plaque burden as assessed pathologically and to have significant predictive value for subsequent cardiac events in symptomatic and asymptomatic adults.[34,35] A recent meta-analysis of predictive utility concluded that this score is an independent predictor of subsequent CAD events.[36] Most of the data on these scores come from studies on men; data for women must be interpreted with caution at this time.[37] With these caveats in mind, it is of interest to consider recent studies of these scores as a surrogate endpoint for CAD in women using or not using HT.[38–41] Each study demonstrated evidence of reduced subclinical vascular disease among women who were compliant with HT. The WHI investigators[41] performed a substudy on 1064 women aged 50 to 59 years in the estrogen-only arm of the WHI. Coronary-artery calcium scores were significantly lower among the women randomly assigned to ET than among the women assigned to placebo after a mean of 7.4 years of treatment. In women who remained at least 80% adherent to the treatment protocol the OR for a high score in users compared with non-users was 0.39 ($P = 0.004$).

The National Institute on Aging's Early versus Late Intervention Trial with Estradiol (ELITE) is designed to test the hypothesis that 17β-estradiol therapy will reduce the progression of early atherosclerosis if initiated soon after menopause, when the vascular endothelium is relatively healthy, versus later, when the endothelium has lost its responsiveness to estrogen.

Considering all these studies, healthy recently menopausal women who are considering HT for relief of symptoms should be reassured that there does not appear to be significant cardiovascular risk; some argue that there is benefit. However, most women will be using HT for a limited time: a survey of hormone use in the United States before the WHI results were reported revealed that only 3% of women using EPT and only 10% using estrogen alone stayed on their HT for more than 5 years.[42] Therefore, the key cardiovascular preventive advice will remain the reduction of modifiable risk factors.

PREMATURE LOSS OF OVARIAN FUNCTION AND CVD

Large numbers of women continue to face early loss of ovarian function because of either surgical oophorectomy or chemotherapy-associated ovarian failure. Several studies have suggested that women have a greater risk for CAD after bilateral oophorectomy.[43–48] An increased risk of stroke has been found in women with surgical premature menopause.[49] WHI investigators reported that oophorectomized women who subsequently received ET had less coronary-artery calcium accumulation than

those who did not receive ET, and they concluded that "the findings are consistent with the thesis that estrogen deficiency associated with bilateral oophorectomy is related to an increased burden of calcified plaque in the coronary arteries that can be countered by the use of HT".[50] This finding supports the need for ET after premature loss of ovarian function at least until the natural age of menopause if estrogen is not contraindicated for other reasons.

STROKE

Risk factors for stroke (obesity, hypertension, smoking, and diabetes) are common among North American women as they enter menopause. Certain segments of the population are more likely to have these risk factors. Seventy-three percent of women entering the WHI trial were classified as being in the Framingham medium-risk (36%) or high-risk (37%) category for stroke.[51] Among the various racial and ethnic groups, black women had the highest risk of stroke (HR 2.52; 95% CI 1.05 to 6.08).

Studies of HT (predominantly with estrogen) have provided inconsistent evidence about the effects on the risk of stroke.[8,19,52] In the WISDOM trial[53] there was no excess incidence of cerebrovascular accidents among 2196 women randomly assigned to EPT compared with 2189 randomly assigned to placebo therapy, with an average of 1 year of follow-up. A meta-analysis of RCTs performed before the WISDOM trial found an HR of 1.30 (95% CI 1.13 to 1.47) for total stroke.[54] Dose of estrogen, use of a progestin, and route of administration have all been studied as potential contributors to these inconsistent findings.

In a case–control study using data from the General Practice Research Database (GPRD), lower doses of transdermal estrogen (50 μg/d of estradiol or less) were not significantly associated with stroke (RR 0.81; 95% CI 0.62 to 1.05), but doses greater than 50 μg/d were associated with an increased risk of stroke (RR 1.89; 95% CI 1.15 to 3.11).[55] Whereas in the Nurses' Health Study lower doses of oral estrogens (< 0.625 mg daily of CEE) were not associated with any increase in risk,[8] in the GPRD study an increased risk was observed with both standard and low-dose CEE therapy (RR 1.35; 95% CI 1.16 to 1.58).[55]

The absolute risk of ischemic stroke due to HT in younger menopausal women is low, but the health consequences can be severe. The additional risk conferred by the use of HT was found to be 8/10 000 woman-years in the EPT arm of the WHI[51] and 13/10 000 woman-years in the estrogen arm.[56] Risk factors for stroke should be assessed and addressed in all menopausal women and particularly in those seeking HT for distressing VMS.

DIABETES AND METABOLIC SYNDROME

The results of large RCTs have suggested that HT reduces the incidence of new-onset diabetes mellitus. Women receiving active treatment in the EPT arm of the WHI had an annualized incidence of diabetes requiring treatment of 0.61% versus 0.76% in placebo-treated women. This translated into a 21% reduction (HR 0.79; 95% CI 0.67 to 0.93) in incident-treated diabetes, or 15 fewer cases per 10 000 women per year of therapy.[57] A similar risk reduction was noted in the HERS trial (HR 0.65; 95% CI 0.48 to 0.89).[58] In the estrogen arm of the WHI there was a 12% reduction (HR 0.88; 95% CI 0.77 to 1.01) in incident diabetes, or 14 fewer cases per 10 000 women per year of therapy. It is unclear whether the mechanism for this benefit is through lesser centripetal weight gain or reduced insulin resistance in women receiving combined EPT or some other factor.

A meta-analysis of 107 trials examining components of the metabolic syndrome concluded that HT reduced abdominal obesity, insulin resistance, the incidence of new-onset diabetes, lipid levels, and blood pressure in women without diabetes and reduced insulin resistance and fasting glucose levels in women with diabetes.[59]

There is inadequate evidence to recommend HT solely to prevent or ameliorate diabetes.

VENOUS THROMBOEMBOLISM

The risk of DVT has been discussed in the NAMS 2012 Consensus Position Statement.[60] The risk of DVT roughly doubles with each decade of aging. Women with obesity, prior history of DVT, and factor V Leiden gene mutations are at increased risk of venous thrombosis.[61–62] Women who have underlying prothrombotic disorders of factor V and factor VIII appear to be at particularly high risk: the combination of oral EPT and an underlying coagulation disorder carries 17 times the risk of DVT.[63] Although the highest risks are in women who are carriers of the factor V Leiden gene defect, screening is not recommended for this condition owing to low cost-effectiveness. Calculations suggest that screening of 795 women would be required to prevent 1 episode of VTE in 5 years.[64]

The risk of DVT appears to be higher with EPT than with ET. Douketis et al.[65] studied 1168 women with suspected DVT and found the risk of thrombosis not to be significantly elevated in women on ET but to be significantly elevated in those on EPT (OR 2.70; 95% CI 1.44 to 5.07).

Oral HT results in an increased risk of VTE that is greatest in the first year after the start of therapy.[66] In the WHI the HR was 4.0 in year 1 and fell to 1.04 by year 6.[61,64]

In the WHI, compared with women aged 50 to 59 years, those aged 60 to 69 years had a doubled risk of DVT (HR 2.03; 95% CI 1.43 to 2.88), and those aged 70 to 79 years had an almost quadruple risk (HR 3.72; 95% CI 2.57 to 5.36).[64] A large population study revealed that the absolute incidence is 2 to 3 per 10 000 for women aged 50 to 54 years and increases to 20 to 30 per 10 000 at age 80.[67]

In the WHI, being overweight doubled the risk of DVT (HR 1.96; 95% CI 1.33 to 2.88) and obesity tripled it (HR 3.09; 95% CI 2.13 to 4.49).[64] The overall risk was lower with ET alone (HR 1.32; 95% CI 0.99 to 1.75) than with EPT (HR 2.06; 95% CI 1.57 to 2.70). The risk attributable to HT was not synergistic with the risk factors of obesity and advancing age.[61]

There is increasing and consistent evidence that the risk of thrombosis is associated more with oral than with transdermal delivery. The European Menopause and Andropause Society in its 2011 position statement noted that a personal history of DVT, or a strong family history, is a contraindication to oral HT but that consideration can be given to transdermal therapy in those circumstances.[68] The Estrogen and Thromboembolism Risk (ESTHER) Study, a multicentre case–control evaluation of the risk of thromboembolism in postmenopausal users of estrogen, reported more risk associated with oral than with transdermal ET.[69] The prospective E3N cohort study of 80 308 postmenopausal women found that the risk of thromboembolism was increased with oral but not transdermal therapy and was most increased in women using EPT involving norpregnane progestins.[70]

Differences in lipid and coagulation responses to oral and transdermal HT have led to the suggestion that the route be selected on the basis of individual risk profile.[71,72]

Recommendations

1. Health care providers should not initiate hormone therapy for the sole purpose of preventing cardiovascular disease (coronary artery disease and stroke) in older postmenopausal women since there are no data to support this indication for hormone therapy. (I-A)
2. The risk of venous thromboembolism increases with age and obesity, in carriers of a factor V Leiden mutation, and in women with a history of deep vein thrombosis. Transdermal therapy is associated with a lower risk of deep vein thrombosis than oral therapy and should be considered only if the benefits overcome the risks. (III-C) Health care providers should abstain from prescribing oral hormone therapy for women at high risk of venous thromboembolism. (I-A)
3. Health care providers should initiate other evidence-based therapies and interventions to effectively reduce the risk of cardiovascular events in women with or without vascular disease. (I-A)
4. Risk factors for stroke (obesity, hypertension, elevated cholesterol levels, diabetes, and cigarette smoking) should be addressed in all postmenopausal women. (I-A)
5. If prescribing hormone therapy to older postmenopausal women, health care providers should address cardiovascular risk factors; low- or ultralow-dose estrogen therapy is preferred. (I-B)
6. Health care providers may prescribe hormone therapy to diabetic women for the relief of menopausal symptoms. (I-A)

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