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**Postmenopausal Hormone Replacement Therapy
for Primary Prevention of Cardiovascular
and Cerebrovascular Disease
Systematic Review and Recommendations**

March 2003

TECHNICAL REPORT

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**Postmenopausal Hormone Replacement Therapy for the Primary Prevention
of Cardiovascular and Cerebrovascular Disease:
Systematic Review and Recommendations**

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Running head: *Abramson with CTF – HRT & CVD*

ABSTRACT

Objectives: To systematically review the current evidence and make recommendations for the use of hormone replacement therapy (HRT) for primary prevention of cardiovascular and cerebrovascular disease.

Options: Hormone replacement therapy for primary prevention of cardiovascular and cerebrovascular disease in peri-menopausal women without established disease.

Outcomes: *Cardiac disease outcomes:* myocardial infarction incidence or cardiovascular disease mortality; *Cerebrovascular disease outcomes:* stroke incidence and mortality.

Evidence: A MEDLINE search was conducted for all English language articles published from 1966 to February 2001 that related to Hormone Replacement Therapy and Mortality, Myocardial Infarction, and Stroke. Selection criteria were used to limit the analysis to prospective cohort studies with internal controls or randomised controlled trials (RCT) with a minimum follow-up of 5 years. The addition of a recent large RCT published in 2002 has been added to the analysis.

Benefits, Harms, and Costs: Four out of every ten female deaths in Canada each year are due to heart disease and stroke. Until recently, the role of HRT for *primary* prevention of both cardio and cerebrovascular disease was not clear, with variable levels of evidence available. Prior to July 2002, seventeen studies meeting inclusion criteria were published, one small RCT and 16 prospective cohort studies. Most showed a protective association with estrogen, alone or in combination with a progestin, on myocardial infarction or death from cardiovascular disease in peri-menopausal women without established CAD. This is in contrast to the recent Women's Health Initiative trial, which showed evidence of potential harm. There is no beneficial effect from HRT on rates of stroke or stroke related death in the available studies. HRT for the sole purpose of prevention of cardiac disease is therefore not indicated.

Values: The strength of evidence was evaluated using the evidence-based methods of the Canadian Task Force on Preventive Health Care.

Recommendations: There is fair evidence to recommend against the use of HRT for the primary prevention of myocardial infarction and death from cardiovascular disease in peri-menopausal women without established CAD (**D recommendation**). 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. There is insufficient evidence to make a recommendation on the use of HRT for the primary prevention of stroke and death from cerebrovascular disease.

Validation: The members of the Canadian Task Force on Preventive Health Care reviewed the findings of this analysis through an iterative process. The Task Force sent the final review and recommendations to two external expert reviewers and their feedback was incorporated.

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Background:

Coronary heart disease (CHD) is a leading cause of morbidity and mortality among North American women.^{1,2} Four out of every ten female deaths in Canada,³ and up to 3.8 million days in hospital,⁴ are due to heart disease and stroke annually. Prevention of CV disease through various risk factor modifications (i.e. lipid lowering, control of hypertension) has been shown to decrease morbidity and mortality in both men and women.⁵ A unique risk factor in older women is the hypo-estrogenemic, post-menopausal state.

Until recently, the role of Hormone Replacement Therapy (HRT) for *primary* prevention of both cardio and cerebrovascular disease was contentious. Early observational and cohort studies showed promise for the cardio-protective role of HRT generally. This was later tempered by the results of the HERS⁶ and ERA⁷ trials assessing HRT for *secondary* prevention in women with established coronary disease, which showed no benefit in reduction of death or coronary events over 4 years;⁶ review of high risk women in observational studies suggests the same.⁸ The HERS cohort was followed in an observational format for a further 2.7 years:⁹ HERS II did not find any benefit of the assigned HRT regimen in these women with coronary artery disease, although only 45% of women were still on HRT by the end of year 6. Furthermore, HRT did not reduce the risk of ischemic stroke in women with established coronary artery disease in HERS and HERS II.

Until recently, HRT was postulated to have a role in the primary prevention of CV disease in women without established disease. Large randomized trials, including the Women's Health Initiative, were designed to assess long-term benefit of various HRT regimens on CHD and non-CHD outcomes for women without a previous history of CHD. Initially scheduled for completion in 2005,¹⁰ the Women's Health Initiative was stopped early in July 2002 and the data regarding the use of HRT for primary prevention of CVD, and other chronic diseases, is now more clear.¹¹

This paper provides a systematic review of currently available evidence and makes recommendations for the use of HRT for primary prevention of cardiovascular and cerebrovascular disease.

METHODS

MEDLINE was searched for all English language articles published from 1966 to February 2001 using the MeSH terms: “Estrogen Replacement Therapy” from 1991 forward, in addition “Estrogens – conjugated” and “Estrogens –synthetic” from 1966 to 1990 AND [“cardiovascular diseases”, OR “cerebrovascular disorders”, OR “myocardial infarction” OR “coronary disease” OR the keyword “mortality” as a text word in the title or abstract]. Scanning the bibliographies of the retrieved articles and review articles identified additional articles. Key studies published after the search end date were also added.

To limit the analysis to studies with the highest methodologic quality, study-selection criteria were developed *a priori* (Table 1). All eligible studies were systematically reviewed using the methodology of the Canadian Task Force on Preventive Health Care.¹² The Task Force, comprising expert clinicians and methodologists from a variety of medical specialties, uses a standardized evidence-based method for evaluating effectiveness. Appendix 1 describes the methodology and review process in more detail and provides definitions of the levels of evidence and recommendation grades.

RESULTS:

Understanding both the recent trial data, as well as the previous evidence, is useful since the clinician is still faced with patients in need of relevant information – especially in the face of better-informed patients, who come to their physicians with specific questions that require discussion.

Randomized controlled trials:

Recently, principal results were reported for one trial arm of the long-awaited Women’s Health Initiative (WHI), involving 16,608 women with an intact uterus aged 50-79 years (mean age 63 years), randomized to continuous Premarin and Provera vs. Placebo. Although this important trial of primary prevention was scheduled for completion in 2005, it was stopped after 5.2 years of follow-up, based on an assessment of greater risk than benefit. Although its primary outcome was non-fatal myocardial infarction (MI) and coronary death, interim results showed a small but significant increased risk of invasive breast cancer (8 more cases/10,000 women), which increased with duration of treatment, a diagnosis that was a pre-determined primary

adverse outcome. For cardiovascular disease, there was an increased risk (7 more cases/10,000) of non-fatal MI and coronary death. This was seen early on, within the first year of treatment, remaining neutral over the ensuing years. There was an excess risk of stroke (8 more cases/10,000), which persisted throughout the trial, and a doubling of risk for venous thromboembolism (18 more cases/10,000). This translates into an increased relative risk of 22% of an adverse outcome for cardiovascular disease, with early harm for acute myocardial infarction and continuing harm for stroke and venous thromboembolism with use of this HRT regimen. The study was stopped too early to see if these statistically non-significant trends would persist over time, however there was a lack of any statistical suggestion of potential benefit if the trial were to be continued; at most a “neutral” cardiovascular effect could be speculated.

The WHI also showed evidence of benefit for hip fractures (5 fewer cases/10,000) and colorectal cancer (6 fewer cases/10,000) – again trends were seen here, but the study was stopped too early to give absolute confidence in these numbers. However, these outcomes did not result in an overall benefit for this treatment over the 5.2 years of the trial.

In summary, for the duration reported in this trial, 100 more women per 10,000 taking this HRT regimen will experience an adverse event compared to placebo. This excess risk is small but important given that this therapy has been advocated for prevention of disease. This large randomized trial therefore does not support the use of this HRT regimen for the primary prevention of coronary artery disease.

It should be noted that another trial under the auspices of WHI is still in progress comparing unopposed estrogen to placebo in women who have had hysterectomies. Interim analyses to date have indicated that the trial should continue until planned termination in 2005. A large European trial, WISDOM, has been stopped as well.

Observational studies:

Prior to the publication of the WHI results for combined therapy, there was a significant body of epidemiological literature for HRT and how it relates to mortality, and cardiac events. The quality of the data is variable and has been reviewed in three ‘meta-analyses’.¹³⁻¹⁵ Since these comprehensive overviews, several other large studies have been published.¹⁶⁻²⁵

Most studies on HRT in women have observed lower rates of death among users than non-users, largely from a reduction in coronary heart disease. The summary relative risk of these studies has been calculated previously to be 0.5 (95% CI 0.43–0.56)¹⁵ and 0.65 (95% CI 0.59–0.71).¹³ Recent publications subsequent to these meta-analyses show consensus with this result - a reduction of coronary heart disease in the range of 30% associated with those women taking hormone replacement. Why were the results of the WHI so different than previously reported cohorts? A review of the previous studies is helpful to understand the issues for the female patient.

Quality of the Evidence:

An initial inspection of some of the “landmark” studies often quoted in the area revealed several methodological weaknesses. Of 732 retrieved studies, 33 satisfied the inclusion criteria on review of abstracts and titles, of which 16 were excluded because of one or more exclusion criteria, this left 17 studies for critical appraisal.^{16-20,22-33} Of specific note, the HERS trial⁶ was not included in this review, as the women in the trial had established coronary disease and were not taking hormones for *primary* prevention. The women in the HERS trial represent a very different patient population. Over 80% of these women had received revascularization and may not represent a group from which one can widely generalize regarding *secondary* prevention.

One study is a very small, randomised, placebo controlled, clinical trial³¹ (grade I evidence). The majority of publications reviewed were well conducted, large prospective cohort studies, often with a nested case-control analysis within (all grade II-2). Two of the most methodologically sound studies, the Lipid Research Clinics (LRC) Follow-up Program²⁷ and the Nurses’ Health Study^{21,29} are presented in greater detail. The LRC study evaluated 2270 perimenopausal women age 40-69 in 10 North American sites. Although 10% of women in the study had “CV” disease, this may be an over-estimate as included in the definition was angina on history. 26% of the cohort were estrogen users (99% unopposed estrogen). The cohort was followed for 8.5 years. The Nurses’ Health Study followed over 120,000 nurses across the United States, of whom 37, 611 were postmenopausal during follow-up. Only the data of HRT use in postmenopausal women were included from this study. Approximately 40% of nurses had used HRT at some point, with approximately 15% currently using hormones. Ongoing evaluation occurred in assessment of hormone use, with information on both unopposed

estrogen, and combination estrogen plus progestin. A nested case-control design within the study had 10 controls for every case. To date, 16-year follow-up is 98% complete. The publications are summarized for important study variables: participants, assessment of estrogen use, duration of estrogen use, and type of hormones.

Participants:

Cohort studies are subject to volunteer bias because volunteers tend to be healthier people.^{16,19,27,33} Another potential bias is introduced by the healthy user effect, i.e., healthier individuals may be predisposed to suffer fewer adverse effects from estrogen use. This may partially explain differences seen in the primary and secondary prevention studies. However, several large studies capitalized on information from large databases from Health Maintenance Organizations²⁶ or national medical databases.^{17,18,23} Other studies sent questionnaires to entire retirement communities,³⁰ communities as a whole,³² or working nurses nation-wide.²⁹ One study followed women in a private gynaecology practise for 25 years.²² Most of the women in these studies were white and well educated. The single randomised, placebo controlled, trial of HRT for primary prevention of CAD occurred in a chronic care hospital setting with bed-ridden women.³¹ By and large, within these cohorts, hormone users tended to have different profiles than non-users. Unless stated otherwise, the results given for risk reduction in events are adjusted for co-variates. The possibility still exists however that there are intangible confounding factors in these studies for which adjustment could not take place due to lack of randomization in the study design. As well, higher rates of hormone use in most of the studies compared to national averages reflect potential volunteer bias. The WHI helped confirm this criticism.

Assessment of Estrogen Use:

A potential problem with most prospective studies is that estrogen use was ascertained only at baseline, and often not updated, potentially leading to misclassification and an underestimate of the effect of the treatment. This is especially pertinent as the protective effects of estrogen are more pronounced in current than past users.^{25,30} Most studies determined estrogen use via a questionnaire, and two cohorts had estrogen use ascertained via linkage systems to pharmacy databases²⁶ – albeit with smaller sampling for internal controls.^{17,18,23} Exceptions to this were the Nurses' Health Study, which had biannual, and the U.S. BDDP study, which had annual, assessments of hormone use.^{21,25}

Duration of Estrogen Use:

The limitation of a single assessment of estrogen use also prevents answering the question as to the optimal duration of hormone use to prevent disease. Two smaller studies evaluated women (n = 83 and 168 respectively) for at least 10 years (25 years and 10 years respectively).^{22,31} Other questionnaire-based studies attempted to ascertain duration of hormone use, but were potentially susceptible to recall bias. Despite this, several studies showed a trend to reduction in mortality with over 5 years of use. Folsom et al.²⁰ showed a relative risk reduction in all cause, multi-variate adjusted mortality to be slightly greater in those who took HRT for more than 5 years compared with those who used HRT for five years or less (> 5 years 0.77 (0.61-0.96), ≤ 5 years 0.85 (.62-1.15) [RR (95% CI)], p trend =0.02). Henderson et al.³⁰ analysed all cause mortality for more than 15 years of use, in comparison to 4-14 years and ≤ 3 years. The reduction in all cause mortality appears greatest with longest use (> 15 years: 0.69 (.58-.82) 4-14 years: 0.76 (.65-.89), ≤ 3 years: 0.83 (.71-.96)). In contrast, in a 16 year follow-up of the Nurses' Health Study, Grodstein et al.²¹ showed that although over-all mortality was still reduced with hormone use after 10 years, mostly due to a reduction in cardiac deaths. The benefit was less in those with longer use, as the incidence of breast cancer increased (RR of death for current users: < 5 years 0.56 (.48-.65), 5-9 years 0.6 (.5-.72), ≥10 years 0.8 (.67-.96)). This increase in breast cancer was confirmed in the Women's Health Initiative combined therapy trial.

Type of Hormone:

In women with an intact uterus, estrogen given in combination with a progestin to reduce the risk of endometrial cancer is indicated. Although there is much physiologic evidence for vascular benefit from estrogen alone, there is some concern that progestins may negate estrogen's beneficial effects.³⁴⁻³⁷ Many studies have assessed the effect of unopposed estrogen on CV morbidity and mortality^{16,24,26,27} and many have not addressed the issue of combination HRT.^{19,20,25,33} Because the knowledge of endometrial cancer risk is relatively recent, there is more long-term data with unopposed estrogen than combination therapy, and there are now several published studies assessing combination HRT and cardio and cerebrovascular outcomes.^{16-18,23} The Study of Osteoporotic Fractures had 20% combination HRT use in more than 1200 women.¹⁶ The Uppsala Region Swedish study had 31% combination use in the 23,000 women prescribed hormones (over 7000 women). All cause death decreased in the combination HRT group with an unadjusted relative risk of 0.7 (0.6-0.8), as was death due to ischemic heart disease 0.4 (0.2-0.6).^{17,18,23} An analysis of the effects of combination HRT in the Nurses' Health Study showed no difference in events in women on combination HRT compared to those on unopposed estrogen. There were 27,161 person-years evaluating combination HRT and 82,626 person-years studying unopposed estrogen. Of those participating in the study in 1990, 7776 women were taking unopposed estrogen and 6224 were on combined estrogen-progestin. The multivariate adjusted relative risk of having major coronary disease in combination users was 0.39 (0.19-0.78) and 0.60 (0.43-0.83) in unopposed estrogen users.²⁹ Subsequent analyses combined the data on use of estrogen alone and combination therapy.²¹

In addition to variation in combination vs. unopposed estrogen use, the doses and types of HRT prescribed have varied between studies. Although most studies used oral compounds, given the timing of the observation, most prospective studies do not provide detailed data. It is interesting to note that the unopposed estrogen arm of the Women's Health Initiative is still ongoing.

Effectiveness of HRT for Primary Prevention

Protection from Coronary Heart Disease

Most studies on HRT replacement in women have observed lower rates of death among users than non-users, largely from a reduction in coronary heart disease. The summary relative risk of these studies has been calculated previously to be 0.5 (95% CI 0.43-0.56)¹⁵ and 0.65 (95% CI 0.59-.71).¹³ With the exception of the recent, randomized Women's Health Initiative, publications subsequent to these meta-analyses are consistent with this result (Table 2).

There is one study in which the results originally appeared contrary to others (with the exception of the WHI). An initial evaluation of the Framingham cohort, showed an increase in morbidity (i.e. angina - a soft endpoint in women, in addition to myocardial infarction) from coronary heart disease in estrogen users.³² Although there was no statistically significant increase in mortality or rate of myocardial infarction, the trends are in the opposite direction of data from other studies. A separate analysis of the Framingham Study data, excluding angina as an endpoint, showed a significant protective association with estrogen use for women aged 50-59 and no association in older women.³⁸

As the studies prior to the WHI were primarily observational, concern existed that some of the effect may be confounded by the fact that healthier women chose to take hormone replacement. Most studies (with the exception of the large Swedish studies^{17,18,23}) corrected for co-morbidity in their analyses. Although the validity of assessing the numbers needed to treat based on observational data has been questioned, the analysis does raise the point that the various observational studies had different death rates, with an implication of different women studied. In the Lipid Research Clinics Program follow-up,²⁷ there were 44 deaths in 1677 women not on estrogen replacement, and 6 deaths in 593 women taking estrogen for almost 10 years, suggesting that 61 women would need to be treated with estrogen to prevent one death due to cardiovascular disease. Of note, the cardiovascular death rate in the non-hormone user group was 2/3 that for the white U.S. postmenopausal population, suggesting a healthy participant effect in this study.

In contrast, Criqui et al.²⁸ assessed hormone use in a retirement community in California. Of the 1868 women, there were 364 deaths over approximately 8 years. An 11% absolute risk reduction in all cause death was seen, and a 3% absolute reduction was seen in deaths due to ischemic heart disease. Using the data from this cohort, 9 older women would need to be treated

with HRT to prevent one death and 34 women would need to be treated to prevent one death due primarily to ischemic heart disease. The numbers are calculated for unopposed estrogen users. The number of women needed to treat with combination HRT for cardiovascular protection should be an ongoing research priority.

The Nurses' Health Study was a relatively healthy population, with approximately 37,000 post-menopausal women followed in the cohort over 16 years. In this healthy cohort, 289 deaths due to cardiovascular disease were reported, assuming most cardiovascular deaths were in the postmenopausal women followed, the baseline cardiovascular death rate is $289/37,611$ or 0.0077. Based on the relative risk reduction of 0.47, theoretically one would have needed to treat 246 women to prevent one death due to ischemic heart disease. This study differs from the others in that the number needed to treat is based on from data in the subgroup of current hormone users. For primary prevention, treating women with risks for cardiovascular disease may be more effective than treating the entire healthy population. But one needs to be cautious that a preventive strategy is not harmful. This points to some of the discrepancies in previous cohort studies.

Protection from Stroke

The overall evidence shows no benefit of HRT for the primary prevention of stroke and death from cerebrovascular disease (Table 3). In the Women's Health Initiative, there was an excess risk of stroke (8 cases/10,000) which persisted throughout the trial.¹¹ Schairer et al. reported cause-specific mortality from the Uppsala Health Care Region in Sweden.²³ As the ascertainment of HRT use was through pharmacy databases connected to national death registries, information on combination HRT use and risk of stroke is available. Although a protective effect was found for the reduction of cerebrovascular disease death from more potent estrogens that are not used routinely in Canada (RR 0.7 (0.6-0.9)), no such effect was found in the group of women on combination HRT. Death from thromboembolic stroke was not changed by estrogen use (RR 1.1 (0.6-1.8)) nor by combination HRT use. This recent large study is consistent with previously published prospective cohorts that show no effect on stroke of post-menopausal hormone use. In all studies to date, the 95% confidence intervals overlap one, suggesting no association between HRT use and stroke.

INTERPRETATION:

Summary of Key Evidence

Prior to the WHI, seventeen studies meeting our inclusion criteria were published, one small RCT and 16 prospective cohort studies. Most showed a protective association with estrogen, alone or in combination with a progestin, on myocardial infarction or death from cardiovascular disease in peri-menopausal women without established CAD. No studies showed a beneficial effect from HRT on stroke incidence or stroke related mortality. The WHI has helped inform us of the risks vs. benefits of HRT. There are some risks to estrogen, including a small but consistent 3-fold increase in thromboembolic events (approximately 4/1000 women-years)⁶ and hyper-triglyceridemia.³⁴

Canadian Task Force Recommendations: (Table 4):

In light of the RCT-level evidence for increased overall harm in women without diagnosed CAD who take combination HRT, the Task Force concludes that there is fair evidence to recommend against the use of HRT for the primary prevention of myocardial infarction and death from cardiovascular disease in peri-menopausal women without established CAD (**D recommendation**). To maintain 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 importantly blood pressure assessment and control, are more likely to limit the tremendous burden of disease in the female population.

There is insufficient evidence to make a recommendation on HRT for the primary prevention of stroke and death from cerebrovascular disease in peri-menopausal women. However, as stroke is a major cause of morbidity and mortality in Canadian women, other beneficial preventive measures, such as aggressive treatment of hypertension, should be used rather than HRT.

Clinical Implications

There will still be many symptomatic postmenopausal women who may choose to take HRT short-term, weighing the symptomatic benefits vs. known risks. In the symptomatic woman, clinicians must be cautious however, in initiating therapy to anyone with thrombotic risk.³⁹ Contraindications to HRT include previous or active deep vein thrombosis, thrombophilic

disease, active liver dysfunction, known or suspected endometrial or breast cancer, and severe elevation in triglycerides. The discussion of risks and benefits of HRT should be based on the individual patient's history and risk profile for cardiac, thrombo-embolic and gallbladder disease, osteoporosis, and breast cancer. Although not covered in this review, women with established coronary disease must also make individual treatment decisions based on potential non-cardiac benefits vs. risks of estrogen use. Many of the cardiac benefits of estrogen may be reproduced by use of specific cardiac medications in select populations. Reviews of HRT related cancer risks, and benefits for osteoporosis have recently been completed by the Canadian Task Force on Preventive Health Care.⁴⁰⁻⁴²

Recommendations of Others:

Several groups have issued updated recommendations following the release of the WHI results. The United States Preventive Services Task Force recommends against combination estrogen-progestin therapy based on an overall balance of harms versus benefits for chronic disease prevention. They found inconclusive evidence to recommend for or against the use of unopposed estrogen for chronic disease prevention in women who have had a hysterectomy.⁴³ The Society of Obstetrics and Gynaecology of Canada (SOGC) maintains that: “the best treatment for distressing menopausal symptoms is combined continuous HRT”. However, they also advised that “combined continuous HRT should not be recommended routinely for all postmenopausal women, as it does not appear to offer cardio-protection and the slightly increased risk of cardiovascular disease and breast cancer outweigh the benefits in asymptomatic women”.⁴⁴ The Heart and Stroke Foundation of Canada, in collaboration with the Canadian Cardiovascular Society and the SGOC state that HRT should not be initiated or continued in women for the sole purpose of preventing future cardiovascular events.⁴⁵

The American Society of Obstetrics and Gynaecology (ACOG) went further to state that “women who take HRT for the management of vasomotor symptoms should be encouraged to take it for as short a time as possible and to use the lowest effective dose”.⁴⁶ They also stated that “long term use of CEE and progesterone therapy should be discontinued in asymptomatic patients”.

The North American Menopause Society recently published the NAMS Report on Hormone Therapy⁴⁷ which stated “no estrogen/progestin therapy regimen should be used for

primary or secondary prevention of coronary heart disease (CHD)”. They also advised 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”.⁴⁷

Research Priorities:

Studies involving women of different ethnic backgrounds, lower socio-economic class, lower education, and frailer health are research priorities. Evaluation of strategies once thought to be beneficial need to be evaluated in RCTs. Ongoing research is needed regarding the safety and efficacy of other types and routes of administration of HRT.

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Table 1: Inclusion and exclusion criteria used to select studies for review of HRT in the primary prevention of cardio- and cerebro-vascular disease.

Inclusion criteria

- the study was either a prospective cohort study with internal controls or a randomised controlled trial investigating the prevention of death, myocardial infarction, or stroke from hormone replacement therapy consisting of either estrogen or estrogen in combination with progestin
- the duration of the patient follow-up was at least 5 years
- the majority of patients initially studied were free from established coronary or cerebrovascular disease ($\leq 10\%$) (d) human females were studied.

Exclusion criteria

- agents such as Selective Estrogen Receptor Modulators (SERMs) were utilized (as these compounds are still under investigation for cardio-protection and have some anti-estrogen properties in addition to estrogen like effects)
- there was no documentation of patients lost to follow-up
- men were included in the study population and data from the female sub-group could not be separated
- the study evaluated pre-menopausal estrogen use
- the study did not have internal controls or had a solely a case-control design, although prospective cohorts with nested case control analyses were included.

NOTE: In studies with multiple publications, the version with the longest follow up duration was included in the analysis.

Table 2: Cardiovascular outcomes (relative risk reductions are adjusted for age and co-morbidity)[†]

| * Author (reference #) | Exposure (% E+P of HRT users) E=estrogen, P=progesterin | N | Average F/U (years) | All Cause mortality RR (95%CI) | IHD mortality RR (95%CI) | Other mortality RR (95%CI) | CV events RR (95%CI) |
|---|--|-------------|--------------------------------|--|---|--|--|
| WHI Writing Group, ¹¹ 2002 | 100% E+P | 16,608 | 5.2 | 0.98 (0.82-1.18) (unadjusted, study stopped early) | 1.18 (0.70-1.97) | 0.92 (0.74-1.14) | |
| Bush et al, ²⁷ 1987 | 1% E+P | 2270 | 8.5 | 0.54 (0.29-0.79) | 0.42 (0.13-1.10) | CV(1°+2°) 0.34 (0.12-0.81) | |
| Grodstein, ²¹ 1997 and Grodstein, ²⁹ 1996 | 44% E+P (for 1990) | 37,611 | 16 years, 662,891 person-years | current vs never: 0.63 (.56-.70) past vs never 1.03 (0.94-1.12) | current vs never: 0.47 (.32-.69) past vs never 0.99 (0.75-1.3) | | CV events 0.60 (0.43-0.83) E 0.39 (0.19-0.78) E+P |
| Schairer, ²³ 1997 | 31% E+P | 23,246 | 5.8 | 0.7 (0.6-0.8) (E+P) | 0.4 (0.2-0.6) (E+P) | Circulatory System 0.5 (0.3-0.7) (E+P) | |
| Falkeborn, ¹⁷ 1992 | 31% E+P | 1.4 million | 5.8 | | | | 1 st MI hospitalization 0.81 (0.71-0.92) 0.50 (0.28-0.80) E+P |
| Criqui, ²⁸ 1988 | Unknown | 1868 | 12 | 0.79 (.62-.1.01) | 0.96(.65-1.43) | CV (400-448.9 ICD) 0.82 (.56-1.2) | |
| Wolf, ³³ 1991 | Unknown | 1910 | 16 | | 0.66 (0.48-0.90) | | |
| Henderson, ³⁰ 1991 | 60% E+P | 8853 | 7.5 | 0.8 (.7-.87) | death from MI 0.60 p<0.001 | | |
| Cauley, ¹⁶ 1997 | 20% E+P | 8947 | 6 | 0.69 (0.54-0.87) | 0.49 (.26-.93) | All CVD 0.46 (0.29-0.73) | |
| Sturgeon, ²⁵ 1995 | Unknown | 49,017 | 10 | 0.7 (.7-.8) | 0.7 (.6-.9) IHD (410-414) | CV (ICD 390-459) 0.7 (.6-.8) | |
| Folsom, ²⁰ 1995 | Unknown | 41,070 | 6 | 0.78 (.65-.94) | 0.74 (.48-1.12) | | |
| Wilson, ³² 1985 | < 5% E+P | 1234 | 8 | 0.97 p=NS | 1.94 p=NS | | MI 1.87 p=NS |
| Nachtigall, ³¹ 1979 | 100% E+P | 168 | 10 | 8.3% vs 3.6% NS (Placebo Vs HRT) | | | (Placebo Vs HRT) MI 3.7% vs 1.2% NS DVT 18.3% vs 15.5%NS |
| Sourander, ²⁴ 1998 | 20% E+P | 7944 | 8 | | Current: 0.19 (.05-.77) Former:0.64(.27-1.47) | Current 0.21 (.08-.59) former 0.75 (.08-.59) CV mortality: | |

[†] with the exception of the Falkeborn¹⁷ & Schairer²³ studies

| | | | | | | | |
|---------------------------------|-----------------------|--------|----|--|--|--|--|
| Lafferty, ²² 1994 | 100% E+P from 1983 on | 157 | 25 | | | | MI 0.34 (.09-1.34) |
| Avila, ²⁶ 1990 | Unknown | 24,900 | 5 | | | | 1 st time MI 0.7 (0.4-1.3) |

* Studies are arranged to reflect relative importance/quality of methodology, with higher-ranking studies shown first.

Table 3: Stroke outcomes

| Author (ref. #) | Exposure (% E+P of HRT users) E=estrogen, P=progestin | N, | Average F/U (years) | Endpoints | Results RR (95%CI) |
|---|---|---------|------------------------|---|---|
| WHI Writing Group, ¹¹ 2002 | 100% E+P | 16,608 | 5.2 | Stroke, fatal and Non-fatal (unadjusted, study stopped early) | 1.41 (1.07-1.85) 1.50 (1.08-2.08) |
| Grodstein, ²¹ 1997 and Grodstein, ²⁹ 1996 | 44% E+P (for 1990) | 121,700 | 16 | Deaths from stroke n= 167 | 0.68 (.39-1.16) current vs never 1.07 (0.68-1.69) past vs never |
| Schairer, ²³ 1997 | 31% E+P | 23,246 | 5.8 | Mortality:* from cerebrovascular diseases Acute stroke(unadjusted) Intracerebral hemmorage Thromboembolic stroke Acute- ill defined | 0.6 (0.3-1.1) (E+P) 0.8 (0.3-1.6) (E+P) 0.6 (0.1-1.7) (E+P) 0.8 (0.1-2.8) (E+P) 1.2 (0.1-4.4) (E+P) |
| Henderson, ³⁰ 1991 | 60% E+P | 8853 | 7.5 | Death from occlusive stroke n= 60 in non-users, n= 32 in users | 0.63 p= NS |
| Sturgeon, ²⁵ 1995 | Unknown | 49,017 | 10 | Mortality due to cerebrovascular disease ICD430-438 | ever vs never: 1.0 (.7-1.4) |
| Falkeborn, ¹⁷ 1992 | 31% E+P | 23,088 | 5.8 | Stroke | 0.9 (0.81-0.99) |
| Finucane, ¹⁹ 1993 | 31% E+P | 1910 | 11.9 | Stroke, fatal and non-fatal N=250, 8.3%(33) ever vs14.3% (217) never | 0.69 (0.47-1.00) |
| Folsom, ²⁰ 1995 | Unknown | 41,070 | 6 | Mortality from stroke: | 1.31 (.64-2.67) 0.95 (.37-2.43) * *excluding baseline CAD and cancer |
| Wilson, ³² 1985 | < 5% E+P | 1234 | 8 | Cerebrovascular disease Atherothrombotic brain infarction | 2.27 p < 0.01 2.60 p < 0.01 |
| Sourander, ²⁴ 1998 | 20% E+P | 7944 | 8 | stroke mortality N=386 | current 0.16 (0.02-1.18) former 1.05 (0.41-.2.68) |
| Cauley, ¹⁶ 1997 | 20% E+P | 8947 | 6 | Stroke mortality: | 0.47 (0.2-1.08) current vs never 0.85 (0.48-1.49) past vs never |

| | | | | | |
|------------------------------|--------------------|-----|----|------------------|-------------------|
| Lafferty, ²² 1994 | 100% E+P from 1983 | 157 | 25 | Stroke mortality | 4.15 vs 0 p=0.025 |
|------------------------------|--------------------|-----|----|------------------|-------------------|

Table 4: Recommendation Table: Hormone Replacement to Prevent Cardiovascular Disease and Stroke

| Maneuver | Effectiveness | Level of Evidence <refs> | Recommendation |
|---|---|--------------------------------|--|
| Hormone replacement therapy for the primary prevention of cardiac disease and cardiac mortality in peri-menopausal women. | <p>For combined estrogen plus progestin therapy:</p> <ul style="list-style-type: none"> - increased risk of non-fatal MI and coronary death (7 more cases/10,000) - increased risk of stroke (8 more cases/10,000), venous thrombo-embolism (18 more cases/10,000). <p>Overall increased relative risk of 22% of an adverse outcome for cardiovascular disease.</p> | Level I, II-2 <16-20,22-33> | There is fair evidence to recommend against the use of HRT for the primary prevention of myocardial infarction and death from cardiovascular disease in peri-menopausal women without established CAD (D recommendation). |

* To maintain 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.

** There is insufficient evidence to make a recommendation on HRT for the primary prevention of stroke and death from CVD. Since stroke is a major cause of morbidity and mortality in Canadian women, other beneficial preventive measures, such as aggressive treatment of hypertension, should be used rather than HRT.

| Appendix 1: Methodology of the Canadian Task Force on Preventive Health Care | |
|---|---|
| <p>Critical appraisal</p> <p>The Task Force reviewed 1) the initial analytic framework and key questions for the proposed review; 2) the subsequent draft(s) of the complete manuscript providing critical appraisal of the evidence prepared by the lead author(s), including identification and critical appraisal of key studies, and ratings of the quality of this evidence using the task force's established methodological hierarchy (sidebar); and 3) a summary of the evidence and proposed recommendations.</p> | <p>Levels of evidence</p> <p>I Evidence from well-designed randomized controlled trial(s)</p> <p>II-1 Evidence from well-designed controlled trial(s) without randomization</p> <p>II-2 Evidence from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group</p> <p>II-3 Evidence from comparisons between times or places with or without the intervention; dramatic results from uncontrolled studies could be included here</p> <p>III Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees</p> |
| <p>Consensus development</p> <p>Evidence for this topic was presented by the lead author(s) and deliberated upon during task force meetings in June and October 1999, May 2002 and February 2003. Expert panelists addressed critical issues, clarified ambiguous concepts and analyzed the synthesis of the evidence. At the end of this process, the specific clinical recommendations proposed by the lead author were discussed, as were issues related to clarification of the recommendations for clinical application and any gaps in evidence. The results of this process are reflected in the description of the decision criteria presented with the specific recommendations. The group and lead author(s) arrived at final decisions on recommendations unanimously.</p> <p>Subsequent to the meetings, the lead author revised the manuscript accordingly. After final revision, the manuscript was sent by the Task Force to two experts in the field (identified by Task Force members at the meeting). Feedback from these experts was incorporated into a subsequent draft of the manuscript.</p> <p>Procedures to achieve explicit documentation, consistency, comprehensiveness, objectivity and adherence to the task force methodology were maintained at all stages during review development, the consensus process and beyond to ensure uniformity and impartiality throughout.</p> | <p>*General design specific criteria are outlined in Harris et al.⁴⁸ Inclusion/exclusion criteria are detailed in Table 1.</p> <p>Recommendation Grades</p> <p>A The CTF concludes that there is good evidence to recommend the clinical preventive action.</p> <p>B The CTF concludes that there is fair evidence to recommend the clinical preventive action.</p> <p>C The CTF concludes that the existing evidence is conflicting and does not allow making a recommendation for or against use of the clinical preventive action, however other factors may influence decision-making.</p> <p>D The CTF concludes that there is fair evidence to recommend against the clinical preventive action.</p> <p>E The CTF concludes that there is good evidence to recommend against the clinical preventive action.</p> <p>I The CTF concludes that there is insufficient evidence (in quantity and/or quality) to make a recommendation, however other factors may influence decision-making.</p> <p><i>The CTF recognizes that in many cases patient specific factors need to be considered and discussed, such as the value the patient places on the clinical preventive action; its possible positive and negative outcomes; and the context and/or personal circumstances of the patient (medical and other). In certain circumstances where the evidence is complex, conflicting or insufficient, a more detailed discussion may be required.</i></p> |