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Systematic Evidence Review
Number 10

Postmenopausal Hormone Replacement Therapy and Cardiovascular Disease

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Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) through its Evidence-based Practice Program. With guidance from the third U.S. Preventive Services Task Force* (USPSTF) and input from Federal partners and primary care specialty societies, two Evidence-based Practice Centers—one at the Oregon Health Sciences University and the other at Research Triangle Institute-University of North Carolina—systematically review the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, immunizations, and chemoprevention, in the primary care setting. The SERs—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services—serve as the foundation for the recommendations of the third USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the "Methods" section of each SER.

The SERs document the evidence regarding the benefits, limitations, and cost-effectiveness of a broad range of clinical preventive services and will help to further awareness, delivery, and coverage of preventive care as an integral part of quality primary health care.

AHRQ also disseminates the SERs on the AHRQ Web site (http://www.ahrq.gov/uspstfix.htm) and disseminates summaries of the evidence (summaries of the SERs) and recommendations of the third USPSTF in print and on the Web. These are available through the AHRQ Web site (http://www.ahrgq.gov/uspstfix.htm), through the National Guideline Clearinghouse (http://www.ncg.gov), and in print through the AHRQ Publications Clearinghouse (1-800-358-9295).

We welcome written comments on this SER. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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* The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services--including screening, counseling, immunization, and chemoprevention--in the primary care setting. AHRQ convened the third USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.

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Structured Abstract

Objective: Cardiovascular disease (CVD) is the leading cause of death among women in the United States (US), and hormone replacement therapy (HRT) is commonly used, often for the prevention of CVD. The goal of this systematic evidence review and meta-analysis is to evaluate the association between HRT and the primary prevention of CVD, including total CVD, coronary artery disease (CAD), and stroke, when they were evaluated as separate subsets.

Data Sources: The MEDLINE (1966-2000) and Cochrane databases were searched for all published studies reporting CVD, CAD, and stroke incidence and/or mortality in association with HRT among the general population of women; reference lists, letters, editorials, and reviews were also reviewed.

Methods: All studies were reviewed, abstracted and rated in quality; only studies of good or fair quality according to U.S. Preventive Services Task Force (USPSTF) criteria were included in the detailed review and meta-analysis. Meta-analysis was conducted using a random effects model.

Results: The summary relative risk for CVD mortality with any HRT use was 0.75 (95% CI, 0.42-1.23) and for current users was 0.64 (95% CI, 0.44-0.93). CAD mortality was associated with a relative risk of 0.74 (95% CI, 0.36-1.45) for any use and 0.62 (95% CI, 0.40-0.91) for current use. No significant association between HRT and risk of stroke death was identified. In contrast to the mortality findings, the summary relative risk for

CVD incidence is 1.28 (95% CI, 0.86-2.00) for any use and 1.27 (95% CI, 0.80-2.00) for current use. Stroke incidence was significantly increased among women using HRT, with a summary relative risk of 1.12 (95% CI 1.01-1.23), largely due to a significant increase in atherothrombotic stroke among women using HRT.

In our meta-analysis, the pooled relative risk of CAD associated with any use of HRT was 0.87 (95% CI, 0.62-1.21) and for current use was 0.80 (95% CI, 0.68-0.95). When studies adjust for socioeconomic status (SES) as well as other major CAD risk factors, the summary relative risk of CAD is 0.97 (95% CI, 0.82-1.16) among current users and 1.04 (95% CI, 0.79-1.44) among ever users. Similar results were found when the analysis stratified by studies adjusting for alcohol consumption and/or exercise, in addition to other major risk factors.

Conclusion: The association between HRT and CVD incidence and mortality, as well as CAD and stroke incidence and mortality, is uncertain, based on conflicting findings, and limited by lack of randomization and consequent selection biases among women using HRT in the observational studies. Our meta-analysis differs from prior meta-analyses by evaluating potential explanatory variables of the HRT-CVD/CAD relationship, as well as different measures of HRT exposure. It shows a small decrease in CVD and CAD deaths only among current HRT users and no effect on stroke, and suggests that SES, alcohol use, and exercise are important confounders of the HRT/CVD/CAD relationship. A valid answer to the potential role of HRT in the primary prevention of CVD will best come from randomized controlled trials.

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Chapter 1. Introduction

Postmenopausal hormone replacement therapy (HRT) is one of the most commonly prescribed drug regimens in the United States. This use largely reflects the significant number of postmenopausal women in the United States, many of whom are choosing to take HRT to treat symptoms of menopause. A recent survey showed that 40% to 55% of postmenopausal women have used hormone replacement therapy at some time in their lives, with higher rates of use in women who have undergone hysterectomy.[1] Also contributing to the high prevalence of use has been significant publicity to physicians and women regarding HRT's effect on bone density and its potential effect in decreasing cardiovascular disease (CVD) morbidity and mortality, as well as potentially reducing several other serious diseases, such as Alzheimer's Disease and colon cancer. Finally, because estrogen replacement therapy has been shown to favorably alter lipids, estrogen use is recommended as part of the National Cholesterol Education Program Guidelines for managing cholesterol, and this too has contributed to its frequent use.[2]

Of all the potential benefits of HRT, the one with the greatest potential public health impact is its possible role in preventing CVD, the leading cause of death among women in the United States. CVD includes coronary artery disease (CAD) and stroke. Unfortunately, despite many observational studies of HRT and CVD, a valid answer to the question of whether HRT is protective against CVD has not yet been provided in the medical literature, due to limitations of observational studies. However, evidence from 3 randomized controlled trials has recently been published and aids in evaluating this relationship. This systematic evidence review will summarize all epidemiologic studies evaluating the role of HRT in the primary prevention of CVD. Two important recent studies of the secondary prevention of CAD in postmenopausal women will also be reviewed because they are the only published randomized controlled trials of HRT in CVD and may provide insight to the primary prevention discussion.

Background

CVD, which includes CAD and stroke, is the leading cause of death in women in the United States. At every age, women have less CAD than men, even with adjustment

for risk factors.[3] The one risk factor exception is diabetes, where women and men have equal rates of CAD.[4] To explain this gender difference, it has been suggested that women have less CAD than men because of exposure to female hormones, specifically estrogen. Animal studies showing that estrogen is protective against heart disease and vascular disease have suggested an important role for estrogen in atherosclerosis.[5-7] The relationship between estrogen and CVD has also been considered because of epidemiologic studies showing low rates of CVD in premenopausal women, with significant increases in incidence occurring after menopause,[4] although other physiologic parameters, such as progesterone and pituitary hormones, also change with menopause.

Adding to the hypothesis that estrogen mediates the reduced risk of CVD observed among women are multiple epidemiologic studies showing reduced rates of CVD, particularly CAD, among women using HRT.[8] Evidence of a relationship between female reproductive hormones and CVD also comes from studies evaluating CVD in women who undergo premature menopause. In the Nurses' Health Study (NHS), early menopause increased the risk of CVD when compared to later menopause, suggesting an important role of estrogen or other reproductive hormones.[9] This change in risk of CVD was reversed or normalized with HRT,[9, 10] suggesting that estrogen with or without progesterone was important etiologically. However, other explanations may also be important, such as confounding by factors associated with early menopause and CVD (e.g., smoking and body weight). Other physiologic parameters that change with menopause may also be important etiologically. In addition, the fact that women in different countries have dramatically different rates of CVD suggests that genetic, environmental, and lifestyle characteristics are much more important than exposure to estrogens in determining CVD risk among women.

Multiple observational epidemiologic studies evaluating the relationship between HRT (usually estrogen) and CVD have been conducted, and many suggest that HRT is associated with lower risk of CVD.[8] Some, however, have suggested increased risk[11] or no difference in risk.[12] Critical in evaluating this relationship has been the issue of confounding, and the fact that women who use estrogen are systematically different from women who do not in ways that influence their risk of CAD.[11] However, because of the many studies suggesting benefit, multiple studies

have been conducted in attempts to understand the potential mechanisms of benefit from HRT. These biological mechanisms will be briefly discussed.

Cardiovascular Disease: Proposed Biological Actions of Estrogen and Progesterone

This section briefly summarizes proposed mechanisms by which estrogen might influence CVD risk. For excellent, in-depth reviews, see papers by Bush and Barrett-Connor[6] and Mendelsohn.[13] Because recent randomized controlled trials have evaluated HRT and lipids, and because estrogen has been proposed as a potential therapy for hyperlipidemia,[2] the review of lipids is more detailed than other topics in this section.

Lipids. In general, observational studies[14-17] and clinical trials of estrogen use[18-20] have shown that estrogen alone decreases low-density lipoprotein (LDL) and apoprotein B, and increases high-density lipoprotein (HDL) and triglycerides.[21] These findings have been shown in diverse population groups, among healthy and non-healthy women, and among those with natural and surgical menopause. Adding progesterone has been shown to diminish, though not reverse, the improvement in HDL that occurs among women taking estrogen, and the magnitude varies with the type of progestin used. Because women who use HRT often have health characteristics associated with better lipid profiles, the most important data in this area come from randomized controlled trials of HRT and lipids.

The best data may come from the Postmenopausal Estrogen/Progestin Inverventions (PEPI) trial,[21] in which 875 healthy postmenopausal women were randomized to placebo, conjugated equine estrogen (CEE) alone, CEE plus cyclic medroxyprogesterone acetate (MPA), CEE plus continuous daily MPA, or CEE plus cyclic micronized progesterone (MP). All active therapies decreased mean LDL-cholesterol and increased mean triglyceride levels when compared to placebo. All estrogen therapies also increased HDL-cholesterol, with the greatest increase among women taking CEE alone (5.6 mg/dl) or CEE plus MP (4.1 mg/dl). Combination therapy with CEE and cyclic MPA, or CEE with continuous MPA, was associated with increased HDL levels of 1.6 and 1.2 mg/dl, respectively. Women taking placebo experienced a decrease in HDL of 1.2 mg/dl. The effect of estrogen and progestins on HDL is an important one because

HDL has been shown to be an important predictor of major CAD among women.[4, 22] Transdermal estrogen has less effect on lipids than oral administration of estrogen and no effect on HDL cholesterol.[13]

Another important independent risk factor for atherosclerosis is lipoprotein(a). Randomized trials of CEE and 17 B estradiol have shown that estrogen also reduces lipoprotein (a).[23-25] However, some studies have shown that this benefit may be modified[26] or attenuated[19] by adding progestins.

Adding progestins to estrogen may reduce the decrease in LDL and increase in HDL[27] among women taking estrogen (as discussed above in the PEPI trial), although usually not to pre-estrogen or placebo levels. The PEPI trial was important in showing that the action of progestins on lipids varies between MPA and MP.[21] Adding progestins to estrogen also may reduce the increase in triglycerides observed when estrogen is used alone.[27] Also, the effects of progestins on cholesterol levels vary significantly by dose and type of progestin, particularly their androgenicity.[19, 27, 28]

The Heart and Estrogen/Progestin Replacement (HERS) trial,[29] a randomized controlled trial of combined hormone replacement therapy (CHRT) in the secondary prevention of CAD, contributed important findings to the evaluation of lipid changes associated with CHRT. The study involved 2,763 postmenopausal women younger than age 80 with known CAD randomized to either placebo or CEE (0.625 mg per day) and MPA (2.5 mg per day) and followed for 4.1 years for non-fatal myocardial infarction (MI) or coronary death. During the first year of the study, LDL cholesterol decreased 14% in those randomized to CHRT and 3% in the placebo group. Among those women randomized to hormones, HDL cholesterol increased by 8% and triglycerides by 10%. In the placebo group, HDL decreased by 2% and triglycerides increased by 2%.[29]

In another recently reported randomized controlled trial of secondary prevention[30] involving 309 women with coronary disease, women randomized to CEE (0.625 mg per day) had a decrease in LDL of 9.4%, an increase in HDL of 18.8%, and an increase in triglycerides of 6.1%. Women randomized to CEE (0.625 mg per day) plus MPA (2.5 mg per day) had an LDL decrease of 16.5%, an HDL increase of 14.2%, and an increase in triglycerides of 10.1%. Among

the women randomized to placebo, LDL decreased by 1.3%, HDL increased by 6.8%, and triglycerides increased by 2.2%.[30]

Endothelial wall function. Studies of postmenopausal women with atherosclerosis have shown that sustained estrogen enhances endothelium-dependent vasodilation.[31, 32] One study showed that estrogen restored coronary vasodilation in response to acetylcholine among women but not men with coronary disease, suggesting a gender-specific effect.[33] Estrogen-associated vasodilation occurs within minutes after estrogen administration and is not dependent on changes in gene expression; in addition, estrogen inhibits the response of blood vessels to vascular injury, a response occurring over hours to days and dependent on changes in gene expression.[13]

Carbohydrate metabolism. The role of estrogens in carbohydrate metabolism is complex. Some studies have suggested that estrogens may predispose women to impaired glucose tolerance; others have suggested favorable effects on glucose and insulin that may depend on the type of estrogen and progestin used.[34] Another important finding from the PEPI trial was that mean changes in 2-hour insulin levels did not differ significantly among treatment groups.[21] However, 2-hour glucose levels increased significantly in women on active treatment compared to placebo. Fasting insulin levels slightly, though not significantly, decreased among women assigned to active treatment. Also, fasting glucose levels decreased slightly in all treatment arms compared with placebo ($p = 0.03$). The overall clinical significance of these changes is uncertain at this time.

Hypertension. The induction of hypertension among women taking estrogen has been a concern because estrogen regulates vascular tone, both through long-term and short-term effects.[13] Long-term administration of estrogen is associated with decreases in renin, angiotensin-converting enzyme inhibitor, and endothelin I, as well as other vascular changes, with a net vasodilatory effect.[13] However, studies evaluating this relationship have been contradictory, with some showing elevations and some showing decreases in blood pressure among women using estrogen. These studies, though, have had methodologic weaknesses.[21] The addition of progesterone to

estrogen and the effect on blood pressure has been less well studied. In the PEPI trial, systolic and diastolic blood pressure did not differ significantly among treatment groups.[21]

Coagulation factors. The role of coagulation factors in atherosclerotic vascular disease is complex. Estrogen has been shown to regulate the hepatic synthesis of several coagulation factors and fibrinolytic proteins,[13] resulting in reduced levels of fibrinogen,[21] antithrombin III,[34] and plasminogen-activator inhibitor type 1.[35, 36] The effect of estrogen on coagulation varies with type and dose of estrogen, as well as with duration of use.[13] Some studies have shown that estrogen alone increases plasminogen, protein C, and factor VII.[16] Estrogen may also favor vasodilation and anti-aggregation by increasing prostacyclin production and thromboboxane A2 platelet aggregation.[37] The net effect of these changes on CVD incidence is uncertain, although the data on HRT from both observational and randomized controlled trials are consistent and strong in showing an increase in deep venous thrombosis and pulmonary emboli among women using HRT.[38, 39] Given the known importance of plaque formation and rupture with associated thrombosis in myocardial infarction and stroke, the balance among these factors and their association with CVD is critically important.

Weight. Obesity and/or increased abdominal adiposity are associated with increased risk of CAD in women.[40] The PEPI study showed that women in all treatment groups gained weight over the 3 years of the study, but weight gain was greater among women assigned to placebo (2.1 kg) and least among women using CEE (0.7 kg) over 36 months.[21] The mean waist-to-hip ratio increased slightly over time among all groups, unrelated to treatment.

Inflammation. C-reactive protein, a marker of inflammation, was recently shown to be an independent predictor of CVD in women.[41] Two recent studies have shown that women taking estrogen, or estrogen with progesterone, had higher levels of C-reactive protein than women not taking HRT.[42, 43]

Antioxidant Effects. The role of estrogen as an antioxidant or pro-oxidant has been suggested in some studies.[44] Estrogen also has been found to inhibit LDL oxidation in vitro.[45]

In aggregate, the changes in intermediate biological outcomes have potentially favorable results, including lower LDL, lower lipoprotein (a), and increased HDL, and potentially unfavorable results, such as increased triglycerides, factor VII and c-reactive protein, and decreased plasminogen and antithrombin III.[16, 21, 34] These physiologic changes may explain a biological relationship between HRT and CVD. However, whether the favorable changes in these biological intermediates translate into improved CVD outcomes is uncertain. Given the mix of intermediate biological outcomes and limitations of the observational data, it is imperative that the relationship be critically examined prior to speculation of benefit. Several important questions regarding HRT and CVD among postmenopausal women have not yet been answered in the medical literature. These questions primarily relate to the cardiovascular risks/benefits associated with short-term and long-term hormone use, as well as risks/benefits associated with combination therapy involving estrogen and progesterone. These questions are outlined in detail below.

This report reviews the epidemiologic literature evaluating these benefits and risks in association with CVD. In some studies, CVD was explicitly described as a global outcome involving any cardiovascular event, such as stroke, transient ischemic attack, sudden cardiac death attributed to ischemic heart disease, myocardial infarction, peripheral vascular disease, coronary artery surgery (CABG), percutaneous transluminal coronary angioplasty (PTCA), or congestive heart failure (CHF). In other studies, the components of cardiovascular disease were not described but presumably comprised CAD and stroke. In an effort to include the breadth of available information, for the purposes of this review, CVD is considered as a global outcome when described, or as a measure of CAD and stroke when not described. CAD includes MI, PTCA, CABG, sudden cardiac death attributed to CAD, CHF, and occasionally, angina. Stroke includes different types of stroke, such as subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), thromboembolic infarction, and transient ischemic attack.

Analytic Framework and Key Questions

The analytic frameworks in Figures 1 and 2 show the target populations, interventions, and health outcome measures we examined for the overall question of the benefits and risks of postmenopausal HRT.

The key questions to consider when evaluating the research describing the role of exogenous estrogen or estrogen/progesterone in CVD incidence and mortality include:

1. *What is the role of postmenopausal HRT in the primary prevention of CVD death?*
2. *What is the role of postmenopausal HRT in the primary prevention of CAD death?*
3. *Does postmenopausal HRT alter the risk of stroke death?*
4. *What is the role of postmenopausal HRT in the primary prevention of CVD?*
5. *What is the role of postmenopausal HRT in the primary prevention of CAD?*
6. *Does postmenopausal HRT alter the risk of stroke as well as subtypes of stroke?*
7. *Does postmenopausal HRT reduce cardiovascular events or progression of disease in women with known CAD?*

Because we were concerned with HRT as chemoprophylaxis against chronic conditions, not as treatment of menopausal symptoms, we focused on the use of either estrogen alone or estrogen combined with progesterone in healthy, postmenopausal women. However, because there are important recent data from secondary prevention studies of HRT in women with known CVD and these are the only clinical trials with published information to date, we have also included information on 2 randomized controlled trials of secondary prevention of CVD with HRT, since they may provide insight to the issue of primary prevention. This evaluation will be part of an overall chapter reviewing the risks and potential benefits of HRT. Shared decision making and patient preferences will also be discussed in that chapter.

Chapter 2. Methods

Literature Search

We sought to review all published English-language literature with quantitative data evaluating the relationship between HRT use and CVD, CAD, and stroke in postmenopausal women. We conducted 2 MEDLINE searches. First, the topic of HRT and CVD was searched in the MEDLINE database from 1966 to December 2000. Second, the search was narrowed to specifically look for stroke and cerebrovascular disorders. Full search strings are listed in Appendix 1. The Cochrane Library was also reviewed. Two investigators reviewed all abstracts to identify papers for full-text review and also evaluated editorials, letters, and reviews to ensure that no key papers were missed in the MEDLINE and Cochrane searches. We searched the bibliographies of all review papers, meta-analyses, and original research studies to ensure that all papers evaluating the epidemiologic relationship between HRT use and CVD outcomes were retrieved from the medical literature, reviewed, and abstracted, including those predating the search dates.

Criteria for inclusion in the systematic review were that the study included postmenopausal women and that it was in the English language or in a key non-English journal. We included meta-analyses, randomized controlled trials, and observational cohort and case-control studies if they reported CVD (as defined above), stroke, or CAD incidence or mortality. We did not review articles dealing with the use of estrogen in men, or in association with pregnancy or lactation.

Appendix 2 summarizes the results of the literature searches. A total of 1,926 abstracts were identified and reviewed: 1,668 in the CVD search and 258 in the stroke search. Sixty-five studies about HRT and CVD met criteria for full text review. This includes 34 cohort studies, 24 case-control studies, 4 angiography studies of secondary prevention of CAD, 2 randomized controlled trials of secondary prevention of CAD with HRT, and preliminary findings from the Women's Health Initiative. Of these 65 studies, 24 cohort and 8 case-control studies describing stroke and HRT met criteria for full text review. Fourteen of the cohort studies and 3 of the case-control studies overlapped and were used in evidence tables for both the CVD/CAD and stroke sections.

Literature Synthesis and Preparation of Systematic Evidence Review

We abstracted study data onto data-collection forms prepared at the beginning of the review, and then created and organized evidence tables by study type. One difficulty in summarizing and interpreting this literature is that analyses and results are reported differently among studies. The methods used to assess HRT use and to define categories of use in case-control and cohort studies are shown in Tables 1 and 2, respectively. Most studies report point estimates comparing "ever" to "never" or non-use of HRT. Notably, "ever" use can be of any duration, and may reflect as little use as 1 to 2 months or just filling a prescription for HRT, or can be many years of use. However, some studies report their findings only as "current" or "recent" use, or after a specific duration of use. Current or recent use may reflect a broad range of durations of use, which often are not characterized within the studies, and may reflect weeks to years of therapy. These are important differences to note, since some studies have identified reduced risks only in association with current or ever use, and not past use. When possible, we differentiate these findings on the evidence tables and in the text of this report. Since many of the studies only evaluate HRT use on one occasion, there is substantial room for misclassification in many of the studies.

Hormone use was classified in each study as unopposed estrogen (ERT) or combined estrogen and progesterone (CHRT) when it was specified, which was infrequent. When the type of estrogen or progesterone therapy was not specified, or the data were analyzed and/or reported together, the exposure was categorized as HRT.

In general, well-conducted randomized controlled trials provide more valid results than observational studies evaluating causal relationships. However, with the exception of preliminary data from the Women's Health Initiative, there are no randomized controlled trials of primary prevention of CVD with HRT. Therefore, our review involves predominantly observational studies, which are limited by lack of randomization and the potential for substantial selection biases.

In reviewing the quality of the evidence evaluating the relationship between HRT and CVD, cohort studies are methodologically stronger since they assess exposure prior to the onset of disease and are not as dependent on the recall of HRT use as case-control studies. In addition,

case-control studies are limited by the refusals of some patients with disease to participate, as well as by a frequent inability to evaluate patients with severe disease or those who have died. This can be an especially important problem in CVD epidemiology because a significant number of incident CVD events result in death. Women who have died of CVD may have had different HRT exposures from those of the women who did not, which might bias the results of these types of studies. In addition, case-control studies are prone toward recall bias, where cases remember or report exposures differently than controls. Finally, HRT use may be different among those who choose to participate and those who do not, which could bias the findings of the study. These issues will be discussed below. In this review, therefore, we assign more importance to the results from cohort studies. We did not review cross-sectional studies, since they are limited by prevalence/incidence/survivor bias and are often not helpful in evaluating potentially etiologic relationships. In ranking the quality of both cohort and case-control studies, we gave significant weight to adequate control of potential CVD risk factors because of known differences in risk profiles among women who use HRT and those who do not.[11, 46] Criteria for evaluating study quality were created by the third US Preventive Services Task Force and are described in Appendix 3. Table 3 shows each study's rating by quality; reasons for study quality ranking are described in the evidence tables.

After reviewing and rating all of the epidemiological studies displayed in the evidence tables, we limited our formal review and meta-analyses to studies meeting two criteria: 1) the study is a population-based, case-control study evaluating the risk of incident CVD, CAD, or stroke, or death from CVD, CAD, or stroke, with adequate control of major CVD risk factors, or a cohort study with internal controls evaluating CVD, CAD, and/or stroke incidence or mortality with adequate control for major CVD risk factors and at least 3 years of followup, and 2) the study was rated as fair or good quality based on the criteria described in Appendix 3.[47]

Only studies of fair or good quality are described in detail in our report and included in the meta-analyses, although all are summarized in the evidence tables. Some studies might be of fair or good quality in one type of analysis and of poor quality in another analysis. For example, some studies age-adjusted certain findings and used multivariate analyses for others. When this occurred, only the information of fair or good quality from the study was included in the results, discussion, and meta-analyses sections of our report. Unless stated, all relative risk estimates

discussed are adjusted for some important covariables. In studies with multiple publications from the same cohort or population, only data from the most recent publication were included in the discussion and meta-analyses, with reference in the text to older publications if they presented unique findings.

Three other studies discussed include the HERS trial, the Estrogen Replacement and Atherosclerosis (ERA) study, and preliminary information from the Women's Health Initiative (WHI) study. In the last 2 years, data have been published from the HERS and ERA studies, both randomized controlled trials of HRT in women with known CAD. Although these data may not be generalizable to women without CAD, it is important to include these data in this review, since the findings are concerning and provide the only data on secondary prevention among women randomized to HRT or placebo. In addition, preliminary data from the Women's Health Initiative were released in the spring of 2000 in the lay press, and although these data have not yet been published, the preliminary findings are included in this systematic review.[48]

Meta-analyses

We performed meta-analyses using a random-effects model to determine whether HRT has any impact on the risk of total CVD, CAD, and stroke mortality and incidence (see Appendix 4). All studies reported relative risk estimates. The logarithm of the relative risk (logRR) was assumed to have a normal distribution. If confidence intervals or *p*-values were reported, then standard errors for the logRR were calculated. The adjusted logRR and the corresponding standard errors were the data points for the meta-analyses.

The model used allows for stratification by three categories of HRT therapy (HRT unspecified, ERT alone, and combined ERT+HRT). Mean relative risks and confidence intervals are estimated for each HRT type. Separate models were fit on each outcome. When the data were sufficient, summary risks were determined by exposure type (past, current, ever) if the summary relative risks differed by exposure type. Finally, a global measure of use-- "any use"-- was determined based on mutually exclusive data points in the above 3 categories. In the stroke meta-analysis, the estimated relative risks of stroke associated with current, ever, past, or any use of HRT were similar, and therefore only one summary estimate was determined for each stroke outcome. A model was only fit if there were 3 or more data points available.

The Bayesian data analytic framework was used to fit the model. Inference on the parameters was done via posterior probability distributions. WinBUGS was used to analyze the data; this software uses a method of Markov Chain Monte Carlo called Gibbs Sampling to simulate posterior probability distributions. Noninformative prior probability distributions were used. Inference was made on 10,000 simulated draws (2,000 draws from 5 chains) from the posterior distribution after adequate convergence.

Chapter 3. Results

Cardiovascular Disease, Coronary Artery Disease and Stroke Mortality

The literature evaluating total CVD mortality and/or the subsets of CVD, CAD, and stroke mortality includes 8 studies reporting total CVD mortality, 5 reporting CAD mortality, and 8 reporting stroke mortality. In an effort to report all CVD, we first report data from studies evaluating the global outcome of CVD mortality when it was reported either alone or in addition to the subsets of CAD or stroke mortality. All of the studies providing information to this discussion and the meta-analyses are summarized in detail in Evidence Tables 1 through 5.

1. What is the Role of Postmenopausal HRT in the Primary Prevention of Cardiovascular Disease Death?

Definitions of CVD were taken directly from studies evaluating this outcome. In general, these outcomes included stroke, CAD, sudden cardiac death, congestive heart failure, peripheral vascular disease, CABG, or PTCA. In some studies, however, CVD is not clearly defined and likely represents death from a variety of etiologies coded as CVD. Alternatively, CVD may really represent only or primarily CAD events, but was used in a less specific manner by the authors. For these reasons we evaluated CVD rates in addition to its components of CAD and stroke when these were reported.

Among the observational studies reviewed, 8 studies of good or fair quality provided information to this analysis[11, 22, 49-54] (Table 4, Evidence Tables 1 and 2). Six of the 8 studies[22, 49-53] reported lower CVD mortality among women using HRT, but only 4 reported statistically significant findings.[50-53]

Among the studies suggesting benefit is the Lipid Research Clinic (LRC) study, in which 2,270 women ages 40 to 69 identified in the Lipid Clinics Prevalence Study were followed for an average of 8.5 years.[22] Women participated in a clinical exam, laboratory evaluation, and cardiologic evaluation, as well as an interview. Subjects were classified as current users if they were using HRT at the second visit. After age adjustment, the relative risk of CVD death among women using HRT was 0.34 (95% CI 0.12-0.81). However, with the addition of HDL levels to the multivariate model, the protection associated with HRT use was reduced from a relative risk

of 0.44 to a relative risk of 0.63, which was not statistically significant (p=0.29). This finding is very important because it suggests that HDL is an important risk factor for CVD mortality in women. It also suggests that HDL levels among HRT users may be a mechanism of the benefit of HRT and/or that women who use HRT have higher HDL levels independent of HRT, and that HDL is an important confounder of the HRT-CVD mortality relationship. As will be discussed, women taking HRT tend to exercise more, drink more alcohol, and be leaner, characteristics that are associated with increased HDL levels. The LRC Study highlights the importance of adding HDL levels to multivariate models evaluating the HRT-CVD relationship.

The NHS evaluated CVD mortality using nested case-control methodology.[53] In this study, 3,637 women dying of CVD were divided into groups at high and low risk for CVD and matched to 10 controls. Among high-risk women, the relative risk of CVD death with current HRT use was 0.51 (95% CI 0.45-0.57); among low-risk women it was 0.89 (95% CI 0.62-1.28).

In the Study of Osteoporotic Fractures (SOF), 9,704 women above the age of 60 were followed for CVD death. The risk of CVD death was reduced only among current HRT users (RR 0.46; 95% CI 0.29-0.73). For past HRT use the relative risk of CVD death was 0.86 (0.65-1.15).[50]

A study by Wolf and colleagues[52] involved a national sample of 1,944 white, postmenopausal women age 55 or older from the epidemiologic followup study of National Health and Nutrition Examination Survey I (NHANES I). All women underwent a baseline interview, physical, and laboratory exam, with HRT use evaluated as "ever" or "never," and were followed for an average of 16 years. There were 631 deaths among the cohort, and the relative risk of CVD death was 0.66 (95% CI 0.48-0.90). The findings were similar for women with natural and surgical menopause.

A cohort of 6,093 postmenopausal women identified between 1968 and 1972 in Walnut Creek, California was followed until 1983 for mortality.[49] In this cohort, the adjusted all-cause mortality was 0.80 (95% CI 0.6-1.0) among HRT users. The relative risk of death from CVD was 0.60 (95% CI 0.3-1.1) among estrogen users.

A Southern California cohort study involving 1,868 white, upper-middle class women, aged 50 to 79, residing in a planned community in Southern California, was followed from 1972

to 1984 for CVD. No difference in CVD mortality was shown among ever users of HRT (RR 0.96; 95% CI 0.65-1.43).[54]

An important exception to the above studies, however, is the Framingham Heart Study (FHS),[11] which showed increased mortality among ever HRT users. This is a prospective cohort study involving 1,234 women from Framingham, Massachusetts who were above age 50 and postmenopausal, and who participated in the 12th biennial survey. During the study, women were evaluated biennially and HRT use was considered positive if reported in the 8 years prior to the baseline of the 12th biennial exam. These 1,234 women were followed for an average of 8 years, but HRT use was not re-evaluated during that time period. The overall rate of HRT use in this study was 24%, with fewer than 5% of women using progestins. Cardiovascular disease death was defined broadly and included death from coronary heart disease, sudden cardiac death, congestive heart failure, and stroke. After 8 years of followup, the relative risk of death was 1.94 and not statistically significant.

A cohort of 7,944 Finnish women, ages 57 to 64, participating in a mammography study, was followed an average of 7 years for CVD death.[51] Among women currently using HRT, the risk of CVD death was reduced (RR 0.21; 95% CI 0.08-0.59). Former use was associated with a relative risk of 0.75 (95% CI 0.41-1.37).

Two cohort studies evaluated risk of CVD death by duration of HRT use (see Table 5). Criqui[54] found elevated relative risk among women using HRT for fewer than 8 years (RR 1.2-1.55) and lower relative risk among women using HRT for more than 8 years (RR 0.40). However, none of the findings were statistically significant. Cauley[50] identified reduced risk among women using HRT for 10 or more years (RR 0.36; 95% CI 0.16-0.57).

The reasons for different results among the studies is unclear. As shown in Table 4, each study adjusted for different sets of confounders, but review of the table does not help in understanding the different results. In addition, the differences do not seem to be explained by differences in the studies' quality or methods by which HRT use was assessed. The findings from the FHS differ from many of the other good quality studies and will be discussed below. Many studies of HRT show a number of biases that may influence mortality estimates among women using HRT; this will also be discussed below.

Our meta-analysis (Table 6, Figure 3) estimated summary relative risks for CVD death in association with HRT using several measures of use. Current HRT use was associated with a summary relative risk of 0.64 (95% CI 0.44-0.93), ever use with a summary relative risk of 0.81 (95% CI 0.58-1.13), and past use with a summary relative risk of 0.79 (95% CI 0.52-1.09). Any use was associated with a summary relative risk of 0.75 (95% CI 0.42-1.23).

Summary

- Seven cohort studies and one nested case-control study evaluating the risk of CVD death associated with HRT use were of good or fair quality.
- Six of these studies suggest decreased risk of CVD death, with relative risks ranging from 0.21 to 0.80 among current or ever users. However, only 4 had statistically significant findings.
- One cohort study showed no association between HRT and CVD death (RR 0.96; 95% CI 0.65-1.43).
- The FHS showed an almost 2-fold (RR 1.94) increased risk of CVD death, which was not statistically significant.
- A nested case-control study conducted among the NHS cohort showed decreased risk among women at high risk of CVD (RR 0.51; 95% CI 0.45-0.57) with current HRT use. For women at low risk of CVD, the relative risk associated with current use was 0.89 (95% CI 0.62-1.28).
- Past HRT use was evaluated in 2 studies with relative risks of 0.75-0.86 that were not statistically significant.
- Two studies evaluated risk by duration of use; one study showed significantly reduced risk with use for 10 or more years (RR 0.36; 95% CI 0.16-0.57). The other showed non-statistically significant increased risk in the first 8 years of use, with reduced risk after 8 years.
- When evaluated with meta-analysis, only current HRT use is associated with reduced risk of CVD death (RR 0.64; 95% CI 0.44-0.93). Past, ever, and any use showed no benefit in our meta-analysis.

2. What is the Role of Postmenopausal HRT in the Primary Prevention of Coronary Artery Disease Death?

Among the observational studies evaluating the relationship between HRT and CVD, 5 studies of good or fair quality specifically evaluated the risk of CAD death (Table 7).[50, 51, 53-55] Four of these reported total CVD mortality in addition to the subset of CAD mortality, and one, the Iowa Women's Health Study (IWHS),[55] reported only CAD (not CVD) mortality. For the purposes of this review, the definition of CAD death was taken directly from the studies reviewed and most often included fatal MI and/or sudden cardiac death attributed to CAD.

The two largest studies are the Nurse's Health Study and the IWHS, both from the United States. The IWHS[55] involved 41,070 Iowa women aged 55 to 69, who were evaluated at baseline using a mailed questionnaire and followed for coronary mortality for 6 years. Hormone use was characterized as "ever," "never," or "former," and duration was evaluated. Overall coronary mortality was decreased significantly in former users, and decreased but not statistically significant among current users, with relative risks of 0.57 (95% CI 0.38-0.85) and 0.82 (95% CI 0.47-1.43), respectively. Women using HRT for 5 or fewer years also had reduced CAD mortality (RR 0.57), although this was not statistically significant. Use over 5 years was associated with a relative risk of 0.90 (95% CI 0.47-1.72).

The NHS published data in 1997 evaluating CAD mortality using nested case-control methodology.[53] The study evaluated 3,637 deaths among women in the cohort between 1976 and 1994. Each case was matched to 10 controls and after adjustment for most coronary disease risk factors, mortality was reduced among current users (RR 0.47; 95% CI 0.32-0.69) but not among past users (RR 0.99; 95% CI 0.75-1.30).

Coronary disease mortality was evaluated in 9,704 women above age 65 in the SOF study.[50] Among women in the cohort with current HRT use, the relative risk of CAD death was 0.49 (95% CI 0.26-0.93). Women using HRT from 1 to 9 years had no reduction in CAD mortality (RR 0.97), but women using HRT for 10 or more years had a significantly decreased rate of CAD death (RR 0.25; 95% CI 0.09-0.68). Notably, women currently using HRT had reduced all-cause mortality (RR 0.69; 95% CI 0.54-0.87), as did past HRT users (RR 0.79; 95% CI 0.66-0.95).

A cohort of 7,944 women ages 57 to 64 from Finland participating in a mammography study was followed for an average of 7 years for CAD death.[51] Among current HRT users, the

relative risk of CAD mortality was 0.19 (95% CI 0.05-0.77). One difference between this study and others is that the mean dose of estrogen was 1.46 mg, higher than the usual doses found in other studies.

A cohort of 1,868 white, upper-middle-class women, ages 50 to 79, residing in a planned community in Southern California was followed for 12 years from 1972 on for CAD.[54] Among women using HRT, the CAD mortality was unchanged after multivariate adjustment for most CAD risk factors (RR 0.99; 95% CI 0.59-1.67).

Among the 3 studies evaluating CAD mortality by duration of HRT,[50, 54, 55] the findings are inconsistent (Table 8). The Criqui study[54] observed decreased risk of CAD among those using HRT for more than 8 years, with a relative risk of CAD mortality of 0.36 (95% CI 0.04-3.02). However, among women using HRT for fewer than 8 years, CAD mortality was increased, with relative risks ranging from 1.24 to 2.62, depending on the order of HRT use in the 8 years of follow-up (off then on, or on then off). Neither finding was statistically significant. Another study shows decreased risk for use of fewer than 5 years (RR 0.57),[55] and one shows no difference in risk (RR 0.97).[50] None of these findings was statistically significant. Two studies suggest decreased risk for very long-term use. In the SOF study, more than 10 years of HRT use was associated with a relative risk of 0.25 (95% CI 0.09-0.68).[50] Use for 8 or more years was also associated with decreased risk of CAD mortality in the Southern California cohort (RR 0.36), but was not statistically significant. The relative risk of CAD death was 0.90 and not significant in the IWHS among women using HRT longer than 5 years.[55]

Many of these studies differentiated past HRT use from current use (as opposed to "ever" use), as shown in Table 7. Among them, the SOF, Finnish, and NHS cohorts showed statistically reduced risk of CAD mortality with current HRT use (RR 0.19-0.49). The IWHS had a non-statistically significant relative risk of 0.82 for current use. For past use, the IWHS had a statistically significant relative risk of 0.57 (95% CI 0.38-0.85); the other 3 studies had relative risks ranging from 0.64 to 0.99, and were not statistically significant.[50, 51, 54] None of the fair or good quality studies evaluated CAD mortality by type of HRT used.

In our meta-analysis of HRT and CAD mortality (Table 6, Figure 4), current HRT use was associated with a summary relative risk of 0.62 (95% CI 0.40-0.91), ever use was associated with a summary relative risk of 0.81 (95% CI 0.37-1.60) and past use with a summary relative

risk of 0.76 (95% CI 0.53-1.02). "Any use," the global measure of use, had a summary relative risk of 0.74 (95% CI 0.36-1.45).

Summary

- Five studies of good or fair quality evaluated CAD death among women using HRT. No studies evaluated CAD mortality by type or dose of HRT.
- Four of the 5 showed reduced risk of CAD death associated with current use of HRT, with relative risks ranging from 0.19 to 0.82, although only 3 were statistically significant.
- Past use was associated with relative risks ranging from 0.57 to 0.99, with only one result statistically significant.
- The 3 studies evaluating risk of CAD death by duration of use had inconsistent findings, with relative risks ranging from 0.57 to 2.62 for fewer than 5-10 years of use, and 0.25 to 0.90 for more than 5 to 10 years of use.
- Only current HRT use was associated with reduced CAD mortality in our meta-analysis; no association was shown with past, ever, or any use.

3. Does Postmenopausal HRT Alter the Risk of Stroke Death?

Eight cohort studies[22, 49-51, 55-58] of good or fair quality addressed the issue of HRT and stroke death (Table 9, see also Evidence Tables 3 and 4). Most of these studies found reduced relative risk point estimates, though none was statistically significant. The Rancho Bernardo study found no significant association between stroke death among current HRT users (RR 0.92; 95% CI 0.34-2.49).[57] The Finnish cohort[51] also found no significant risk of stroke death in former users (RR 1.05; 95% CI 0.41-2.68) or current users (RR 0.16; 95% CI 0.02-1.18). The SOF study[50] identified no significant risk of stroke death in current users (RR 0.47; 95% CI 0.20-1.08) or past users of HRT (RR 0.85; 95% CI 0.48-1.49). The IWHS[55] also found no significant association between HRT use and stroke death; the relative risk was 0.95 for current use (95% CI 0.37-2.43) and 0.88 for past use (95% CI 0.48-1.61). The NHANES I cohort study[56] identified a significant decreased risk of stroke death (RR 0.86; 95% CI 0.14-0.92) when proxy responses were included; when proxy responses were eliminated, however, there was no reduction in stroke

death (RR 0.86; 95% CI 0.28-2.66). The NHS cohort identified no association between current HRT use and stroke mortality (RR 0.81; 95% CI 0.54-1.22).[58] Finally, the Lipid Research Clinics study[22], a well-designed cohort study, found no significant association between HRT and stroke death (RR 0.40; 95% CI 0.01-3.07) after adjustment for many CVD risk factors. Although none of these studies adjusted for lipids or socioeconomic status (SES), variable adjustment for confounders does not seem to explain different findings among the studies (see Table 9).

Two good-quality cohort studies evaluated long-term use of estrogen and risk of stroke death (Table 10). The SOF study[50] identified no significant risk of stroke death for use for 10 or more years (RR 0.38; 95% CI 0.13-1.10), or for use from 1 to 9 years (RR 0.66; 95% CI 0.20-2.20). Similarly, after 6 years of followup, the IWHS,[55] identified no significant change in stroke death with HRT use of more than 5 years (RR 1.05; 95% CI 0.41-2.64) or 5 or fewer years (RR 2.08; 95% CI 0.74-5.82).

We performed a meta-analysis of data from the 8 cohort studies that reported data on HRT and stroke mortality (Table 6, Figure 5). The summary relative risk for stroke death was 0.79 (95% CI 0.60-1.01). No differences were found for ever, past, or current use, and, therefore, only one summary relative risk is reported.

Summary

- No significant association between HRT and risk of stroke death was identified in the observational studies of good to fair quality, although most point estimates showed reduced risk.
- Two good-quality cohort studies evaluated long-term use of estrogen and did not show any significant association between long-term HRT use and stroke death.
- Meta-analysis of 8 studies showed no significant association between HRT and stroke mortality.

Cardiovascular Disease, Coronary Artery Disease and Stroke Incidence

4. What is the Role of Postmenopausal HRT in the Primary Prevention of Cardiovascular Disease?

Three observational studies of fair or good quality have evaluated the overall risk of CVD[11, 51, 59] (Table 11). The FHS[11] defined CVD broadly and included coronary heart disease (angina, MI, coronary death, sudden cardiac death), cerebrovascular disease (stroke and transient ischemic attack [TIA]), claudication, and congestive heart failure. After 8 years of followup, the total CVD rate was increased among HRT users by 76% (RR 1.76; $p<0.01$). CVD events in this study were ascertained by physician review of clinic notes, hospital and physician records, and death certificates on a biennial basis. This process is unique to this study and involved evaluating unrecognized MI with electrocardiograms and including angina and TIAs, each more difficult endpoints to define. In addition, the multivariate model used in this study included the cholesterol:HDL ratio, which also may have influenced the findings, since adding the HDL level to multivariable models has been shown to significantly change results towards less benefit from HRT.[22] The FHS also differs in its assessment of HRT use. In this study, nearly two-thirds of the cohort reported use of HRT at 2 or more of the biennial examinations, suggesting that the findings are most relevant to longer-term use of HRT. Interestingly, the authors reanalyzed their data, categorizing women as users or nonusers at the 11th biennial exam, and repeated similar analyses. When estrogen use was characterized in this manner (at a single point in time), the findings suggested an inverse relation between HRT and CVD mortality in women ages 50-59. Also, when total CVD was evaluated in this way, there was no association between HRT and CVD in the youngest women, but a strong positive relation (increase in risk) among women over age 60. These findings indicate that how HRT use is measured or characterized can significantly affect the findings of a study.

A case-control study conducted in the United Kingdom evaluated CVD incidence and involved 603 women ages 45 to 69 with MI or stroke.[59] Two controls per case were matched by age, race, and general practitioner, and all were evaluated with a questionnaire completed by a nurse, as well as a review of all medical records. After adjustment for several important confounding variables (though not including lipids), the relative risk of CVD events was 1.29

(95% CI 0.82-2.00) for any HRT use, 1.09 (95% CI 0.65-1.82) for ERT use, and 1.16 (95% CI 0.43-3.12) for CHRT use.[59]

In the Finnish cohort[51] described above, the relative risk of CVD events was 1.07 (95% CI 0.86-1.32) among current HRT users and 1.11 (95% CI 0.89-1.39) among past users.

A 1997 meta-analysis combined data from 22 randomized controlled trials of short-term HRT use for several outcomes other than CVD, such as bone density or lipids.[60] In these studies, cardiovascular events were reported as complications or side effects of therapy, not as primary outcomes of interest. Of approximately 1,700 women randomized to placebo or HRT (of varying composition), there were 12 cardiovascular events in the HRT group and 5 in the control subjects, with a relative risk of 1.39 (95% CI 0.48-3.95). The authors also calculated probabilities for finding this result if 0.7 or 0.5 was the true odds ratio, and these probabilities were 0.10 and 0.03, respectively. This suggests that it is highly unlikely that a short-term benefit of HRT was missed by chance alone in this study.

The WHI is a randomized controlled trial of hormone replacement therapy in the primary prevention of CVD involving 27,348 postmenopausal US women. The study began several years ago and was to report findings initially in the year 2005. However, in the spring of 2000, the data and safety monitoring board identified an increased rate of MI, stroke, and "blood clots" among the women randomized to hormone therapy (HRT or CHRT) occurring in the first 2 years of the study. To date, no information on the number of events is available, although the April 3, 2000 press release from the National Heart, Lung and Blood Institute (NHLBI)[48] stated that the number was less than 1% among women using HRT. The increased rates did not meet statistical criteria for stopping the trial. Over time, the trends may diminish and, as the press release states, "may even go away." This information was considered preliminary and did not address the issue of long-term benefits. Therefore, the authors did not recommend that the findings influence current medical practice.

We performed a meta-analysis of the studies of HRT and CVD incidence (Table 6, Figure 6), and found summary relative risk estimates of 1.35 (95% CI 0.92-2.00) for ever use and 1.26 (95% CI 0.79-2.08) for past use. Current use of HRT was associated with a summary relative risk of 1.27 (95% CI 0.80-2.00). Any use of HRT, the overall measure of use, was associated with a summary relative risk of 1.28 (95% CI 0.86-2.00).

Summary

- All observational studies evaluating CVD incidence, which includes stroke and coronary disease, show elevated relative risks among women using HRT on the order of 10% to 75%. In only one study, however, was this finding statistically significant, and this study has been criticized for including "angina" as a CVD outcome.
- An important analysis of the FHS showed that how HRT use is assessed and defined can significantly influence calculated rates of CVD events.
- None of the studies evaluating CVD incidence and HRT evaluated risk by duration of HRT use.
- Meta-analysis involving evaluation of only women involved in randomized controlled trials of relatively short-term HRT suggests increased risk of CVD events among women randomized to HRT.
- Preliminary findings from the large Women's Health Initiative randomized controlled trial of HRT and primary prevention released to the public in the spring of 2000 indicate increased rates of stroke, MI, and "blood clots" among women using HRT within the first 2 years of the study. These rates have diminished with increased followup.
- In our meta-analysis, all measures of HRT use were associated with increased risk of CVD events, with relative risks ranging from 1.26 to 1.35.

5. What is the Role of Postmenopausal HRT in the Primary Prevention of Coronary Artery Disease?

Evaluating CAD events is difficult, and each study has used different methods to determine or identify events, as well as different definitions of CAD. For this review, we classified all MIs as coronary events, recognizing that many occur outside the hospital and are not included in this category. This is especially a problem in case-control studies that evaluate the relationship, since most define their cases as women hospitalized with MI while others include only non-fatal MI as cases. As discussed above, some investigators included outcomes of angina and sudden cardiac death in their overall definition of CAD. Typically, if sudden cardiac death was considered in the measurement of CAD, the investigators did so after

excluding other causes. Finally, the FHS[11] included clinically unrecognized MI in its definition of CAD, which is important because approximately one-third of MIs in women are clinically unrecognized or "silent." The data from the studies evaluating CAD incidence and HRT are displayed in Table 12.

The only published randomized controlled trial of the primary prevention of CAD with HRT was conducted among 168 postmenopausal women institutionalized in New York City and followed for 10 years while in the hospital.[61] After 10 years, there were 3 MIs in the control group treated with placebo, and 1 MI in the CHRT treated group (RR 0.33; 95% CI non-significant). This study contributes little to this evaluation however, because of its small size and unique population, and because the dose of estrogen used (2.5 mg) is rarely used in clinical practice.

The association between HRT and CAD incidence was evaluated in 4 cohort studies (1 analyzed as a nested case-control study) of good or fair quality.[8, 11, 51, 62] The FHS identified a relative risk of 1.90 ($p<0.01$) for CAD events associated with HRT use.[11] When this study was reanalyzed by Eaker,[63] excluding the endpoint of angina, the relative risk among women reporting HRT use at exams 11 or 12 was 0.40 ($p > 0.05$) among women ages 50 to 59.[10] Among women ages 60 to 69, the relative risk of those reporting HRT use at exam 11 or 12 was 2.20 ($p > 0.05$).[10, 63] It can be argued that angina is such a poorly defined or difficult-to-define entity, particularly among women, that it is appropriate to exclude angina from the relative risk calculations for CAD. However, the FHS was a very carefully conducted study. Also, it is difficult to know how to interpret or compare the relative risk findings of the studies by Eaker and Wilson without an overall estimate involving the entire cohort, since the number of CAD events would have been larger in the older women in whom the relative risk was elevated. In addition, women in the FHS tended to use higher doses of estrogen.[9]

The Finnish cohort study[51] identified elevated relative risks of CAD associated with current and past HRT use, although these were not statistically significant. Among current users of HRT, the risk of CAD was 1.05 (95% CI 0.76-1.46). Past users had a relative risk of 1.23 (95% CI 0.88-1.71). Women in this study also used higher doses of estrogen.

The NHS[8] reported a relative risk of CAD of 0.60 (95% CI 0.47-0.76) among women currently using HRT and a relative risk among past users of 0.85 (95% CI 0.71-1.01). These data

were also analyzed by type of HRT use. Among current users of CHRT, the relative risk of CAD was 0.39 (95% CI 0.19-0.78); women currently using ERT had a relative risk of 0.60 (95% CI 0.43-0.83), suggesting reduced risk with both types of HRT, consistent with the overall risk identified.

A cohort study involving women ages 50 to 64 from the GroupHealth Cooperative in Seattle, who were identified between 1978 and 1984, included a nested case-control analysis among 120 women with first MI.[62] After adjustment for drug treatment of hypertension and diabetes, as well as age, the relative risk for current HRT use was 0.70 (95% CI 0.40-1.40) and for past use was 0.60 (95% CI 0.10-2.10). These results should be interpreted cautiously because they are not statistically significant and adjustment for confounding by CAD risk factors was limited.

Among the 8 case-control studies evaluating CAD incidence that were of fair or good quality,[12, 62, 64-69] 2 of good quality investigated the relationship between HRT and incident coronary disease.[12, 67] The best of these studies was a population-based study conducted by Rosenberg and involved 858 cases with first, non-fatal MI.[67] Each case was geographically and age matched (within 5 years) to one control. Estrogen use was considered present with any use more than one month in duration, and its use, as well as CAD risk factors, was evaluated by questionnaire. The odds ratio for ever use of ERT was 0.90 (95% CI 0.70-1.20) and for CHRT was 1.2 (95% CI 0.60-2.40). Overall, recent use of any HRT was associated with a non-statistically significant decrease in first MI of 20%. Past use was associated with an odds ratio of 0.9 (95% CI 0.7-1.3). All relative confounders were included in the analyses except for the cholesterol: HDL ratio, which has been identified as an important explanatory variable in multivariate models.[4, 22] When ERT use was evaluated by duration, relative risks were elevated in the first 4 years of use, and after 4 years were below 1.0 with positive trend ($p = 0.08$) for reduced risk of first MI with increasing ERT duration, though none of the strata of years was statistically significant. CHRT use of 5 or fewer years was associated with an odds ratio of 0.50 (95% CI 0.20-1.50) and more than 5 years with an odds ratio of 2.60 (95% CI 0.80-8.40). It is important to note that this study evaluated only survivors of first MI.

Another good-quality population-based case-control study[12] was conducted in a Northern California HMO population and involved 438 postmenopausal women with first MI. An equal

number of controls were matched by age and medical center. Medical records were reviewed for estrogen exposure, and some major risk factors for CAD were identified and adjusted for (family history, lipids, and BMI were not adjusted for). The adjusted odds ratio for current ERT or CHRT use was 0.96 (95% CI 0.66-1.40) and for past use was 1.07 (0.72-1.58). For CHRT, there was an increased, though non-statistically significant, risk in the first year of use (OR 1.27; 95% CI 0.40-4.02). There was no trend associated with increasing duration of either CHRT or ERT.

Only one case-control study evaluating CAD incidence showed statistically significant reduced risk of CAD among HRT users.[69] This study was conducted in the Seattle GroupHealth Cooperative and involved 850 postmenopausal women ages 30 to 79 with incident fatal or non-fatal MI. Controls were frequency matched, and record review, pharmacy review, and telephone interviews were conducted to measure exposure and CAD risk factors. The odds ratios for ever use, current use, and past use of HRT were 0.72 (95% CI 0.59-0.88), 0.70 (95% CI 0.55-0.89), and 0.74 (95% CI 0.57-0.96), respectively. This study had relatively little adjustment for CAD risk factors, however.

Four other population-based case-control studies of fair quality identified odds ratios ranging from 0.55 to 0.93 for current, recent, or ever use of HRT, though none was statistically significant.[62, 65, 66, 68]

Past use of HRT was evaluated in 6 studies of CAD incidence. The risks were elevated in 2 studies (RR 1.07-1.23),[12, 51] but were not statistically significant. The risks were reduced in 3 studies (RR 0.60-0.90),[8, 62, 67] but again were not statistically significant. The GroupHealth Study[69] did show significantly reduced risk with past use (OR 0.74; 95% CI 0.57-0.96), though it is limited by lack of adjustment for many CAD risk factors.

The use of combined therapy (CHRT) was evaluated in 3 observational studies. In the NHS,[8] the relative risk of current CHRT use was 0.39 (95% CI 0.19-0.78). In the Rosenberg case-control study,[67] ever use of CHRT was associated with an odds ratio of 1.2 (95% CI 0.60-2.4). Finally, in the UK study,[59] recent CHRT use was associated with an odds ratio of 0.68 (95% 0.47-0.97).

Although review of Table 10 indicates that many studies had point estimates below 1.0, suggesting benefit, only 3 of these were statistically significant. The most notable finding is that, with the exception of the NHS,[11] the good quality studies were consistent in showing no benefit

or an increased risk of CAD events among HRT users. The reason(s) for disparity among the best studies is uncertain. There were great differences among the studies in their adjustment for confounders. What is striking in reviewing the table however, is that none of the studies that included adjustment for SES or education in their models found HRT use beneficial. This is an important finding and suggests that SES may confound the relationship between HRT and CAD incidence. Similarly, none of the studies with adjustment for alcohol use or exercise, both known to be more common in women who use HRT and to be protective against CAD, showed benefit with HRT use. As Tables 1 and 2 indicate, all studies included in this systematic review assessed and defined HRT use differently. As Wilson very effectively showed,[11] how this is done can significantly influence relative risk estimates. Unfortunately, however, no clear pattern emerges from Tables 1 and 2 that helps further explain disparate findings among studies evaluating CAD incidence.

Results of our meta-analysis evaluating the association between CAD incidence and HRT use varied by exposure status (Table 6, Figure 7). Current use of HRT was associated with a summary relative risk of 0.80 (95% CI 0.68-0.95). Ever use of HRT was associated with a relative risk of 0.91 (95% CI 0.67-1.33), and past use with a summary relative risk of 0.87 (95% CI 0.75-1.05). We also conducted the meta-analyses and compared the summary relative risks among the studies that adjusted for SES and those that did not adjust. Among the studies that adjusted for SES, there was no association between any measure of HRT use and CAD events, with relative risks ranging from 0.98-1.07. However, the summary relative risks among studies that did not adjust for SES were reduced with current exposure (RR 0.72; 95% CI 0.61-0.84) and past exposure (RR 0.77; 95% CI 0.65-0.91). This finding suggests that SES status may significantly confound observations of reduced CAD among women using HRT. This is a very important issue as SES is powerfully and inversely linked with CVD.[70] Our finding of no association between any measure of HRT use and coronary incidence was similar when the meta-analyses were stratified by alcohol consumption and exercise, in addition to other major coronary disease risk factors, suggesting confounding by these factors as well.

Summary

- Among 3 cohort studies of good or fair quality, 2 suggest increased risk of CAD in association with HRT, although only the FHS findings were statistically significant (RR 1.05-1.90). Reanalysis of FHS data without angina as an endpoint showed a trend towards reduced risk among women aged 50 to 59 (RR 0.40) and increased risk among women aged 60-69 (RR 2.20). The NHS showed reduced risk among current users of any type of hormone therapy.
- Eight case-control studies (1 nested case control study) evaluated HRT use and CAD incidence. Among them only one showed statistically significant reduced risk of approximately 30% with HRT use.[11, 51, 56-58, 69] The two best studies suggested elevated risks (RR 0.96-1.20) among women using HRT, but the findings were not statistically significant. The others showed relative risks ranging from 0.55 to 0.93 and were not statistically significant.
- The findings among the 6 studies evaluating past use of HRT were inconsistent, showing both increased and decreased risks.
- With the exception of the NHS, none of the good quality studies showed reduced coronary events among women using HRT.
- None of the studies including adjustment for SES, education, exercise, or alcohol use in their models showed a benefit of HRT in reducing CAD events.
- Two of 3 observational studies evaluating CHRT use showed statistically significant reduced risk among current, recent, or ever users.
- In our meta-analysis, there was no association between HRT use and CAD events in studies that adjusted for SES, but summary relative risks for studies that did not adjust for SES were reduced. These results suggest that SES may significantly confound observations of reduced CAD among women using HRT.

6. Does Postmenopausal HRT Alter the Risk of Stroke?

6a. Total stroke

Among the 24 cohort studies reviewed (representing 15 cohorts), 5 cohort studies[11, 51, 56-58] and 4 case-control studies[59, 64, 71, 72] of good or fair quality were analyzed in depth (Table 13a, Evidence Table 3 and 4).

Four of the 5 cohort studies found no association between stroke and postmenopausal estrogen.[51, 56-58] Only the FHS[11] found an increase in stroke rates in women using HRT.

The Rancho Bernado cohort[57] consisted primarily of white, middle- to upper-class women from California, aged 60 or older, with no history of stroke. In this study 1,031 women, of which 278 (27%) were current HRT users, were followed for approximately 8.75 years. After controlling for age, smoking, systolic blood pressure and diabetes, no significant association between stroke or TIA and HRT use was identified (RR 4.43; 95% CI 0.83-23.58).

A population-based study included 7,944 women ages 57 to 64 from Finland participating in mammography screening in 1987 to 1988 who were followed every 2 years for stroke.[51] After approximately 6 years of followup, there was no significant association[11, 51, 56-58] between non-fatal stroke and the use of HRT, with a relative risk of 0.86 (95% CI 0.42-1.75) in current users and 1.08 (95% CI 0.55-2.10) in former users.

A cohort of 1,910 women without a history of stroke, ages 55-74, was evaluated in the NHANES I followup study from 1971 to 1975.[56] No significant decrease in risk of non-fatal stroke (RR 0.69; 95% CI 0.47-1.00) was identified. Although most major confounders were adjusted for, family history of CVD and lipids were not.

The NHS evaluated stroke incidence after 20 years of followup.[58] Non-fatal strokes were verified by medical record review, and required typical neurological symptoms of stroke lasting more than 24 hours and meeting the criteria of the National Survey of Stroke. Strokes were classified into ischemic stroke (IS), (thrombotic or embolic), SAH, and intraparenchymal hemorrhage (IPH). Deaths were verified by family, medical, and autopsy records, and by the National Death Index. No association between the risk of total stroke and current (RR 1.13; 95% CI 0.94-1.35) or past (RR 1.02; 95% CI 0.85-1.24) use of HRT was shown;[58] however, an increased risk of total stroke (RR 1.54; 95% CI 1.12-2.11) was observed in women currently using CHRT. No association was identified in women taking 0.625 mg of oral CEE compared

to non-users (RR 1.24; 95% CI 0.95-1.62). This good-quality study adjusted for major confounders, including age, smoking, cholesterol, history of hypertension and myocardial infarction, diabetes, lipids, alcohol use, BMI, and family history of cardiovascular disease (see Table 13a). In addition, a significant dose-response relationship was shown for stroke with graded risks of 0.54, 1.35, and 1.63 for conjugated estrogen doses of 0.3 mg, 0.625 mg and 1.25 mg or more per day.[58]

The FHS found a significant increase in stroke rates among women using HRT.[11] On average, women took estrogen for approximately 3 years, and primarily used CEE; fewer than 5% used CHRT. After 8 years of followup, 45 cases of fatal and non-fatal cerebrovascular disease events (total stroke), including 21 cases of atherothrombotic brain infarction had occured. Women taking HRT had greater than a 2-fold risk of total stroke (RR 2.27, $p<0.01$). A limitation of this study is that diabetes, a known major risk factor for stroke, was not assessed or adjusted for.

Four case-control studies have evaluated the association between short-term estrogen use and risk of stroke.[59, 64, 71, 72] Though several have elevated point estimates, none of the studies has shown a significantly increased risk of stroke. All the studies were of fair quality, limited primarily by lack of control for confounding factors (refer to Evidence Table 4).

The results of the studies evaluating stroke incidence are relatively consistent in showing elevated, though non-statistically significant, relative risks of stroke in association with HRT. The major outlier is the FHS, which found significantly increased rates of stroke and brain infarction among women using HRT. The reason for the disparity between the FHS and other studies is not clear. However, since most women in the FHS were on estrogen alone, this result is consistent with the increase in risk of ischemic stroke shown among women using estrogen alone in the NHS (discussed below).[58] Because event ascertainment in the FHS was similar among women using and not using HRT, differential ascertainment is unlikely to explain the results. Two other issues with the FHS should be considered. These include the use of higher doses of estrogen among women in the study,[9] and the lack of adjustment for diabetes in their analysis, an important stroke risk factor. However, the FHS evaluated risk profiles among women using HRT, and these women were at lower CVD risk than women not using HRT based

on traditional risk factors. Thus, the data somewhat compellingly suggest increased stroke risk among HRT users.

Long-term use of HRT has not clearly been defined. Many of the cohort studies do not address duration of use, and among those that do, the definition of "long-term" often varies from a few months to more than 15 years. Also, duration of use has been evaluated in past users by time since last use as well as time since the first use. The NHS[58] evaluated the effect of long-term use of HRT on the risk of stroke, and it showed no association, with relative risks ranging from 1.04 to 1.32 for less than one year to 10 or more years of use (see Table 10).

Of the 4 case-control studies reviewed, only one study of fair quality, the Northern California Kaiser Permanente study,[71] addressed the duration of estrogen use and risk of stroke. This study identified no significant association between stroke and HRT use by duration. HRT use of less than one year had an odds ratio of 0.75 (95% CI 0.23-2.42); for use of more than 10 years, the odds ratio of stroke was 1.37 (95% CI 0.79-2.38). There was also no association between HRT and stroke with past use (OR 0.84; 95% CI 0.54-1.32).

Evaluating exposure from estrogen and progesterone therapy is difficult. Most studies that include combination therapy rarely present these data independently. Often they report that a certain percentage of women was on combination therapy, but do not differentiate further. The majority of studies had fewer than 20% of subjects on combination therapy. The NHS evaluated the risk of stroke and CHRT use in 70,533 women.[58] A significant increase in total stroke (RR 1.54; 95% CI 1.12-2.11) was identified in association with CHRT. Two case-control studies evaluated CHRT and stroke risk. The first study[72] (previously discussed in detail) involved a cohort of 1,422 Danish women. Among women on CHRT, odds ratios of stroke ranged from 1.20 to 1.30 for various types of stroke (SAH, ICH, thromboembolic stroke, TIA), and none were significant. A study from the UK[59] found no increase in stroke in women on CHRT (OR 0.86; 95% CI 0.43-1.74) (see Evidence Table 4.)

Although there are no randomized trials of HRT and the primary prevention of stroke, the WHI is a CVD primary prevention trial involving 27,348 postmenopausal women randomized to either CHRT, ERT, or placebo. In the spring of 2000, women in the trial were notified that there were increased rates of stroke occurring among women randomized to HRT.[48]

For the reasons discussed above and because there are no randomized controlled trials of HRT for the primary prevention of stroke, valuable information may come from the HERS trial, a secondary prevention study involving 2,763 women with known CAD randomized to either placebo (n=1383) or Prempro (CEE 0.625 mg and medroxyprogesterone acetate 2.5 mg) (n=1380). Stroke and TIA were secondary cardiovascular outcomes. Details of stroke diagnosis and classification were not reported. After 4 years of followup, 108 strokes or TIAs had occurred in the CHRT group, and the risk hazard was 1.13 (95% CI 0.85-1.48).

In our meta-analysis of total stroke incidence and HRT (Table 6, Figure 8), 5 cohort studies[11, 51, 56-58] and 4 case-control studies[59, 64, 71, 72] were included in the analysis. The summary relative risk was 1.12 (95% CI 1.01-1.23), identifying a slightly significant increase in stroke incidence, consistent with the early results from the WHI.

Summary

- One meta-analysis showed no association between HRT and stroke.
- Twenty-five cohort studies representing 15 cohorts have evaluated the use of HRT. Five of these were of fair or good quality, and 4 of the 5 found no association between stroke HRT use.
- Of the 4 good to fair case-control studies, none showed a significant association between HRT and stroke, though several had elevated point estimates.
- Although no randomized trials have evaluated HRT and primary prevention of stroke, preliminary findings of the Women's Health Initiative, as reported by the lay press, found an increased risk of stroke in women treated with HRT.
- The NHS found no association with long-term use of HRT and stroke incidence. One fair-quality case-control study evaluated the effect of long-term use of HRT on the risk of stroke, and found no significant association.
- The majority of the studies do not analyze risk associated with CHRT independently. The NHS found an increased risk of stroke in current users of CHRT compared to never-users, but no increased risk in women on ERT compared to never-users. Other studies to date have not found a significant association between stroke and CHRT, though some have suggested increased risk. The HERS trial of secondary prevention identified no

increase risk of stroke or TIA in association with CHRT. However, this was a secondary prevention trial and may not be generalizable to a healthy population.

- Data from the NHS found an increasing risk of stroke with increasing doses of estrogen.
- Our meta-analysis identified a significant increased risk of stroke associated with ever use of HRT (RR 1.12; 95% CI 1.01-1.23).

6b. Ischemic stroke

Ischemic, or thromboembolic, strokes are the most common type of stroke. HRT is a known thromboembolic agent and thus may be important etiologically in ischemic stroke. The majority of studies report their results as total stroke, and epidemiologically, ischemic stroke is the major contributor to total stroke. However, 4 studies of good or fair quality specifically report ischemic stroke separately.[11, 58, 64, 72](Table 13b, Evidence Tables 3 and 4)

Two cohort studies specifically evaluate ischemic stroke in their analyses.[11, 58] The FHS, discussed previously, found that women with ever-use of HRT had an increased risk of ischemic stroke (RR 2.60; $p<0.01$).[11] The NHS[58] found that women who currently use HRT had an increased risk of ischemic stroke (RR 1.26; 95% CI 1.00-1.61); past use of HRT was not associated with ischemic stroke (RR 1.01; 95% CI 0.79-1.30).[58]

Two case-control studies have evaluated the risk of ischemic stroke.[64, 72] An older study of primarily white women from a Southern California retirement community found no significant increase in risk (OR 1.13; 95% CI 0.71-1.77) associated with ever use.[64] In the Denmark study,[72] previously described, there was no significant increased risk of ischemic stroke among current (OR 1.24 95% CI 0.91-1.70) or past ERT users (OR 1.12 95% CI 0.88-1.42), or current CHRT users (OR 1.27 95% CI 1.00-1.62), though all had elevated point estimates suggesting increased risk.

In our meta-analysis (Figure 9), the results of these 4 studies[11, 58, 64, 72] were pooled to estimate risk of ischemic stroke. Because there were no apparent differences between study type, type of hormone use, or ever-use, past use or current use, these results were pooled. The summary relative risk was 1.20 (95% CI 1.05-1.40), indicating a significant increased risk of ischemic stroke in women with HRT exposure.

Summary

- The NHS and FHS identified statistically significant increased risk of ischemic stroke.
- 2 case-control studies of fair to good quality evaluated the risk of ischemic stroke and found no association.
- Our meta-analysis of these studies found increased risk of ischemic stroke with HRT use (RR 1.20; 95% CI 1.05-1.40).

6c. Subarachnoid hemorrhage

Risk factors for SAH are different from those of ischemic and hemorrhagic stroke. In a systematic review of risk factors for SAH, the significant risk factors included smoking, hypertension, and drinking 150 grams or more of alcohol per week.[73] Use of oral contraceptives, use of HRT, hypercholesterolemia, and physical activity were not shown to be significantly related to the risk of SAH. With this in mind, only a few studies have evaluated the association between HRT and SAH independently. These studies are summarized in Table 13c and Evidence Table 3 and 4.

Of the 10 observational studies of fair or good quality that evaluated stroke, only one cohort study specifically evaluated SAH.[8] After 16 years of followup in the NHS, no clear association between SAH and current (RR 0.90; 95% CI 0.57-1.41) or past (RR 0.81; 95% CI 0.52-1.25) use of HRT was identified.[8] There was an increased risk of SAH observed in subjects using ERT only (RR 1.35), but no confidence interval or p-value was reported.

Only two case-control studies[72, 74] of fair quality evaluated the relationship between HRT and SAH (see Table 13c and Evidence Table 4). One population-based case-control study from Denmark[72] included 1,422 women aged 45 to 64 who had a first-ever, non-fatal stroke between 1990 and 1992. Cases were identified from the Danish National Patient Register. Randomly selected from the Central National Person Register were 3,171 age-matched controls. There was no significant association between SAH and current use of ERT (OR 0.53; 95% CI 0.23-1.25), current use of CHRT (RR 1.30; 95% CI 0.84-2.02), or former use of HRT (RR 0.78; 95% CI 0.46-1.30).

The other study[74] was a population-based case-control study from King County, Washington. This study included 103 women with spontaneous SAH invited into the study by a

treating physician in the King County area. There were 206 age- and sex-matched controls identified through random-digit dialing. A significant decrease in risk of SAH in women who ever (RR 0.47; 95% CI 0.26-0.86) or currently (RR 0.38; 95% CI 0.17-0.84) used HRT in comparison to never-users was identified. No association was found with former use of HRT and SAH (RR 0.58; 95% CI 0.28-1.21).

In our meta-analysis, these 3 studies[8, 72, 74] were pooled to estimate the risk of SAH associated with HRT use (Figure 10). No association was identified, with a summary relative risk of 0.80 (95% CI 0.57-1.05).

Summary

- The NHS found no clear association between SAH and current or past use of HRT.
- Of the 2 case-control studies that evaluated SAH and HRT use, one identified no significant association, and the other found a significant decrease in risk of SAH in current and ever users compared to never users.
- Our meta-analysis estimated a pooled relative risk of 0.80 (95% CI 0.57-1.05).

6d. Intracerebral hemorrhage

Three cohort studies, among 2 cohorts, evaluated the risk of intracerebral hemorrhage (ICH) specifically.[8, 75, 76] The NHS reported a decreased risk of ICH in ERT users (RR 0.53), but there were only 3 cases, and confidence intervals or p-value were not reported.[8] The other studies, involving a Swedish cohort, are of poor quality.[75, 76] These studies based exposure on pharmacy databases, used external controls from the general Swedish population, and presented data as standard mortality ratios with no adjustment for confounding. However, a small, but significant decrease in risk of ICH was observed in the estrogen-treated group.

Four case-control studies of good or fair quality evaluated ICH (Table 13d, Evidence Table 4).[64, 71, 72, 77] A population-based case-control study from Denmark[72] analyzed the association between ICH and HRT use. There were 95 cases of ICH, and no significant association between ICH and estrogen use was identified with either former or current use of ERT (OR 0.18; 95% CI 0.02-1.27) or CHRT (OR 1.22; 95% CI 0.66-2.23).

The Northern California study,[71] involving women hospitalized for stroke, identified a total of 83 cases of hemorrhagic stroke. Each case was matched to a control by birth year and facility of care. HRT exposure history was obtained by interview or by proxy. Smoking, hypertension, diabetes, prior stroke or TIA, BMI, ethnicity, and education were assessed and included in their multivariate models. This study found a significant decrease in risk of hemorrhagic stroke in current users of HRT (OR 0.33; 95% CI 0.12-0.96).

A study conducted in Australia evaluated 105 cases of ICH occurring between 1990 and 1992 among women ages 18-80 years old, with a mean age of 63.4 years.[77] Each case was matched to a control by age, sex, and neighborhood and was recruited and interviewed by the nurse who interviewed the corresponding patient. ICH was verified by CT scan (94.9%), autopsy (4.8%), and MRI (0.3%). Estrogen exposure was considered present if ever used. Among women with ICH, there was a significantly decreased risk of ICH in ever users of HRT (OR 0.36; 95% CI 0.14-0.95).

The population-based case-control study from a Southern California retirement community also assessed the risk of hemorrhagic stroke and HRT use.[64] This study, reviewed in detail above, involved 258 women with first stroke resulting in hospitalization or death. A total of 1,260 controls were drawn from the resident population and matched to each case by age. Estrogen exposure was defined as "ever" or "never" use, and was assessed from a prescription database. Results were adjusted for hypertension, diabetes, and age, but not for smoking, family history of CAD, or lipids. No association between hemorrhagic stroke and estrogen use (OR 0.49; 95% CI 0.00-9.19x10^3) was identified.

Four studies[64, 71, 72, 77] were pooled to estimate the risk of ICH associated with HRT in our meta-analysis (Figure 11). No significant decrease in risk of ICH was found (RR 0.71; 95% CI 0.25-1.29). Of note, the most recent NHS[58] combined both SAH and ICH (due to small numbers of cases) and found no association in current or past users of HRT compared to never users (RR 0.93-0.95).

Summary

- The recent NHS found no association between HRT and ICH. Among 4 case-control studies, 2 observed no association between HRT and hemorrhagic stroke,[64, 72] and the other 2 identified a significant decrease in risk.[71, 77]
- Meta-analysis identified no association between HRT and ICH.

7. Does HRT Reduce Cardiovascular Events and Death in Women with Known Coronary Artery Disease?

Although this report concerns the prevention of CVD in healthy postmenopausal women, CVD is present in nearly one-third of women over age 65.[3] Because CVD is such a prevalent disorder, it can be argued that evaluation of some of the literature about secondary prevention of CVD is useful in developing prevention guidelines. In addition, because almost all of the studies evaluating HRT and CVD incidence and mortality are observational, it is useful to review the best evidence to date on secondary prevention, since it might lend important insight to understanding the primary prevention literature. Furthermore, because the role of HRT in reducing CVD has been promoted to women and physicians by some health care leaders as well as by the media, based largely on observational studies suggesting benefit, and because this promotion may have been more directed towards women at high risk for CVD or with known CVD, it is useful to review the best evidence on secondary prevention. Observational studies of HRT and CVD are often limited by lack of control for known confounders and inability to control for unknown confounders. Therefore, we focus this discussion on randomized controlled trials of HRT in the secondary prevention of CVD.

The most important randomized controlled trial of HRT in the secondary prevention of CAD is the HERS trial,[29] a randomized, placebo-controlled trial of HRT conducted at 20 clinical centers in the United States between January 1993 and September 1994. In the trial, 2,763 postmenopausal women ages 44 to 79 (mean age 66.7) with known CVD were randomized to either HRT or placebo. CAD was defined as evidence of at least one of the following: MI, CABG, PCTA, or angiographic evidence of at least 50% occlusion of one or more major coronary arteries. There were a number of exclusions, but most important to this topic were a CAD event within 6 months of randomization, triglycerides over 300 mg/dL, history of pulmonary embolism or deep venous thrombosis, history of recent hormone use, history of breast or endometrial cancer, endometrial hyperplasia, and/or presence of a disease likely to be fatal in 4 years. Study participants were randomized to CEE 0.625 mg per day and MPA 2.5 mg per day in one pill, or placebo. The primary outcomes evaluated were fatal and non-fatal MI (symptomatic or silent), sudden cardiac death in the absence of known cause, death due to a coronary

revascularization procedure, or congestive heart failure. Secondary cardiovascular events included CABG, PTCA, hospitalization for unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke, TIA, or peripheral vascular disease.

There were no significant differences between the women randomized to placebo or intervention. After 4.1 years there were 172 primary CAD events in the intervention group (33.1/1,000 women per year) and 176 in the placebo group (33.6/1,000 women per year) (RR 0.99; 95% CI 0.80-1.22). The relative risk for CAD death was 1.24 (95% CI 0.87-1.75). Although the findings were not statistically significant, the survival curves for CAD death diverged during year 2 with survival lower in the hormone-treated group. Also, the incidence curves for non-fatal MI diverged in the first year, with more events occurring in the CHRT group, and then converged and crossed during the third year of the study. Calculating non-fatal MI events by months of treatment, the relative risk was 2.30 for the first 4 months, 1.46 for the second 4 months, and 1.18 for the third 4 months of CHRT. For primary coronary heart disease events, the incidence curves diverged early in year one, with a greater number of events in the CHRT group, and converged at approximately year 3. Overall, the relative risk of primary CAD outcome was 0.95 (95% CI, 0.76-1.17) in those randomized to HRT.

An important finding in this study was that LDL cholesterol decreased 14% in the hormone treated group and 3% in the placebo group, and that HDL increased 8% in the hormone group and decreased 2% in the placebo group. Overall, the relative risk of primary CAD outcome after adjustment for lipid levels and use of statin drugs was 0.94 (95% CI, 0.76-1.17). These findings are important because they are consistent with multiple other studies showing that HRT decreases LDL and increases HDL,[21] yet in this study these changes occur in the absence of improved CAD outcomes, suggesting that other biological mechanisms are important in the CAD and HRT relationship. A recent analysis comparing women in the HERS study to women with presumed CAD in the NHANES III survey highlighted the issue that women in the general population have more CAD risk factors than those in the HERS study, and that secondary prevention strategies should also be tested in populations more representative of the general population.[78]

Another important finding in this study was that deep venous thrombosis and pulmonary embolism occurred in 34 women in the hormone group (6.3/1,000 women-years) and in 12

women in the placebo group (2.2/1,000 women-years). This finding is an important one, both for its intrinsic risk and because it suggests a pathway by which HRT might increase CAD events in the setting of reduced lipid levels, since thrombosis is part of the pathophysiology of several CVD events. It was suggested by Hulley and others that the early increase in CAD events in the HERS study might be explained by an immediate prothrombotic, proischemic, or proarrhythmic effect of CHRT that is gradually outweighed by a reduction in atherosclerosis progression.

The ERA study[30] involved randomization of 309 women with angiographically-confirmed CAD to either placebo, CEE 0.625 mg per day, or CEE 0.625 mg per day plus MPA 2.5 mg per day. All women received a baseline coronary angiogram, were followed for a mean of 3.2 years, and had a followup angiogram. Each of the estrogen arms of the study produced significant decreases in LDL cholesterol when compared to placebo. However, neither active treatment regimen changed the progression of atherosclerosis when evaluated with repeat angiogram. In addition, coronary disease event rates did not differ among the treatment groups. Whether lack of angiographic disease progression correlates with no difference in event rates over time is unclear. This lack of benefit of estrogen with or without progestin among women with established coronary disease is consistent with the HERS study, but differs in not finding higher early event rates in the treatment groups. One of the questions raised with the HERS study was whether the addition of progestins contributed to a lack of benefit in the study; the ERA study helps dispel that concern.

We reviewed 4 studies involving women undergoing angiography (Evidence Table 5).[79-82] We considered these as studies of secondary prevention since women undergoing angiography represent a select group of women, and the results are not generalizable to the general population. In addition, they are effectively cross-sectional studies in which estrogen use was evaluated at the time of angiography, and these types of studies provide little insight into causal relationships.

Summary

- There is currently no evidence that HRT reduces either progression of CAD or CAD events among women with known CAD.

Chapter 4. Discussion

The data on HRT and CVD events, previously fairly consistent in showing benefit to users, have recently become more uncertain because of the publication of new observational studies, the HERS and ERA studies of secondary prevention, and preliminary, though unpublished, data from the Women's Health Initiative. The major points from this review are:

- HRT has been shown in randomized trials to influence a number of biological intermediates that might in turn influence the risk of CVD, CAD, or stroke. HRT raises triglycerides and HDL, and lowers LDL. In addition, it has important effects on endothelial function, fibrinolysis and clotting, and carbohydrate metabolism; may have oxidant (pro- or anti-oxidant) activity; and may be associated with a proinflammatory response. The balance among these biological intermediates in determining CVD, CAD, and stroke risk is uncertain at this time.
- Forty-two observational studies have evaluated the relationship between CVD and HRT. However, only 20 of them are of sufficient quality to allow a valid evaluation of the association and only these were included in our meta-analyses.
- The best evidence from observational studies suggests increased rates of CVD events, but the findings have not been statistically significant in most studies. When combined in meta-analyses, no statistically significant association is shown, although the point estimates are increased for any measure of use.
- The best evidence from observational studies suggests reduced risk of coronary disease events on the order of 20-40%, although many point estimates are not statistically significant and none of the studies that adjust for SES, alcohol use, or exercise show this benefit.
- The findings from the best observational studies are inconsistent in their findings of risk or benefit from longer duration of HRT and any CVD event.
- The vast majority of observational studies and our meta-analysis show no association between HRT and stroke mortality.
- Our meta-analysis estimate for stroke incidence indicates increased risk with a relative risk of 1.12 (95% CI 1.01-1.23)

- Currently, few data suggest that adding progesterone to estrogen influences the risk of any CVD event associated with HRT.
- When women were randomized to HRT or placebo, one clinical trial of secondary prevention convincingly showed no benefit to women in the first 2 years of HRT use, with a non-statistically significant increase in non-fatal MI until year 3 and in CAD death that persists to at least 4 years. Another trial of secondary prevention also showed no benefit in preventing angiographic progression of CAD among HRT users.
- Preliminary evidence from the Women's Health Initiative, the only randomized controlled trial of primary prevention with HRT, has also suggested increased CVD event rates (including stroke and MI) in the first 2 years of the study among women randomized to HRT.
- Observational studies suggest that HRT is associated with reduced relative risks for CVD and CAD death. In our meta-analysis, however, only current use of HRT was associated with significantly reduced risks of death from CVD and CAD. No significant association was identified between past, ever, or any use of HRT and CVD or CAD death.
- Our meta-analysis evaluating CAD incidence and HRT shows no benefit among the studies that adjust for SES and benefit among studies that do not adjust for SES, suggesting confounding.
- Several observational studies suggest increased risk of ischemic stroke among HRT users. Our meta-analysis identified a significant increase in ischemic stroke among ever users of HRT (RR 1.20; 95% CI 1.05-1.40).

We approached this review differently from others who have reviewed this topic.[10, 83] First, we evaluated the overall issue of CVD and then the two major components of it, stroke and CAD. Second, we conducted separate analyses of incidence and mortality for each of the outcomes, as well as a global measure of CVD. Separating these analyses by type of CVD outcome, as well as by incidence and mortality, made sense from both a clinical and epidemiological standpoint because, in spite of many shared risk factors, they are quite different outcomes. Our analysis is also different because we limited our detailed review and meta-analyses to only studies of good or fair quality. With few exceptions, all were population-based,

had some assessment of important CVD risk factors, and had no evidence of bias in classification of exposures. We paid particular attention to CVD risk factors, given the known use of HRT by women at lower risk for CVD based on behavioral and environmental factors (discussed below). Finally, we evaluated risks in our meta-analyses using different measures of exposure (current, past, ever) as well as a global (any) measure.

One of the difficulties in assessing the literature evaluating the HRT-CVD relationship is the large span of years (1962-mid 1990s) represented in the observational studies, during which there were dramatic changes in clinical practice and knowledge about CVD. There have also been significant secular changes in the use of estrogen, including type, administration, and dose, as well as the relatively recent practice of adding progesterone to estrogen therapy. Complicating this evaluation is that many studies use only measurements of estrogen use at one point in time or asked women if they had "ever" used HRT. Thus, "ever" and "current" use could reflect very short exposure or very long exposure to HRT. These differences are illustrated in Tables 1 and 2. Also shown is that several studies combined past use with non-use, which would dilute any potential association between HRT use and CVD. The importance of how HRT use is characterized is illustrated in the FHS, where a change in how HRT use was assessed changed relative risk estimates significantly.

The findings of our review evaluating CVD and CAD mortality show relatively consistent decreases in relative risk of CAD and CVD death in association with exposure to HRT, particularly current exposure. Our meta-analyses differed, however, in showing benefit only with current use of HRT with pooled relative risk estimates of 0.64 (95% CI 0.44-0.93) and 0.62 (95%CI 0.40-0.91) for CVD and CAD death, respectively. Other measures of exposure, and in particular, any use of HRT, showed no benefit in CVD/CAD death in our meta-analyses. The major exception to the consistency among the studies is the FHS, where the relative risk of CVD death was non-statistically significantly elevated at 1.94. The FHS, though older than many, was an excellent study, and why their mortality findings differ from most other studies is not clear. One possiblity is that women in the study used higher doses of estrogen than in more recent studies.[9] Unfortunately, little information is available about the dose of HRT used in this study. Selection of higher risk women for HRT use can be considered, but is not supported by their data, which shows that women using HRT had lower CAD risk than those not choosing HRT.[11]

Therefore, it is unclear why the mortality rate among women using HRT in the FHS was increased.

Most other studies show mortality benefits, but this may be explained by many of the biases discussed below. This is supported by the finding of reduced all-cause mortality among women using HRT shown in several studies,[49, 50, 55, 84, 85] even from causes unlikely to be influenced by HRT. Adjustment or lack of adjustment for important confounders does not explain variable findings among the studies (see Tables 4 and 7). Finally, review of how HRT use is assessed and defined (see Tables 1 and 2) does not explain different findings among studies.

Many studies have evaluated CAD incidence, and many have shown reduced, though non-statistically significant, relative risks (Table 12). The summary relative risk estimate for CAD incidence from our meta-analysis shows a reduced relative risk of CAD of 0.81 (95% CI 0.69-0.96) for current use when no adjustment for SES is made. This is of lower magnitude than prior meta-analyses have found. No benefit was shown in our meta-analyses for any other measure of HRT use in reducing CAD events. This difference between our meta-analysis and others is likely due to our use of fairly rigorous study inclusion criteria, as well as the inclusion of more recent studies, 2 of which show no benefit.[12, 51] It is notable that of the 3 cohort studies evaluating CAD incidence, only the NHS shows reduced risk and the 2 others show non-significantly elevated risks. However, because of the size of the NHS, any meta-analytic estimate will be weighted towards its results. An interesting finding among the studies evaluating CAD incidence is that none of the studies that included adjustment for SES or education in their multivariate models showed reduced CAD incidence.[12, 51, 65, 67] This is an important finding, since lower SES is an important risk factor for CAD, as well as for most other poor outcomes,[70] and women using HRT tend to be of higher SES, and their better outcomes may be explained by higher SES rather than HRT.

To better evaluate this observation, we conducted the meta-analysis stratifying by adjustment for SES. When this was done, the summary risk derived from studies not adjusting for SES showed benefit for current and past use of HRT. However, when SES was accounted for, no benefit was seen for any type of HRT use. These findings suggest confounding of the HRT/CAD relationship by SES.

To the best of our knowledge, no other meta-analyses have rigorously evaluated studies or included this type of sensitivity analysis. In the area of CAD, Stampfer and colleagues[9] conducted a meta-analysis in 1991 that included 6 case-control studies, 16 cohort studies, and 3 cross-sectional angiography studies and found a relative risk of 0.56 (95% CI 0.50-0.61) for CAD events (incidence and mortality). In 1992, Grady and colleagues[83] conducted a meta-analysis of HRT and CAD and calculated a relative risk for CAD events of 0.65 (95% CI 0.59-0.71) and CAD death 0.63 (95% CI 0.55-0.72) when comparing ever-users to non-users. More recently, Barrett-Connor and Grady[86] conducted another meta-analysis and calculated a summary risk estimate for CAD of 0.70 (95% CI 0.65-0.75) for ERT/CHRT use. In each of these meta-analyses, studies were included which we rated of poor quality and excluded from our review. Several of the studies we excluded from our review did not provide risk-adjusted estimates of relative risk or used data from proxies. In addition, angiography studies that involve symptomatic women and are limited by their cross-sectional design were included in the above meta-analyses. These meta-analyses also differ from ours because they combine mortality and incidence relative risks for HRT. Finally, we evaluated current, past, and ever use in several of our meta-analyses and found significant results only among current users, and this approach differs from all of the above. These differences may partially explain why our review suggests less benefit from HRT in preventing CAD.

Our review and meta-analysis suggest increased rates of CVD among women using HRT, with summary estimates of 1.35 for ever use and 1.27 for current use, which are not statistically significant. This finding differs from prior analyses and likely results from our reviewing total CVD separate from CAD, as well as inclusion of new data from the Hemminki analysis[60] and the Finnish cohort.[51] Our findings of reduced CVD mortality among current HRT users and no association with CVD incidence were also shown in the Sourander[51] and Pettiti[49] studies.

The relationship between stroke and HRT is very difficult to study for many reasons. These include inconsistencies in defining stroke endpoints, as well as differences in estrogen formulations and dose, length of use, and time since last use. Not surprisingly, therefore, studies that have been conducted on stroke and HRT have conflicting results. One meta-analysis pooled 15 studies (3 case-control, 3 uncontrolled cohort, and 9 cohort) and found a pooled estimate of the relative risk of stroke among estrogen users of 0.96 (95% CI 0.82-1.13),[83] indicating no

association between HRT and stroke. This review pooled numerous studies that varied in size and quality. The summary relative risk was estimated by assigning a weight for the relative risk from each study, thereby giving more weight to larger studies. No allowance was made for the quality of the study, allowing poor-quality studies to carry weight equal to that of good-quality studies. A review by Paganini-Hill[87] in 1995 analyzed 26 studies, representing 19 cohorts, and found mixed results. Our results differ from prior analyses of this relationship in showing a significantly increased risk of stroke (summary RR 1.12) and ischemic stroke (summary RR 1.15) among HRT users and no association with stroke death. Again, these different findings likely reflect our exclusion of poor quality studies and inclusion of recent studies, many of which have elevated point estimates.

Several biases complicate the interpretation of our results, as well as those of others. The first consideration is selection bias. Women who use HRT tend to be more affluent, leaner, more educated, exercise more often, and drink more alcohol, and all of these factors have been shown to be protective against cardiovascular disease.[88] This has been shown in several studies, including the FHS, NHS, IWHS, and NHANES. They are also different premenopausally. Longitudinal data among women who are premenopausal and followed into menopause show that prior to menopause, women who take estrogen postmenopausally are different in significant ways from those who do not.[46, 89] In one study,[11] the premenopausal women who subsequently took HRT were better educated, drank more alcohol, were leaner and exercised more, and had less comorbidity, and all of these lifestyle characteristics are associated with reduced rates of cardiovascular disease in epidemiologic studies. Thus, the role of estrogen in CVD may be confounded by its relationship with these other important known protective factors for cardiovascular disease. Interestingly, none of the studies evaluating CAD that adjusted for alcohol or exercise showed benefit, supporting evidence of confounding by these factors. These protective factors can be adjusted for analytically when measured; what cannot be adjusted for statistically, however, are lifestyle and/or environmental exposures and/or genetic characteristics that are not measured, or may not yet be identified as important etiologically in cardiovascular disease. This is particularly an issue in CVD, where 50% of it is unexplained by traditional risk factors.[3]

We know that women who take HRT have access to health care, since they are receiving prescriptions, and they are therefore more likely to be treated for comorbid conditions such as high cholesterol or high blood pressure, which would also lower their risk of cardiovascular disease.[90] This has been called "prevention bias" by Barrett-Connor and was effectively demonstrated in an upper-middle-class cohort where current HRT users were significantly more likely than non-users to have several preventive health care measures performed.[90] Several studies have suggested that even when known cardiovascular disease risk factors are adjusted for, the social class difference in cardiovascular disease remains, suggesting that social class should be included in multivariate models and that there are as yet unmeasured risk factors for cardiovascular disease that are associated with lower socioeconomic class.[70] None of the studies evaluating CAD incidence that adjusted for SES showed benefit, and our meta-analysis showed markedly different relative risks depending on the inclusion or exclusion of SES in the studies' multivariate analyses.

Another type of selection bias that is very difficult to quantify or characterize is selection bias among physicians. Do physicians select women at lower risk of cardiovascular disease for HRT use? This is clearly shown when the characteristics of women who take HRT are evaluated. Significant secular trends have been observed in estrogen use,[91] and it is notable that many of the studies of estrogen use were conducted at a time when physicians were concerned about the risk of HRT and CVD, based on the Coronary Drug Project findings among men and MI rates in women taking oral contraceptives.[91] In addition, for many of the years represented in these studies, hypertension, diabetes and heart disease were considered contraindications to the use of HRT.[86] What is more subtle, though likely apparent to practicing physicians, may be a tendency to offer and prescribe HRT to women for whom the physicians' sense of their overall "health" is higher. This type of selection bias is more difficult to measure and could lead to systematic overestimates of the benefit of HRT in cardiovascular disease.

These types of selection bias have been termed "healthy user bias." Another aspect of healthy user bias is the common finding that women often quit HRT when they become ill. This tendency would bias studies that evaluate recent use, by underestimating use in ill patients, resulting in reduced relative risk estimates associated with exposure suggesting protection by HRT. This is suggested in studies where current or recent users may have a reduced risk of

cardiovascular disease compared to non-users or past users of HRT. It is even more strongly suggested in studies where past users have higher rates of cardiovascular disease than nonusers or current users, suggesting that they may have stopped HRT because of illness.[92] In our meta-analyses evaluating CVD and CAD mortality, only current use of HRT was associated with decreased risk of death; other measures of use showed no association. In particular, any use, which combined mutually exclusive point estimates by type of use (past, current, ever) showed no association with decreased risk. This measure of use should have had sufficient power to show benefit if benefit existed, given that current use had enough power. One interpretation of these data is that current use reflects healthy user bias. That is, women currently using HRT are healthier, and when data are combined to reflect any use (current, past or ever), the pool of women is less enriched with healthy users, and benefit is therefore not shown. Clinically, it makes sense that HRT is less likely to be used in women who have become ill, and that when HRT use is evaluated using observational methods, current use actually reflects current health. Supporting the concept of healthy use bias among women using HRT is that several studies have shown reduced all-cause mortality, as well as reduced mortality from accidents and homicides, among women who take HRT, possibly reflecting multiple benefits, but more likely indicating systematic differences among users and non-users.[22, 49]

Another consideration in evaluating the HRT-CVD relationship is the issue of compliance bias. Women who take HRT, especially for long periods of time, are by definition compliant with therapy. Several epidemiologic studies have shown that compliance itself is associated with reduced risk of disease of many types, often of the same magnitude seen with HRT use.[93] Women who comply with treatment are different from those who do not in ways that are protective against cardiovascular disease. In randomized controlled trials, good compliance with placebo has been shown to decrease CAD events by 40 to 60%.[94, 95] Because the studies of HRT are almost entirely observational, compliance bias itself may explain much of the benefit seen in studies of HRT and CVD.

Another area of potential bias in evaluating the HRT-CVD relationship, possibly leading to an underestimation of benefit from HRT, is that HRT is more often used by women who have undergone hysterectomy and oophorectomy. Women who undergo premenopausal hysterectomy are at increased risk of CVD, possibly because of loss of estrogen, although this is not clearly

delineated as causal in the medical literature.[4] This could lead to a systematic underestimate of the benefit of HRT if their baseline risk is higher, since they have a higher likelihood of using HRT. Also, estimating age at menopause in women who have had simple hysterectomies may lead to misclassification of a CVD risk factor that would result in estimates of the association between HRT and cardiovascular disease moving closer to the null if it is nonbiased. However, often the oldest potential age for menopause is used as an estimate for age at menopause, and this could result in bias towards a systematic underestimate of the intrinsic risk of CVD in women with surgical menopause. Finally, women undergoing hysterectomy and receiving HRT are selected for health, since they are able to undergo and survive surgery, which is typically elective.

In the last 2 years, important data from 2 randomized controlled trials of HRT in the secondary prevention of CVD[29, 30] and one trial of HRT in the primary prevention of CVD[48] have been published, or have released information to the public. Results from these studies are very important because randomization is the only way to deal with the above biases and to ensure equal distribution of known and unknown CVD risk factors or confounders. The HERS study of secondary prevention showed no benefit of HRT in the first 2 years of use, and, in fact, showed an increased rate of MI during the first 2 years of use.[29] The ERA study of secondary prevention showed no benefit from HRT in reducing angiographic CHD progression.[30] In both these studies of secondary prevention, HRT was initiated long after menopause, which likely differs from most observational studies of primary prevention. It is important to consider that the HERS results may not apply to ERT alone, or to other types of estrogen or progesterone, or other progestin dose schedules. Also, whether these secondary prevention results can be extrapolated to the primary prevention of CVD with HRT is unclear in the absence of further data from randomized controlled trials. The WHI released early results to participants in the spring of 2000.[48] These results, as yet unpublished, suggest that women randomized to HRT had rates of stroke, ischemic heart disease, and blood clots higher than those of women randomized to placebo. Again, similar to the secondary prevention studies, the excess rate of these events was found to be highest in the first 2 years of the study, with risks decreasing at approximately 2 years.

How can the results of these 3 studies, and especially the WHI study of primary prevention, be explained, given the observational data described above showing benefit? As discussed at length in this report, it is possible, and even likely, that selection and compliance

bias play a major role in the findings from the observational studies. What is especially surprising in these 3 studies, however, is not just the lack of benefit among users, but the suggestion of harm in the first 2 years in 2 of the studies.[29, 48] For years it has been thought that the most likely biological explanation for some of the observed reduction in cardiovascular disease risk among HRT users was an improvement in lipid profiles. However, the fact that randomized controlled studies have shown that women had higher CVD risks in the first 2 years of the study in the setting of more favorable lipid profiles, suggests that other important biological effects occur in women who take HRT. As discussed above, estrogen has many other biological effects, and one of these is a complex role in clotting and thrombolysis. The role of clotting is a major issue that must be considered, since stroke, MI, and unstable angina are thought to be partially mediated through clotting mechanisms. These biological changes may result in a shift in balance towards increased blood clotting, which may be a more immediate or acute effect of estrogen, and is consistent with the observation of increased risk among women during the early years of estrogen use. Notably, women at high risk for thrombotic disorders were excluded from these trials. Women who are able to stay on estrogen may be able to benefit from the more chronic benefit of reduced lipids or other changes in physiology.

With the publication of the HERS results and the preliminary reporting of increased event rates in the first 2 years of the WHI, one of the most pressing questions facing investigators and clinicians is whether this early increase in events is later offset by a reduction. Among the fair and good quality studies we reviewed and included in our meta-analyses, only a few provide information that is helpful in evaluating this issue. The Hemminki analysis,[60] which used only trial data, suggests (though the finding is not statistically significant) an increase in CVD event with HRT use of relatively short duration. The Criqui data[54] suggest an increased risk of CAD death among women using HRT for fewer than 8 years. These authors also investigated order of use among women using HRT for fewer than 8 years. Among women on HRT at the beginning of the study who went off it before 8 years follow-up, the relative risk was 1.24 (95% CI 0.55-2.78). However, for women who were not on HRT at the beginning of the study who began estrogen and used it for fewer than 8 years, the relative risk of CAD death was 2.62 (95% CI 0.59-11.61). A similar pattern of early increased risk, though with smaller relative risk, was also observed with CVD mortality in this cohort. Rosenberg and colleagues[67] reported a similar

pattern in a large US case-control study where the adjusted relative risk of MI was 1.5 in ERT users of less than 1 year, 1.2 for 1-4 years of use, 0.6 for 5-9 years of use, and 0.5 for more than 10 years of use, suggesting early increased risk. Data from 2 other sources evaluating estrogen use in the secondary prevention of CAD also support an increase in early event rates in association with estrogen. Wenger and colleagues[96] report a similar pattern of early events among men involved in the Coronary Drug Project, a randomized controlled trial of estrogen and other therapies in the secondary prevention of CAD. Specifically, among men randomized to estrogen (2.5 mg), the relative risk of CAD events was 1.58 (95% CI 1.04-2.40) in months 0-4 compared to placebo and 0.96 for months 13-60. The relative risk of CAD events associated with months 0-4 compared to months 13-60 of estrogen exposure was 1.65 (95% CI 1.04-2.60). In addition, in the group of men randomized to 5.0 mg of estrogen, this trial arm was stopped because of an increase of adverse events in the first 2 years of use. Among 2,245 women in the NHS with prior MI or coronary atherosclerosis the overall risk of recurrent events associated with estrogen use was 0.65 (95% CI 0.45-0.95).[97] However, marked differences were observed with duration of use. In the first year of use, the relative risk of recurrent events was 2.10 (95% CI 0.88-4.99). For years 1 to 2 the relative risk was 1.01 (95% CI 0.31-3.27) and for greater than 2 years use it was 0.56 (95% CI 0.37-0.85). Thus, several studies suggest an early increase in CVD risk in association with HRT which diminishes over 1 to 2 years, consistent with both the HERS and WHI study findings.

In recent years, many new hypercoaguable states have been identified, one of which is the Factor V Leiden mutation. This mutation is a relatively common disorder in the US population, with prevalence of 4-6%, and has been shown to increase the risk of primary and recurrent venous thrombolism 3-6 fold.[98] A very interesting recent observation has been the marked interaction and increased risk of blood clotting among women with the Factor V Leiden mutation who use oral contraceptive agents.[99] There are theoretical reasons that HRT may interact with this deficiency similarly to oral contraceptives, and recent work suggests a 13-fold increase in risk of clot associated with HRT in women with Factor V Leiden mutations.[100] Could an excess number of early CVD events in women with this relatively common disorder or other hypercoagulative states explain some of the HRT findings from randomized controlled trials? Supporting this possibility is a recent case-control study among women with first non-fatal MI

which suggests an important interaction with current HRT and the presence of a pro-thrombotic genetic variant among women with hypertension, resulting in a markedly elevated risk of recurrent MI.[101] No interaction was observed among non-hypertensive women or those with Factor V Leiden. Also, are there subgroups of women where most of the increased risk is conferred, such that those women at lower risk of clot could benefit from the potential long-term benefits of HRT? The answers to these questions are unknown but are important to pursue.

Based on this review, and extrapolating somewhat from the 2 trials of secondary prevention, there is good reason to question the results of observational studies supporting the use of HRT in the primary or secondary prevention of CVD. Randomized controlled trials are the best way to determine whether these biases explain the effects observed in observational studies. We hope that better information will come from randomized trials in the near future.

Chapter 5. Research Priorities

- Investigate whether subgroups of women are at particularly increased risk of CVD or CAD in association with HRT.
- Almost all studies involve Caucasian women; further research should be conducted among non-Caucasian women.
- Homocysteine levels have recently been identified as important risk factors for CVD. Evaluate whether adding homocysteine levels to multivariate models changes the association with HRT. Consider interaction between homocystiene levels and HRT use.
- The most commonly used estrogen compound is conjugated equine estrogen, which is composed of multiple chemicals. Evaluate whether particular components are associated with different physiologic effects.
- Conduct studies to evaluate whether aspirin might modify the early risk of increased MI, stroke, and clotting, as seen in 2 of the randomized controlled trials.
- Further evaluate the role of transdermal estrogen in CVD, as well as other formulations.
- Evaluate childhood and adolescent exposures that might influence the risk of CVD and might be associated with HRT use.
- Investigate the potential interaction with HRT in women with hypercoaguable states.
- Conduct/complete randomized controlled trials evaluating the role of ERT and CHRT in CVD.
- Conduct more research on lower-dose estrogen preparations.

Addendum

This evidence review was completed in December 2001, and the meta-analyses evaluating stroke death and incidence were updated in February 2002. A summary of the findings will be published in the *Journal of the American Medical Association* on August 20, 2002.

On May 31, 2002 after approximately 5.2 years of follow-up, the Women's Health Initiative (WHI) randomized controlled trial was stopped on the recommendation of the data safety and monitoring board because the test statistic for invasive breast cancer exceeded the stopping boundary for this outcome. At the time the study was stopped, the findings for several cardiovascular outcomes, including coronary heart disease (defined as acute MI, silent MI or CHD death) and stroke were reported. Among the 8,506 women randomized to conjugated estrogen 0.625mg per day and medroxyprogesterone acetate 2.5mg per day combined in 1 pill, the annual rate of CHD was 37 per 10,000 compared with 30 per 10,000 among women randomized to placebo (n=8,102). The hazard ratio for CHD was 1.29 (nominal 95% CI; 1.02-1.63). When the confidence interval was adjusted for multiple analyses over time the confidence interval was 0.85-1.97. Rates of CABG and PTCA were similar among the 2 groups. The annualized stroke rates were 29 per 10,000 among women randomized to estrogen and progesterone and 21 per 10,000 among those randomized to placebo. The hazard ratio for stroke was 1.41 (95% nominal CI; 1.07-1.85). After adjustment for multiple analyses over time the confidence interval was 0.86-2.31. The curves showing the cumulative hazards for CHD began to diverge shortly after randomization with little evidence of convergence after 6 years of follow-up. The cumulative hazard for stroke began to diverge between 1 and 2 years after

randomization and persists beyond the fifth year. Subgroup analyses among women with prior MI or revascularization procedures (conditions that would have made them eligible for the HERS) identified a hazard ratio of 1.28 (95% CI; 0.64-2.56). Among the remaining women (without prior CHD) the hazard ratio was 1.28 (95% CI; 1.00-1.65). An important limitation of the study was a very high rate of discontinuation of study drugs during the trial (42% among CHRT users and 38% for placebo); this should result in dilution of any effect.

Notably, a separate arm of the WHI evaluating whether oral estrogen prevents cardiovascular disease among women with prior hysterectomy (n=10,739) was not terminated so the association between ERT and CVD in this trial remains uncertain, with results expected in 2005.

These findings support the main findings of our review and meta-analyses showing no benefit in preventing CAD events and increased rates of ischemic stroke.

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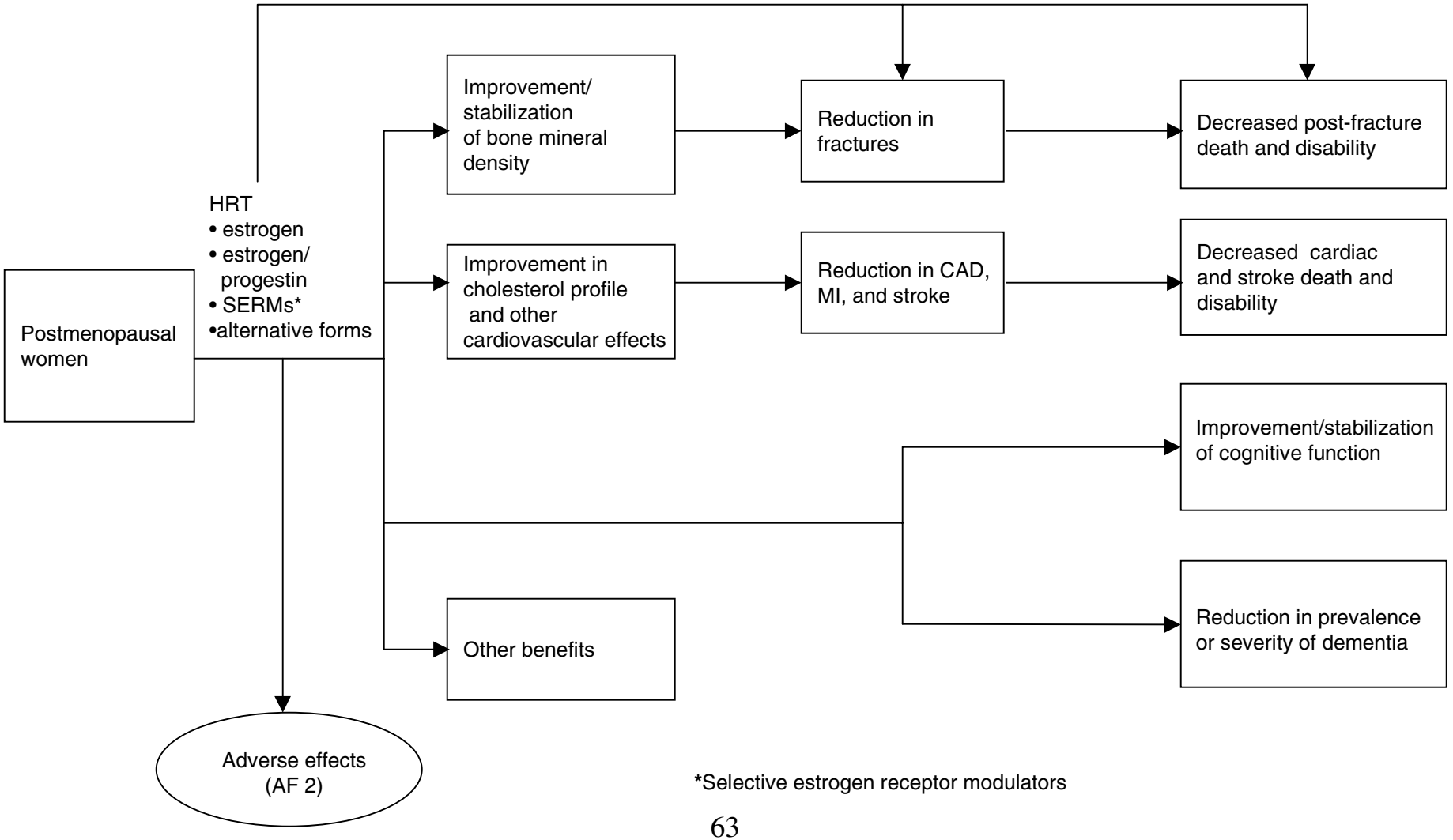
Figure 1. Analytic Framework 1: Benefits of Hormone Replacement Therapy



*Selective estrogen receptor modulators

Figure 2. Analytic Framework 2: Adverse Effects of Hormone Replacement Therapy

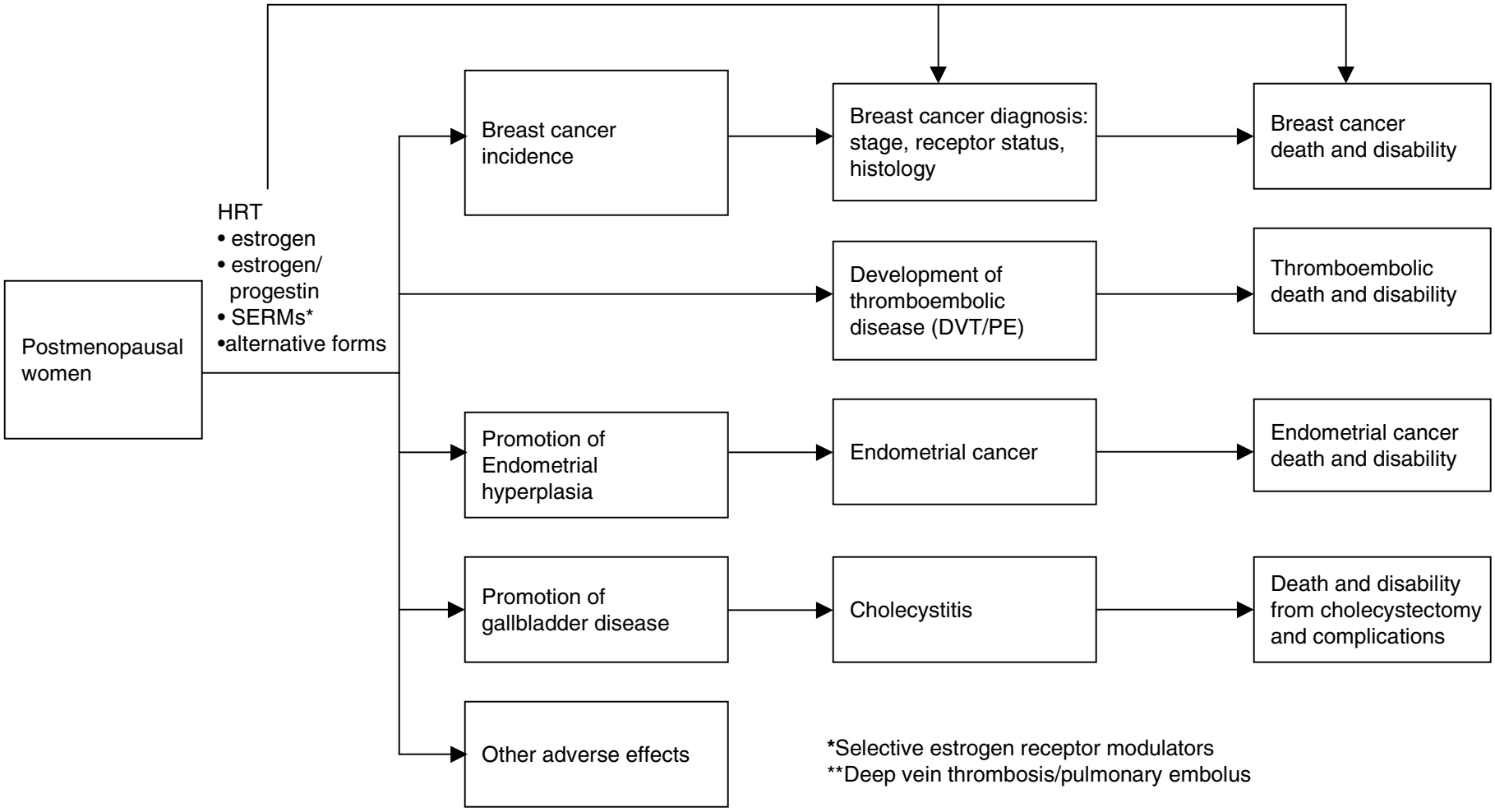


Figure 3. Cardiovascular disease mortality and hormone replacement therapy.

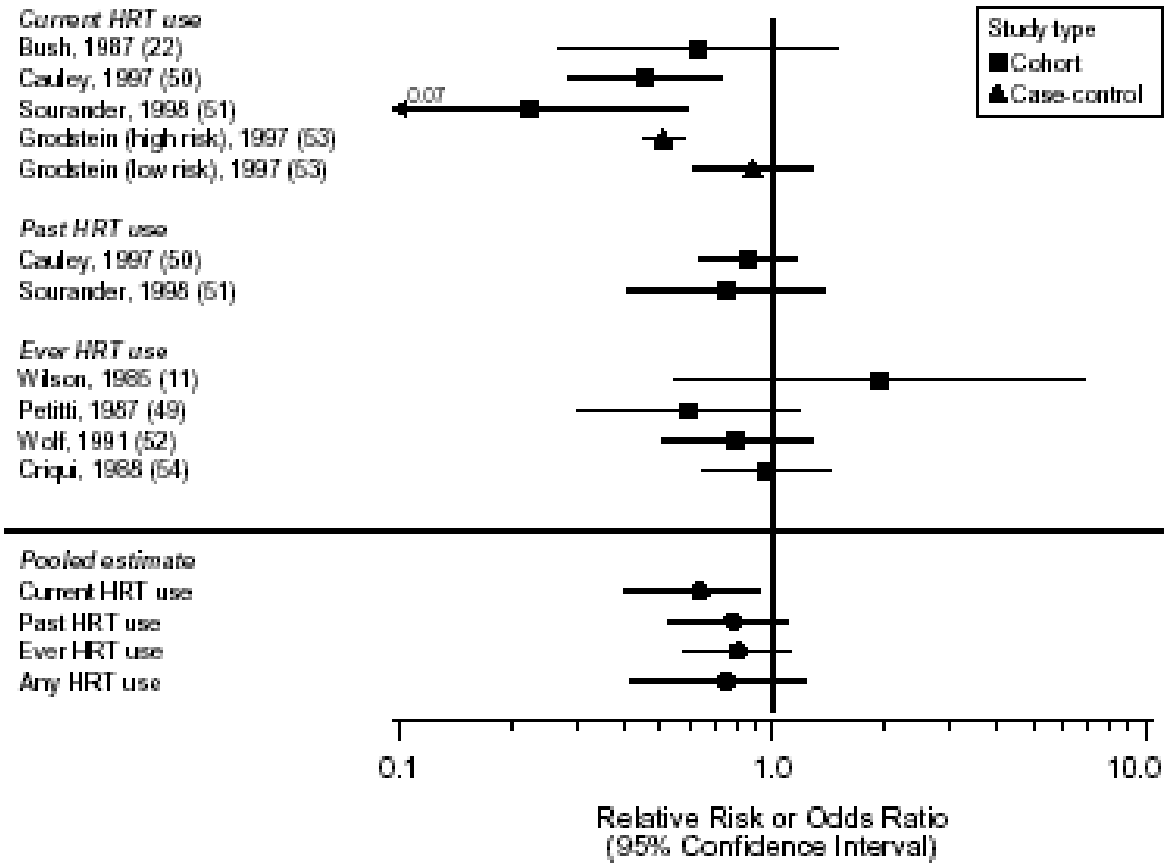


Figure 4. Coronary artery disease mortality and hormone replacement therapy.

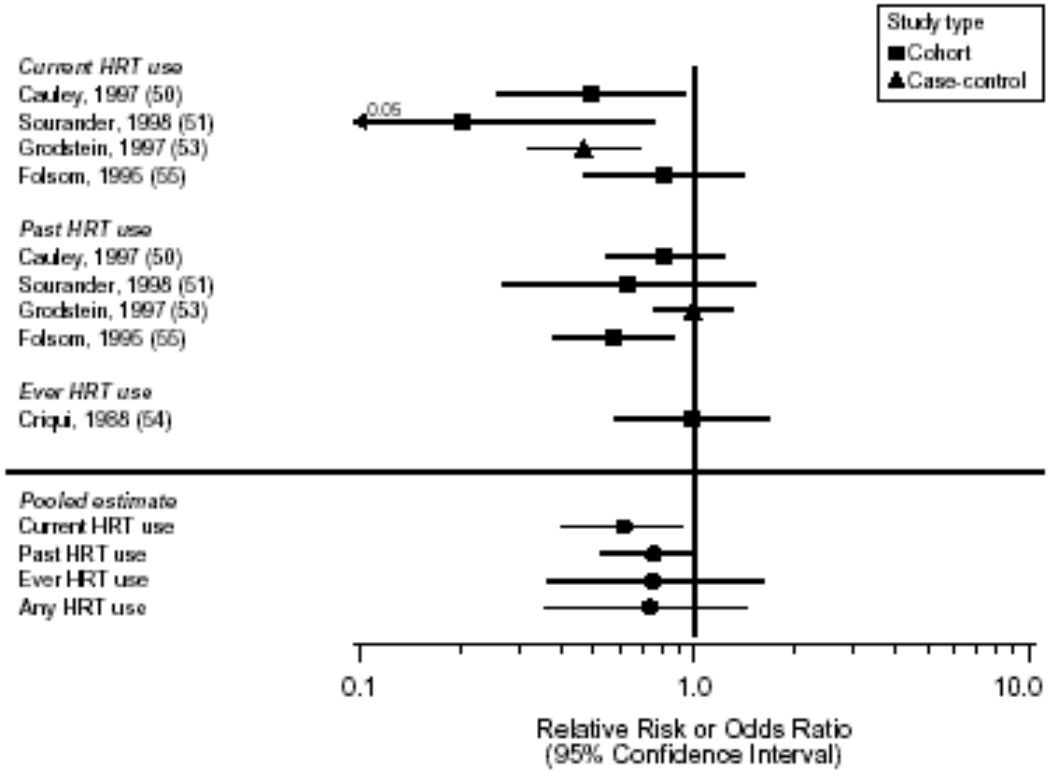


Figure 5. Stroke mortality and hormone replacement therapy.

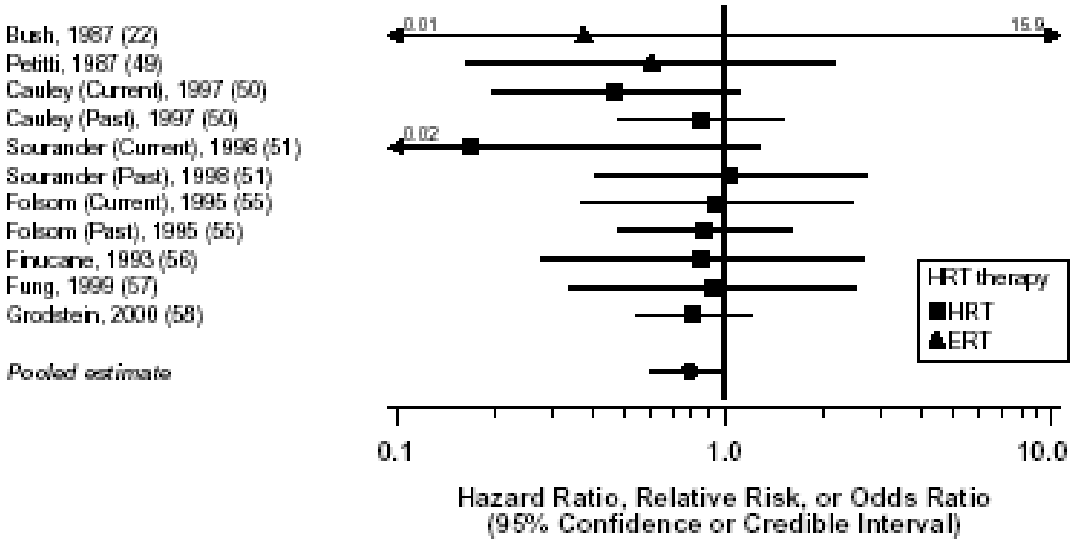


Figure 6. Cardiovascular disease incidence and hormone replacement therapy.

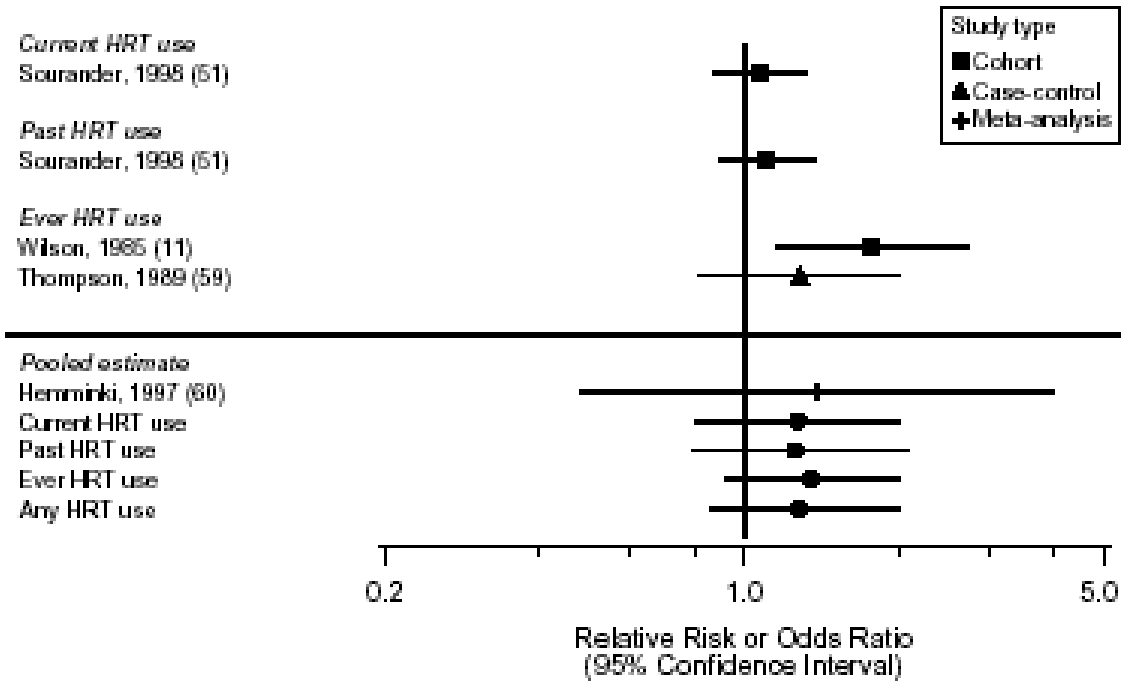


Figure 7. Coronary artery disease incidence and hormone replacement therapy.

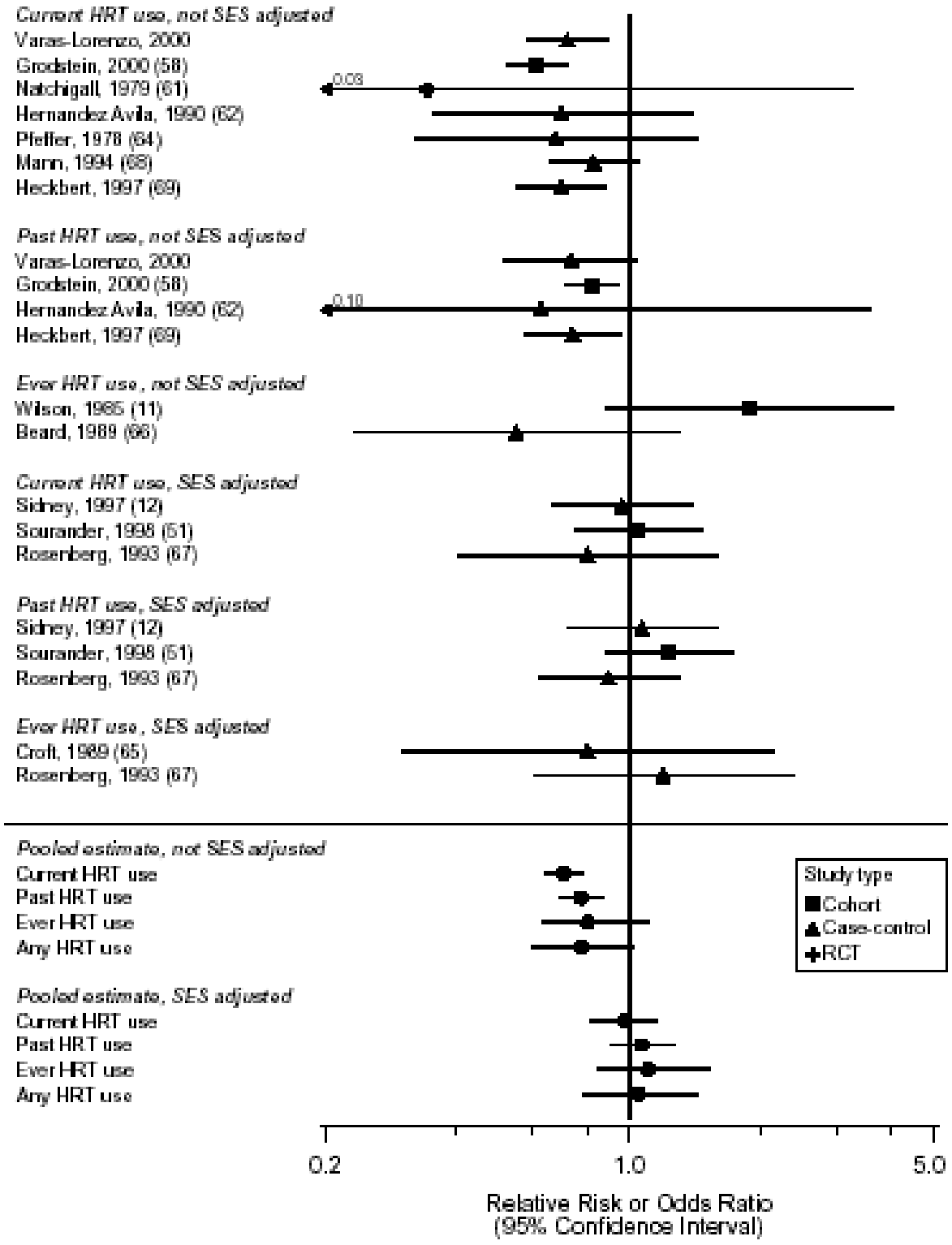


Figure 8. Stroke incidence and hormone replacement therapy.

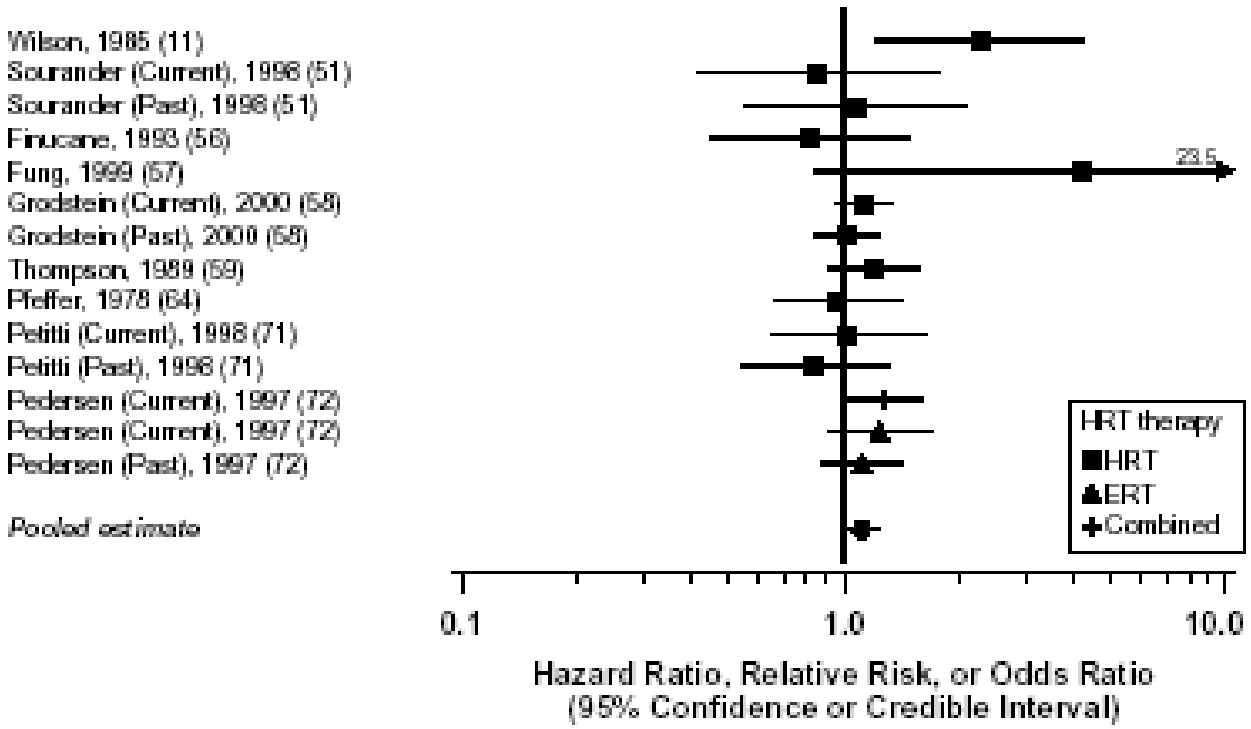


Figure 9. Atherothrombotic brain infarction incidence and hormone replacement therapy.

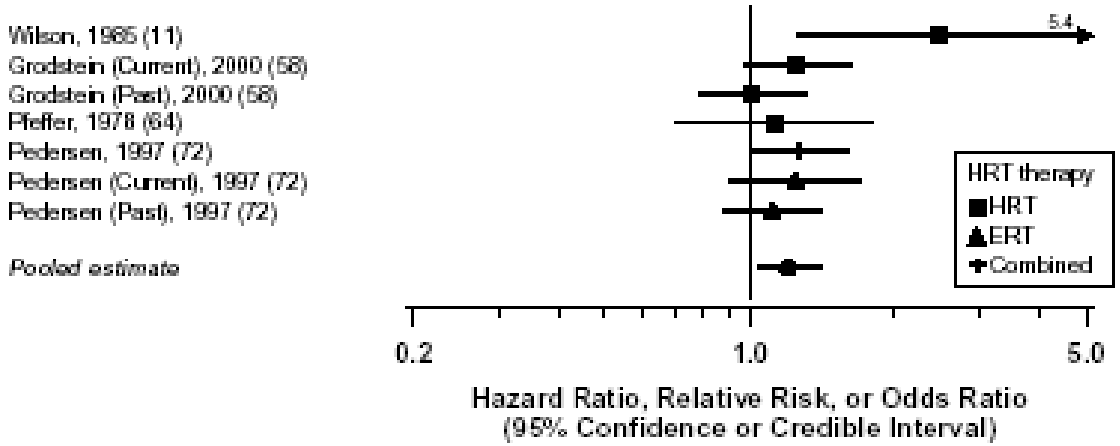


Figure 10. Subarachnoid hemorrhage incidence and hormone replacement therapy.

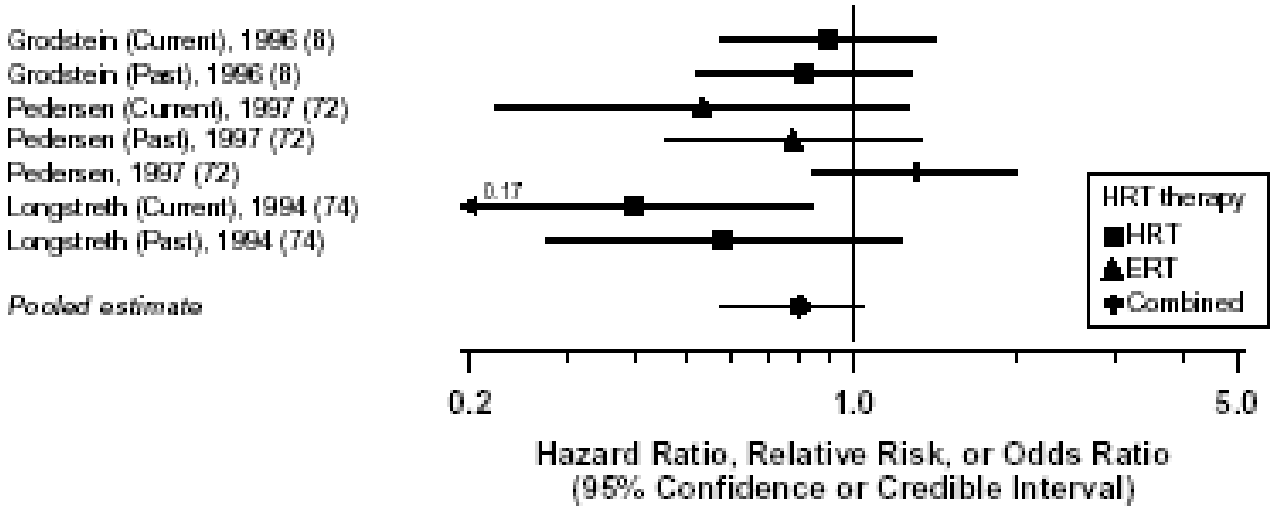


Figure 11. Intracerebral hemorrhage incidence and hormone replacement therapy.

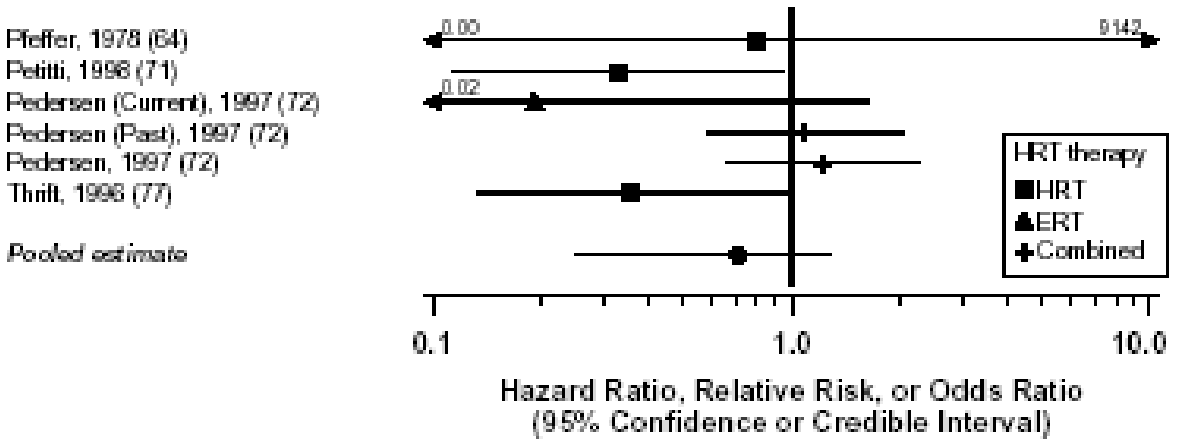


Table 1. Characterization of hormone replacement therapy use in case-control studies: assessment and definitions

Study, year	Quality	How HRT Use Assessed and Defined
Pfeffer, 1978[64]	Fair	File of estrogen prescriptions 1964-1974. Ever, current and never use not defined. Continuous use: not interrupted over 30 days.
Thompson, 1989[59]	Good	Medical record review. Use: receiving 2 or more prescriptions
Croft, 1989[65]	Fair	Medical records. Use/non-use not defined.
Beard, 1989[66]	Fair	Medical record review. Current, ever, former not specified.
Rosenberg, 1993[67]	Good	Personal or telephone interview. Use: greater than one month's use. Non-use: less than 1 month of use.
Mann, 1994[68]	Fair	Computer records. Current: record of HRT prescription in 6 months prior to index date.
Longstreth, 1994[74]	Fair	Personal interview; current, ever, or former use not defined.
Grodstein, 1996[8]	Good	Baseline questionnaires beginning 1976 and updated biennially to 1992. Hormone use defined according to questionnaire prior to case's death or disease leading to death. Current and past not defined.
Thrift, 1996[77]	Fair	Personal interview. Ever use: use ever in lifetime.
Heckbert, 1997[69]	Fair	Pharmacy database. Ever: 2 prescriptions. Current: filled enough to reach index date.
Sidney, 1997[12]	Good	Personal interview. Lifetime HRT use assessed - both current use and past. Current and past not specifically defined.
Pedersen, 1997[72]	Good	Baseline questionnaire. Current use: use at time of stroke in cases and at time of questionnaire in controls.
Pettiti, 1998[71]	Fair	Personal interview. Current and past use not defined.

Table 2. Characterization of hormone replacement therapy use in cohort studies: assessment, prevalence and definitions

Study, year	Quality	Prevalence ever use HRT	How HRT Use Assessed and Defined
Wilson, 1985[11]	Good		Biennial questionnaire over 10 years. Ever use: one report of use. Non-use not defined.
Bush, 1987[22]	Good	26%	Personal interview. Use: used within 2 weeks of second visit.
Pettiti, 1987[49]	Fair	NR	Questionnaire with annual updates through 1977. Never/ever not defined.
Criqui, 1988[54]	Fair	39%	One questionnaire 1972, repeated nine years later. Current use/non use not defined but characterized with both questionnaires.
Hernandez-Avila, 1990[62]	Fair		Pharmacy record review. Current : using 12 months after receiving prescription. Recent if used 12-23 months after last prescription. Non-use if no use ever or greater than 23 months since last use.
Wolf, 1991[52]	Fair	21%	Questionnaires between 1982-1984 2 years apart. Ever or non-use not defined.
Finucane, 1993[56]	Good	21%	Obtained at first follow-up visit. Ever use: use ever in lifetime; never use: not before baseline.
Folsom, 1995[55]	Good	38%	Questionnaire 1985. Former, current, ever not defined.
Grodstein, 1996[8]	Good	51%	Questionnaires beginning 1976 and updated biennially to 1992. Current and ever use not defined.
Cauley, 1997[50]	Good	36%	Questionnaire at baseline with one update in 1991. Never: less than one year. Current: use of >1 year. Former: past use of < 1 year.
Sourander, 1998[51]	Fair	22%	Baseline questionnaire 1987 and 3 biennial follow-up questionnaires. Current use: use at baseline. Former use: use before baseline. Never use: not before or after baseline.
Fung, 1999[57]	Fair	33% (current)	Baseline interview and questionnaire (1972-1974). Follow-up questionnaire (1984-1987). Current use: use within 2 weeks of interview.

Table 3. Studies contributing to CVD review by quality ranking

	Cohort	Case Control
Good:	Wilson, 1985[11]	Thompson, 1989[59]
	Bush, 1987[22]	Rosenberg, 1993[67]
	Grodstein, 1996[8]	Grodstein, 1996[8]
	Folsom, 1995[55]	Sidney, 1997[12]
	Cauley, 1997[50]	Pedersen, 1997[72]
	Finucane, 1993[56]	
Fair:	Criqui, 1988[54]	Pfeffer, 1978[64]
	Hernandez-Avila, 1990[62]	Beard, 1989[66]
	Wolf, 1991[52]	Croft, 1989[65]
	Pettiti, 1987[49]	Mann, 1994[68]
	Sourander, 1998[51]	Heckbert, 1997[69]
	Fung, 1999[57]	Pettiti, 1998[71]
		Thrift, 1996[77]
		Longstreth, 1994[74]

Table 4. Cardiovascular disease mortality and hormone replacement therapy

Study, year Quality	N	Design	Hormone Type	Hormone Exposure Status	RR	95% Confidence Intervals	Age	BP	DM	Family History	Chol	LDL/ HDL	Smok-ing	BMI	Alco-hol	Educ SES	Exer-cise	Other
Wilson, 1985[11] Good	1234	Cohort	HRT	Ever	1.94	NS	X	X				X	X	X	X			
Pettiti, 1987[49] Fair	6093	Cohort	HRT	Ever	0.60	0.3 -1.1	X	X					X	X	X	X		Marital status
Bush, 1987[22] Good	2270	Cohort	HRT	Current	0.63	P=0.29	X	X				X	X	X				
Criqui, 1988[54] Fair	1868	Cohort	HRT	Ever	0.96	0.65 - 1.43	X	X	X		X		X	X		X		Glucose
Wolf, 1991[52] Fair	1944	Cohort	HRT	Ever	**0.66**	**0.48 - 0.90**	X	X			X		X	X		X		Previous MI
Cauley, 1997[50] Good	9704	Cohort	HRT	Current Past	**0.46** 0.86	**0.29 - 0.73** 0.65 - 1.15	X	X	X				X	X	X	X	X	Surgical menopause, health status, clinic, stroke
Grodstein, 199[69] Good	3637	Nested CC	HRT	Current High CVD risk Current low CVD risk	**0.51** 0.89	**0.45 - 0.57** 0.62 - 1.28	X	X	X	X	X		X	X				Age at menopause, type menopause, OCP use
Sourander, 1998[51] Fair	7944	Cohort	HRT	Current Past	**0.21** 0.75	**0.08 - 0.59** 0.41 - 1.37	X	X	X				X	X		X		CAD, CHF

Table 5. Cardiovascular disease mortality and hormone replacement therapy by duration

Study, year	HRT Status	Duration (years)	RR	95% Confidence Intervals
Criqui, 1988[54]	Ever	≤8 (on-off)¶	1.20	0.62 - 2.35
		8 (off-on)¶¶	1.55	0.32 - 6.62
		>8	0.40	0.05 - 3.19
Cauley, 1997[50]	Current	1-9	0.78	0.44 - 1.38
		≥10	**0.36**	**0.16 - 0.57**

¶ On HRT at first evaluation, off at second

¶¶ Off HRT at first evaluation, on at second

Table 6. Meta-analysis summary table

	Current	Past	Ever	Any
Mortality - Meta-analysis				
Total cardiovascular disease	**0.64 (0.44-0.93)**	0.79 (0.52-1.09)	0.81 (0.58-1.13)	0.75 (0.42-1.23)
Coronary artery disease	**0.62 (0.40-0.90)**	0.76 (0.53-1.02)	0.81 (0.37-1.60)	0.74 (0.36-1.45)
Stroke				[¶] 0.79 (0.60-1.01)
Incidence- Meta-analysis				
Total cardiovascular disease	1.27 (0.80-2.00)	1.26 (0.79-2.08)	1.35 (0.92-2.00)	1.28 (0.86-2.00)
Coronary artery disease	**0.72 (0.61-0.84)** [¶¶]0.98 (0.79-1.18)	**0.77 (0.65-0.91)** [¶¶]1.06 (0.84-1.31)	0.79 (0.59-1.15) [¶¶]1.09 (0.77-1.58)	0.75 (0.56-1.04) [¶¶]1.04 (0.75-1.40)
Stroke			**[¶]1.12 (1.01-1.23)**	

[¶] Risks similar for current, past and ever use

[¶¶] Adjusted for socioeconomic status

Table 7. Coronary artery disease mortality and hormone replacement therapy

Study, year Quality	N	Design	Hormone Type	Hormone Exposure Status	RR	95% Confidence Intervals	Age	BP	DM	Family History	Chol	LDL/ HDL	Smok-ing	BMI	Alco-hol	Educ SES	Exer-cise	Other
Criqui, 1988[54] Fair	1868	Cohort	HRT	Ever	0.99	0.59 - 1.67	X	X	X		X		X	X		X		Glucose
Folsom, 1995[55] Good	41,000	Cohort	HRT	Current Past	0.82 **0.57**	0.47 - 1.43 **0.38 - 0.85**	X	X	X					X	X		X	Waist/hip, marital status
Grodstein, 1996[8]	3637 cases	Nested CC	HRT	Current Past	**0.47** 0.99	**0.32 - 0.69** 0.75 - 1.30	X	X	X	X	X		X	X				
Cauley, 1997[50] Good	9704	Cohort	HRT	Current Past	**0.49** 0.82	**0.26 - 0.93** 0.55 - 1.23	X	X	X				X	X	X	X	X	Surgical menopause, clinic, stroke, health
Sourander, 1998[51] Fair	7944	Cohort	HRT	Current Past	**0.19** 0.64	**0.05 - 0.77** 0.27 - 1.47	X	X	X				X	X		X		CAD, CHF

Table 8. Coronary heart disease mortality and hormone replacement therapy by duration

Study, year	Design	Duration (years)	RR	95% Confidence Intervals
Criqui, 1988[54]	Cohort	≤8 (on-off)¶	1.24	0.55 - 2.78
		8 (off-on)¶¶	2.62	0.59 - 11.61
		>8	0.36	0.04 - 3.02
Folsom, 1995[55]	Cohort	≤5	0.57	0.18 - 1.75
		>5	0.90	0.47 - 1.72
Cauley, 1997[50]	Cohort	1-9	0.97	0.46 - 2.05
		>10	**0.25**	**0.09 - 0.68**

¶ On HRT at first evaluation, off at second

¶¶ Off HRT at first evaluation, on at second

Table 9. Stroke mortality and hormone replacement therapy

Study, year Quality	N	Design Type	Hormone Type	Hormone Exposure Status	RR/OR	95% CI	Age	BP	DM	Family History	Chol	LDL/ HDL	Smok-ing	BMI	Alco-hol	Educ SES	Exer-cise	Other
Bush, 1987[22] Good	2270	cohort	ERT	Ever	0.4	0.01-3.07	X	X				X	X	X		X		
Petitti, 1987[49] Fair	16,638	cohort	ERT	Ever	0.6	0.2-2.2	X	X					X	X	X	X		Marital status
Finucane, 1993[56] Good	1910	cohort	HRT	Ever	0.86	0.28-2.66	X	X	X				X	X		X		
Folsom, 1995[55] Good	41,070	cohort	HRT	Current Past	0.95 0.88	0.37-2.43 0.48-1.61	X	X	X				X	X	X		X	
Cauley, 1997[50] Good	9,704	cohort	HRT	Current Past	0.47 0.85	0.20-1.08 0.48-1.49	X	X	X				X	X	X	X	X	Surgical menopause, health status, clinic, stroke
Grodstein, 2000[58] Good	70,533	cohort	HRT	Current	0.81	0.54-1.22	X	X	X	X	X		X	X				
			ERT CHRT	Current Current	0.81 1.22	0.49-1.34 0.65-2.28												
Sourander, 1998[51] Fair	7944	cohort	HRT	Current Past	0.16 1.05	0.02-1.18 0.41-2.68	X	X	X				X	X X		X X		CAD CHF
Fung, 1999[57] Fair	1031	cohort	HRT	Current	0.92	0.34-2.49	X	X	X				X			X		

Table 10. Summary of stroke and hormone replacement therapy by duration

Study, year	Design Type	HRT Duration (years)	Outcome	RR/OR	95% CI
Folsom, 1995[55]	Cohort	≤ 5	Stroke mortality	2.08	0.74-5.82
		>5		1.05	0.41-2.64
Cauley, 1997[50]	Cohort	1-9	Stroke mortality	0.66	0.20-2.20
		≥10		0.38	0.13-1.10
Petitti, 1998[71]	CC	<1	Stroke incidence	0.75	0.23-2.42
		1-4		0.67	0.26-1.73
		5-9		0.69	0.28-1.72
		≥10		1.37	0.79-2.38
Grodstein, 2000[58]	Cohort	<1	Stroke incidence	1.32	0.76-2.32
		1-1.9		1.04	0.55-1.97
		2-4.9		1.14	0.86-1.52
		5-9.9		1.05	0.79-1.38
		≥10		1.17	0.91-1.49

Table 11. Cardiovascular disease incidence and hormone replacement therapy

Study (Year) Quality	N	Design	Hormone Type	Hormone Exposure Status	RR	95% Confidence Intervals	Age	BP	DM	Family History	Chol	LDL/ HDL	Smok-ing	BMI	Alco-hol	Educ SES	Exer-cise	Other
Wilson, 1985[11] Fair	1234	Cohort	HRT	Ever	**1.76**	**P<.01**	X	X			X	X	X	X	X			
Thompson, 1989[59] Good	603	CC	HRT ERT CHRT	Ever Ever Ever	1.29 1.09 1.16	0.82-2.00 0.65-1.82 0.43-3.12	X	X	X	X			X					Marital status, MI, stroke, DVT
Hemminki, 1997[60] Good		Meta-analysis	HRT	Short-term	1.39	0.48-3.95												
Sourander, 1998[51] Fair	7944	Cohort	HRT	Current Past	1.07 1.11	0.86-1.32 0.89-1.39	X	X	X				X	X		X		Glucose

Table 12. Coronary disease incidence and hormone replacement therapy

Study, year	N	Design Type	Hormone Type	Hormone Exposure Status	RR/OR	95% CI	Age	BP	DM	Family History	Chol.	LDL/HDL	Smoking	BMI	Alcohol	Educ. SES	Exercise	Other
Pfeffer, 1978[64]	274	CC	HRT	Ever	0.86	0.54-1.37	X	X										
			HRT	Current	0.68	0.32-1.42	X	X										
Nachtigall, 1979[61]	168	RCT	CHRT	10 years	0.33	NS	X											
Wilson, 1985[11]	1234	Cohort	HRT	Ever	**1.9**	**P<.01**	X	X			X	X	X	X	X			
Croft, 1989[65]	158	CC	HRT	Ever	0.8	0.3-1.8	X						X			X		OCP use, hysterectomy
Beard, 1989[66]	133	CC	HRT	Ever	0.55	0.24-1.30	X	X	X				X					Menopausal status,type,year
Hernandez-Avila, 1990[62]	120	Nested case control from cohort study	HRT	Current	0.7	0.4-1.4	X	X	X									Drug treated anti-arhythmic therapy
Rosenberg, 1993[67]	858	CC	ERT	Ever	0.9	0.7-1.2	X	X	X		X		X	X	X	X	X	Coffee, angina,
			CHRT	Ever	1.2	0.6-2.4	X	X	X		X		X	X	X	X	X	MI<60, age/type
			ERT	Past	0.9	0.7-1.3	X	X	X		X		X	X	X	X	X	menopause,
			ERT	Recent	0.8	0.4-1.3	X	X	X		X		X	X	X	X	X	physician visits
Mann, 1994[68]	1521	CC	HRT	Recent	0.83	0.66-1.03	X	X	X		X							Hysterectomy, surgical menopause
			CHRT		**0.68**	**0.47-0.97**	X	X	X		X							
			ERT		0.93	0.47-1.86	X	X	X		X							
Grodstein, 1996[8]	59,337	Cohort	ERT	Current	**0.6**	**0.43-0.83**	X	X	X	X	X		X	X				OCP use, parity, menarche
			CHRT	Current	**0.39**	**0.19-0.78**	X	X	X	X	X		X	X				
			HRT	Current	**0.6**	**0.47-0.76**	X	X	X	X	X		X	X				
			HRT	Past	0.85	0.71-1.01	X	X	X	X	X		X	X				
Heckbert, 1997[69]	850	CC	HRT	Ever	**0.72**	**0.59-0.88**	X		X				X					Year, angina
			HRT	Current	**0.7**	**0.55-0.89**	X		X				X					
			HRT	Past	**0.74**	**0.57-0.96**	X		X				X					
Sidney, 1997[12]	438	CC	HRT	Current	0.96	0.66-1.40	X	X	X				X		X	X	X	HO, CAD, race,
			HRT	Past	1.07	0.72-1.58	X	X	X				X		X	X	X	facility
Sourander, 1998[51]	7944	Cohort	HRT	Current	1.05	0.76-1.46	X	X	X				X			X	X	
				Past	1.21	0.88-1.71	X	X	X				X			X	X	
Eaker[¶]	1234	Cohort	HRT	Ever	50-59:0.4	P>0.05	X	X	X		X	X	X	X			X	CAD, CHF
					60-69:2.2	P>0.05	X	X	X		X	X	X	X			X	

[¶] Reanalysis of Framingham data excluding angina adapted by Stampfer (Stampfer 1991[9])

Table 13a. Summary of total stroke incidence and hormone replacement therapy

Study, Year Quality	N	Design Type	Hormone Type	Hormone Exposure Status	RR/OR	95% CI	Age	BP	DM	Family History	Cholesterol	LDL/HDL	Smoking	BMI	Alcohol	Education SES	Exercise	Other
Pfeffer 1978[64] Fair	258 cases	CC	HRT	Ever	0.97 TIA 2.79	0.65-1.44 0.67-11.62	X	X	X									
Wilson 1985[11] Good	1234	cohort	HRT	Ever	**2.27**	**p<0.01**	X	X			X	X	X	X	X			
Thompson 1989[59] Good	244 cases	CC	HRT	Ever	1.2	p>0.02	X	X	X	X	X							Marital status, clot, stroke, MI
Finucane 1993[56] Good	1910	cohort	HRT	Ever	0.82	0.46-1.47	X	X	X				X	X		X		MI
Grodstein 2000[58] Good	70,533	cohort	ERT	Current	1.24	0.95-1.46	X	X	X	X	X	X	X	X	X			OCP use, parity, menarche
			CHRT	Current	**1.54**	**1.12-2.11**												
			HRT	Current Past	1.13 1.02	0.94-1.35 0.85-1.24												
Pedersen 1997[72] Good	1422 cases	CC	ERT	Current	1.24	0.91-1.70	X	X	X				X	X		X	X	CAD, CHF
				Past	1.12	0.88-1.42												
			CHRT	Current	1.27	1.00-1.62												
			ERT	Current	**TIA 2.13**	**1.41-3.22**												
				Past	**TIA 1.83**	**1.33-2.51**												
			CHRT	Current	TIA 1.20	0.81-1.76												
Petitti 1998[71] Fair	349 cases	CC	HRT	Current	1.03	0.65-1.65	X	X	X				X	X		X		Stroke
				Past	0.84	0.54-1.32												
Sourander 1998[51] Fair	7944	cohort	HRT	Current	0.86	0.42-1.75	X	X	X				X	X		X		CAD, CHF
				Past	1.08	0.55-2.10												
Fung, 1999[57] Fair	1031	cohort	HRT	Ever	stroke/TIA 4.43	0.83-23.58	X	X	X				X	X		X		

TIA - Transient Ischemic Attack

Table 13b. Summary of ischemic stroke incidence and hormone replacement therapy

Study Year Quality	N	Design Type	Hormone Type	Hormone Exposure Status	RR/ OR	95% CI	Age	BP	DM	Family History	Choles-terol	LDL/ HDL	Smok-ing	BMI	Alco-hol	Educ SES	Exer-cise	Other
Pfeffer 1978[64] Fair	258 cases	CC	HRT	Ever	NES 1.13 ES 0.49	0.71-1.77 0.00-5.38	X	X	X									
Wilson 1985[11] Good	1234	cohort	HRT	Ever	**2.6**	**p<0.01**	X	X			X	X	X	X	X			
Grodstein 2000[58] Good	70,533	cohort	HRT	Current	**1.26**	**1.00-1.61**	X	X	X	X	X	X	X	X	X			OCP use, parity, menarche
			HRT	Past	1.01	0.79-1.30												
Pedersen 1997[72] Good	1422 cases	CC	ERT	Current	1.24	0.91-1.70	X	X	X				X	X		X	X	CAD, CHF
				Past	1.12	0.88-1.42												
			CHRT	Current	1.27	1.00-1.62												

Ischemic Stroke includes: nonembolic and embolic stroke (NES/ES), thromboembolic stroke and atherothrombotic stroke

Table 13c. Subarachnoid hemorrhage and hormone replacement therapy

Study, Year Quality	N	Design Type	Hormone Type	Hormone Exposure Status	RR/OR	95% CI
Longstreth 1994[74] Fair	103 cases	CC	HRT	Ever	**0.47**	**0.26-0.86**
				Current	**0.38**	**0.17-0.84**
				Past	0.58	0.28-1.21
Grodstein 199[69] Good	59,337	cohort	ERT	Current	1.35	nr
			HRT	Current	0.90	0.57-1.41
			HRT	Past	0.81	0.52-1.25
Pedersen 1997[72] Good	1422 cases	CC	ERT	Current	0.53	0.23-1.25
			ERT	Past	0.78	0.46-1.30
			CHRT	Current	1.30	0.84-2.02

nr - not reported

Table 13d. Intracerebral hemorrhage and hormone replacement therapy

Study Year Quality	N	Design Type	Hormone Type	Hormone Exposure Status	RR/OR	95% CI
Pfeffer 1978[64] Fair	258 cases	CC	HRT	Ever	0.86	0.00-9.19 x 10^3
Grodstein 1996[8] Good	59,337	cohort	CHRT	Current	0.53	nr
Thrift 1996[77] Fair	331 cases	CC	HRT	Ever	**0.36**	**0.14-0.95**
Pedersen 1997[72] Good	1422 cases	CC	ERT	Current	0.18	0.02-1.27
			ERT	Past	1.09	0.58-2.03
			CHRT	Current	1.22	0.66-2.23
Petitti 1998[71] Fair	349 cases	CC	HRT	Ever	**0.33**	**0.12-0.96**

nr - not reported

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention

Author, Journal, Date	Setting, Study Population Date	Measurement of Hormone Exposure, Co-morbidity, Other Risk Factors	Type Controls	Outcomes Evaluated, Documentation	FU Length Loss to FU
Byrd BF, Jr., Burch JC, Vaughn WK. The impact of long term estrogen support after hysterectomy. A report of 1016 cases. *Ann Surg.* 1977;185(5):574-580.	1016 with hysterectomy ages 22-78 and placed on estrogen who used over 3 years. Caucasian females from middle TN.	Medical records		Death cert.	100% FU
McMahon B. *Cardiovascular disease and non-contraceptive oestrogen therapy.* Edinburgh, Scotland: Churchill Livingstone; 1978.	Use data of Hoover and Gray, 1977				Average 12 years
Hammond CB, Jelovsek FR, Lee KL, Creasman WT, Parker RT. Effects of long-term estrogen replacement therapy. I. Metabolic effects. *Am J Obstet Gynecol.* 1979;133(5):525-536.	Duke University cohort of hypoestrogenic women diagnosed 1940-1969. Only followed if returned for FU for 5 years and must have been seen after Jan. 1, 1974 2 groups: no HRT: n = 309 yes HRT: n = 301			Medical record review	5 years at least.

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Study	Assessment of CVD risk factors	RR CVD Among Users Compared to Non-Users	RR by Duration HRT	RR CVD Associated With Current Use and By Duration	RR CVD Associated With Pass Use and By Duration	CVD Mortality RR Among Users Compared to Non-Users	Comments
Byrd BF, Jr., Burch JC, Vaughn WK. The impact of long term estrogen support after hysterectomy. A report of 1016 cases. *Ann Surg.* 1977;185(5):574-580.	No adjustment					Heart dis SMR 0/E 13/35 SMR 0/E – CVA 8/15	Premarin 1.25 mg/day No adj. for confounding Poor generalizability Quality: poor
McMahon B. *Cardiovascular disease and non-contraceptive oestrogen therapy.* Edinburgh, Scotland: Churchill Livingstone; 1978.	No adj.		CVD Mortality use/non use: < 5 yr: 0 deaths > 15 yr: 0.8 NS Stroke Mortality: >15 y: 1.7 NS		All cause: 40% expected CVD: RR 0.4 Stroke: RR 0.8		Highest risk stroke in women taking higher doses E. Quality: poor
Hammond CB, Jelovsek FR, Lee KL, Creasman WT, Parker RT. Effects of long-term estrogen replacement therapy. I. Metabolic effects. *Am J Obstet Gynecol.* 1979;133(5):525-536.	Adj. for age, race, duration FU: **37 events CVD in NoE** **7 events CVD in E** **p<.001**						Poor generalizability Survivors not clear how outcome defined. Quality: poor

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Author, Journal, Date	Setting, Study Population Date	Measurement of Hormone Exposure, Co-morbidity, Other Risk Factors	Type Controls	Outcomes Evaluated, Documentation	FU Length Loss to FU
Wilson, 1985[11]	Framingham Age >50 and post-menopausal Patients included if they participated in 12th biennial survey n=1234	Biennial exam only includes information on HRT use at baseline Almost all conjugated estrogen Progestin use rare (>5%) HRT use classified as ever use if reported in any 8-12 biennial exams. Duration assessed, dose not assessed Overall rate use 24%	Internal	Physician review of notes and death certificates <u>Coronary heart disease</u> includes: Angina, MI, SCD and coronary death <u>Cerebrovascular disease (CVD)</u> includes: 1st CVA or TIA <u>Cardiovascular disease (CVD)</u> includes: CHD, CVA, Claudication & CHF	8 years
Henderson BE, Ross RK, Paganini-Hill A, Mack TM. Estrogen use and cardiovascular disease. *Am J Obstet Gynecol.* 1986;154(6):1181-1186.	Leisure world retirement community, 1981. White, affluent, well educated. After 3 mailings 62% returned questionnaires. N = 7610 Mean age 74	Detailed mailed health questionnaire all hospital admissions evaluated. Biannual remailings. Hormone use = ever/never,	Internal	435 deaths all cause acute MI. Death certificates used to code deaths	

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Study	Assessment of CVD risk factors	RR CVD Among Users Compared to Non-Users	RR by Duration HRT	RR CVD Associated With Current Use and By Duration	RR CVD Associated With Pass Use and By Duration	CVD Mortality RR Among Users Compared to Non-Users	Comments
Wilson, 1985[11]	Adj for Cholesterol, BMI, smoking BP, age, and alcohol Not Adj for DM FMH	Total CVD **1.76, *P* < 0.01** Cerebrovascular **2.27 (*P* <0.01)** CHD **1.9 (*P* <0.1)** CHF 1.15				Death total CVD 1.94 (NS) Death cancer 0.7 (p=NS) Death all causes 0.97 (NS)	Throughout the study (exams 1-7) age adjusted, wt, and cholesterol lower in women who later reported ERT use. Evaluated confounding by surgical menopause and no relationship + interaction with smoking. 35% MI's unrecognized (by ECG) Quality: good
Henderson BE, Ross RK, Paganini-Hill A, Mack TM. Estrogen use and cardiovascular disease. *Am J Obstet Gynecol.* 1986;154(6):1181-1186.	No adj. except age					All cause: 0.84(p = .06) MI: 0.54(p = .07)	Dose/duration not eval No. adj. confounding Definitions use unclear Definition MI unclear Poor generalizability Quality: poor

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Author, Journal, Date	Setting, Study Population Date	Measurement of Hormone Exposure, Co-morbidity, Other Risk Factors	Type Controls	Outcomes Evaluated, Documentation	FU Length Loss to FU
Bush, 1987[22]	2270 white women ages 40-69 in Lipid Research Clinics Prevalence Study recruited. 1972-1976, n=2270, 593 used, 1677 non-use	Lab, questionnaire, EKG exam, ETT, obtained at 2nd visit (current users)	Internal	44 deaths Death certificates, Medical record review. Interview next of kin.	
Eaker, 1987[63] *Re-analysis of Framingham study excluding angina – adapted from Stampfer	Reanalysis of Framingham as above excluding angina	Biennial exam only includes information on HRT use at baseline Almost all conjugated estrogen Progestin use rare (>5%) HRT use classified as ever use if reported in any 8-12 biennial exams. Duration assessed, dose not assessed Overall rate use 24%	Internal	Coronary heart disease - no angina	8 years

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Study	Assessment of CVD risk factors	RR CVD Among Users Compared to Non-Users	RR by Duration HRT	RR CVD Associated With Current Use and By Duration	RR CVD Associated With Pass Use and By Duration	CVD Mortality RR Among Users Compared to Non-Users	Comments
Bush, 1987[22]	Adj for: Age, HTN, Tobacco, education, BMI, LDL Not adj: DM, exercise, FMH, alcohol	Age adj. Current 0.34(0.12-0.81) among all cox model B= -0.47 P= 0.29 Stroke 0.40(0.01-3.07)				All cause: Age adj. **0.54(0.29-0.79)** SMR of non-users 67 sug "healthy participant effect"	E use only evaluated at one time. Adding HDL/LDL to model B from – 0.82 to – 0.47 Users/non-users similar in CVD disease prevalence. Very important paper in suggesting much, though not all decreased risk due to Inc HDL. Quality: good
Eaker, 1987[63]		Ages 50-59: 0.4 p>.05 Ages 60-69: 2.2 p>.05					Excludes angina as endpoint Quality: good

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Author, Journal, Date	Setting, Study Population Date	Measurement of Hormone Exposure, Co-morbidity, Other Risk Factors	Type Controls	Outcomes Evaluated, Documentation	FU Length Loss to FU
Pettiti, 1987[49]	12/68 - 2/72 16,638 women 18-54 Walnut Creek California N= 6093	Complete multiphasic examination through 1977 contacted yearly or returned for exam. Classified: ever/never	Internal	Deaths, NDI, death certificates	1983
Criqui, 1988[54]	1868 50-79 women residing in planned community, California 1972. White, upper-middle class 39.9% used HRT	Interview, exam, lab 1972; Re-eval 1981 and these women followed. Current use, non-use	Internal	Vital status, death certificates reviewed by nosologist coded ICD. Compared 3 year subsequent mortality among 9 year survivors.	12 99.8% complete

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Study	Assessment of CVD risk factors	RR CVD Among Users Compared to Non-Users	RR by Duration HRT	RR CVD Associated With Current Use and By Duration	RR CVD Associated With Pass Use and By Duration	CVD Mortality RR Among Users Compared to Non-Users	Comments
Pettiti, 1987[49]	DM Lipids FMH					All diseases of circulatory systems (adj) 0.6 (0.3 – 1.1) Multivariate adj Ischemic heart disease (age – adj) 1.3 (0.2 – 7.7) Acute MI (age-adj) 0.3 (0.1 – 1.3) All cerebrovascular disease (age-adj) 0.6 (0.2 – 2.2)	Overall mortality in users from accidents, homicide, suicide was lower (RR 0.8) Almost all ERT No information on occupation or income but differences persisted after adj. edu/marital. FU through 83 but no data on HRT past 77 Quality: fair (misclassification potential problem)
Criqui, 1988[54]	Adj. for BMI Chol GWC BP Age Social class Not adj. for Family history Exercise Alcohol		**Mortality by duration** < 8 y use (on-off) all: 0.88(0.56-1.36) CVD: 1.20 (0.62 –2.35) CHD: 1.24 (0.55-2.78) < 8 y use (off-on) all: 1.58(0.68-3.65) CVD: 1.55(0.32-6.62) CHD: 2.62(0.59-11.61) ≥ 8 y use all: 0.35(0.1-1.22) CVD: 0.40(0.05-3.19) CHD: 0.36(0.04-3.02)			Age adj All cause **0.69(0.55-0.87)** CVD 0.81(0.61-1.08) CHD 0.75(0.45-1.24) Multivar adj. All cause: 0.79(0.62-1.01) CVD: 0.96(0.65-1.43) CHD: 0.99(0.59-1.67) CVD mortality not decreased in women who never smoked	Relied on death certificate review Definitions CVD, CHD not provided 70% women discontinued estrogen Interaction with tobacco highly significant Never/current users: lower risk Past users: higher risk Quality: fair

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Author, Journal, Date	Setting, Study Population Date	Measurement of Hormone Exposure, Co-morbidity, Other Risk Factors	Type Controls	Outcomes Evaluated, Documentation	FU Length Loss to FU
Hernandez-Avila, 1990[62] see Evidence Table 2 case-control	All female members group health Seattle, ages 50 – 64 1978-1984	Pharmacy and medical records. Current users for 12 mos. after filling prescription year, dose, duration evaluated	Internal Also preformed nested case control study to control for confounding N=721 controls	First MI N=120	1978-1983
Hunt K, Vessey M, McPherson K. Mortality in a cohort of long-term users of hormone replacement therapy: an updated analysis. *Br J Obstet Gynaecol.* 1990;97(12):1080-1086.	4544 long term HRT users (≥ 1 year) England & Wales recruited from menopause clinics ages 45-54	Interview, exam, detailed HRT history	External	All cause, CVD, mortality. Deaths coded using ICD codes.	1988

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Study	Assessment of CVD risk factors	RR CVD Among Users Compared to Non-Users	RR by Duration HRT	RR CVD Associated With Current Use and By Duration	RR CVD Associated With Pass Use and By Duration	CVD Mortality RR Among Users Compared to Non-Users	Comments
Hernandez-Avila, 1990[62] see Evidence Table 2 case-control	Not adj: BMI Smoking Lipids	Age/calendar year adj. Current/non 0.7(0.4-1.3) CCS analysis current: 0.7(0.4-1.4) past: 0.6(0.12.1)	First MI duration > 1 year 0.7(0.3-1.3)				Drug prescriptions used as markers for risk factors. Survivors (made it to hospital) No evaluation for type of menopause. Quality: fair – poor control of confounding
Hunt K, Vessey M, McPherson K. Mortality in a cohort of long-term users of hormone replacement therapy: an updated analysis. *Br J Obstet Gynaecol.* 1990;97(12):1080-1086.	No adj.					SMR All cause: **0.56(0.47 – 0.66)** Ischemic heart dis: **0.41(0.20 – 0.61)** All CVD **0.44(0.28 – 0.59)** Stroke **0.54(0.24 – 0.84)**	Not generalizable. Tended to be of higher social class. Mean duration use 66.9 months No definition IHD Quality: poor

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Author, Journal, Date	Setting, Study Population Date	Measurement of Hormone Exposure, Co-morbidity, Other Risk Factors	Type Controls	Outcomes Evaluated, Documentation	FU Length Loss to FU
Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. *Arch Intern Med.* 1991;151(1):75-78.	Leisure world retirement community. 8881 women returned health questionnaire. Mean age 73.	Mailed health questionnaire. Estrogen use: ever/never	Internal	Death Death certificates obtained Follow-up mailings '83, '85. 1477 deaths	Dec. 88 56,020 py
Wolf, 1991[52]	National sample n=1944 White post-menopausal women $\geq$ 55 from epidemiologic follow up of NHANE"s I 1971-1975. Mean age 66	Baseline exam, lab Categorized as ever never	Internal	631 deaths. Outcomes CVD death. Death certificate review ICD, codes, underlying cause. Hospital, medical record review, vital status ascertained 82-84, 86, 87	16 years

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Study	Assessment of CVD risk factors	RR CVD Among Users Compared to Non-Users	RR by Duration HRT	RR CVD Associated With Current Use and By Duration	RR CVD Associated With Pass Use and By Duration	CVD Mortality RR Among Users Compared to Non-Users	Comments
Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. *Arch Intern Med.* 1991;151(1) :75-78.	Adj. for: BP History angina/MI Smoking Alcohol BMI Exercise Age menopause Not Adj. Lipids DM Family hst.					Multivar adj. use/non All cause: **0.79(0.71-0.88)** Only age adjusted; use/non Acute MI: **0.60 p< .001** Ischemic HD: 0.79 p Other heart Dis: 0.68 NS Occlusive Stroke/age 0.63 NS	Mean duration use 10 years >50% used HRT Quality: poor – no adjustment for CVD RF/confounding in CVD analyses.
Wolf, 1991[52]	Adj for: HTN DM BMI Tos CHOL MI Age Age men. Education					Multivar (CVD) ever/never **0.66(0.48-0.90)** natural menopause 0.69(0.45-1.06) surgical menopause 0.80(0.39-1.67)	

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Author, Journal, Date	Setting, Study Population Date	Measurement of Hormone Exposure, Co-morbidity, Other Risk Factors	Type Controls	Outcomes Evaluated, Documentation	FU Length Loss to FU
Falkeborn, 1992[76]	Population based prospective study of 23,247 who had at least 1 prescription for estrogen 1977-1980 in Uppsala, Sweden	Random sample of 735 provided data on confounders	External; Population rates used	1st MI	133,372 p-y Average observation time per persons 5.8 years.
Lafferty FW, Fiske ME. Postmenopausal estrogen replacement: a long-term cohort study. *Am J Med.* 1994;97(1):66-77.	Non-random prospective 1964 – 1983 All post-menopausal women 43-60 from private practice offered ERT candidates: healthy, white normal exam, EKG, labs 76 declined ERT 96 used ERT 58 ineligible	0.625 – 1.25 mg premarin all 1964-1983 no progesterone used 1983 on the remaining 24 women with uterus received progesterone days 14-25 of every 6th months <u>Follow-up</u> Annual PE, labs, EKG	76 women with same eligibility declined HRT	Prospective: biennial exams, labs EKG Outcome: MI, EKG changes	Followed until 1989

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Study	Assessment of CVD risk factors	RR CVD Among Users Compared to Non-Users	RR by Duration HRT	RR CVD Associated With Current Use and By Duration	RR CVD Associated With Pass Use and By Duration	CVD Mortality RR Among Users Compared to Non-Users	Comments
Falkeborn, 1992[76]	Not adj for DM HTN Lipids FMH Exercise BMI SES Only age adjusted	Univariate ERT SIR: 0.81 (0.71 – 0.92) Univariate CHRT SIR: 0.50 (0.28 – 0.80) Multivariate SIR (conjugated or estradiol) ERT: 0.73 (0.59 – 0.90) Multivar SIR all ERT (0.88 (0.64-1.19)					
Lafferty FW, Fiske ME. Postmenopausal estrogen replacement: a long-term cohort study. *Am J Med.* 1994;97(1):66-77.	No adjustment	Age-adjusted RR user/non-users Ischemic changes on EKG 0.84 (0.39 – 1.03) MI 0.34 (0.09 – 1.34) CVA (no strokes in ERT cohort) $p \leq 0.025$					Small numbers Poor design Non-random Non-population based Not generalizable RR estimate without adjustment for confounders Unconventional progesterone use Quality: poor, bias

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Author, Journal, Date	Setting, Study Population Date	Measurement of Hormone Exposure, Co-morbidity, Other Risk Factors	Type Controls	Outcomes Evaluated, Documentation	FU Length Loss to FU
Sturgeon, 1995[92]	Cohort of 49,000 women followed 1979-1989 in BCDDP follow-up study menopausal	Baseline questionnaire up to 6 annual follow-up interviews Use, duration, repeated measures	Internal	Death- Vital status evaluated by phone interview, tracing by mail death certificates obtained/reviewed underlying cause death code	

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Study	Assessment of CVD risk factors	RR CVD Among Users Compared to Non-Users	RR by Duration HRT	RR CVD Associated With Current Use and By Duration	RR CVD Associated With Pass Use and By Duration	CVD Mortality RR Among Users Compared to Non-Users	Comments
Sturgeon, 1995[92]	Only age adjusted	< 5yr use CVD 0.9 CHD 1.0 Stroke 0.8 Mortality stroke Current/never:0.4 (0.2-1.0) 2-3.9 years since use:3.3 (1.9-5.8) Mortality CHD Current/never: **0.3 (0.2-0.5)** 2-3.9 yrs since last use 0.9 (0.5-1.9)	>5 yr use CVD 0.8 CHD 0.8 Stroke 1.1			Ever/never **CVD:0.7(0.6-0.8)** **CHD 0.7(0.6-0.9)** Stoke 1.0(0.7-1.4)	Current use all cause mortality **0.3 (0.2-0.4)** All cause mortality **(0.7 (0.7-0.8)** Women recently stop HRT have all cause mortality 1.4 (1.2-1.7) (stopped 2-3 years prior Women stopping more distant past similar to non-users Quality: Poor

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Author, Journal, Date	Setting, Study Population Date	Measurement of Hormone Exposure, Co-morbidity, Other Risk Factors	Type Controls	Outcomes Evaluated, Documentation	FU Length Loss to FU
Folsom, 1995[55]	Iowa 41,837 ages 55-69 analyses restricted to post-menopausal with information on HRT n=41,070	Mailed questionnaire anthopometric measure used, HRT use categorized as current, former, never and duration	Internal	Coronary disease, mortality, stroke	6 years

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Study	Assessment of CVD risk factors	RR CVD Among Users Compared to Non-Users	RR by Duration HRT	RR CVD Associated With Current Use and By Duration	RR CVD Associated With Pass Use and By Duration	CVD Mortality RR Among Users Compared to Non-Users	Comments
Folsom, 1995[55]	Excellent control of confounders					CHD Mortality Former/never: **0.57 (0.38 – 0.85)** Current: 0.82 (0.47 – 1.43) <5 yrs: 0.57 (0.18 – 1.75) >5 yrs: 0.90 (0.47 – 1.72) Stroke Former 0.88 (0.48 – 1.61) Current 0.95 (0.37 – 2.43) <5 yrs: 2.08 (0.74 – 5.82) >5 yrs: 1.05 (0.41 – 2.64)	No data on prog use All Cause mortality: RR 0.95(0.76–1.19) Quality: good

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Author, Journal, Date	Setting, Study Population Date	Measurement of Hormone Exposure, Co-morbidity, Other Risk Factors	Type Controls	Outcomes Evaluated, Documentation	FU Length Loss to FU
Ettinger, 1996[84]	Kaiser-women identified 1969-1973 who had used HRT ≥5yrs and women with ≤1 yr use Date menopause known for ERT begun within 3 yrs. of menopause exclusions (many) n=232 ERT users Non-users age matched and not used E >1yr. n=222	Prescription filled known date menopause Medical records reviewed	Same cohort age matched had filled prescription for ERT but not used >1yr. n=222 13% had used estrogen	Deaths 68% validated CHD CVD	

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Study	Assessment of CVD risk factors	RR CVD Among Users Compared to Non-Users	RR by Duration HRT	RR CVD Associated With Current Use and By Duration	RR CVD Associated With Pass Use and By Duration	CVD Mortality RR Among Users Compared to Non-Users	Comments
Ettinger, 1996[84]	Adj. for Age, tob, BMI, alcohol TC, EKG					Coronary disease 0.40 (0.16 – 1.02) Cardiovascular disease **0.27 (0.10 – 0.71)** All cause **0.54 (0.38 – 0.76)**	5.6% ever use progesterone. Mean ERT 0.9 mg. then 0.5 mg. Biased cohort. Fair control of confounding Quality: poor

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Author, Journal, Date	Setting, Study Population Date	Measurement of Hormone Exposure, Co-morbidity, Other Risk Factors	Type Controls	Outcomes Evaluated, Documentation	FU Length Loss to FU
Grodstein, 1996[8]	Nurses Health Study began 1976 n=59,337 post-menopausal	Mailed questionnaire with biennial follow-up 1976 – HRT use assessed 1978 – Type HRT 1980 – Dose, menopause classified	Internal	CVD - Who criteria 1. Non-fatal MI 2. Fatal CHD 3. CABG/PTCA 4. CVA Medical records reviewed when possible NDI also used 584 non-fatal MI 186 CHD deaths 572 CVA's 553 PTCA/CABG Maj. CHD = non fatal + fatal MI	

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Study	Assessment of CVD risk factors	RR CVD Among Users Compared to Non-Users	RR by Duration HRT	RR CVD Associated With Current Use and By Duration	RR CVD Associated With Pass Use and By Duration	CVD Mortality RR Among Users Compared to Non-Users	Comments
Grodstein, 1996[8]	Age, HTN, FMH, Chol, Age men., DM and BMI	Time since last use <3 yrs. 0.69 (0.48 – 1.0) 3-4.9 yrs. 0.81 (0.5 – 1.2) ***p* trend ≤0.05**	Major Coronary dis <2 yrs HRT current 0.53 (0.31 – 0.93) >10yrs HRT current 0.70 (0.47 – 1.04) Stroke ≥10yrs 1.01 (0.69 – 1.46)	Major CHD (adj) ERT 0.60 **(0.43-0.83)** CHRT 0.39 **(0.19–0.78)** HRT 0.60**(0.47-0.76)** Stroke (adj) ERT 1.27 (0.95-1.69) CHRT 1.09 (0.66-1.8) HRT 1.03(0.82-1.31) Ischemic Stroke (adj) ERT 1.63 (1.10-2.39) CHRT 1.42 (0.73-2.75) HRT 1.40(1.02-1.92) Subarachnoid ERT 1.35 CHRT 0.53 HRT 0.90(0.57-1.41) CABG/PTCA HRT 0.99	Multivar adj major CHD 0.85 (0.71-1.01) Stroke 0.99(0.80-1.22)		**Coronary heart disease by dose** 0.3 ERT RR 0.57 *0.625 E RR 0.53 1.25 E RR 0.82 >1.25 RR 0.92 trend 0.22 Stroke 0.3 0.64 0.625 1.24 1.25 1.44 >1.25 1.86 **p tend 0.047** No significant interaction No change RR with # visits Silent MI excluded. Current Users: Decrease FMH, TOB and DM, Increase MVI, ASA, ETOH, Vitamin E and leaner Quality: good

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Author, Journal, Date	Setting, Study Population Date	Measurement of Hormone Exposure, Co-morbidity, Other Risk Factors	Type Controls	Outcomes Evaluated, Documentation	FU Length Loss to FU
Sourander, 1998[51]	7944 women ages 57-64 who participated in mam screening program Turku, Finland 1987-1988	Biennial questionnaire linked hospital data, death registry Trained nurses helped with questionnaire baseline +3 for most Exposure = never, ever, current, former	Internal	CVD CAD AMI CVA	53,305 person-years

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Study	Assessment of CVD risk factors	RR CVD Among Users Compared to Non-Users	RR by Duration HRT	RR CVD Associated With Current Use and By Duration	RR CVD Associated With Pass Use and By Duration	CVD Mortality RR Among Users Compared to Non-Users	Comments
Sourander, 1998[51]	Not adj. for lipids.. exercise, alcohol	CVD morbidity Former 1.11 (0.89 – 1.39) Current 1.07 (0.86 – 1.32 CAD morbidity Former 1.23 (0.88 – 1.71) Current 1.05 (0.76 – 1.46) Stroke morbidity Former 1.08 (0.55 – 2.10) Current 0.86 (0.42 – 1.75)				CVD Former 0.75 (0.41 – 1.37) Current **0.21 (0.08 – 0.59)** CAD death Former 0.64 (0.27 – 1.47) Current **0.19 (0.05 – 0.77)** CVA death Former 1.05 (0.41 – 2.68) Current 0.16 (0.02 – 1.18)	Mean oral dose 1.46 mg Lipids not in model Adj. for social class Quality: fair

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Author, Journal Date	Setting, Study Population Date	Measurement of Hormone Exposure, Co-morbidity, Other Risk Factors	Type Control	Outcomes Evaluated, Documentation	FU Length Loss to FU
Schairer, 1996[75]	Uppsala Health Care Regiou, Sweden Cohort = all women prescribed HRT 4/77 - 3/80 n=23, 246 women >35 yrs. Mean age 54.5	3 groups 1. Estradiol or CE-more potent 2. Other estrogens 3. combined	External	Mortality	199,810 p-y 1472 deaths

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Study	Assessment of CVD risk factors	RR CVD Among Users Compared to Non-Users	RR by Duration HRT	RR CVD Associated With Current Use and By Duration	RR CVD Associated With Pass Use and By Duration	CVD Mortality RR Among Users Compared to Non-Users	Comments
Schairer, 1996[75]						SMR circulatory disease **0.69 (0.64 – 0.75)** IHD: **0.69 (0.55 – 0.69)** Cerebrovasc: **0.79 (0.67 – 0.91**) IHD: other **0.7 (0.6-0.8)** more potent **0.6 (0.5-0.7)** CHRT 0.4 **(0.2-0.6)** Cerebrovasc: other 0.9 (0.7-1.0) more potent **0.7(0.6-0.9)** CHRT 0.6 (0.3-1.1)	No adj for confounding All cause mortality decreased 23% Compare: Falkeborn 92 incidence rates (lower) - ? selection for low risk Quality: poor

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Author, Journal Date	Setting, Study Population Date	Measurement of Hormone Exposure, Co-morbidity, Other Risk Factors	Type Control	Outcomes Evaluated, Documentation	FU Length Loss to FU
Cauley, 1997[50]	9704 > 65 yrs. Recruited osteoporotic fractures analyses restricted to women with known HRT use	Detailed information collected at baseline interview Updated at 3rd visit 14% currently using oral HRT (of those, 20% CHRT, 88% ERT	External- US Internal- white women	Death - ascertained through study protocol 99% complete Copies of discharge summaries and death certificates obtained	

Evidence Table 1. HRT and CVD: Incidence and Mortality – Cohort Studies of Primary Prevention (continued)

Study	Assessment of CVD risk factors	RR CVD Among Users Compared to Non-Users	RR by Duration HRT	RR CVD Associated With Current Use and By Duration	RR CVD Associated With Pass Use and By Duration	CVD Mortality RR Among Users Compared to Non-Users	Comments
Cauley, 1997[50]	SES				Death- use 1-9 yrs: CVD: 6.78 (0.44 – 1.38) CHD: 0.97 (0.46 – 2.05) CVA: 0.66 (0.2 – 2.2) Death – use > 10 year: CVD: **0.3 (0.16 – 0.57)** CHD: **0.25 (0.09 – 0.68)** CVA: 0.38 (0.13 – 1.10)	Current All CVD deaths **0.46 (0.29 – 0.73)** All CHD deaths **0.49 (0.26 – 0.93)** CVA 0.47 (0.2 – 1.08) Past All CVD: 0.86 (0.65 – 1.15) All CHD: 0.82 (0.55 – 1.23) CVA: 0.85 (0.48 – 1.49)	Women using HRT All cause mortality current **0.69(0.54 - 0.87)** past **0.79(0.66 – 0.95)** Quality: good

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention

Study, Year, Journal	Setting/Study Population Date	Cases	Controls	Exposure Assessment/ Classification	Important Confounders Not adjusted for
Rosenberg L, Armstrong B, Jick H. Myocardial infarction and estrogen therapy in post-menopausal women. N Engl J Med. 1976;294(23):1256-1259.	①US UK New Zealand Canada Germany Italy Israel ② 24 Boston area hospitals	2 sets hospitalized patients Set ① from several countries Set ② from Boston post-menopausal women ages 40-75 n=336 with acute MI	Women without Estrogen related or possible Estrogen related admissions n=2536① n=4194 ② considered controls	Nurse interview	Lipids
Talbott E, Kuller LH, Detre K, Perper J. Biologic and psychosocial risk factors of sudden death from coronary disease in white women. *Am J Cardiol.* 1977;39(6):858-864.	Allegheny County, Penn	All cases sudden death from otheroslerotic heart disease while women ages 25-64 without known heart disease. Identified using coroner's records, death certificates, letters to physicians n=64.	Matched by block age +/- 1-10 yr., n = 64	Family interview, some physician contact	

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Major Findings Multivariable Adjusted Odds Rating (MAOR) 95% CI	Major Findings by Duration Use HRT (MAOR) 95% CI	Time Since Last Use	Time Since Starting Estrogen	Findings by Other Sub-group Analyses (MAOR)	Comments
Rosenberg L, Armstrong B, Jick H. Myocardial infarction and estrogen therapy in post-menopausal women. N Engl J Med. 1976;294(23) :1256-1259.	49% CO HRT users 4.3% CA HRT users 0.97 (0.48 – 1.95) Conjugated estrogen alone 0.85 (0.38 – 1.91)	No difference in duration use				Premarin most commonly used Quality: fair
Talbott E, Kuller LH, Detre K, Perper J. Biologic and psychosocial risk factors of sudden death from coronary disease in white women. *Am J Cardiol.* 1977;39(6):858-864.	3 cases use HRT 8 controls use HRT					Few cases No eval if post menopausal No adj. confounding Exposure collected from case proxy Quality: poor: no evaluation control

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Setting/Study Population Date	Cases	Controls	Exposure Assessment/ Classification	Important Confounders Not adjusted for
Jick H, Dinan B, Rothman KJ. Noncontraceptive estrogens and nonfatal myocardial infarction. JAMA. 1978;239(14):1407-1409.		Non-fatal MI discharged from hospital 1-6/1975 n=107<age 46 47/107 had natural menopause, hysterectomy, tubule laceration, spouse vasectomy n=30 MI 39-46, but only 17 healthy prior to MI Final n=17 healthy menopausal	n=165 ? discharged from hospital – not explicitly stated 86 had natural menopause or she or spouse sterilized n=89 of these 61 apparently healthy	Telephone interview	Adjusted for type of sterilization
Pfeffer[64]	Cohort of 15, 500 living in community 3/64 – 12/74 ages 57-98 No African Americans Southern California Retirement community with centralization of care	Potential cases first MI, history angnia, unattended death of cardiac etiology Cases: n=274 MI=220 Sudden death = 13 Angina = 14	File of all women residents 3:1 ratio	Medical records, necropsy reports, EKG's, laboratory, all reviewed.	Exercise Alcohol

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Major Findings Multivariable Adjusted Odds Rating (MAOR) 95% CI	Major Findings by Duration Use HRT (MAOR) 95% CI	Time Since Last Use	Time Since Starting Estrogen	Findings by Other Sub-group Analyses (MAOR)	Comments
Jick H, Dinan B, Rothman KJ. Noncontraceptive estrogens and nonfatal myocardial infarction. JAMA. 1978;239(14):1407-1409.	Not adjusted (non-fatal MI) RR 7.5 (2.4 – 24)					Duration E use in users ave. 2.6 years in cases and 1.7 years in controls *Non-fatal MI Of the 17 MI's 16 use tobacco Quality; poor, based on poor inclusion criteria, no adjustment, poor characterization of estrogen use.
Pfeffer, 1978[64]	Adjusted For age, DM, HTN Ever use: 0.86 (0.54 – 1.37) Current use: 0.68 (0.32 – 1.42) For severe CAD: adj, age, DM, HTN Ever use: 0.87 (0.57 – 1.34) Current use: 0.78 (0.38 – 1.63)					Mean daily dose 0.408 mg. in cases 0.315 mg. in controls Quality: fair (little assessment of confounding) Mean duration recent use 72 days

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Setting/Study Population Date	Cases	Controls	Exposure Assessment/ Classification	Important Confounders Not adjusted for
Rosenberg L, Slone D, Shapiro S, Kaufman D, Stolley PD, Miettinen OS. Noncontraceptive estrogens and myocardial infarction in young women. *JAMA.* 1980;244(4):339-342.	US Northeast 7/76 – 7/77	Women 30-49 admitted to coronary care units with MI N=477 Median age 45	Women 30-49 admitted to hospitals with diagnosis other than MI from medical, ortho, surg wards. n=1832 Median age 41	Nurse interviews Standard questionnaire	Lipids
Adam S, Williams V, Vessey MP. Cardiovascular disease and hormone replacement treatment: a pilot case-control study. *British Medical Journal Clinical Research Ed.* 1981;282(6272):1277-1278.	Wales, England	248 death certificates Women ages 50-59 during 11/78 with cause of death MI or SAH Exclusions: n=58 see comments n=76 MI n=23 SAH	Controls drawn from practice list of the general practioner submitting names of cases randomly selected by procedure and age	Post-mortem wrote to general practitioners who used hospital records to fill out questionnaire	

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Major Findings Multivariable Adjusted Odds Rating (MAOR)	Major Findings by Duration Use HRT (MAOR)	Time Since Last Use	Time Since Starting Estrogen	Findings by Other Sub-group Analyses (MAOR)	Comments
Rosenberg L, Slone D, Shapiro S, Kaufman D, Stolley PD, Miettinen OS. Noncontraceptive estrogens and myocardial infarction in young women. *JAMA.* 1980;244(4): 339-342.	Unadjusted Recent 1.3 (0.8 – 2.1) Past 1.2 (0.8 – 1.8) Adjusted Recent 1.0 (0.6 – 1.7) Past 1.2 (0.8 – 1.8) No increase in smokers	<1 yr. 1.9 1-2 0.8 3-4 1.1 ≥5 0.6 Non stat sig				Most estrogen used 1.25 mg or less 90% recent, 75% past, used for symptoms of menopause Young women. Quality: good
Adam S, Williams V, Vessey MP. Cardiovascular disease and hormone replacement treatment: a pilot case-control study. *British Medical Journal Clinical Research Ed.* 1981;282(6272):1277-1278.					Mortality No OR given No relationship identified	Cases excluded if MI or SAH terminal event in long-standing chronic disease No blinding so GP's aware CA/C0 status Only 3% using HRT Quality: poor, non-blind ascertainment, many exclusions ? bias

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Setting/Study Population Date	Cases	Controls	Exposure Assessment/ Classification	Important Confounders Not adjusted for
Ross RK, Paganini-Hill A, Mack TM, Arthur M, Henderson BE. Menopausal oestrogen therapy and protection from death from ischaemic heart disease. *Lancet.* 1981;1(8225):858-860.	Retirement community, 1 yr 20,000 white, highly educated High SES 1971	All females whose primary or underlying cause of death was ischemic, dying 1971-1975 < age 80 N=133	Living controls matched by race, age (year), date of entry into the community Selected by resident registry N=124 2nd control set chosen from register of all who had died 71-76 matched on date of death (year) + above n=124 Exclusions: breast, ovary, uterine cancer, fractures, cerebrovascular, peripheral vascular disease	Medical record interview	Only adj. for matching factors.
Szklo M, Tonascia J, Gordis L, Bloom I. Estrogen use and myocardial infarction risk: a case-control study. *Prev Med.* 1984;13(5):510-516.	5 general hospitals Maryland 1971-1972	White females 35-64 admitted with first MI n=39	2 controls per case from same hospital Discharged lists matched by age $\pm$ 2 years and date admission n=45 Patients with old MI excluded. Only post-menopausal CA/CO pairs analyzed Controls with possible estrogen linked diseases excluded	Records abstracted Interviews conducted 3 months – 3 years of index date (similar time for cases/co	DM Lipids BMI Exercise ASA

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Major Findings Multivariable Adjusted Odds Rating (MAOR) 95% CI	Major Findings by Duration Use HRT (MAOR)	Time Since Last Use	Time Since Starting Estrogen	Findings by Other Sub-group Analyses (MAOR)	Comments
Ross RK, Paganini-Hill A, Mack TM, Arthur M, Henderson BE. Menopausal oestrogen therapy and protection from death from ischaemic heart disease. *Lancet.* 1981;1(8225) :858-860.					Mortality Univariate **OR 0.57 *p*< .05** (deceased control) or **0.43 p<.01** (living control) In women with no history of MI, CVA, angio, DM, HTN, RR living (co) 0.43 RR deceased (co) 0.39 When these factors present **OR 0.48 -0. 58**	When using living controls 1.25 conferred same protection Findings similar, when analyzed using only autopsy cases No adjustment for confounding Quality: poor
Szklo M, Tonascia J, Gordis L, Bloom I. Estrogen use and myocardial infarction risk: a case-control study. *Prev Med.* 1984;13(5):5 10-516.	Unadjusted OR Past use 0.83 Adjusted OR Past use 0.61 (0.20 – 1.87) Natural MP (Adjusted OR) Used/never compared with surgical Never = 0.38 (0.08 – 1.71) Used = 0.29 (.04 – 1.94) Surgical MP (Adj) Never = 1.0 Used = 0.37 (0.04 – 3.23)					Unclear how case limited to 1st MI No proxies Long time between interview and event (≤3 yrs.) Hospital controls ? fatal MI excludes Nothing on dose, duration, composition ? Bias Excluded controls with possible exposure to estrogen (gall bladder, gynecologic d/o breast cancer.) Quality: poor

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Setting/Study Population Date	Cases	Controls	Exposure Assessment/ Classification	Important Confounders Not adjusted for
La Vecchia C, Franceschi S, Decarli A, Pampallona S, Tognoni G. Risk factors for myocardial infarction in young women. *Am J Epidemiol.* 1987;125(5):832-843.	Cases derived from women < age 55 admitted to 5 hospitals in Italy with acute MI	156 women under age 55 with MI. 98% participation	Admitted to same hospitals with acute conditions other than CVD, malignant, hormonal, or gynecologic disease Diagnosed within year of index case. N = 251, ages 23-54, mean 47. Many from orthopedics 98% participation.	Trained interviewers, Physicians. Standard questionnaire. Non fatal MI	Adj. for: Region Lipids Tobacco DM HTN BMI OcP Alcohol Education SES
Thompson, 1989[59]	Northwick, UK	Cases from 83 general practices N=603 white women ages 45-69 Cases were fatal or non-fatal stroke or MI using "WHO" criteria 9/81-9/82 retrospectively identified 9/82-1/86 prospectively identified Fatal cases less represented in first group 244 CVA's 359 MI's Response rate - NR	2 controls each matched by age, race, and general practitioner chosen from registry. 79% were 1st eligible Response rate NR	Research nurse completed a questionnaire for each case and controls, which included information from medical notes, hospital records clinical laboratory tests, autopsy findings, personal interview. HRT= receiving ≥2 prescriptions	Cholesterol

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Major Findings Multivariable Adjusted Odds Rating (MAOR) 95% CI	Major Findings by Duration Use HRT (MAOR)	Time Since Last Use	Time Since Starting Estrogen	Findings by Other Sub-group Analyses (MAOR)	Comments
La Vecchia C, Franceschi S, Decarli A, Pampallona S, Tognoni G. Risk factors for myocardial infarction in young women. *Am J Epidemiol.* 1987;125(5): 832-843.	7 cases: multivar adj. current: 2.95(0.8-10.80) past: 0.77(0.16-3.60)					Only 7 cases in post-menopausal women. Non-fatal MI Quality: poor – pre-menopausal
Thompson, 1989[59]	Univariate (>1 prescription) **OR 1.36** ***P* = 0.04** MI 1.48 CVA 1.20	Univariate (months) 1-3 m 2.14 4-6 m 1.09 7-12 m 1.06 13-24 m 1.14 >24 m 1.19 **p trend = 0.09**			Adjusted for: Marital status Smoking FMH HTN, DVT/TE, MI, CVA, DM Fatal/non-fatal MI/CVA Any HRT 1.29 (0.82 – 2.0) ERT 1.09 (0.65 – 1.82) Progestin alone 1.02 (0.45 – 2.32) CHRT 1.16 (0.43 – 3.12)	Good agreement between nurses HRT assessment Poor ascertainment of confounders among controls. Quality: fair -good

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Setting/Study Population Date	Cases	Controls	Exposure Assessment/ Classification	Important Confounders Not adjusted for
Mann, 1994[68]	6/87 – 5/93 U.K.	Incident MI – fatal and non-fatal among all women in general medical practices in British National Health Service ages 45-64 n=1521	45-64 without MI recorded in their medical histories Matched within 5 years n=6084	Current HRT use defined as computer record of HRT prescription within 6 months prior to event HRT/CHRT Computer records used to identify risk factors	Family history BMI Exercise Alcohol ASA
Psaty BM, Heckbert SR, Atkins D, et al. The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. *Arch Intern Med.* 1994;154(12):1333-1339. See Heckbert, 1997[69]	Population-based Group Health, Seattle	Post-menopausal women with incident fatal or non-fatal MI 1986-1990 n=502 participation 97%; exclusion: prior MI	Stratified GH/random sample frequency matched by age & calendar year. n=1193 exclusion: prior MI participation 96%	Pharmacy database <u>3 categories use</u> 1. non-users 2. ERT 3. CHRT Use = filling 2 prescriptions Medical reviewed for potential confounder Telephone intervews	Family history Exercise Alcohol ASA BMI

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Major Findings Multivariable Adjusted Odds Rating (MAOR) 95% CI	Major Findings by Duration Use HRT (MAOR)	Time Since Last Use	Time Since Starting Estrogen	Findings by Other Sub-group Analyses (MAOR)	Comments
Mann, 1994[68]	Adjusted 0.83 (0.66 – 1.03) 0.70 (0.49 – 1.0) Non-smoker and/or unknown 1.05 (0.71 – 1.53) in smokers CHRT (adj) **0.68 (0.47 – 0.97)** ERT (adj) 0.93 (0.47 – 1.86)					HRT use only evaluated 6 months prior to event Past use not evaluated Prior CAD not excluded Large #: unknown smoking Quality - fair
Psaty BM, Heckbert SR, Atkins D, et al. The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. *Arch Intern Med.* 1994;154(12) :1333-1339. See Heckbert, 1997[69]	Current ERT/(non adj.) 0.69 (0.47 – 1.02) Current CHRT/(non adj) 0.68 (0.38 – 1.22)		Past/CHRT adj 1.04 (0.53 – 2.05) Past ERT adj. 0.69(0.44 – 1.07)			See Heckbert Quality: good Most MPA sequential Average duration ERT/CHRT $\leq$ 2y

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Setting/Study Population Date	Cases	Controls	Exposure Assessment/ Classification	Important Confounders Not adjusted for
Grodstein, 1997[53]	Nested case – control study within Nurses Health Cohort	3637 deaths 1976-1994	10 controls per case randomly chosen, matched by age, age at menopause, type menopause, period of cases death.	Biennial questionnaire ascertained prior to fatal illness to decrease "sick-quitter" bias.	Good adjustment
Heckbert, 1997[69] (see Psaty BM, Heckbert SR, Atkins D, et al. The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. *Arch Intern Med.* 1994;154(12):1333-1339.)	Group Health Seattle	Post-menopausal age 30-79 incident Fatal or non-fatal MI 7/86-12/93 Index date = date 1st MI or death n=850 (participation 94%) women < age 55 of uncertain menopause excluded.	Stratified random sample Frequency matched by age (decade) and year n=1974 (participation 94%)	All collected before index date Review of record Telephone interviews Pharmacy database reviewed Type, dose, date only obtained from pharmacy data Use= filling 2 prescriptions	Lipids Family history SES BMI Exercise Alcohol

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Major Findings Multivariable Adjusted Odds Rating (MAOR) 95% CI	Major Findings by Duration Use HRT (MAOR)	Time Since Last Use	Time Since Starting Estrogen	Findings by Other Sub-group Analyses (MAOR)	Comments
Grodstein, 1997[53]	**Mortality** Coronary Current: **0.47 (0.32 – 0.69)** Past: 0.99(0.75 – 1.30) CVA Current: 0.68 (0.39 – 1.16) Past: 1.07 (0.68 – 1.69) By CVD Risk Current Use: HI 0.51 (0.45 –0.57) Low 0.89 (0.62 – 1.28)					No benefit past exposure ? do women quit when ill, "healthy user" good control Quality: good
Heckbert, 1997[69]	Ever: HRT adj. **0.72 (0.59 – 0.88)** Current: HRT adj. **0.70 (0.55 – 0.89)** Past: HRT adj. **0.74 (0.57 – 0.96)**	Ever use (adj) <1.8 yr: 0.77 (0.58 – 1.02) 1.8-4.2: 0.70 (0.49 – 1.00) 4.2-8.2: 0.74 (0.51 – 1.06) **>8.2: 0.60 (0.39 – 0.93)** No trend	Current (adj) 0.91 (0.60 – 1.38) 0.70 (0.45 – 1.10) 0.65 (0.42 – 1.01) **0.55** **(0.34 – 0.88)** **trend .05**	Past duration **0.69 (0.49 – 0.97)** 0.70 (0.41 – 1.18) 0.93 (0.51 – 1.69) 0.96 (0.36 – 2.52) No trend		Median interval between index date and phone interview 24 mos.CHRT use <14% ✳Adjustment for HDL attenuated association between duration and riskof MI Quality: fair

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Setting/Study Population Date	Cases	Controls	Exposure Assessment/ Classification	Important Confounders Not adjusted for
Sidney, 1997[12]	Kaiser	Women 45-74 hospitalized for MI in 10 medical centers 11/91-11/94 (Kaiser) Exclusions:prevalent heart disease;excluded < 55 if hysterectomy;n=438 Post-menopausal	Age facility matched Post-menopausal Participation 80% N=438	Medical records abstracted Interviews Lifetime use Among women with hysterectomy only evaluated ERT Women without hysterectomy only evaluated CHRT Outcome:	Major RF were adj for (tob, DM, HTN, educ) Family history not adj for exercise, BMI, alcohol
Beard, 1989[66]	Rochester, MN	Female residents 40-59 with incident CHD(SCD, MI, angina) 1960-1982 N=133	2 age matched residents with Mayo health care within 1 year of index date without CHD	Medical record review	<u>Adj. for:</u> Age Dm HTN Tob Menopausal status <u>Not adj.</u> Alcohol BMI Exercise Family history

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Major Findings Multivariable Adjusted Odds Rating (MAOR) 95% CI	Major Findings by Duration Use HRT (MAOR)	Time Since Last Use	Time Since Starting Estrogen	Findings by Other Sub-group Analyses (MAOR)	Comments
Sidney, 1997[12]	Overall ERT use 34% Unadjusted Current ERT: 0.85 (0.6 – 1.21), among women with out hysterectomy Current CHRT **0.59 (0.38 – 0.94)** OR adj Current: (ERT or CHRT) 0.96 (0.66 – 1.40) OR adj Past: (ERT or CHRT) 1.07 (0.72 – 1.58)	No trend ERT (yr) <1: 0.71(0.15-3.34) 1-4: 0.91(0.28-2.92) 5-9: 0.75(0.27-2.07) ≥10: 1.08(0.54-2.14) CHRT (yr) <1: 1.27(0.4-4.02) 1-4: 0.64(0.27-1.51) 5-9: 0.97(0.41-2.29) ≥10: 0.73(0.29-1.80)			By hysterectomy With hysterectomy ERT current: 0.95(0.50-1.80) w/out hysterectomy CHRT current: 0.89(0.52-1.53)	84% of current users conjugated Of current E+P users, 98% used MPA in several regimens Quality: good
Beard, 1989[66]	MI/SCD: Ever/never 0.55(0.24-1.30) angina: 0.82(0.46-1.47)					Young cases Menopausal status unclear # menopausal Quality: fair Limited by size, age, incomplete control confounding.

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Setting/Study Population Date	Cases	Controls	Exposure Assessment/ Classification	Important Confounders Not adjusted for
Croft, 1989[65]	Nested case control within cohort of 23,000 women using OCD and 23, 000 not in Britain.	All women with 1st. MI (fatal/non fatal) n = 158	3 controls each case matched by age +/-2, n = 158	Diagnosis by GD Death cert. Physician records Record review	Adj. for social class Tobacco OCP HTN Hysterectomy No adj. Lipids DM BMI
Hernandez-Avila, 1990[62] see Evidence Table 1 Cohort	Group Health Women ages 50-64 with pharmacy use in last 2 years	First MI 1978-84 ages 50-64 n=102	No history of MI, from records GH lists and pharmacy users n=721	Pharmacy records	Used medicines as surrogates Not adj. for chol, HTN, FMH, DM, smoking, BMI, exercise.
Rosenberg, 1993[67]	Massachusetts 1986-1990 Ages 45-69	1st non fatal MI identified by calling CCU's of 52 hospitals weekly n=858 (97% Caucasians) Participation 90% 21% used ERT	Geographically matched 5 yrs age, no prior MI Identified by use of books n=85% 83% participation	Questionnaire Nurse administered by telephone or in person (27%) Use <1 month = non-user	None

Evidence Table 2. HRT and CVD – Case Control Studies of Primary Prevention (continued)

Study, Year, Journal	Major Findings Multivariable Adjusted Odds Rating (MAOR) 95% CI	Major Findings by Duration Use HRT (MAOR)	Time Since Last Use	Time Since Starting Estrogen	Findings by Other Sub-group Analyses (MAOR)	Comments
Croft, 1989[65]	Adj. RR 1st. MI: 0.8(0.3-1.8)					Major RF not adj. for Exposure not defined. Quality: fair
Hernandez-Avila, 1990[62] See Evidence Table 1 Cohort	Current/ non use: 0.8(0.4 – 1.4) Past use: 0.7(0.2 – 2.4) Multivar adj: Current 0.7(0.4 – 1.4) Past 0.6(0.1 – 2.1)					Only adjusted for other drugs, only survivors Quality: poor
Rosenberg, 1993[67]	Ever ERT 0.9 (0.7 – 1.2) Ever Progestin Only 1.3 (0.4 – 4.9) Ever CHRT 1.2 (0.6 – 2.4)	ERT <1 yr. 0.9 (0.6 – 1.5) 1-2 1.1 (0.6 – 2.0) 3-4 0.8 (0.3 – 1.9) 5-9 0.6 (0.3 – 1.3) ≥15 0.4 (0.2 – 1.0) p = 0.08 trend CHRT ≤5 0.5 (0.2 – 1.5) ≥5 2.6 (0.8 – 8.4) ERT ≥5 0.6 (0.4 – 1.1)	Past ERT Total: 0.9(0.7-1.3) <1y: 0.9(0.5-1.5) 1-4: 1.0(0.6-1.7) 5-9: 0.7(0.3-1.7) ≥10: (0.3-3.6)	Recent ERT Total: 0.8(0.4 - 1.3) <1y: 1.5(0.3 - 8.0) 1-4: 1.2(0.4 - 3.7) 5-9: 0.6(0.2 - 2.0) ≥10: 0.5(0.2 – 1.1)	Recent Use 0.8 (0.4 – 1.3) Past Use 0.9 (0.7 – 1.3) Recent >5 0.5 (0.3 – 1.1) Past >5 0.8 (0.3 – 1.7) Trend for risk increases duration mostly in recent users	Conjugated estrogen most commonly used ✳Only survivors Good participation and adjustment for confounding. Quality: good, best

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Hammond CB, Jelovsek FR, Lee KL, Creasman WT, Parker RT. Effects of long-term estrogen replacement therapy. I. Metabolic effects. Am J Obstet Gynecol. 1979;133(5): 525-536.	Retrospective Cohort 610 women identified through medical records retrieval system of Duke University Medical Center and by systematic review of office records from OB/GYN faculty, likely to have an estrogen-deficient state identified by diagnoses of premature ovarian failure, hypogonadism due to hypopituitarism, osteoporosis, atrophic vaginitis, menopausal syndrome, surgical removal of ovaries, not due to cancer, gonadal dysgenesis. Patients identified from 1940 through 1969; Ages 10 to >50 yr Must have estrogen exposure of at least 5 years, and must have been seen in exam after 1/1/74.	Primarily used CEE, ~96% (31% at 0.625 mg; 33% at 1.25 mg), usually given in cyclic fashion (88%). 27.6% received progestins, in addition to CEE. Estrogen reported as never use (n= 309) and estrogen users (n=301).	stroke syndromes, F/NF CAD Details of stroke or CAD outcomes were not given in this analysis, but presumed to be verified by medical records and discharge diagnosis.	5+ years	none

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Hammond CB, Jelovsek FR, Lee KL, Creasman WT, Parker RT. Effects of long-term estrogen replacement therapy. I. Metabolic effects. Am J Obstet Gynecol. 1979;133(5): 525-536.	P<0.05, no RR given. 14 cases in the never users and 3 cases in the estrogen users.		CAD p<0.01, no RR given 44 cases in never users 14 cases in estrogen users	Poor; not adjusted for confounders; subjects hypoestro-genic, but young age and at low risk of stroke.	Users significantly different from nonusers. Users tended to be younger, lower BMI, have lower blood pressures, white; while nonusers tended to be older, black, hypertensive, lower SES, higher BMI, higher gravidity.

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Byrd BF, Jr., Burch JC, Vaughn WK. The impact of long term estrogen support after hysterectomy. A report of 1016 cases. Ann Surg. 1977;185(5): 574-580.	1016 White women with hysterectomies performed by co-author JC Burch, age 22-78 y/o (avg 44), on estrogen for at least 3+ yrs. 1948-1971, Tennessee	Primarily used CEE, 1.25 mg - no distinction between cyclic therapy; Exposure measurement at contact and questionnaire f/u. Avg yr on estrogen 13.5 yr.	Cancer cerebrovascular accident death Heart Disease Death verified by death certificates; cancer data from the Third National Cancer Survey for the Atlantic area; mortality statistics from Dept. of Vital Statistics, State of Tennessee Public Health Department.	100% f/u 14,318 person-yr +E2	none
Burch JD. Discussion of the effects of long-term estrogen on hysterectomized women. Am J Obstet Gynecol. 1974;118:782.	737 white women with hysterectomies performed by author, ages 20-80's, from 1940's to 1967.	Primarily used CEE, 1.25 mg - no distinction between cyclic therapy; Exposure measurement at contact.	cerebrovascular accident death	100% 9,899 patient years 1973	none

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Byrd BF, Jr., Burch JC, Vaughn WK. The impact of long term estrogen support after hysterectomy. A report of 1016 cases. Ann Surg. 1977;185(5): 574-580.		CVA death SMR (8/15) = 0.53 heart dx death = (13/35) = 0.37, p<0.005		Poor Unadjusted; External controls 100% f/u. Probable not a generalizable population.	
Burch JD. Discussion of the effects of long-term estrogen on hysterectomized women. Am J Obstet Gynecol. 1974;118:782.	8 cases of stroke			Poor; Unadjusted; external controls. 713/737 s/o hysterectomy	

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Petitti DB, Wingerd J, Pellegrin F, Ramcharan S. Risk of vascular disease in women. Smoking, oral contraceptives, noncontraceptive estrogens, and other factors. JAMA. 1979;242(11):1150-1154	Walnut Creek Contraceptive Drug Study. N=16,759 primarily white, suburban middle class women aged 18-54 appearing for routine check ups from 1969-1971. Controls were matched to cases by age/birth year, with varying numbers of controls matched to each case, ranging from 60->200.	Annual Routine Exam between 1969-1971, F/U exam and yearly questionnaires, hospital discharge records and California Death certificates. Info obtained on hormonal use (OCP's, and noncontraceptive estrogen and progestins)	Subarachnoid hemorrhage (SAH) Other Stroke MI Venous thromboembolism Outcomes evaluated by patient self-report; and verified MI's by discharge records with clinical s+sx/EKG changes or inc. CK; SAH by death cert/autopsy, discharge summary and confirmed by angiography or operation; Other stroke by h/o of sudden onset of sx c/w cerebrovascular dx (CVD), absence of predisposing condition, at least one the following: acute onset of hemiplegia, angiographic data of cerebral thrombosis, embolism or hemorrhage or transient episode of one-sided weakness with assoc. sensory or ocular symptoms.	470(2.8%) lost to f/u. 107 (0.7%) deaths; 922 (5.5%) withdrew; f/u from 1969-12/76, avg 6.5 yr.	Excluded at start of study women with h/o stroke and DM

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Petitti DB, Wingerd J, Pellegrin F, Ramcharan S. Risk of vascular disease in women. Smoking, oral contraceptives, noncontraceptive estrogens, and other factors. JAMA. 1979;242(11):1150-1154	SAH (fatal/nonfatal) n=11 RR 1.6(0.7-3.8)* Other stroke (F/NF) n=23 RR 0.9(0.4-1.8)*		MI (F/NF) RR 1.2(0.6-2.3)*	Fair; Unsure if confounders were adjusted for, except for DM and stroke which were eliminated at start of study. F/U 97.2% complete.	*90%CI Analyzed as a case control study.

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Wilson 1985[11]	Framingham cohort, exam 12-16. Postmenopausal women age 50-83. Recruitment from 1970-1972. N=1234; Controls = 932; Cases = 302	Exposure measured on initial exam. Biennial exams were done, but no info on estrogen use during f/u. Almost all were CEE, <5% used progestins; Exposure classified if subject ever reported use during exams 8-12	Cerebrovascular disease (F/NF) Atherothrombotic brain infarction All cause mortality	8 years	Adjusted for surgical menopause, age, SBP, BMI, TC:HDL, smoking, ETOH Not adjusted for DM

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Wilson 1985[11]	cerebrovascular disease (F/NF), n=45 **RR 2.27, p<0.01** Atherothrombotic brain infarction, n=21 **RR = 2.60, p<0.01**		CVD/HRT: Smokers: RR 1.96, not significant **Non-smokers: RR 2.35, p<0.05** Coronary heart dz/HRT: Smokers RR 4.17, p<0.01 Non-smokers RR 1.44, not sig. Total cardiovascular disease/HRT: Smokers: RR 3.16, p<0.01 Nonsmokers: RR 1.26, not sig. All cause mortality, n=130 RR 0.97, not sig.	Good; not adjusted for diabetes	

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Bush 1987[22]	Participants in Lipid Research Clinics Prevalence Study for CVD from 10 N. American clinics between 1972-1976. Women aged 40-69, white. N=2270 Participants initially identified in selected target populations (ie. Occupational grp, school children and parents, whole county surveys) Visit 1 (74% response rate) Visit 2 (84% of invited) - 3449 randomly selected from target groups (58%); 2350 persons with elevated lipids (40%) and 127 taking lipid meds (2%).	Estrogen use determined at baseline by standardized interview -OCP or ERT use before visit 2. Verified by samples drug containers. Estrogen use validated in ~95% (with 2/3 taking premarin and 1% taking progesterone (6 ERT users) never user = 1677; ERT = 593	Cerebrovascular death Death verified by hospital/physician records, interviews with next of kin.	99% f/u; Average 8.5 yr. 10,080 py	Age, BP, smoking, LDL, BMI, education Not adjusted for fhx, DM

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Bush 1987[22]		0.40 (0.01-3.07)	All cause Mortality RR= 0.54(0.29-0.79) Cardiovascular disease mortality (age adj) RR = 0.34(0.12-0.81), after adjustment for prevalent cases RR=0.42(0.13-1.10)	Good; Adjusted for most important confounders; fair response rate; good f/u.	4% of users (n=23) and nonusers (n=60) reported prior MI or stroke. Estrogen type, dose, duration not consistently obtained. Estrogen use ascertained only at one point in time.

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
The American-Canadian Co-Operative Study Group. Persantine aspirin trial in cerebral ischemia--Part III: Risk factors for stroke. Stroke. 1986;17(1):12-18.	890 subjects with one or more TIA's in the carotid territory from 15 centers. 10% female, n=293	Baseline history obtained at time of admission to study. Estrogen never or ever user. Information on confounders obtained in a similar fashion. 293 women (262 never use, 31 ever use)	Stroke Retinal Infarction Death	?100% median f/u `25 mos.	Unadjusted

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
The American-Canadian Co-Operative Study Group. Persantine aspirin trial in cerebral ischemia--Part III: Risk factors for stroke. Stroke. 1986;17(1):12-18.	F/NF Stroke or Retinal Infarction (n=36, 35 never users, 1 user) RR = 0.23, p=0.06	nr		Poor; did not adjust for confounding; Exposure assessment not consistent and possibly unreliable.	Smoking and estrogen use not on questionnaire initially. Included in the study after 1 mos. Some data collected retrospectively.

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Hunt K, Vessey M, McPherson K, Coleman M. Long-term surveillance of mortality and cancer incidence in women receiving hormone replacement therapy. Br J Obstet Gynaecol. 1987;94(7):620-635.	UK (England and Wales); 4544 women recruited from 21 specialty menopause clinics, aged 45-54 (60%) Primarily white, affluent, h/o hysterectomiy ~36%) Retrospective recruitment from before 1974 to 1978 (7% prior to 1974, 29% between 1974-1977) Prospective recruitment from 1978 (53% between 1978-1981, and 11% 1982).Postal questionnaire sent out in 1983 to 4387 of 4544 women recruited. (response rate was almost 80%). Illicited info on HRT use since entry to study and about major morbidity. All on HRT for at least 1 year prior to recruitment, plus attend one of the participating clinics.	HRT info obtained from recruitment interview and PMHx. Risk factor info collected in the same manner. Uncontrolled.	All-Cause mortality Cancer Mortality Cerebrovascular Disease Deaths flagged by the Nat'l Health Service Central Registries.	June 1983	Not adjusted for DM, HTN, smoking, lipids, family h/o, etc.

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Hunt K, Vessey M, McPherson K, Coleman M. Long-term surveillance of mortality and cancer incidence in women receiving hormone replacement therapy. Br J Obstet Gynaecol. 1987;94(7):620-635.		SMR for cerebrovascular disease 0.65(0.35-1.09)	SMR suicide or suspected suicide 2.53(1.26-4.54)	Poor; Uncontrolled; Not adjusted for confounding; Response rate approx. 80%; ? F/U 100%;	Over 175 different hrt preparations, premarin accounted for only 17%. Full HRT histories available for 70% of cohort. 51% had taken HRT for more than 5 years; average duration of use 67 months. 43% "opposed estrogen".

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Petitti 1987[49]	16,638 women aged 18-54 from Walnut Creek Facility at Kaiser Permanente. Recruitment from 12/68 to 2/72 Controls were women who never used OCP or ERT (n=3437)	Health exam, with history obtained on past and current hormone use, as well as info on potential confounders. Final analysis on: Controls: 3437 women who never used OCP or ERT and Cases: 2656 women who used ERT, but not OCP. Estrogen type not mentioned	Death Outcomes evaluated by: next of kin questionnaires, search of California Death Index, and obtained death certificates coded by ICD-8	1968-1977 (active follow up) through 12/31/83 by computer search in CDI Loss to followup not reported	age, smoking, ETOH, Quetelet index, h/o htn, marital status and education. Not adjusted for DM. Lipids, family h/o.

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Petitti 1987[49]	Cerebrovascular Death (4 nonuser deaths/5 user deaths) RR 0.6 (0.2-2.2)	nr	all-Cause Mortality RR = 0.80(0.6-1.1) Death from Acute MI (7 nonusers/4 users) RR = 0.3(0.1-1.3) Death from all ischemic heart disease RR 1.3(0.2-7.7)	Fair; Not adjusted for major confounders; Exposure use equally measured, but only up until 1977, although f/u continued until 1983; Only death as an outcome is measured and losses to f/u not mentioned.	

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Paganini-Hill A, Ross RK, Henderson BE. Postmenopausal oestrogen treatment and stroke: a prospective study. Br Med J. 1988;297(6647):519-522.	California Retirement Community - Laguna Hills. Leisure World Cohort Study from 6/81 to 1985. N=13986, 8882 women, primarily white, affluent, well-educated, median age 73, 2/3 women.	Health questionnaire mailed to residents (initial 60% response rate), 6/82, 6/83, 10/85. Assessed estrogen use and duration as well as confounding factors by questionnaire.	Stroke death Deaths were ascertained by death certificates, records at local county health dept.; obituary columns, info from friends and relatives;	13 lost to follow-up (search by National Death Index, negative); 8/86	Age, HTN, h/o angina, MI or stroke, ETOH, smoking, Quetelet's index, last menstral period. No adjustment for DM, lipids

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Paganini-Hill A, Ross RK, Henderson BE. Postmenopausal oestrogen treatment and stroke: a prospective study. Br Med J. 1988;297(6647):519-522.		N=63 stroke deaths RR = 0.53(0.31-0.91), p=0.02	Duration of use <=8 y = 0.55(0.28-1.08) >=8 y = 0.50(0.23-1.08) Dose <= 0.625 mg = 0.73(0.32-1.66) >= 1.25 mg = 0.49(0.19-1.27)	Poor; Good f/u; Important confounder not adjusted for, DM. Only evaluated for mortality/fatal stroke. 60% response rate.	3845 nonusers 4962 users Primarily CEE

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Hunt K, Vessey M, McPherson K. Mortality in a cohort of long-term users of hormone replacement therapy: an updated analysis. Br J Obstet Gynaecol. 1990;97(12): 1080-1086.	UK (England and Wales); 4544 women recruited from 21 specialty menopause clinics, aged 45-54 Different from general population - 36% had hysterectomy (2-2.5 that of gen pop). 46% social class I or II (affluent) All on HRT for at least 1 year prior to recruitment. Mean duration of HRT use 66.9 mos., 59% still using HRT.	HRT info obtained from recruitment interview and PMHx. Uncontrolled.	All-Cause mortality CV Mortality Deaths flagged by the Nat'l Health Service Central Registries.	1980-12/31/88 F/u 100%	Not adjusted for DM, HTN, smoking

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Hunt K, Vessey M, McPherson K. Mortality in a cohort of long-term users of hormone replacement therapy: an updated analysis. Br J Obstet Gynaecol. 1990;97(12): 1080-1086.		Stroke Mortality (up to 1988), n=23 SMR = 0.54(0.24-0.84)		Poor; Uncontrolled; Not adjusted for confounding; F/U 100%;	Select population of women, from specialty menopause clinics. All affluent. Not adjusted for significant confounders.

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Henderson 1991[85]	All residents of Leisure World, Laguna Hills; Retirement community in Southern Ca. Primarily white, affluent, well educated, mean age 73; N=13987 (respondents out of 22,781, men and women). N=8853 women (8881-28 b/c no info given on HRT) Internal controls. 1981-1985.	Questionnaires sent 6/81, 6/82, 6/83, 10/85. (PMHx, type and duration of estrogen use.) N=4988 of 8853 used ERT Mean duration of use ~10 yr. 932 (19%) took ERT <=1 yr. 37 took ERT > 40 yr. Majority of ERT taken immediately postmenopausal years and d/c'd prior to study entry.	Stroke death Deaths were ascertained by death certificates, records at local county health dept.; obituary columns, info from friends and relatives.	7.5 years; 56,020 py 22 subjects unavailable for f/u (review of Nat'l Death Index)	Age only.

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Henderson 1991[85]		0.63 (primarily CEE), not statistically significant Actual # of deaths due to stoke = 92 (60 in nonusers, 32 in users) RR of death from occlusive stroke by duration of use: <3 y 0.51 4-14 y 0.74 **>= 15 y 0.53, p<0.05** RR of death from occlusive stroke by time since last use: >= 15 y 0.67 2-14 y 0.63 **0-1 y 0.30, p<0.05**	Age-adjusted data: All-Cause Mortality: RR by h/o of use of ERT, users vs. never users RR 0.8 (0.70-0.87); p<0.0001. All-Cause Mortality and RR by h/o of ERT use: Duration of use (yr): **<= 3** **0.83(0.71-0.96), p<0.05** 4-14 0.76(0.65-0.89) **>= 15** **0.69(0.58-0.82), p<0.001, test for trend** years since last use: **>= 15**	Poor; Good f/u; Not adjusted for major confounders in CVD and stroke analysis. Only evaluated for mortality/fatal stroke.	Premarin used most commonly.

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Stampfer 1991[9]	48,470 postmenopausal women, nurses, aged 30-63 who participated in the Nurses' Health Study. Overall healthy, white, no h/o cvd and cancer. 1976-1986. (initial cohort 22,950 in 1976, up to 48,470 as women became menopausal).	Hormone use obtained by biennial questionnaire. HRT use and duration obtained.	Strokes F/NF Ischemic Stroke SAH Major coronary disease (NF MI, death due to coronary dz) CABG All-cause mortality Info from PMHx/questionnaire verified by medical records. NF strokes verified by med record if typical neurologic symptoms lasting at least 24 hours and meeting criteria of the Nat'l Survey of Stroke. Stroke classified as ischemic (thrombotic or embolic), SAH, IPH. If no medical record available, case defined as probable if they required hosp-italization and letter of interview corroborated event. Death reported by subjects family; verified by medical & autopsy records. Non-respondents - searched Nat'l Death Index	F/u up to 10 years (337,854 person years) F/U 88.4% complete for NF outcomes and 98% complete for fatal outcomes. F/u ended with diagnosis of stroke or death. Women were excluded from analysis who reported CVD at the start of each 2 year interval.	Adjusted for age, smoking, HTN, DM, hypercholesterolemia, FH of MI before 60 y, quetelet index, past OCP use.

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Stampfer 1991[9]	Total strokes (F=52/NF=172) - (ischemic 113, SAH 36, NOS 75) Never use (n=123) 1.0 Current (n=39) 0.97(0.65-1.45) Former (n=62) 0.99(0.72-1.36) Ischemic stroke (113) Never use (n=56) 1.0 Current (n=23) 1.46(0.85-2.51) Former (n=34) 1.19(0.77-1.86) SAH (36) Never use (n=19) 1.0 Current (n=5) 0.53(0.18-1.57) Former (n=12) 1.03 (0.47-2.25) Number of Strokes (177 confirmed, 47 probable) 224 total strokes 52 fatal and 172 nonfatal		All-Cause Mortality RR = 0.89 (0.78-1.00) CV mortality RR = 0.72 (0.55-0.95), p=0.02	Good; Good f/u; confounders adjusted for; important outcomes measured, comparable groups maintained.	No association between current estrogen use and total stroke. RR = 0.97.

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Folsom 1995[55]	Subjects are part of the Iowa Women's Health Study cohort, consisting of 41,837 (41,070 after exclusions) women aged 55-69 with valid IA drivers license in 1985. Analyses restricted to PM women with HRT data. 1986-1991.	Estrogen exposure obtained from initial mailed questionaire and updated in follow up Estrogen use = current, former and never use at baseline; duration of use, <=5 y or >5 yr.	CHD death Stroke death All cause mortality Death identified through the Health Registry and national Death Index, with recorded underlying cause of death coded by ICD9.	6 years	Adjustment for age, marital status, physical activity, ETOH use, pack-years of smoking, BMI, waist/hip ratio, HTN, DM Not adjusted for lipids, SES
Finucane 1993[56]	Subjects were participants in the NHANES I trial. Women were white, civilian, noninstitutionalized women, without h/o of stroke, aged 55-74 y/o. Out of total 2371 women, N=1910 after exclusions; 1971-1975	HRT use is obtained at first f/u appt (NHEFS) and not at NHANES baseline. Dose, duration of use of HRT was not obtained. Info obtained by interview and classified as ever users vs. never users. (Ever users may have taken HRT years ago; never users may have begun taking HRT after the first f/u appt.)	Nonfatal and fatal stroke. Stroke determined from discharge diagnosis coded from hospital/nursing home records, death certificates and f/u up interviews.	1971-1987 average f/u ~11.9 yr. 4% of original cohort is lost to f/u.	adjustment for age, SBP, DM, smoking, BMI, h/o HTN, MI, education, poverty ratio. Not adjusted for family hx, lipids

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Folsom 1995[55]		current users RR= 0.95(0.37-2.43) former users RR= 0.88(0.48-1.61)	Duration of use <=5 y RR = 2.08(0.74-5.82) >5 y RR = 1.05(0.41-2.64)	Good; f/u 100%; All important confounders adjusted for.	Estimated ~20% CHRT current users
Finucane 1993[56]	RR of stroke (subject + proxy/ n=1910) = 0.69(0.47-1.00) RR of stroke (subject only/n=1474) = 0.82 (0.46-1.47)	RR of stroke (subject + proxy): 0.37 (0.14-0.92) RR of stroke (subject only): 0.86 (0.28-2.66)		good; F/u complete; Important confounders adjusted for; pertinent outcomes studied	21% of study subjects took HRT (n=397).

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Lindenstrom E, Boysen G, Nyboe J. Lifestyle factors and risk of cerebrovascular disease in women. The Copenhagen City Heart Study. Stroke. 1993;24(10): 1468-1472.	Subjects were participants in the Copenhagen City Heart Study. Random sample(after age stratification) of Danish women from urban population in Copenhagen, served by Rigshospitalet. 10,317 women invited by letter for exam. N =7060; Exam 1: 3/76-3/78; Exam 2: 4/81-7/83; N=4716 postmenopausal women.	Exposure history obtained from questionnaires and by 2 exams. Type of estrogen, duration of use, past use, not specified.	First stroke and TIA (SAH excluded) Outcomes evaluated by history and PE with neurologic assessment; Natl pt. Register (hospital records); Nat'l health service register of deaths; patient's MD, family or nursing home.	F/U of 12 years (1976-1988)	Adjusted for age, education, income, smoking, ETOH, BMI, activity, current use of OCP or HRT. Did not account for HTN and DM.

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Lindenstrom E, Boysen G, Nyboe J. Lifestyle factors and risk of cerebrovascular disease in women. The Copenhagen City Heart Study. Stroke. 1993;24(10): 1468-1472.	RR not reported, 95% CI = 0.5-1.9.		In Smokers + HRT: RR = 0.57 (0.29-1.13) In Smokers/ no HRT: RR = 1.50 (1.09-2.08) Nonsmokers/ HRT: RR = 1.01 (0.55-1.84) Nonsmokers/ no HRT: RR = 1	Poor; % of F/U uncertain; Did not adjust for DM and HTN; 68% response rate.	Interaction between smoking and HRT, p<0.041; (HRT protective among smokers RR 0.57, compared to non-users RR 1.50) In non-smokers, use of HRT did not influence risk of stroke.

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Boysen G, Nyboe J, Appleyard M, et al. Stroke incidence and risk factors for stroke in Copenhagen, Denmark. Stroke. 1988;19(11): 1345-1353.	Participants in the Copenhagen City Heart Study (see above). N = 5602 women age 45-74	Questionnaire	First stroke/TIA ICD-9 430-438	5 years Between 4/1981 and 9/1983	HTN, DM, age, income, smoking, cholesterol

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Boysen G, Nyboe J, Appleyard M, et al. Stroke incidence and risk factors for stroke in Copenhagen, Denmark. Stroke. 1988;19(11): 1345-1353.	In model with age, income, smoking, SBP, DM and cholesterol, no indication that PM estrogen influences stroke risk. RR= not reported 95% CI = 0.5-1.9		stroke cases= 238	Poor	Unable to calculate RR from data presented in study

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Falkeborn M, Persson I, Terent A, Adami HO, Lithell H, Bergstrom R. Hormone replacement therapy and the risk of stroke. Follow-up of a population-based cohort in Sweden. Arch Intern Med. 1993;153(10):1201-1209.	23,088 women older than age 35, from Uppsala, Sweden Health Care Region. 1977-1983 N=23,247(-159 w/hx of stroke) Median age 53.9 yr.	Hormone use established by pharmacies in Uppsala Health Care Region from 1977-1980. Random sample of 1/30 of cohort received questionnaires. Subcohort, N=735. External controls Questionnaire to age-matched sample, n=1039 (78% response rate). Median duration of ERT was 3.5 years & 23% continued treatment through 1983. Groups: Potent estrogens (estradiol cmpds, CEE)-N=17,143 (5639 combined e+p; 81% of subcohort) Other estrogens (weak estrogens, primarily estriol 1 mg/d)-N=5945 18,869 <60 yr old at time of first Rx; 4219 >60 yrs. old	First stroke: -acute stroke (AS) -subarachnoid hemorrhage (SAH) -intracerebral hemorrhage (ICH) -thromboembolic stroke (including TIA) (TES) Outcomes evaluated by record linkages by National Registration number and verified with hospital admissions and the Inpatient Registry. Classification based on ICD-9 codes	f/u started at date of first prescription or 1977 - 12/31/83 133,718 person years of observation; avg. observation time per person = 5.8 yrs. 26 women emigrated and were lost to f/u. 876 deaths	Age only. Could not adjust for confounders b/c database was from prescriptions.

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers				Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Falkeborn M, Persson I, Terent A, Adami HO, Lithell H, Bergstrom R. Hormone replacement therapy and the risk of stroke. Follow-up of a population-based cohort in Sweden. Arch Intern Med. 1993;153(10):1201-1209.	Stroke	All	E2/CE	Comb.	OE			Poor. Unable to adjust for confounders; however small subset analyzed.	Distribution of risk factors between subcohort and female population were found to be no different in respect to age at menarche, menopause and DM, HTN. 361 cases of first stroke. - hormone use before and after study not ascertained. Only one brand of estrogen-progestin combination included; but classified all women on estrogenic compounds
	All strokes	0.90 (0.81-0.99)	**0.79 (0.67-0.92)**	**0.61 (0.40-0.88)**	1.02 (0.88-1.17)				
	Acute strokes	0.85 (0.75-0.97)	**0.72 (0.59-0.86)**	**0.56 (0.33-0.90)**	1.00 (0.85-1.18)				
	SAH	1.19 (0.86-1.61)	1.24 (0.85-1.74)	0.83 (0.33-1.71)	1.03 (0.47-1.96)				
	ICH	**0.68 (0.45-0.99)**	**0.57 (0.30-0.97)**	0.20 (0.01-1.11)	0.84 (0.46-1.41)				
	TES	0.91 (0.76-1.09)	0.78 (0.59-1.01)	0.57 (0.26-1.09)	1.08 (0.83-1.38)				

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Grodstein 1996[8]	Women from the Nurses Health Study; age 30-55 y/o. 1976-1992. N=59,337	Hormone use obtained by biennial questionnaire. N=27,034 never users N=12,503 past users N=7776 current users of estrogen only N=6224 current users of estrogen + progestin	NF/F strokes; MI/CABG/Angioplasty, death from CAD. Positive report in questionnaire resulted in review of medical records; NF strokes verified by med. Record if typical neurologic symptoms lasting at least 24 hours and meeting criteria of the Nat'l Survey of Stroke. Stroke classified as ischemic (thrombotic or embolic), SAH, IPH. If no medical record available, case defined as probable if they required hosp-italization and letter of interview corrobaorated event. Death reported by subjects family and verified by medical records, autopsy records. Non-respondents - searched Nat'l Death Index	16 yr f/u from 1976-1992 (662,891 person-yrs) 59,337 women Mortality data >98%	Adjusted for age, age at menopause, BMI, smoking, DM, HTN, hypercholesterolemia, FH h/o of MI before age 60; prior use of OCP, type of menopause, sat. fat intake, ETOH use, vit E or MVI use, ASA use, physical activity.

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Grodstein 1996[8]	stroke(all)(572) ischemic stroke (285) SAH (155) Current 1.03(0.82-1.31) 1.40(1.02-1.92) 0.90(0.57-1.41) Past 0.99(0.80-1.22) 1.01(0.74-1.36) 0.81(0.52-1.25) ERT only 1.27(0.95-1.69) 1.63(1.10-2.39) 1.35(nr) Est+Prog 1.09(0.66-1.80) 1.42(0.73-2.75)	Deaths due to stroke not reported.	RR of stroke + dose Dose RR of Stroke 0.3 0.64(0.30-1.36) 0.625 1.24(0.90-1.70) 1.25 1.44(0.94-2.22) >1.25 1.86(0.59-5.90) Ptrend = 0.047 Data for RR by duration of HRT not reported in detail, but association found to be unrelated to duration of use. RR for 10+ years of use = 1.01(0.69-1.46).	Good; Comparable groups, all outcomes considered, although stroke deaths not reported. Adjusted for major risk factors. F/U not clear in terms of losses to f/u and those completing study.	Relative Risk of hemorrhagic stroke in ERT users 0.53, only 3 cases; no confidence interval, p-value reported.

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Schairer 1997[75]	Swedish women from Uppsala Health Care Region (Sweden). Cohort of 23,246 women older than 35 years of age, on prescribed estrogen (reported from regional pharmacies). Mean age ~54.4 yrs. Estrogen prescribed for HRT and not contraception. External controls ("background group") Compared to background group, women on "more potent estrogens" had higher rates of TAH/BSO, less DM, smoked more and were more physically active. 4/77-3/80	Prescription-based exposure group. A random-selected subset of cohort (n=753) received questionnaires to evaluate concordance between presription data and those given questionnaire. External controls. Same questionnaire sent to sample of 1324 women from general population of the region and age-matched to distribution of cohort. 1034 respondants (79%). Exposure groups: A. Estrogen grp: 1) Combined: {estradiol/valerate (2 mg) + levonorgestrel (250 ug)} 2) More Potent Estrogen {estradiol/conjugated estrogen} B. Other: predominantly estriol	All cause mortality Cardiovascular deaths CVA (SAH, ICH, TES) Outcomes verified by linkage to National Causes of Death Registry, according to ICD-9 code	8.6 years (199,810 person-years) 3/77-12/86	Confounders were not adjusted for b/c all data was obtained from pharmacy database. No adjustment for smoking, hypertension, diabetes, etc. Small subset of cohort received questionnaires (n=1034) to evaluate for possible confounding.

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Schairer 1997[75]		SMR by HRT regimen: no nonuser group *Other:* CVD 0.9 (0.7-1.0) SAH 1.7 (0.9-2.9) Stroke 0.8 (0.6-1.0) ICH 0.9 (0.6-1.3) TES 0.8 (0.5-1.3) nos 0.7 (0.4-1.1) *More Potent Estrogen:* CVD 0.7 (0.6-0.9) SAH 0.9 (0.5-1.5) Stroke 0.8 (0.6-1.1) ICH 0.4 (0.2-0.7) TES 1.1 (0.6-1.8) nos 1.2 (0.7-1.9)	SMR by HRT regimen (continued) Combined 0.6 (0.3-1.1) 0.5 (0.1-1.4) 0.8 (0.3-1.6) 0.6 (0.1-1.7) 0.6 (0.1-1.7) 1.2 (0.1-4.4)	Poor; External controls; Unadjusted F/u appears to be complete	Unable to adjust for confounders no comparison to nonusers.

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Lafferty FW, Fiske ME. Postmenopausal estrogen replacement: a long-term cohort study. Am J Med. 1994;97(1):66-77.	All postmenopausal women, aged 43-60, who were healthy, white, ambulatory women from the private practice of FWL(author) between 1964-1983, were offered ERT. N=176 (out of 234, after exclusions, cancer, severe HTN, CVD, osteoporosis, DM, etoh, misc. illness;) N= 81 long term estrogen subjects; Controls, N = 76, women who declined ERT use.	ERT prescribed as premarin at 0.625 mg by the study author to each of the 81 patients. No measure of compliance noted. Risk factors collected by history by examiner.	stroke/cardiovascular events (htn, MI, ischemic changes on EKG, CVA). (also BMD, lipids). No measure of how CVA was determined.	min. 3 years (5-14 yr) avg. 8.6 years. 1964-1989 15 of ERT users dc'd estrogen prior to the 3 yr min. obs period. (quit b/c of fear of endom. ca (9), cystic breast dx(2), fear of breast ca, mastalgia, menses, depression (4) At end of study, 67-68% of both groups were under direct f/u of deceased. 26-29% were contacted by questionnaire.	adjusted for HTN, BMI, smoking, cholesterol, age, ETOH, bil. Oophorectomy; Diabetics were excluded from study at the beginning.

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Lafferty FW, Fiske ME. Postmenopausal estrogen replacement: a long-term cohort study. Am J Med. 1994;97(1):66-77.	p=0.025; however only 4 cases of CVA in controls and 0 in the ERT group.			Poor; f/u almost 98%. Study population possibly not generalizable (only from one physician's practice); Documention of CVA, MI scant. Compliance of therapy not known.	Small number of cerebrovascular events (4 in control group, 0 in ERT group); Standardized useage of premarin. Outcome classification/documentation not clear.

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Sourander 1998[51]	7944 women aged 57-64 participating in mammography screening program in Turku, Finland in 1987-1988.	Initial questionnaire filled out by participants with the help of trained nurses. RF info obtained and former and present use of hormone therapy. Use of hormones verified by nurse and presriptions checked. Interviews occurred q 2 years for three times. Estrogen exposure = never, former and current users. Mean oral dose of estradiol was 1.46 mg, mean duration of current use was 8.2 yr. 1707 women had hysterectomies; Non-hysterectomised women, N=514, unopposed current ERT use, and N=139 used opposed ERT.	Cardiovascular disease Coronary artery disease (CAD) Acute myocardial infarction (AMI) Stroke National Death Register in Finland/death certificates bu ICD9 codes. National Agency for Welfare and Health kept nat'l register of hospital discharges for cardiovascular disease and stroke.	53,305 person-yrs.	social class, smoking, age, BMI, DM, HTN, CAD and cardiac failure. Not adjusted for lipids, exercise, ETOH and family history.

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Sourander 1998[51]	Stroke Morbidity Former users RR 1.08(0.88-1.71) Current users RR 0.86(0.42-1.75)	Former users RR 1.05 (0.41-2.68) Current users RR 0.16(0.02-1.18)	Cardiovasc. Disease mortality Former RR 0.75(0.41-1.37) **Current RR 0.21(0.08-0.59)** CAD mortality Former RR 0.64(0.27-1.47) **Current RR 0.19(0.05-0.77)**	Good; F/U 100% ; homogeneous population; appropriate adjustment of confounders. 97% response rate.	Not adjusted for lipids.

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Cauley 1997[50]	N=9704 non-African American women, >= 65 yrs old. Recruited for the Study of Osteoporotic Fractures from 4 communities: Portland, OR, Minneapolis, MN; Baltimore County, MD; Monongahela Valley near Pittsburgh, PA. Women recruited from population-based lists (licensed drivers, registered voters and HMOs). Analyses restricted to women with known oral HRT use.	Estrogen +/- progesterone exposure obtained at baseline interview and updated on third clinical visit (1991). 14% currently using oral HRT, 80% ERT, 20% CHRT. ~22% past use of HRT. HRT use = never, never (n=4995) or less than 1 year (n=745); past, past use 1 yr or longer; current, use for >= 1 yr.	Death due to: Stroke All cardiovascular disease Coronary Heart disease (CHD), (incl. MI and sudden death) All cancers All cause mortality Death Certificates	~6 years 99% complete through 10/31/94.	Adjusted for age, clinic, education, h/o surgical menopause, DM, stroke or HTN, ETOH, health status, smoking, exercise, BMI, waist-hip ratio. No adjustment for lipids, SES.

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Cauley 1997[50]		Past users RR 0.85(0.48-1.49) Current users RR 0.47(0.20-1.08)	Duration of use 1-9 y RR = 0.66 (0.20-2.20) >=10 y RR = 0.38 (0.13-1.10)	Good; 99% f/u. Good adjustment for confounding. Internal controls, with external US controls.	RR of all CVD and CHD on HRT >= 10 years was significant decrease, **RR 0.30(0.16-0.57)** and RR **0.25(0.09-0.68)**, respectively. Current users: all CVD **RR 0.46(0.29-0.73)**; CHD **RR 0.49(0.26-0.93)**; All cause mortality: **current** **RR 0.69(0.54-0.87)** **past** **RR 0.79(0.66-0.95)** Healthy user effect Comparison of SMR on internal controls to US population, white women. Low ERT prevalence and limited power

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Singh PN, Lindsted KD, Fraser GE. Body weight and mortality among adults who never smoked. Am J Epidemiol. 1999;150(11):1152-1164.	Adventist Health Study Cohort I N=20,346(13281 women; 7065 men) Health, SDA's, white, never-smoking, no CAD, stroke or cancer at baseline, aged 25-84. Younger cohort (25-54 yr) - 29% menopausal Older cohort (55-84 yr) - 96% menopausal; 47% participated in Adventist mortality study (1960-1985) - subcohort. 1976-1988	HRT info obtained from census questionnaires, classified as never, current and past use. Duration of use also obtained.	BMI and mortality cerebrovascular mortality Deaths ascertained by record linkage with California Death Certificate File and National Death Index and church records.	F/U 12 years (1976-1988); F/U 96-97% complete	Age; All were never smokers at baseline; Not adjusted for DM or HTN.

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Singh PN, Lindsted KD, Fraser GE. Body weight and mortality among adults who never smoked. Am J Epidemiol. 1999;150(11):1152-1164.	RR of Death due to cerebrovasc. dz, HTN and other CV dz: ***HRT>5 yrs:*** (Quartile BMI) 1 5 Baseline BMI 1.4 1.4 n = 480 (0.7-2.6) (0.7-2.6) Stable wt. 0.4 2.0 n = 149 (0.05-3.4) (0.5-7.5) ***HRT <5 yrs:*** (Quartile BMI) 1 5 Baseline BMI 0.8 1.9 n=480 (0.3-2.0) (0.9-3.7) Stable wt. 3.11 2.0 n=149 (0.8-11.6) (0.4-9.3)	Control group Nonusers Deaths n=480 1 5 1.9 (1.3-3.0) 1.7 (1.1-2.7) n=149 1 5 1.8 (0.4-9.3) 2.0 (0.9-4.2)		Poor Used death certificate data only; strokes not classified (ie. SAH, TES, ICH); Not adjusted for HTN, DM. Good F/U. Defined, comparable population.	Comparison/referent group NOT non-users

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Fung, 1999[57]	Cohort of middle to upper class Caucasian women from Rancho Bernado, CA; aged 60 or older; no h/o of stroke. Initial survey 1972-74 Repeat survey/questionnaires 1984-1987 (80% of surviving cohort) - baseline survey N=1031 Cohort (84-87 survey) divided into current users(CU) N=278, past users(PU) N=459; and never users(NU) N=294	Info obtained by trained interviewer using standard Rancho Bernardo Study and Rose questionnaires; HRT use validated by examining pills and/or prescriptions by nurse. (92.4% of CU was validated) Current use (within the past two weeks). (76% taking CEE; 29% also taking progestin, mainly MPA F/U visit 1995 - 433 participants: 32.6% - CU; 45.3% PU; 22.2% NU	Fatal/Nonfatal Strokes Deaths = 263 (25.5% of cohort) 178 death certificates listed CVD (67.7%) and 37 listed stroke as cause or contributing to cause of death. Fatal Strokes: 7 in current users 16 in former users 14 in never users Vital status determined by annual mailers. Deaths verified with death certificates, ICD-9 codes; in random 1/3 of subjects, validation of cause of death attempted by interviews with next of kin, MD and hosp. records. Fatal CVD confirmed by panel of cardiologists in 85% of cases.	average 8.75 years; Vital status determined for 99% of participants	adjusted for age, current smoking, systolic blood pressure and diabetes. Not adjusted for ethnicity or SES (restricted at entry by population location)

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Fung, 1999[57]	For TIA or non-fatal stroke, N=20 (8 CU, 9 PU, and 3 NU's) CU vs NU = 4.43 (0.83-23.58)	For fatal stroke CU vs. NU = 0.92(0.34-2.49) PU vs. NU = 0.85(0.40-1.81) CU vs. PU = 1.14(0.44-2.93)		Fair; Outcome was stroke death only; F/U 99% complete; homogeneous population; appropriate adjustment of confounders.	Despite small number of events, statistical power sufficient to detect 40% protection from stroke death (1-B = 0.83). Didn't differentiate thrombotic from hemorrhagic strokes. -Recruitment ends 1987; f/u questionnaire in 1995 given to survivors; 433 responded (?out of how many survivors); nonfatal stroke & TIA's addressed at that time. Current users compared to never users were significantly younger (avg. 70.6 vs. 75; p<0.001); had lower BMI (p<0.001); had lower total cholesterol (~224 mg/dl; p<0.001); Lower LDL (126 mg/dl; p<0.001) and higher HDL (74.1 mg/dl p<0.001)

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Grodstein 2000[58]	Women from the Nurses Health Study; age 30-55 y/o, no prev. h/o CVD. 1976-1996. N=70,533	1976 - duration of use obtained 1978 - type of HRT noted 1980 - dose of oral estrogen obtained. Hormone use updated by biennial questionnaire. 44.3% never users f/u time 22.9% past users f/u time 32.8% current users f/u time	Total (NF/F) strokes, Ischemic stroke, SAH, IPH; MI/CABG/Angioplasty, death from CAD. Positive report in questionnaire resulted in review of medical records; NF strokes verified by med. Record if typical neurologic symptoms lasting at least 24 hours and meeting criteria of the Nat'l Survey of Stroke. Stroke classified as ischemic (thrombotic or embolic), SAH, IPH. If no medical record available, case defined as probable if they required hospitalization and letter of interview corrobaorated event. Death reported by subjects family and verified by medical records, autopsy records. Non-respondents searched Nat'l Death Index	up to 20 yr f/u from 1976-1996 (808,825 person-yrs) >90% F/U Mortality data >98%	Adjusted for age, age at menopause, BMI, smoking, DM, HTN, hypercholesterolemia, FH h/o of MI before age 60

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Grodstein 2000[58]	AS (767) IS (432) HS (174) Current 1.13(0.94-1.35) 1.26(1.00-1.61) 0.93(0.64-1.34) Past 1.02(0.85-1.24) 1.01(0.79-1.30) 0.95(0.65-1.40) Any dose: ERT only 1.18(0.95-1.46) CHRT **1.45(1.10-1.92)** 0.625 mg only: ERT only 1.24(0.95-1.62) CHRT **1.54(1.12-2.11)** Duration of use: AS IS HS <1 y 1.32(0.76-2.32) 1.07(0.44-2.61) 1.56(0.63-3.90) 1-1.9 y 1.04(0.55-1.97) 1.32(0.58-3.00) 0.63(0.15-2.59) 2-4.9 y 1.14(0.86-1.52) 1.31(0.90-1.92) 0.95(0.54-1.67) 5-9.9 y 1.05(0.79-1.38) 1.36(0.96-1.92) 0.74(0.40-1.36) >10 y 1.17(0.91-1.49) 1.17(0.84-1.63) 1.03(0.59-1.78) Dose response: AS IS HS 0.3 mg 0.54(0.28-1.06) 0.43(0.16-1.16) 0.51(0.13-2.10) 0.625 mg **1.35(1.08-1.68)** **1.44(1.07-1.93)** 1.41(0.91-2.19) >1.25 mg **1.63(1.18-2.26)** **2.00(1.32-3.05)** 1.18(0.58-2.38) AS = all stroke IS = ischemic stroke HS = hemorrhagic stroke	Current: HRT 0.81(0.54-1.22) ERT 0.81(0.49-1.34) CHRT 1.22(0.65-2.28) N=119 stroke deaths.		Good; Comparable groups, all outcomes considered. Adjusted for major risk factors.	73% strokes confirmed; Major coronary heart dz + stroke: HRT RR 0.71(0.69-0.87), significant due to a preponderance of CHD end points. ERT RR 0.75(0.65-0.87) CHRT RR 0.91(0.75-1.11)

Evidence Table 3. HRT and stroke - cohort studies

Reference	Setting/Study Population	Exposure Measurement/ Risk Factors	Outcomes	Follow-up	Exposure Adjustment
Luoto R, Manolio T, Meilahn E, et al. Estrogen replacement therapy and MRI-demonstrated cerebral infarcts, white matter changes, and brain atrophy in older women: the Cardiovascular Health Study [see comments]. J Am Geriatr Soc. 2000;48(5):467-472.	Cardiovascular health study cohort 2133 women randomly recruited from N. Carolina, California, Maryland & Pennsylvania aged 65-95 y/o between 1992-1994 population-based prospective study	HRT use determined at baseline annual exam by self report and/or prescription check Current, past or never use. ERT current users (n=272) 12.8% ERT past users (n=429) 20.1% CHRT current users (n=87)2.7% CHRT past users (n=54) 2.5% Combined ERT/CHRT HRT current users (n=329) 15% HRT past users (n=483) 23%	MRI infarcts cerebral atrophy white matter changes	Not clear	Only age adjusted for MRI infarcts Adjusted for age, education, race, BP, smoking, hysterectomy, menopause type, medications, ETOH, BMI, live births for cerebral atrophy and white matter changes

Evidence Table 3. HRT and stroke - cohort studies

Reference	MARR of stroke in users vs. nonusers	Stroke Mortality in users compared to nonusers	RR of stroke + Other	Quality of Study	Comments
Luoto R, Manolio T, Meilahn E, et al. Estrogen replacement therapy and MRI-demonstrated cerebral infarcts, white matter changes, and brain atrophy in older women: the Cardiovascular Health Study [see comments]. J Am Geriatr Soc. 2000;48(5):467-472.	MRI infarcts (%) HRT Current (n=88) 28.6% Past (n=142) 29.9% Never (n=403) 29.9% Ptrend= 0.70* (age adjusted)* total number MRI infarcts = 744 (35%)	N/A	Current vs. past vs. never Sulcal warning: Ptrend = 0.07 Bifrontal distance Ptrend = 0.01 Ventricular size Ptrend = 0.01 MMSE score HRT use: 89.2 CI (88.3-90.2) Never use: 87.8 CI (87.3-88.3) Past use: 89.9 CI (89-90.7)	Poor Only age adjusted data for MRI infarcts 63% response rate: (2133 out of 3393 women eligible had MRI scans)	HRT users showed no difference from current, past or never users in terms of prevalence of MRI infarcts Current users had significantly higher education, lower BMI, higher ETOH use No significant dose response relationship found. Also for duration of use. No significant association between white matter change and use of ERT.

Evidence Table 4. HRT and stroke - case control studies

Reference	Setting/Study Population/Date	Cases	Controls	Exposure Assessment/Classification	Confounders Adjusted For
Rosenberg SH, Fausone V, Clark R. The role of estrogens as a risk factor for stroke in postmenopausal women. West J Med. 1980;133(4):292-296.	Case control study involving women 50-80 y/o with Kaiser Foundation Health Plan, from the SF, Redwood City, South SF, Hayward and Santa Clara area. From 1972-1974.	Women >45 yr. Discharged from Northern California Kaiser Foundation Hospital with a diagnosis of stroke from 1972-1974. N=198, 20.7% taking estrogen. After diabetics removed from study, 24% on estrogen	2 matched controls by age with in 5 years and geographic location (same city), randomly selected from Kaiser databank, no history of stroke. N=396, 18.4% taking estrogen; 19.3% on estrogen after diabetics removed from analysis. Primarily used CEE 0.625 mg or 1.25 mg. Average duration of use on 0.625 mg was 7.6 yr, 1/3 of patients; avg. duration of use for 1.25 mg was 7.15 yr, 2/3 patient.	Inpatient and outpatient charts were reviewed by two physician investigators for the use of estrogen. Also for risk factors, cerebral vascular ds., cardiovascular ds., DM, Htn, CAD. Smoking history was unable to obtained reliable b/c of variation in charts. Estrogen use defined as subject cases had to be taking ERT at time of stroke and control case had to be using ERT at the time subject case were matched, when they had stroke. Mailed questionnaires to patients covering info sought in chart review. 84 out of 215 returned. Of those that responded, showed excellent concordance. Stroke data obtained by review of medical records, those with diagnosis of stroke; defined further as occlusive cererovascular disease referable to a specific artery. Excluded intracerebral hematoma and vague diagnosis such as cerebrovascular insufficiency and dizziness. Examined H&P's, labs, xrays and angiograms if available.	Adjusted for age only.

Evidence Table 4. HRT and stroke - case control studies

Reference	HRT & Stroke (MAOR)	HRT Duration (MAOR)	HRT and Time Since Last Use	Other Findings (MAOR)	Quality of Study	Comments
Rosenberg SH, Fausone V, Clark R. The role of estrogens as a risk factor for stroke in postmenopausal women. West J Med. 1980;133(4):292-296.	Stroke F/NF 1.16(0.75-1.77) unadj 1.32(0.84-2.09), after diabetics were eliminated.	nr	nr		Poor - good ascertainment of cases and controls; important confounders not adjusted for, htn, smoking , lipids, FHx.	17 cases eliminated b/c no matched controls could be found. Occurred in the 80-90 year old group; none were on ERT.

Evidence Table 4. HRT and stroke - case control studies

Reference	Setting/Study Population/Date	Cases	Controls	Exposure Assessment/Classification	Confounders Adjusted For
Pfeffer 1978[64]	Case control study involving 15,500 women living in a retirement community in Southern California from 3/64-12/74. Ages 44-100, avg 70.	Female residents in community with first stroke resulting in hospitalization or death. N=258	Drawn from resident populations and matched by age with in 1 year; controls matched to case in 5:1 ratio. N=1260	Estrogen exposure defined as ever vs. never use. Estrogen use assessed from a file of 25,300 original and refill prescriptions filled at the medical center pharmacy between 1964 and 1974. (Of note 81% of cases and controls obtained care from the medical center and of those 92% obtained their prescriptions from that pharmacy.) On second survey on 1/76 or 2/76 79.8% of female residents used the medical center pharmacy as the sole source of prescribed medications. Stroke cases detected by review of discharge diagnostic indices in five hospitals and review of death reports in community medical center. Data of first stroke was abstracted by a neurologist who was blinded to ERT use, BP and glucose tolerance.	Adjusted for HTN, DM and age. Not adjusted for lipids, family history, smoking

Evidence Table 4. HRT and stroke - case control studies

Reference	HRT & Stroke (MAOR)	HRT Duration (MAOR)	HRT and Time Since Last Use	Other Findings (MAOR)	Quality of Study	Comments
Pfeffer 1978[64]	Stroke F/NF 0.97(0.65-1.44) nonembolic infarction 1.13(0.71-1.77) hemorrhagic stroke 0.86(0.00-9.19x10^3) embolic infarction 0.49(0.00-5.38) TIA 2.79(0.67-11.62)	nr	nr		Fair - good ascertainment of cases with nonbiases selection of cases/controls. May have some exposure error given that RX data used and individual info not obtained. Attention to some confounders, but not important ones such as smoking and family history.	There were 6 cases and 22 controls who were identified as ERT users from outpatient charts and not from RX data. Primarily used CEE

Evidence Table 4. HRT and stroke - case control studies

Reference	Setting/Study Population/Date	Cases	Controls	Exposure Assessment/Classification	Confounders Adjusted For
Thompson 1989[59]	Case-control study; Patients from 83 general practices belonging to the Medical Research Council's General Practice Research Framework. Women from UK, white, ages 45-69; 9/81-9/82 - retrospective case retrieval (part 1) N=148, (5 fatal) 9/82-1/86 - part 2 of study N=455 (126 fatal)	N=603; white women age 45-69; 244 cases of stroke; 359 cases of MI;	N=1206; controls were white women, matched to case for age (within 2 years) and for general practitioner. Selected from age/sex register; Difficulty finding controls b/c of non-attendance of interviews (79% selection of first trial)	Coordinating centre(Northwick Park) followed up all notifications of suspected stroke, or MI; copies of med.records, clinical, lab testing and autopsy findings. Classification by WHO criteria; Questionnaires obtained from cases and controls. HRT use info obtained from recorded prescriptions and PMHx; HRT use defined as receiving at least two prescriptions.	Adjusted for marital status, smoking, family h/o MI, h/o htn, venous thrombosis, stroke, MI and DM. No adjustment for SES

Evidence Table 4. HRT and stroke - case control studies

Reference	HRT & Stroke (MAOR)	HRT Duration (MAOR)	HRT and Time Since Last Use	Other Findings (MAOR)	Quality of Study	Comments
Thompson 1989[59]	CVA & MI in women with confounding factors Any HRT = 1.29 (0.82-2.0) Estrogen only = 1.09 (0.65-1.82) Progestogen only = 1.02 (0.45-2.32) Combined E/P = 1.16 (0.43-3.12) OR CVA 1.20, p>0.2	Estimated RR of CVA & MI by duration of use **1-3 mos = 2.14** 4-6 mos = 1.09 7-12 mos = 1.06 13-24 mos = 1.14 >24 mos = 1.19 **p-trend = 0.09**	Estimated RR of CVA & MI 0-1 yr = 1.06 2-5 yrs = 0.74 6-10 yrs = 1.34 11-15 yrs = 1.73 **>15 yrs = 2.44** **p-trend = 0.009**	RR of CVA & MI by # of Prescriptions: 1 rx = 1.02(0.68-1.53); >1Rx = 1.36 (1.01-1.81); p=0.04. (risk of stroke (RR=1.2) vs. MI(RR=1.48) not statistically sig./ no statistical diff between fatal and nonfatal events). *RR by HRT type (>1Rx) Estrogen only = 1.12 (0.79-1.57) **Progestogen only = 1.90 (1.11-3.25); p=0.02 (corresponding RR for fatal events = 5.27; nonfatal events = 1.46; p=0.08 for difference between F/NF events; no diff. between MI or stroke, p=0.2).** Combined = 0.86 (0.43-1.74)	Fair - Good; asc. Cases ok; selection of controls may have some bias - intial 79% response rate; adj for most conf. Except for SES.	Only 1% current users.

Evidence Table 4. HRT and stroke - case control studies

Reference	Setting/Study Population/Date	Cases	Controls	Exposure Assessment/Classification	Confounders Adjusted For
Adam S, Williams V, Vessey MP. Cardiovascular disease and hormone replacement treatment: a pilot case-control study. British Medical Journal Clinical Research Ed. 1981;282(6272):1277-1278.	Women aged 50-59 from England/Wales. 11/78	women aged 50-59 who died in England/Wales during 11/78 due to acute myocardial infarction (AMI) or subarachnoid hemorrhage (SAH) N=23 SAH 4% of cases on ERT.	N=45, randomly selected matched for age from practice list using defined procedure. Unclear where practice list obtained. 7% of controls on ERT	Questionnaire was mailed to 190 practitioners who cared for the women who died of AMI and SAH. Data obtained on medical history, smoking, HRT and menopausal status. 97/190 questionnaires received. Deaths verified by death certificate. No other data given.	Unadjusted.

Evidence Table 4. HRT and stroke - case control studies

Reference	HRT & Stroke (MAOR)	HRT Duration (MAOR)	HRT and Time Since Last Use	Other Findings (MAOR)	Quality of Study	Comments
Adam S, Williams V, Vessey MP. Cardiovascular disease and hormone replacement treatment: a pilot case-control study. British Medical Journal Clinical Research Ed. 1981;282(6272):1277-1278.	RR not reported, unable to estimate from data provided.				Poor. Not adjusted for confounding. Poor response rate from physicians.	

Evidence Table 4. HRT and stroke - case control studies

Reference	Setting/Study Population/Date	Cases	Controls	Exposure Assessment/Classification	Confounders Adjusted For
Longstreth 1994[74]	Population-based case control study; King County, WA. from 7/87 - 6/89	N=103; women 18 yrs. Or older; pre and post-menopausal; Avg. age 57.6 +/- 17.4. Patients recruited from King County, WA from 7/87 - 6/89; invited by PCP; pt. >18 y/o with spontaneous SAH; Primarily white, mean age ~57 +/- 17 yrs. English speaking; Had telephone;	N=206; Identified using random-digit telephone dialing; Two-matched controls per case by age, sex with in 5 yr.; English speaking only; Avg. age 57.4 +/-16.9;	Interview in person,usually at home; info obtained by self-report or proxy. Cases identified by surveillance system relying on physician, hospital and EMS, and King County Medical examiner. Excluded primary intraparenchymal hemorrhage, AVM, trauma and neoplasm.	Controlled for self-reported data vs. proxy derived data.

Evidence Table 4. HRT and stroke - case control studies

Reference	HRT & Stroke (MAOR)	HRT Duration (MAOR)	HRT and Time Since Last Use	Other Findings (MAOR)	Quality of Study	Comments
Longstreth 1994[74]	Age-adjusted OR for risk of SAH in women on HRT. Never user = 1.00 **Ever user = 0.47 (0.26-0.86);** Former user = 0.58 (0.28-1.21); **Current user = 0.38 (0.17-0.84)**	Age adjusted OR for risk of SAH for duration of use of HRT: Never user = 1.00 <1 year = 0.65 (0.26-1.60) **1-5 years = 0.24 (0.07-0.85)** **>=5 years = 0.33 (0.12-0.88)**	Age adjusted OR for risk of SAH by time since last use: Never = 1.00 >15 years = 0.67 (0.21-2.20) 1-15 years = 0.40 (0.11-1.50) **<1 year = 0.32 (0.15-0.69)**	Menopausal status and risk of SAH (age adjusted): Postmenopausal = 1.00 Premenopausal = 0.24(0.09-0.68)	Fair; possibility of inaccurate ascertainment of cases, as it relies on PCP to invite into study; selection of controls by random digit dialing; comparable; Resp. rate: out of 466 elligible controls, 313 participated (67%)	Did not assess estrogen dose or progestins. Cases represented 69% of total cases (103/149); Cases had less education (12.6+/- 2.4 y vs. 13.5+/-2.5 yr); Index and proxy agreement, kappa = 0.58-0.96

Evidence Table 4. HRT and stroke - case control studies

Reference	Setting/Study Population/Date	Cases	Controls	Exposure Assessment/Classification	Confounders Adjusted For
Thrift 1996[77]	Melbourne, Australia; 1990-1992	Pt. With primary ICH between 1990-1992; Ages 18-80 y/o. N=331(total number of cases); 60% men, 90% white; mean age 63.4 y/o;	Controls recruited by nurse home visits and matched with case by age and sex, in the same neighborhood.Total number of controls N=331	Structured questionnaire given by trained research nurses; avg. 6-7 mos after event; controls with in 2 mos of case interview; HRT present if used ever in lifetime. ICH classified by sudden onset of symptoms; CT evidence (~95% cases); Autopsy (<5%); MRI (<1%)	Htn, cholesterol, prev. cardiovascular ds, exercise, BMI, smoking, ETOH; Not Adjusted for DM, Fam. History

Evidence Table 4. HRT and stroke - case control studies

Reference	HRT & Stroke (MAOR)	HRT Duration (MAOR)	HRT and Time Since Last Use	Other Findings (MAOR)	Quality of Study	Comments
Thrift 1996[77]	0.36 (0.14-0.95) N=11, ever-users of HRT N=26, never users	NR	NR		Fair; Good asc. of cases; control select. ok; Resp. rate not clear; not adj for DM	HRT may be associated with decrease risk of ICH (but results only borderline significance). Type of estrogen, whether progestin present not assessed. Duration of use, time of last use not evaluated; Small number of cases of women on HRT.

Evidence Table 4. HRT and stroke - case control studies

Reference	Setting/Study Population/Date	Cases	Controls	Exposure Assessment/Classification	Confounders Adjusted For
Pedersen 1997[72]	Population-based casecontrol study. Denmark, women aged 45-64 1990-1992	Danish women from Danish Nat'l Pt. Register in Denmark. Age 45-64 who had first ever, non-fatal CVA between 1990-1992. N=1422/2584 after exclusions; SAH = 160 ICH = 95 Thromboembolic infarction (TES)= 846; TIA = 321 Strokes defined by WHO, ICD-9 codes 430-438; Validity of stroke diagnoses investigated in random sample of 347 case records (15% of cases)- confirmation of stroke diagnoses based on evidence of acute onset, localized brain dysfunction, results of CT, MRI or arteriography; Diagnoses compared in hospital records, ICD-9 codes.	N=3171/4370 after exclusions; 2 controls matched to each case by age within 3 mos. Controls identified in the Central National Person Register and selected randomly.	Exposure divided into never, former and current use of unopposed estrogen, and current use of combined estrogen-progestagen therapy. Information obtained from questionnaires.	Adjusted for: h/o thromboembolic disorder (other than CVA); treatment of htn; heart disease, anticoagulant therapy; DM, migraine, former use of oral contraceptives; body weight/ height education, marital status, occupational status; smoking habits, physical activity.

Evidence Table 4. HRT and stroke - case control studies

Reference	HRT & Stroke (MAOR)	HRT Duration (MAOR)	HRT and Time Since Last Use	Other Findings (MAOR)	Quality of Study	Comments
Pedersen 1997[72]	HRT/SAH: Adjusted Never use 1.00 Former 0.78(0.46-1.30) UE 0.53(0.23-1.25) combined 1.30(0.84-2.02) ====== HRT/ICH: Never use 1.00 Former 1.09(0.58-2.03) UE 0.18(0.02-1.27) Combined 1.22(0.66-2.23) HRT/TES: Never use 1.00 Former 1.12(0.88-1.42) UE 1.24(0.91-1.70) Combined 1.27(1.00-1.62) ====== HRT & risk of TIA's: Never use 1.00 Former **1.83(1.33-2.51)** UE **2.13(1.41-3.22)** Combined 1.20(0.81-1.76) ======	nr	nr		Good; Accurate case asc. Selection of controls ok; exclusion criteria equally applied; exposure measured by questionnaire and supported by picture of pills; appropriate adjustment for confounders. Response rate 84.3% for cases and 86.3% for controls.	Number of deaths not evaluated.

Evidence Table 4. HRT and stroke - case control studies

Reference	Setting/Study Population/Date	Cases	Controls	Exposure Assessment/Classification	Confounders Adjusted For
Grodstein 1997[53]	Nested case control study within the Nurses Health cohort	Total deaths = 3637 Total stroke deaths = 167 Deaths from stroke from 1976 - 6/1/94 Deaths obtained from Natural Death Index	10 controls per case randomly selected Postmenopausal women free of cancer and cardiovascular disease Matched to case by age (within 1 year) age at menopause	HRT exposure obtained at baseline interview and subsequent biennial questionnaire For each death, HRT status defined by last questionnaire before death or before diagnosis of disease that led to death ICD defined codes 430-438	Adjusted for age, age at menopause, type of menopause, BMI, DM, BP, cholesterol, smoking, past OCP use, family h/o MI and breast cancer, parity, age at menarche, time period
Petitti 1998[71]	Postmenopausal women 45-74 hospitalized for stroke in Northern Calif. Kaiser Facilities (10) 11/91-11/94;	N=349; Initially 885 possible stroke cases, 758 of which confirmed; (550 - ischemic; 201 -hemorrhagic; After exclusions, number of ischemic strokes was 349; no. of hemorrhagic strokes = 83; Detailed data on hemorrhagic stroke not presented in study secondary to small number of cases. cases identified from hospital admissions/discharge records, ER logs, payments for out of plan hospitalization; 69% white.	N=349; controls matched on birth year and facility of care for each case subject. 81% white	HRT exposure obtained by interview; proxy responses excluded secondary to underreporting; did not use medical records for analysis of HRT use. Info about confounders determined by history, questionnaire. Outcome: Stroke diagnosis established by records reviewed by 2 physicians with discrepancies adjudicated by project neurologist. Had defined protocol, subclassified into hemorrhagic or ischemic infarctions. Was hemorrhagic if: blood found on CT or MRI; nontraumatic LP with blood or xanthochromia, or if intracerebral blood found at autopsy, cerebral angioography or at surgery. Remaining strokes were classified as ischemic.	Adjusted for smoking, htn, DM, prior CVA or TIA, BMI, ethnicity, education

Evidence Table 4. HRT and stroke - case control studies

Reference	HRT & Stroke (MAOR)	HRT Duration (MAOR)	HRT and Time Since Last Use	Other Findings (MAOR)	Quality of Study	Comments
Grodstein 1997[53]	Never use = 1.00 Current HRT use: 0.68 (0.39-1.16) past HRT use: 1.07 (0.68-1.69)				Good	
Petitti 1998[71]	Never use = 1.00 Current HRT/ERT use = 1.03 (0.65-1.65) Past HRT/ERT use = 0.84 (0.54-1.32)	Never use = 1.0 < 1 y use = 0.75 (0.23-2.42) 1-4 y use = 0.67 (0.26-1.73) 5-9 y use = 0.69 (0.28-1.72) >10 y use = 1.37 (0.79-2.38) Past HRT/ERT use = 0.85 (0.54-1.33)		Risk of Hemorrhagic stroke in current users compared with never users was OR = 0.33 (0.12-0.96), based on 83 case/control sets (after adjusting for smoking, HTN, DM, BMI, ethnicity and education.)	Fair- eliminated fair number of cases due to various reasons; exposure equally ascertained, but by interview only.	No mention of fatal case numbers. ~201/550 cases of IS excluded (pt/md refusal; proxy interview; missing HRT data): 118/201 cases of HS excluded for similar reasons. No significant difference in previous/current use of HRT between cases and controls.

Evidence Table 5. Angiography Studies – HRT and Coronary Artery Disease – Secondary Prevention

Author, Journal, Date	Setting, Study Population Date	Measurement of Hormone Exposure, Co-mobidity, Other Risk Factors	Type Controls	Outcomes Evaluated, Documentation	FU Length Loss to FU
Gruchow, 1988[79]	993 female patients undergoing angiography ages 50-75 in Milwaukee CVD Data Registry 1972-1985	Questionnaire Lab Exam Use = at time of angio or in 3 months proceeding	Internal	Degree coronary stenosis	NA
Sullivan, 1990[81]	Cohort of all women consecutively undergoing angiography at Baptist Memorial, TN 1972-1985 referred from 5 states. 3 Cohorts 1. ≥ 70% stenosis 2. < 70% stenosis 3. 0 stenosis	History, exam, labs, questionnaires sent to physicians. Estrogen use not specifically obtained.	Internal	Follow-up questionnaires, not exactly specified	1985

Evidence Table 5. Angiography Studies – HRT and Coronary Artery Disease – Secondary Prevention (continued)

Study	Assessment of CVD risk factors	RR CVD Among Users Compared to Non-Users	RR by Duration HRT	RR CVD Associated With Current Use and By Duration	RR CVD Associated With Pass Use and By Duration	CVD Mortality RR Among Users Compared to Non-Users	Comments
Gruchow, 1988[79]	Adj. for: age tos exercise BMI	B= -0.15 P< 0.1 OR severe CAD use/non **0.37(0.46-0.29)** OR mod CAD use/non **0.59(0.73-0.48)** ✲ After HDL/LDL levels entered estrogen not associated with decreased risk					Prevalence cases not excluded (38% past MI, 69% unstable ? angina) Survivors Poor classification use (sick may have gone off) ?Generalizability ✲ Important covariance with HDL Quality: poor
Sullivan, 1990[81]	Adj for: age smoking HTN DM Chol Not Adj. BMI Alcohol Family HDL					RR death among women > 70% stenosis: use/non (adj) ***0.16 (0.04 – 0.66)** Moderate CAD 10 yr. surv. (unadj): use 96% **non 85%** **p = 0.027** no CAD 10 yr surv. (unadj): use 98% non 91% p = NS	No duration/dose data Fatal CAD/MI excluded – Prevalence/incidence bias ? if controls representative of populations without CAD. Quality: fair

Evidence Table 5. Angiography Studies – HRT and Coronary Artery Disease – Secondary Prevention (continued)

Study, Year, Journal	Setting/Study Population Date	Cases	Controls	Exposure Assessment/ Classification	Important Confounders Not adjusted for
Sullivan, 1988[80]	6452 consecutive women having coronary angiography at Baptist Memorial, TN 1972-1984	n=1444 defined as > 70% stenosis in one or more epicardial arteries	N=744 No stenosis at angiography	Medical records Defined as estrogen users if using at time of angiography, risk factors obtained from records. No duration data available	Family history Exercise BMI
McFarland, 1989[82]	2 hospital cardiology practices in South Carolina	All women ages 35-59 who had undergone angiography and had $\geq$ 70% stenosis. N=137	From this group all women with normal coronaries N=208	Use < 6 months = non-use	Only age adjusted

Evidence Table 5. Angiography Studies – HRT and Coronary Artery Disease – Secondary Prevention (continued)

Study, Year, Journal	Major Findings Multivariable Adjusted Odds Rating (MAOR) 95% CI	Major Findings by Duration Use HRT (MAOR)	Time Since Last Use	Time Since Starting Estrogen	Findings by Other Sub-group Analyses (MAOR)	Comments
Sullivan, 1988[80]	Stratified by age (unadj) <59 **0.44 (0.26 – 0.76)** 60-69 **0.42 (0.18 – 0.93)** 70+ 0.56 (0.11 – 2.96) Multivar adjusted-OR of having > 70% **0.58(0.38-0.97)**					Symptomatic patients, Quality: fair, medical records likely bias in risk factor assessment.
McFarland, 1989[82]	Age adj use/non use **0.50(0.3-0.8)** Age adj – natural menopause 0.7(0.3-1.9) Hysterectomy 0.6(0.3-1.2) Bilateral oopherectomy **0.3(0.1-0.8)**					Quality: poor no adjustment for confounding no response rates reported

Appendix 1. Search Strategies

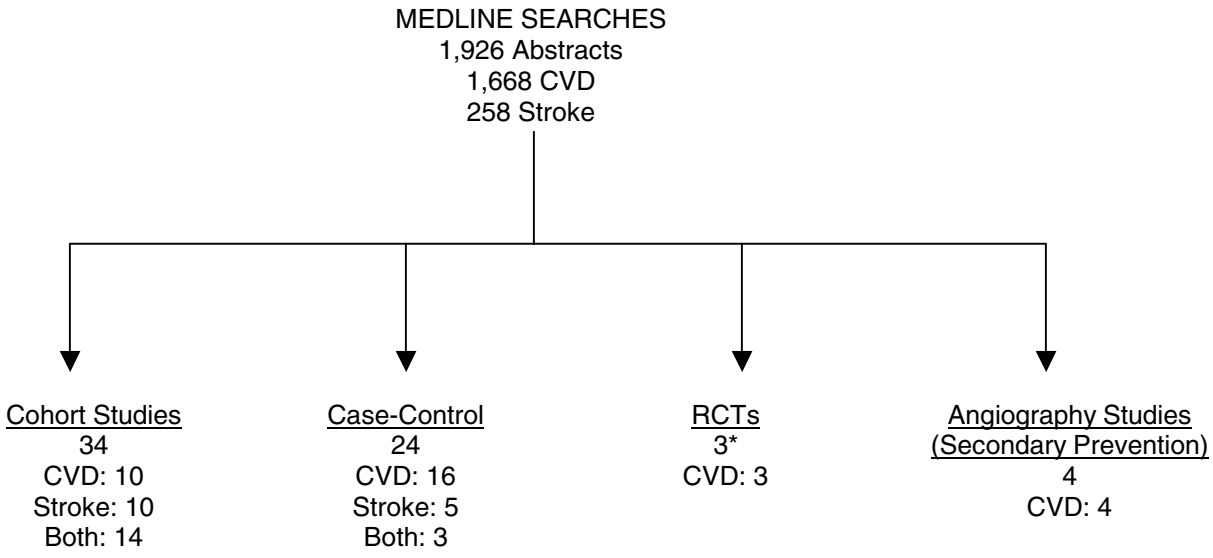
Hormone Replacement Therapy and Cardiovascular Disease

1 exp hormone replacement therapy/
2 hormone replacement.tw.
3 estrogen replacement.tw.
4 exp estrogens/ad,tu
5 exp estrogens, synthetic/ad,tu
6 1 or 2 or 3 or 4 or 5
7 exp cardiovascular diseases/
8 exp myocardial infarction/
9 heart disease$.tw.
10 cardiovascular disease$.tw.
11 (heart attack or myocardial infarct$).tw. [tw=abstract, title]
12 7 or 8 or 9 or 10 or 11
13 6 and 12
14 limit 13 to human
15 limit 14 to english language
16 14 not 15
17 limit 16 to abstracts
18 15 or 17

HRT and Stroke Search

1 exp hormone replacement therapy/
2 hormone replacement.tw.
3 estrogen replacement.tw.
4 exp estrogens/ad,tu
5 exp estrogens, synthetic/ad,tu
6 1 or 2 or 3 or 4 or 5
7 exp cerebrovascular disorders/ or "stroke".mp.
8 6 and 7
9 limit 8 to human

Appendix 2. Hormone Replacement Therapy and Cardiovascular Disease
Included Studies



*Includes preliminary findings from the Women's Health Initiative

Appendix 3
Criteria for Grading Individual Studies and Linkages in the Analytic Framework

Largely during 1999, the Methods Work Group for the US Preventive Services Task Force (USPSTF) developed a set of criteria by which the quality of individual studies could be evaluated in terms of both internal validity and external validity and a related set of criteria relating to the linkages within the analytic framework for the topic of a given systematic evidence review (SER). The USPSTF provisionally accepted these approaches and criteria, and the associated definitions of quality categories, at two quarterly meetings in mid-1999.

The first part of this Appendix describes the criteria relating to internal validity and the procedures that topic teams follow for all updates and new assessments in making these judgments. The overall evaluation for each study is recorded in the Evidence Tables typically provided in Appendix D of any SER. The second part of this Appendix provides similar information relating to aggregate internal validity, aggregate external validity (generalizability), and consistency of the results from related sets of articles (also referred to as coherence).

Criteria for Grading the Internal Validity of of Individual Studies

Introduction

All topic teams will use initial "filters" to select studies for review that deal most directly with the question at issue and that are applicable to the population at issue. Thus, studies of any design that use outdated technologies or technologies that are not feasible for primary care practice may be screened out before the abstraction stage, depending on the topic and the

decisions of the topic team. The teams will justify such exclusion decisions if there could be reasonable disagreement about this step. The criteria below are meant for those studies that pass this initial filter.

Design-Specific Criteria and Quality Category Definitions

Presented below are categories of criteria for which to judge internal validity; they are given for several major study designs (systematic reviews, case-control studies, randomized trials and cohort studies). With these are given general definitions of three ratings — "good," "fair," and "poor" — relating to those criteria. These specifications are not meant to be rigid rules. Rather, they are intended to be general guidelines, and topic teams can make individual exceptions when those are cexplicitly explained and justified.

In general, a "good" study is one that meets all criteria well. A "fair" study is one that meets all but one criterion but has no known "fatal flaw." "Poor" studies have at least one fatal flaw.

Systematic Reviews

Four categories of criteria apply to systematic reviews. They are:

1. Comprehensiveness of sources considered/search strategy used;
2. Standard appraisal of included studies;
3. Validity of conclusions; and
4. Recency and relevance of the included studies.

The definitions of the three rating categories for these types of studies are as follows:

Good: Recent, relevant review that has comprehensive sources and systematic search strategies; explicit and relevant selection criteria; standard appraisal of studies; and valid conclusions.

Fair: Recent, relevant review that lacks comprehensive sources and systematic search strategies but is not clearly biased and meets the other criteria for a rating of "good."

Poor: Outdated, irrelevant, or biased review that lacks comprehensive sources and/or systematic search strategies, explicit and relevant selection criteria, and/or standard appraisal of studies or that draws invalid conclusions.

Case-Control Studies

Six categories of criteria apply to case-control studies. They include:

1. Accurate ascertainment of cases.
2. Nonbiased selection of cases and controls with exclusion criteria applied equally to both.
3. Response rate.
4. Diagnostic testing procedures applied equally to each group.
5. Measurement of exposure accurate and applied equally to each group.
6. Appropriate attention to potential confounding variables.

The definitions of the three rating categories for these types of studies are as follows:

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.

Fair: Appropriate ascertainment of cases and controls and exclusion criteria applied equally to cases and controls, and without major apparent selection or diagnostic work-up bias;

response rate less than 80 percent; or attention to some but not all important confounding variables.

Poor: Major selection or diagnostic work-up biases; response rates less than 50 percent; or inattention to confounding variables.

Randomized Controlled Trials and Cohort Studies

Seven categories of criteria apply to RCTs and cohort studies. They include:

1. Initial assembly of comparable groups.
   a. For RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups.
   b. For cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts.
2. Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination).
3. Levels of follow-up: differential loss between groups; overall loss to follow-up.
4. Measurements: equal, reliable, and valid, and including masking of outcome assessment.
5. Clear definition of interventions.
6. All important outcomes considered.
7. Analysis:
   a. For RCTs: intention-to-treat analysis.
   b. For cohort studies: adjustment for potential confounders.

The definitions of the three rating categories for these types of studies are as follows:

Good: Comparable groups assembled initially and maintained throughout the study; follow-up at least 80 percent; reliable and valid measurement instruments applied equally to the groups; outcome assessment masked; interventions defined clearly; all important

outcomes considered; appropriate attention to confounders in analysis; for RCTs, intention-to-treat analysis.

Fair: Generally comparable groups assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments acceptable (although not the best) and generally applied equally; outcome assessment masked; some, but not all important, outcomes considered; appropriate attention to some, but not all, potential confounders; for RCTs, intention-to-treat analysis.

Poor: Groups assembled initially not close to being comparable or not maintained throughout the study; measurement instruments unreliable or invalid or not applied at all equally among groups; outcome assessment not masked; key confounders given little or no attention; for RCTs, no intention-to-treat analysis.

Diagnostic Accuracy Studies

Seven categories of criteria apply to diagnostic accuracy studies. They include:

1. Screening test relevant, available for primary care, adequately described.
2. Study uses a credible reference standard, performed regardless of test results.
3. Reference standard interpreted independently of screening test .
4. Handles indeterminate results in a reasonable manner.
5. Spectrum of patients included in study.
6. Sample size.
7. Administration of reliable screening test

The definitions of the three rating categories for these types of studies are as follows:

Good: Relevant, available screening test; credible reference standard; interpretation of reference standard independent of interpretation of screening test; reliability of test assessed; few indeterminate results, or indeterminate results handled in a reasonable manner; large

same size (more than 100 subjects) and a broad spectrum of patients with and without disease.

Fair: Relevant, available screening test; reasonable although not best reference standard; interpretation of reference standard independent of interpretation of screening test; moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size or very narrow spectrum of patients.

Criteria for Grading Linkages in the Analytic Framework

Introduction

As documented just above, the USPSTF Methods Work Group developed a set of criteria by which the quality of individual studies could be evaluated in terms of both internal validity. The Methods Work Group also developed definitions and criteria for judging the strength or quality of evidence for key questions — i.e., linkages in the analytic frameworks — for the topics of SERs. These quality criteria were discussed at the May 1999 quarterly meeting and were essentially adopted for use by the Evidence-based Practice Centers in developing their first set of SERs. This document describes the criteria relating specifically to linkages in the analytic framework.[1]

[1] The USPSTF is developing a separate set of criteria for rating its recommendations about an entire preventive service, including policies for appropriate extrapolation to populations or settings not reflected in the reviewed literature. These criteria are expected to be put into final form in early 2000. However, because the SERs do not contain USPSTF recommendations, those ways of grading recommendations are not dealt with here.

Linkage Category Definitions

The rating scheme for grading the evidence for a linkage in the analytic framework rests on three classes of criteria: aggregate internal validity, aggregate external validity, and consistency or coherence. The Methods Work Group did not establish set formulae for arriving at any linkage score for these criteria sets. As with the criteria for quality of individual articles, they are intended to be applied as general guidelines, and the judgments are made implicitly. Judgments can be made about evidence of benefits and evidence of harms. In addition, a summative grade — i.e., an overall rating — combining the evaluations of the three categories defined below can be given.

Also as with the criteria for individual studies, these three categories can be labeled as "good," "fair," or "poor." That is, the linkages can be understood to be supported by good evidence, fair evidence, or poor evidence. The summative, overall rating can also range from good to poor.

Aggregate Internal Validity

This category refers to the overall extent to which data are valid for conditions addressed within studies. It would be rated according to quality grading information about individual studies.

Aggregate External Validity

This category concerns the generalizability of evidence to questions addressed by the linkage. This would include the concordance between populations, interventions, and outcomes in the studies reviewed (on the one hand) and those to which the linkage pertains (on the other). In short, this category reflects the applicability of the evidence to real-world conditions.

The Methods Work Group expects that differences between conditions examined in studies and those addressed by the linkages should be considered if they could potentially influence outcomes. These might include (but not necessarily be limited to): (a) biologic or pathologic characteristics; (b) incidence and prevalence of clinical conditions; (c) distribution of comorbid conditions that might affect outcomes; and (d) likelihood of acceptability and adherence on the part of patients or providers (or both).

Consistency

This category relates to the overall "coherence" of the body of evidence relating to the linkage. Specifically, it includes the number of studies, the homogeneity of those studies (in terms of clinical conditions, populations, settings, and the like), the level of precision of findings in the studies, and the direction of results. In addition, it can include dose-response relationships.

Appendix 4. Statistical analysis report for postmenopausal hormone replacement therapy and cardiovascular disease

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August 20, 2002

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Cardiovascular disease

Four outcomes were analyzed separately: the incidence and mortality of cardiovascular disease and coronary artery disease. Studies contributed multiple data points if they reported separate results for current and past hormone replacement therapy (HRT) users. Such studies almost always did not report results for the combined group of *ever* HRT users. The results from studies that did not distinguish current users from past users were categorized under *ever* users. All studies reported relative risk (RR) estimates using either odds ratios or hazard ratios. Adjusted relative risks were used because they represent the original authors' best estimate of the relative risk. The logarithm of the relative risk (logRR) is used as the effect size data point since it is assumed to be Normally distributed. Standard errors for logRR were calculated from reported confidence intervals or p-values.

1 Hierarchical model

Because of the nature of how the studies reported their results we wanted to preserve the stratification by exposure status but also allow for the estimation of a global measure of relative risk under any HRT exposure while allowing for variation between status categories. The linear predictor for study i is defined as μ_i.

$$\mu_i = \beta_{\text{current}} x_{i,\text{current}} + \beta_{\text{past}} x_{i,\text{past}} + \beta_{\text{ever}} x_{i,\text{ever}} \tag{1}$$

where $x_{i,\text{current}}$, $x_{i,\text{past}}$, and $x_{i,\text{ever}}$ are indicator variables for whether data point i corresponds to the exposure category. The relative risk of each exposure status is a sample from a hyperdistribution of relative risks for any HRT exposure and are distributed as

$$\beta_{\text{current}}, \beta_{\text{past}}, \beta_{\text{ever}} \sim \text{Normal}\left(\mu_{\text{any HRT}}, \sigma^2_{\text{any HRT}}\right)$$

The global effect of any exposure is represented by $\mu_{\text{any HRT}}$. Variance between exposure categories is represented by $\sigma^2_{\text{any HRT}}$. The model allows for further stratification by adding terms to μ_i, such as $\beta_j x_{ij}$

The logarithm of the relative risk is assumed to have the following distribution:

$$\log(RR_i) \sim \text{Normal}\left(\mu_i + z_i\sqrt{\tau^2}, s_i^2\right)$$

where $z_i \sim \text{Normal}(0, 1)$ and s_i is the standard error calculated from reported confidence intervals or p-values. τ^2 represents between-study variance and z_i represents the deviation between the $\log(RR_i)$ of the individual study or data point and the population. Under a fixed effects model $\tau^2 = 0$ while under a random effects model $\tau^2 > 0$.

Fitting the model with Markov Chain Monte Carlo The model was estimated using a Bayesian data analytic framework. The data were analyzed using WinBUGS, which uses Gibbs sampling to simulate posterior probability distributions. Noninformative, proper, prior probability distributions were used unless otherwise specified. The prior probability distributions used were:

$$\begin{aligned} \beta_j, \beta_{\text{current}}, \beta_{\text{past}}, \beta_{\text{ever}}, \mu_{\text{any HRT}} &\sim \text{Normal}(0, 10^6) \\ \tau^2, \sigma^2_{\text{any HRT}} &\sim \text{Inv-gamma}(0.001, 0.001) \end{aligned}$$

Five separate Markov Chain Monte Carlo chains were used, with overdispersed initial values, to generate draws from posterior distributions. Point estimates (mean) and 95% credible intervals (2.5 and 97.5 percentiles) were derived from the subsequent $5 \times 2,000$ draws after reasonable convergence of the five chains was attained. Iterations that result in very large or very small values were trimmed when calculating means. Kernal density estimation were used to generate smoothed densities.

2 Results

2.1 Cardiovascular disease mortality

The results from the hierarchical random-effects meta-analysis models are shown in Table 1. Figure 1 shows kernal density estimates for the relative risks of each exposure status and for any HRT exposure estimated from the model.

2.2 Coronary disease mortality

The results from the hierarchical random-effects meta-analysis models are shown in Table 2. Figure 2 shows kernal density estimates for the relative risks of each exposure status and for any HRT exposure estimated from the model.

Note that the density for ever HRT exposure is pulled toward the any HRT exposure density and is not similar to the relative risk and confidence interval given for the single study of ever HRT exposure.

2.3 Cardiovascular disease incidence

The results from the hierarchical random-effects meta-analysis model are shown in Table 3. Figure 3 shows kernal density estimates for the relative risks of each exposure status and for any HRT exposure estimated from the model.

Note that the densities for each of the exposure status types closely resemble the density for any HRT exposure.

Since there was a previous meta-analysis done on cardiovascular disease incidence, in addition to a noninformative prior, its results are used as the hyperprior in the M2 model fit

$$\mu_{\text{any HRT}} \sim \text{Normal}(0.33, 0.54^2)$$

The Hemminki, 1997 prior did not significantly affect the results from the model fit using a noninformative prior. This is likely due to the large variability in the Hemminki, 1997 results.

2.4 Coronary disease incidence

An important modification is made to the model for this outcome. It was thought that studies that adjusted for socioeconomic status (SES) in their relative risk models have different estimates than

studies that did not adjust for SES. So, an additional term is included in the linear predictor shown in 1. The linear predictor is

$$\mu_i = \beta_{\text{current}} x_{i,\text{current}} + \beta_{\text{past}} x_{i,\text{past}} + \beta_{\text{ever}} x_{i,\text{ever}} + \beta_{\text{SES}} x_{i,\text{SES}} \tag{2}$$

where $x_{i,\text{SES}}$ is an indicator variable for whether the study adjusted for SES.

The results from the model are shown in Table 4. Figure 4 and 5 show kernal density estimates for the relative risks of each exposure status and for any HRT exposure estimated from the model above.

Stratification by other factors Coronary disease incidence was the only outcome where it was thought that it would be worthwhile to explore stratification by other study-level factors as well. Such factors included study design (cohort, case-control, and randomized controlled trial); HRT exposure type (unopposed estrogen (ERT), combined estrogen plus progesterone (CHRT), and unspecified HRT); study quality (fair and good); HRT exposure status (current, past, and ever use); and whether the study adjusted for socioeconomic status (SES), alcohol use, exercise, or cholesterol level.

Table 1: Meta-analysis results for cardiovascular disease mortality.

	Relative risk		95% CI	
Exposure	Mean	Median	Lower	Upper
Current	0.6401	0.6195	0.4359	0.9311
Ever	0.8104	0.7980	0.5820	1.1250
Past	0.7861	0.7740	0.5235	1.0920
Any*	0.7501	0.7302	0.4159	1.2260

* Trimmed mean; lowest and highest 0.5% are trimmed from each tail.

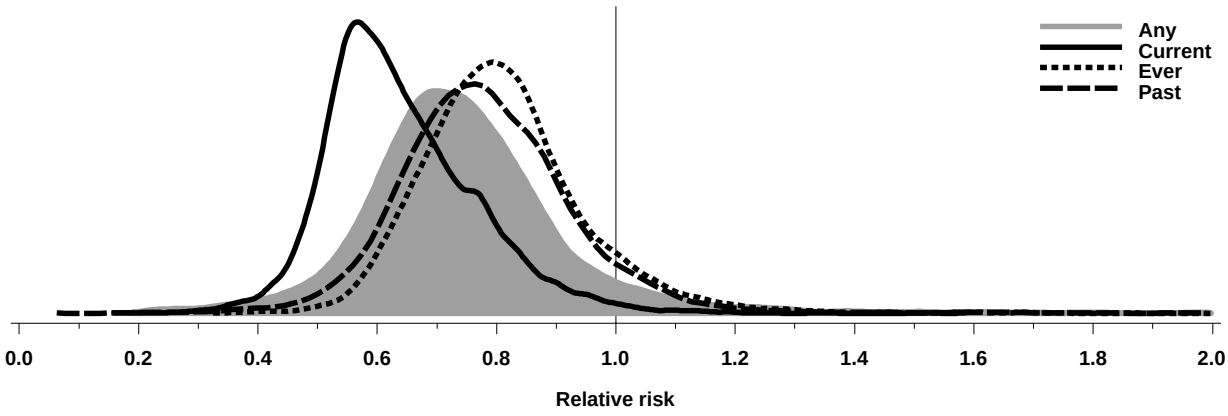

Figure 1: Relative risk densities of cardiovascular disease mortality.

Table 2: Meta-analysis results for coronary disease mortality.

	Relative risk		95% CI	
Exposure	Mean	Median	Lower	Upper
Current	0.6166	0.6023	0.3989	0.9137
Ever*	0.8070	0.7549	0.3663	1.5980
Past	0.7578	0.7538	0.5295	1.0220
Any*	0.7388	0.6997	0.3551	1.4460

* Trimmed mean; lowest and highest 0.5% are trimmed from each tail.

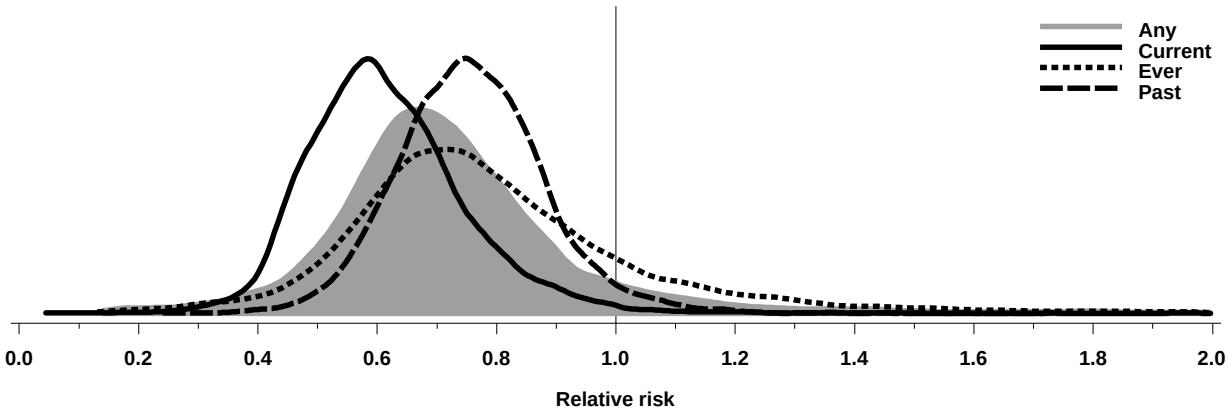

Figure 2: Relative risk densities of coronary disease mortality.

Table 3: Meta-analysis results for cardiovascular disease incidence.

		Relative risk		95% CI	
Prior	Exposure	Mean	Median	Lower	Upper
Non-informative prior	Current*	1.229	1.167	0.7436	2.222
	Ever	1.352	1.302	0.8882	2.065
	Past*	1.241	1.181	0.7089	2.271
	Any*	1.306	1.216	0.6899	2.422
Hemminki, 1997 prior	Current	1.273	1.177	0.8015	1.997
	Ever	1.348	1.307	0.9177	1.997
	Past	1.258	1.188	0.7908	2.082
	Any	1.281	1.232	0.8560	2.004

* Trimmed mean; lowest and highest 0.5% are trimmed from each tail.

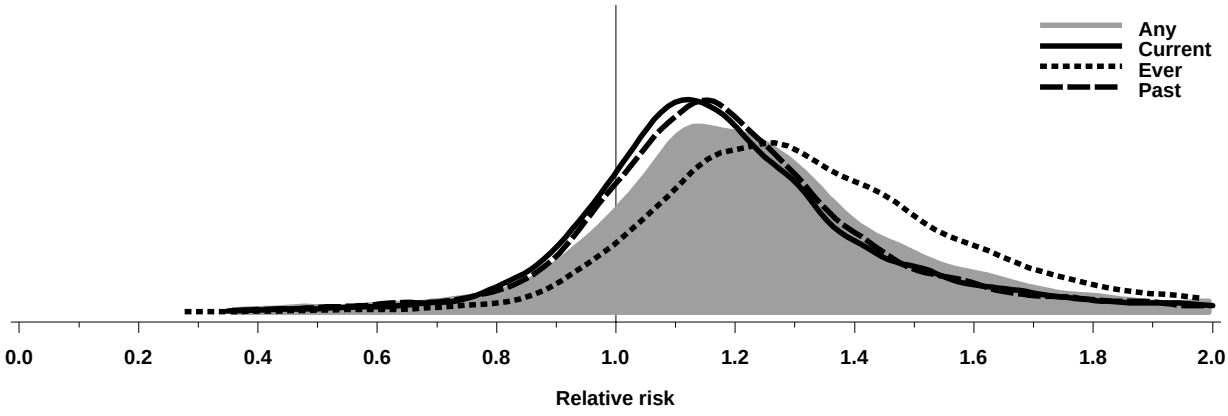

Figure 3: Relative risk densities of cardiovascular disease incidence.

Table 4: Meta-analysis results for coronary disease incidence.

		Relative risk		95% CI	
Model	Exposure	Mean	Median	Lower	Upper
Model 1	Current	0.8057	0.8010	0.6853	0.9555
	Ever	0.9178	0.8871	0.6706	1.3310
	Past	0.8862	0.8795	0.7534	1.0510
	Any	0.8787	0.8551	0.6372	1.2140
Model 2, SES adjusted	Current	0.9743	0.9700	0.8164	1.1570
	Ever	1.1070	1.0820	0.8420	1.5250
	Past	1.0700	1.0660	0.9023	1.2670
	Any*	1.0510	1.0360	0.7862	1.4410
Model 2, not SES adjusted	Current	0.7064	0.7052	0.6379	0.7815
	Ever	0.8022	0.7791	0.6289	1.1030
	Past	0.7751	0.7744	0.6897	0.8654
	Any	0.7747	0.7517	0.5971	1.0180

$\Pr(\beta_{\text{SES}} > 0) = 0.9998$

Results exclude Eaker, 1987 (this study is a reanalysis of the Framingham data reported by Wilson, 1985) and Pfeffer, 1978, ever HRT users (it is assumed that the subjects used in this are a superset of subjects reported as current HRT users). Results including Eaker, 1987 (and excluding Wilson, 1985) and using Pfeffer, 1978, ever HRT users (and not current HRT users) did not produce significantly different results.

* Trimmed mean; lowest and highest 0.5% are trimmed from each tail.

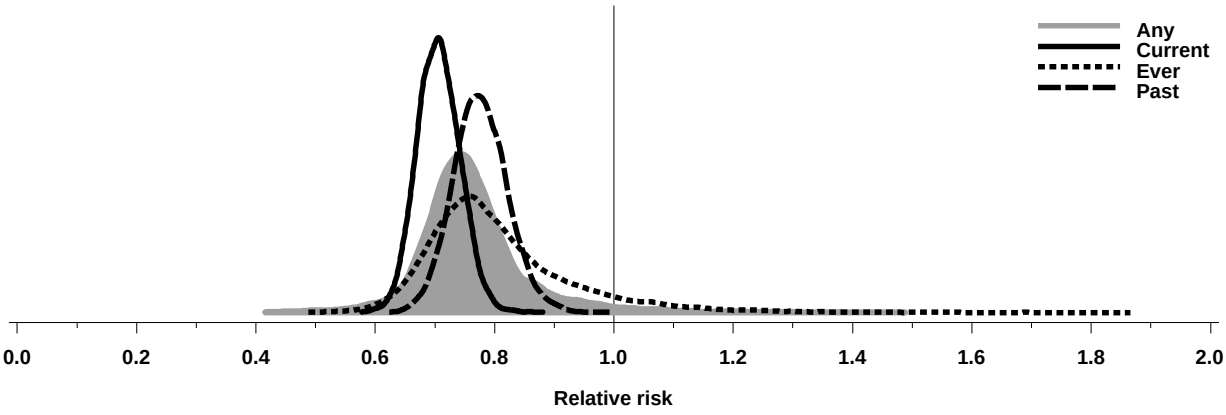

Figure 4: Coronary disease incidence pooled relative risk densities from studies that did not adjust for socioeconomic status.

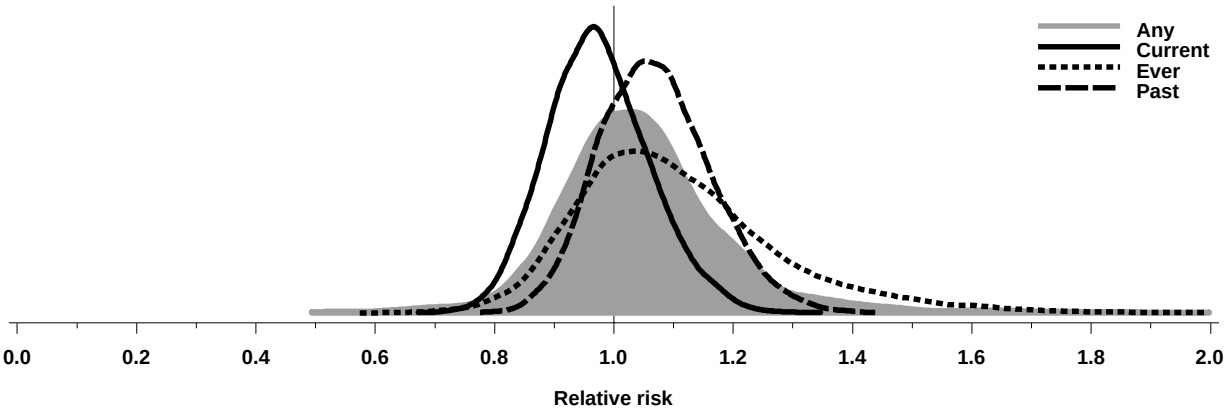

Figure 5: Coronary disease incidence pooled relative risk densities from studies that adjusted for socioeconomic status.

Stroke

Six outcomes were analyzed separately: the mortality from stroke; the incidence from stroke; the incidence from atherothrombotic brain infarction, ischemic stroke, and thromboembolic stroke (ABI, IS, and TES); the incidence from subarachnoid hemorrhage (SAH); the incidence from intracerebral hemorrhage (ICH); and the incidence from hemorrhagic stroke (SAH and ICH combined). Studies contributed multiple data points if they reported separate results for current and past hormone replacement therapy (HRT) users. Such studies almost always did not report results for the combined group of *ever* HRT users. The results from studies that did not distinguish current users from past users were categorized under *ever* users. All studies reported relative risk (RR) estimates using either odds ratios or hazard ratios. Adjusted relative risks were used because they represent the original authors' best estimate of the relative risk. The logarithm of the relative risk (logRR) is used as the effect size data point since it is assumed to be Normally distributed. Standard errors for logRR were calculated from reported confidence intervals or p-values.

3 Random effects model

No differences were found in the results stratified between the three factors of study design (case-control versus cohort design), exposure type (hormone replacement therapy versus estrogen replacement therapy versus combined hormone replacement therapy), and exposure status (current versus past versus ever user). Therefore, the final results presented use an unstratified, intercept-only model, μ.

The logarithm of the relative risk is assumed to have the following distribution:

$$\log(RR_i) \sim \text{Normal}\left(\mu + z_i\sqrt{\tau^2}, s_i^2\right)$$

where $z_i \sim \text{Normal}(0, 1)$ and s_i is the standard error calculated from reported confidence intervals or p-values. τ^2 represents between-study variance and z_i represents the deviation between the $\log(RR_i)$ of the individual study or data point and the population. Under a fixed effects model $\tau^2 = 0$ while under a random effects model $\tau^2 > 0$.

Fitting the model with Markov Chain Monte Carlo The model was estimated using a Bayesian data analytic framework. The data were analyzed using WinBUGS, which uses Gibbs sampling to simulate posterior probability distributions. Noninformative, proper, prior probability distributions were used unless otherwise specified. The prior probability distributions used were:

$$\begin{aligned} \mu &\sim \text{Normal}(0, 10^6) \\ \tau^2, \sigma^2_{\text{any HRT}} &\sim \text{Inv-gamma}(0.001, 0.001) \end{aligned}$$

Five separate Markov Chain Monte Carlo chains were used, with overdispersed initial values, to generate draws from posterior distributions. Point estimates (mean) and 95% credible intervals (2.5 and 97.5 percentiles) were derived from the subsequent $5 \times 2,000$ draws after reasonable convergence of the five chains was attained. Iterations that result in very large or very small values were trimmed when calculating means. Kernal density estimation were used to generate smoothed densities.

4 Results

Results from the meta-analysis are shown in Table 5. Figures 6–11 show kernal density estimates for the relative risks of each outcome.

Table 5: Meta-analysis results from random effects models for stroke.

	Relative risk		95% CI	
Outcome	Mean	Median	Lower	Upper
Stroke mortality	0.7900	0.7844	0.5982	1.014
Stroke incidence	1.118	1.117	1.009	1.233
ABI, IS, and TES incidence	1.202	1.196	1.046	1.404
Subarachnoid hemorrhage (SAH) incidence	0.7997	0.7961	0.5722	1.047
Intracerebral hemorrhage (ICH) incidence	0.7113	0.6877	0.2501	1.287
Hemorrhagic stroke (SAH or ICH) incidence	0.8091	0.8099	0.5931	1.008

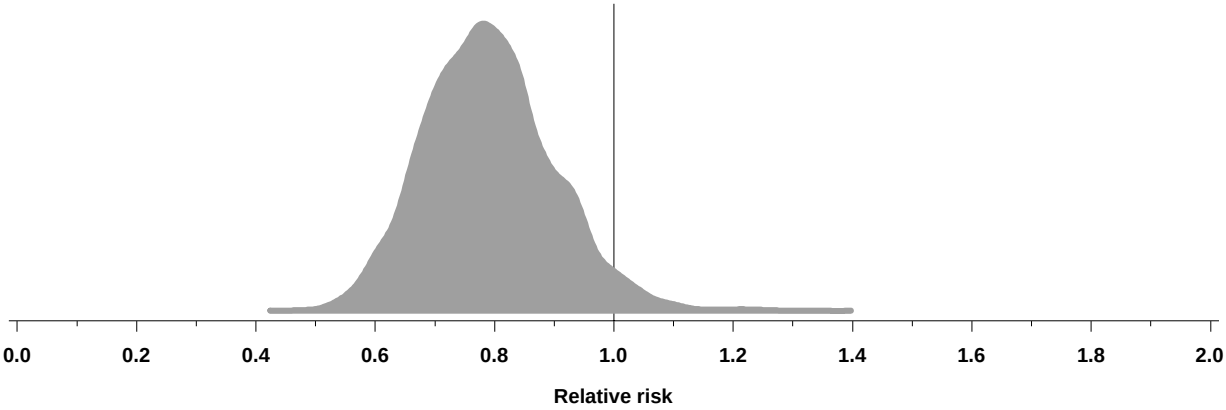

Figure 6: Relative risk density of stroke mortality.

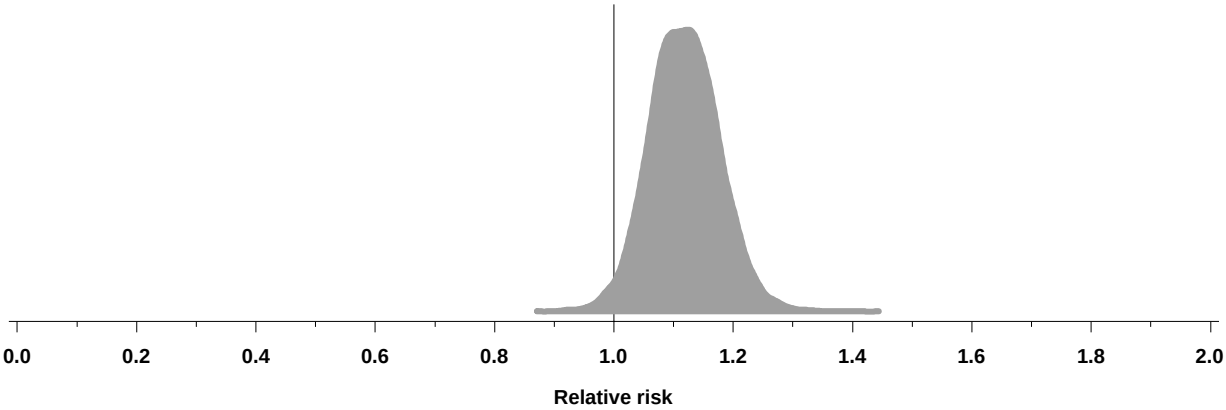

Figure 7: Relative risk density of stroke incidence.

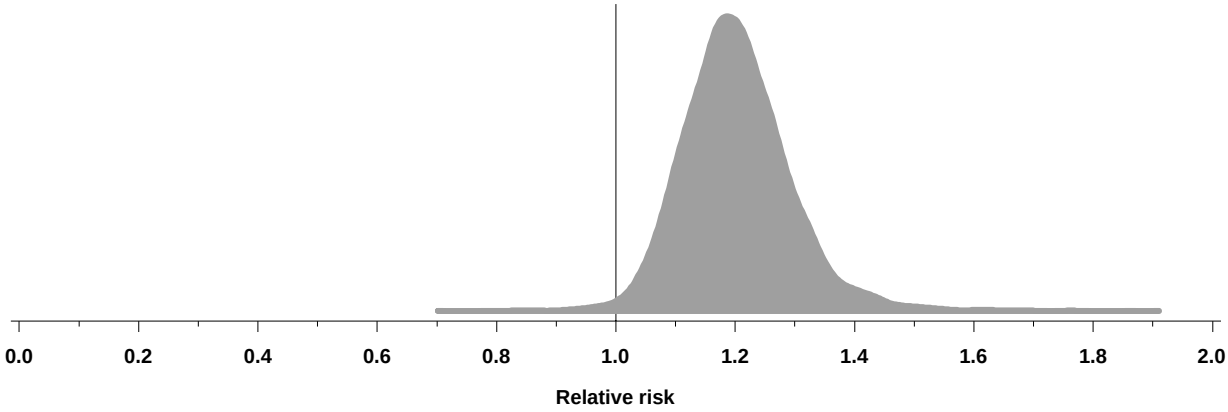

Figure 8: Relative risk density of ABI, IS, and TES incidence.

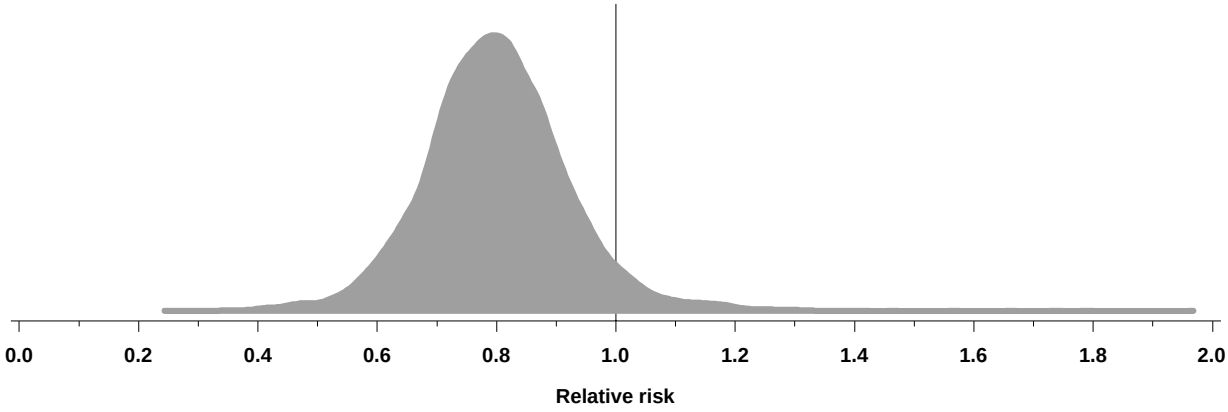

Figure 9: Relative risk density of SAH incidence.

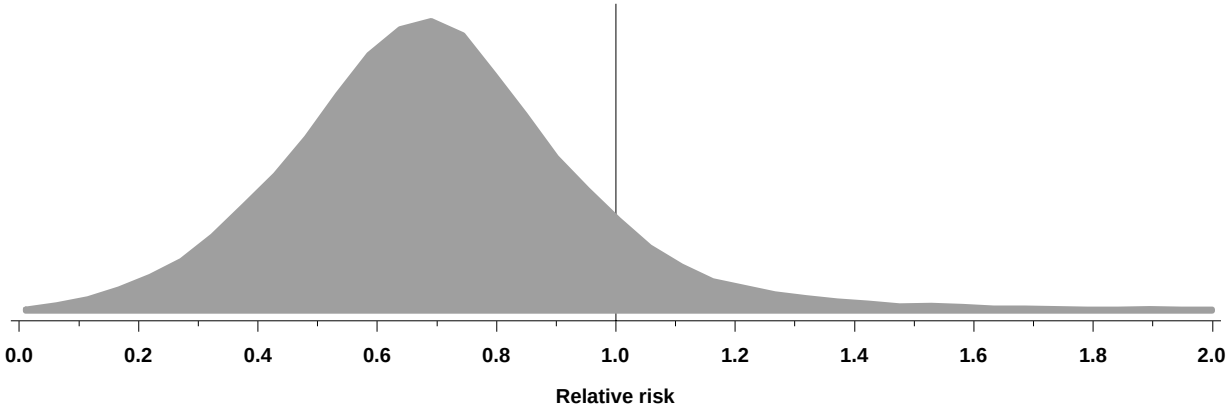

Figure 10: Relative risk density of ICH incidence.

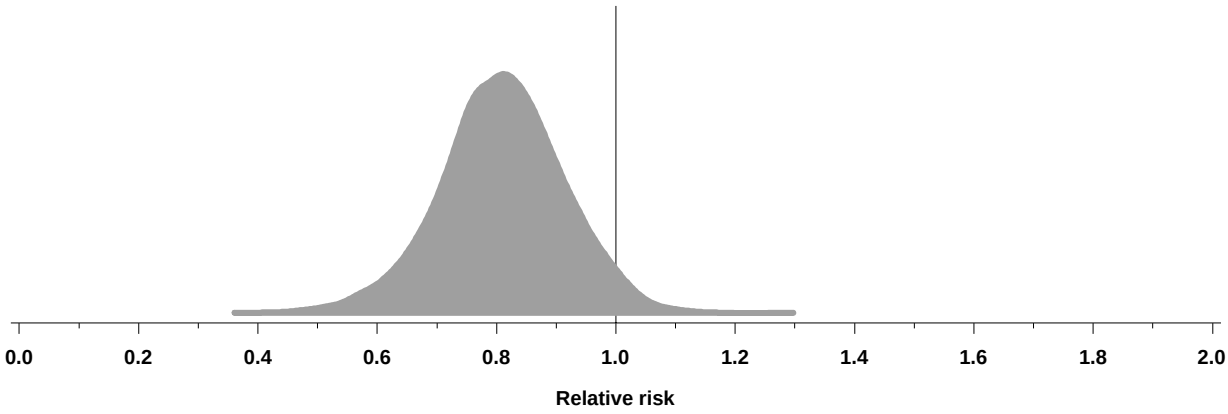

Figure 11: Relative risk density of hemorrhagic stroke (SAH or ICH) incidence.