# ENDEAVOR
## PHARMACEUTICALS

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April 4, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

**RE: Docket No. 98D-0834: Proposed Labeling Guidance - Comments**

To Whom It May Concern:

Reference is made to the Agency's request for comments regarding the January, 2003, <u>Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Prescribing Information for Health Care Providers and Patient Labeling</u>. We appreciate this opportunity to respond.

## INTRODUCTION

Decades of clinical experience and use by millions of women have established estrogen therapy as the gold-standard treatment for relief of vasomotor symptoms associated with menopause. As the only FDA-approved therapy for relief of such symptoms, this is an important consideration given the changing demographics with more women experiencing or approaching menopause than ever before. Class labeling for these products must accurately and fairly portray the benefits and risks associated with their use.

## OVERVIEW

The labeling guidance, as currently proposed, is somewhat misleading when applied to estrogen-only products. The extensive extrapolation of WHI study data to estrogen-only therapies is inconsistent with relevant information pertaining to the relief of vulvar and vaginal atrophy and vasomotor symptoms associated with menopause. The liberal interpretation of these data may preclude use of estrogen therapies by some women who would benefit by them. Specific quotes from the proposed labeling guidance, where

1

applicable, are provided (in bold type) below. Endeavor's commentary, supported by key opinion leaders and literature references, and labeling recommendations are arranged according to the following topics:

- Applicability of findings from the discontinued Estrogen-Progestin Therapy (EPT) arm (Prempro™) of the Women's Health Initiative study to class labeling for Estrogen Therapy (ET) products
  - Fundamental differences between ET and EPT/Hormone Therapy (HT)
  - Fundamental differences between synthetically-derived *conjugated estrogens* (CE) and *conjugated equine estrogens* (CEE)
  - Comparison of medroxyprogesterone (MPA) to other progestins
  - Importance of risk/benefit ratio to indicated population
- Impact of liberal WHI study inclusion criteria, including subject age variability and pre-existing medical conditions

## DISCUSSION

Applicability of findings from the discontinued Estrogen-Progestin Therapy (Prempro™) of the Women's Health Initiative study to class labeling for Estrogen Therapy products

*Fundamental differences between ET and EPT*
   Draft Guidance: PAGE 2, LINES 60-69: **"The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with conjugated equine estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. Other doses of conjugated estrogens with medroxyprogesterone and other combinations of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman."**

   Response:
- The majority of the proposed black box warnings for increased cardiovascular and cancer risks stem from the WHI study, a study involving only one product, an estrogen/progestin combination product. To extend the WHI findings to all products (much less to estrogen-only products) is unfounded. These results are not consistent with the substantial base of data, the majority of which are based on therapies other than Prempro™. For example (as referenced from N Engl J Med 1991; 325:756-62)[1], the ten-year follow-up from the Nurses' Health Study concludes "Current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease, but it is not associated with any change in the risk of stroke." This report was issued almost 5 years prior to the introduction of Prempro™ to the US market, and, therefore, represents experience with other therapies.

2

- It is premature to apply the effects of this one study to the entire class of ET and EPT, as the ET arm of the WHI study is in progress. The ET arm of WHI continues because no equivalent increase in risk has emerged; as such, ET and EPT should not be treated similarly in clinical evaluations, or addressed as such in class labeling guidance.

- The July 20, 2002, British Medical Journal[2] article entitled *Hormone Replacement Therapy: Findings of women's health initiative trial need not alarm users* states: "Given the biological effects of estrogen on the cardiovascular system, the lack of benefit on coronary heart disease is surprising---but these findings apply only to this particular hormone replacement therapy regimen, and other coronary heart disease studies of this hormone replacement therapy have not shown benefit." The article also states "But the metabolic effects of different regimens are clearly different, and this is most likely to have an impact on their cardiovascular effects."

- The aforementioned British Medical Journal[2] article further states "It is most unhelpful that this point about different estrogens and progestogens was not appreciated by the recent recommendations of the Committee for Safety of Medicines and the Medicines Control Agency, which were inappropriate with respect to cardiovascular disease. Particularly for coronary heart disease, the dose (and possibly type) of estrogen and the type of progestogen may be crucial."

- The March 15, 2003, Cancer[3] journal article entitled: *Hormone Replacement Therapy Containing Progestins and Given Continuously Increases Breast Carcinoma Risk in Sweden* discusses outcomes from a population-based cohort of 2,950 women interviewed during 1990-1992 to determine whether there are any differences in breast carcinoma risks according to different types and duration of HRT use. The journal article states "Progestin-containing preparations used continuously are the most hazardous to women." "These data indicate that estrogen-only therapy is a rather safe therapy with little breast carcinoma risk. If there is a need for HRT containing progestins, as in women with intact uterine tissue, an attractive alternative would be to use a more androgenic progestin combination..." The article also states "The results of the...investigation confirm a high risk for breast carcinoma after at least 4 years of HRT use, especially for progestin-containing preparations." ..."The greatest hazard appears to be for continuous combined therapy, whereas combined sequential therapy shows an intermediate risk and estradiol-only preparations are not associated with a significantly increased risk. These results may help physicians to better tailor therapy to avoid breast carcinoma." These data are consistent with the WHI EPT results, the Nurses' Health Study database, and with the fact that the estrogen-only arm of the WHI study is continuing.

- Estrogen alone and estrogen/progestin combination products are different drugs with different pharmacological profiles. This is best exemplified by the fact that

it is well known that estrogen therapy induces endometrial cancer in some patients. Estrogen/progestin therapy inhibits this induction and has an incidence of endometrial cancer equal to or less than that of untreated populations. Estrogen and estrogen/progestin combination products require independent clinical trials and independent registration applications to obtain FDA approval. The data released from WHI to date focus upon EPT (i.e., CEE in combination with MPA).

- Robert L. Barbieri, MD, Chief, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, Massachusetts, and Editor-in-Chief of the OBG Management Journal[4] states the "Agency's position that the findings of WHI should be extended to all estrogen preparations whether or not they contain progestin is shaky scientifically. After all the mere fact that the estrogen-only arm of the WHI continues implies that it is associated with a pattern of benefits and risks superior to that of the estrogen-progestin arm."

- Robert Jaffe, MD, Fredd Gellert Professor of Reproductive Medicine and Biology, University of California, San Francisco, President of the Hormone Foundation, and member of the Endocrine Society's Council of the Endocrine and Hormone Society stated at the NIH Office of Research on Women's Health workshop, October 23-24, 2002, "It is only this estrogen and this progestin that's implicated. Actions are very complex, multiple receptors and organ specificity govern the relationships between these responses."

- Janet Woodcock, MD, Director of CDER, noted in her presentation at the NIH Office of Research on Women's Health workshop, October 23-24, 2002, it is "not possible to establish dose toxicity findings to other products" since WHI defines risks for only one estrogen-progestin product.

*Fundamental differences between synthetically-derived conjugated estrogens (CE) and conjugated equine estrogens (CEE)*

Draft Guidance: Lines 51-53: **"There is no evidence that "natural" estrogens present a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses."**

Response:
- Natural is an ambiguous term with many potential meanings. In the absence of comparable data, and for accuracy and fairness, we suggest the following statement, "It is unknown whether the rate of endometrial carcinomas varies between types of estrogens."

- The guidance does not address the fact that the estrogen component of the combination product investigated in WHI was derived from equine urine sources (i.e., conjugated equine estrogens); it is unfair to compare this with synthetically-derived estrogens that are unique and treated as new chemical entities in the drug approval process. Reference to the WHI study treatment arm should include "conjugated equine estrogens" (instead of "conjugated estrogens"), and "CEE" (instead of "CE"). It is neither fair nor appropriate to differentiate these terms in

4

only some sections of the labeling. Estrogen alone and estrogen/progestin combination products are different drugs with different pharmacological profiles. This is best exemplified by the fact that it is well known that estrogen therapy induces endometrial cancer in some patients. Estrogen/progestin therapy inhibits this induction and has an incidence of endometrial cancer equal to or less than that of untreated populations. Estrogen and estrogen/progestin combination products require independent clinical trials and independent registration applications to obtain FDA approval. The data released from WHI to date focus upon EPT (i.e., CEE in combination with MPA).

- The proposed class labeling guidance neglects to differentiate combination products from estrogen-only products. Such differentiation is key to proper interpretation of study results provided for the drug of interest, as opposed to results from the WHI study.

*Comparison of medroxyprogesterone (MPA) to other progestins*
    Draft Guidance: PAGE 2, LINES 64-67: **"Other doses of conjugated estrogens with medroxyprogesterone and other combination of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar."**

Response:
- The guidance uses a "broad" approach to treat all estrogen and estrogen/progestin products the same, based upon the less-than-favorable results from the Prempro™ study arm. If this logic is applied in reverse, the positive effects associated with the WHI study treatment would automatically be included in labeling for the class (i.e., indications for treatment of osteoporosis/bone fracture and reduction in colon cancer). Hypothetically, had the results from WHI been positive regarding the effect on cardiovascular disease, would the Agency have proposed class (including estrogen-only products) labeling accommodating an indication for prevention of cardiovascular disease?

- The aforementioned British Medical Journal[1] states "The findings may not be the same for types of hormone replacement therapy other than those used in (the WHI) trial, or for lower doses of the regimen that was used---a point that is acknowledged by the authors of the study."

- MPA is known to be the most proliferative progestin on breast tissue. There are other progestins that are more androgenic and more protective of the breast.

- According to the NAMS Position Statement published in Menopause[5], Vol. 10, 2003 "In animal studies, cyclic high-dose MPA (equivalent to 10 mg/day in humans) and continuous low-dose MPA (equivalent to 2.5 mg/day in humans) diminished the beneficial effect of CEE on acetylcholine-induced coronary vascular dilation. However, the addition of nomegestrol acetate to ET did not reverse the beneficial effects of 17$\beta$-estradiol on vascular dilation, indicating that

different progestins exert different effects. In another study, coronary artery vasospasm was avoided with the combination of 17β-estradiol plus progesterone but not with 17β-estradiol plus MPA."

- In the 1995 PEPI trial "good" cholesterol levels increased more in women treated with ET compared to those in the EPT arm, indicating that MPA has negative cardiovascular effects. According to the January 18, 1995, <u>Journal of the American Medical Association</u>[6] (Vol. 273, No. 3) article "Estrogen alone or in combination with a progestin improved lipoproteins and lowers fibrinogen levels without detectable effects on post-challenge insulin or blood pressure. Unopposed estrogen is the optimal regimen for elevation of HDL-C, but the high rate of endometrial hyperplasia restricts use to women without a uterus."

- According to the <u>Climacteric</u>[7] journal (2002;5:332-340) article entitled: *Combined hormone replacement therapy and risk of breast cancer in a French cohort study of 3175 women,* "MPA is a synthetic progestin that may be different from progesterone or other progestins in its effects on breast tissues. According to surgical breast biopsies performed in postmenopausal women, the breast epithelial cell mitotic activity increases during treatment with oral CEE, and even more so during HRT combining oral CEE and MPA."

*Importance of risk/benefit ratio to indicated population*
- Drug package inserts should clarify the intended use of the drug and any associated risks. The addition of WHI study-related information to the extent proposed is specific to Prempro™. Information not specific to the drug of interest is confusing to the health care professional.

- The aforementioned <u>Cancer</u>[3] article states "The authors previously reported an increased risk of breast carcinoma with longer duration of hormone replacement therapy (HRT) use. It is unclear if different types of HRT confer different risks."

- Since the estrogen-only arm of the WHI study is ongoing, and because no equivalent increase in risk has emerged, risks associated with Prempro™ should not be applied to estrogen-only products.

- The <u>Climacteric</u>[8] journal (2002;5:341-350) article entitled: *Differing effects of low-dose estrogen-progestin therapy and pravastatin in postmenopausal hypercholesterolemic women* states "Low-dose estrogen alleviates vasomotor symptoms, protects against bone loss, and is associated with fewer side-effects such as mastalgia and irregular bleeding. Hence, the prescription of low-dose therapy is increasing."

<u>Impact of liberal WHI study inclusion criteria, including subject age variability and pre-existing medical conditions</u>

<u>Draft Guidance</u>: **[Table inserted between lines 247 and 248 and accompanying paragraphs (lines 231 – 247 and lines 257-263)]**

<u>Response:</u>
- Line 242: We endorse the Agency's proposed wording "The CE-only substudy is continuing and results have not been reported." This is a fair and accurate statement and helps to provide important balance.

- The proposed table addresses CE/MPA exclusively. As such, it is more relevant to combination estrogen/progestin products. It is much less relevant to estrogen-only products. Even so, an adaptation to other combination products constitutes a liberal interpretation, as there is no evidence to suggest other progestins or other such combination products will yield a similar safety profile.

- Lines 231-247: The paragraphs preceding the table adequately discuss the results of WHI associated with the combination therapy treatment arm; a separate table is not necessary. The adverse events observed in WHI are appropriately addressed in the WARNINGS section (coronary heart disease (lines 320–350), venous thromboembolism (lines 354-366), breast cancer (lines 391–412) subsections) of the proposed labeling guidance.

- Inclusion of the WHI table may lead the reader to conclude the package insert is intended for Prempro™.

- The phrase on line 247: "…average follow-up of 5.2 years…" is misleading. This does not accurately fully communicate the cumulative time participants were exposed to HRT. Specifically, WHI study participants were enrolled in the study for 5.2 years. Prior to enrollment, they were not HRT naïve. As such, total exposure to HRT is longer than the 5.2 years stated in the labeling guidance. Furthermore, the present wording may be interpreted that these events occurred upon follow-up evaluation 5.2 years <u>after</u> study drug was discontinued, incorrectly implying a lingering safety concern well after therapy was discontinued.

- A statement regarding the liberal inclusion criteria in the WHI "all-comers" study, including previous medical history and the wide age range and average and mean ages of study participants, should be included for accuracy and perspective. The study included patients for whom estrogen was essentially contraindicated.

- The proposed guidance does not clarify that the women studied in WHI were not reflective of the population typically needing treatment for VMS or VVA, nor was the purpose of WHI to study effectiveness for these well-established

indications. According to the May 8, 2003, (pre-publication) <u>New England Journal of Medicine</u>[9] article "It is important to note that the WHI was not designed to test the effect of hormone therapy on vasomotor or other menopausal symptoms. The majority of women enrolled in the WHI did not have menopausal symptoms. Among the 12 percent of women who did report moderate-to-severe vasomotor symptoms at baseline, the symptoms were unlikely to be very bothersome, since the women were willing to be randomly assigned to placebo. In the subgroup, hormone therapy improved vasomotor symptoms and reduced sleep disturbance. Multiple other randomized trials among younger women with hot flashes have shown that systemic estrogen therapy is highly effective in relieving vasomotor symptoms, reducing both the severity and the frequency of hot flashes by about 80 percent and thereby improving the quality of life." This is particularly relevant, considering the labeling guidance is specifically intended for "...the treatment of vasomotor symptoms and vulvar and vaginal atrophy symptoms....".
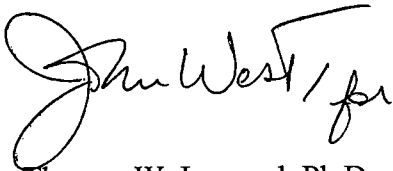
- The results of WHI are not directly applicable to younger women. Two-thirds of the WHI study participants were in the 60-70 year age group, (10+ years post-menopause) rather than at menopause, when women generally begin hormone therapy.

- WHI was intended to be a study of women without heart disease. However, a number of the participants were known to have underlying heart disease. It is well-established that a percentage of women over the age of 60 have undiagnosed heart disease. Since 2/3 of the study population was over 60, this predisposes them to higher rates of undiagnosed heart disease, and could skew the data.

- Women with prior thromboembolic events were admitted to the WHI study. Underlying hypertension or other pre-existing conditions could influence study outcomes. Thirty-six percent of the subjects in the EPT arm of the WHI study had hypertension and 4% were diabetics. Typical practice would not prescribe HT to women with these pre-existing conditions.

- Jacques Rossouw, MD, of NHLBI, noted during the NIH Office of Research on Women's Health workshop, October 23-24, 2002, that the effects attributed to estrogen from progestin must be distinguished. Cardiovascular profiles of women with hysterectomies differ from those of non-hysterectomized women.

- WHI inadequately blinded the study participants. Forty-four percent of the patients in the WHI study were aware of their treatment due to breakthrough bleeding. Once inadvertently unblinded, participants may have had a greater tendency to report adverse events.

**CONCLUSION**

Global application of the WHI study findings regarding estrogens combined with medroxyprogesterone in the class labeling to other combination products, much less estrogen-alone products, is misleading and inappropriate. The proposed draft guidance does not provide fair balance to all ET and EPT products by omitting positive study outcomes, while mandating inclusion of extensive negative findings from WHI and not placing such findings in perspective. Overwhelming consensus of opinion leaders at the NIH Office of Research on Women's Health workshop, October 23-24, 2002, regarding generalization of WHI data was that these data are not applicable to all other products in the class. Furthermore, the medical community has embraced lower dose, shorter duration estrogen and estrogen/progestin therapy in the post-WHI environment. When applied to the intended patient population, it is reasonable to infer that these treatment trends will minimize the likelihood for WHI study safety-related issues to occur.

We appreciate your consideration and this opportunity to comment. Endeavor welcomes this and any other ways we may assist the Agency's efforts to finalize the labeling guidance.

Sincerely,

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Enclosures

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756

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# POSTMENOPAUSAL ESTROGEN THERAPY AND CARDIOVASCULAR DISEASE

## Ten-Year Follow-up from the Nurses' Health Study

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and Charles H. Hennekens, M.D.

**Abstract** *Background.* The effect of postmenopausal estrogen therapy on the risk of cardiovascular disease remains controversial. Our 1985 report in the *Journal*, based on four years of follow-up, suggested that estrogen therapy reduced the risk of coronary heart disease, but a report published simultaneously from the Framingham Study suggested that the risk was increased. In addition, studies of the effect of estrogens on stroke have yielded conflicting results.

*Methods.* We followed 48,470 postmenopausal women, 30 to 63 years old, who were participants in the Nurses' Health Study and who did not have a history of cancer or cardiovascular disease at base line. During up to 10 years of follow-up (337,854 person-years), we documented 224 strokes, 405 cases of major coronary disease (nonfatal myocardial infarctions or deaths from coronary causes), and 1263 deaths from all causes.

*Results.* After adjustment for age and other risk factors, the overall relative risk of major coronary disease in women currently taking estrogen was 0.56 (95 percent confidence interval, 0.40 to 0.80); the risk was significantly reduced among women with either natural or surgical

menopause. We observed no effect of the duration of estrogen use independent of age. The findings were similar in analyses limited to women who had recently visited their physicians (relative risk, 0.45; 95 percent confidence interval, 0.31 to 0.66) and in a low-risk group that excluded women reporting current cigarette smoking, diabetes, hypertension, hypercholesterolemia, or a Quetelet index above the 90th percentile (relative risk, 0.53; 95 percent confidence interval, 0.31 to 0.91). The relative risk for current and former users of estrogen as compared with those who had never used it was 0.89 (95 percent confidence interval, 0.78 to 1.00) for total mortality and 0.72 (95 percent confidence interval, 0.55 to 0.95) for mortality from cardiovascular disease. The relative risk of stroke when current users were compared with those who had never used estrogen was 0.97 (95 percent confidence interval, 0.65 to 1.45), with no marked differences according to type of stroke.

*Conclusions.* Current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease, but it is not associated with any change in the risk of stroke. (N Engl J Med 1991; 325:756-62.)

THE influence of exogenous hormones on the risk of cardiovascular disease has long been controversial. More than 20 studies published in the past decade have addressed the issue of postmenopausal estrogen use and coronary disease.[1] Our earlier report of a benefit from estrogen use in terms of the risk of coronary disease, based on four years of follow-up,[2] was accompanied by a report from the Framingham Study that came to the opposite conclusion.[3] These disparate findings led to considerable confusion.[4] We now report results for both coronary disease and stroke, based on 10 years of follow-up in the Nurses' Health Study, a large cohort study that included 48,470 postmenopausal women with 337,252 person-years of follow-up.

## METHODS

### The Nurses' Health Study Cohort

The Nurses' Health Study began in 1976, when 121,700 female registered nurses in the United States completed questionnaires sent to them by mail about their medical history, including previous cardiovascular disease, menopause, diabetes, hypertension, high serum cholesterol levels, and parental myocardial infarction. We included questions on height, weight, smoking, the use of postmeno-

pausal hormones, and the use of oral contraceptives.[5] Every two years, follow-up questionnaires were mailed to obtain updated information and identify newly diagnosed major illnesses. A dietary questionnaire was added in 1980.[6]

### Ascertainment of Estrogen Use

In 1976 the women were asked whether they had taken hormone supplements after menopause, and if so, for how long. Information on hormone use, including the type taken, was updated in the subsequent questionnaires sent every two years through 1986, with explicit questions about current use and duration of use in the intervening period. Because no information on current use was explicitly requested on the 1976 questionnaire, we considered women to have been current estrogen users for the 1976–1978 period if the duration of their estrogen use was equal (within 12 months) to the interval between menopause and the date of completion of the questionnaire. Women whose duration of hormone use was more than 12 months shorter than this interval were considered former users. The daily dose of conjugated estrogens was obtained beginning in 1980.

### Identification and Confirmation of Cardiovascular End Points

The study end points included nonfatal myocardial infarction, fatal coronary heart disease, coronary-artery bypass grafting or angioplasty, fatal and nonfatal stroke, total cardiovascular mortality, and deaths from all causes after the return of the 1976 questionnaire but before June 1, 1986. Nurses who reported having a nonfatal myocardial infarction or stroke on a follow-up questionnaire were asked for permission for a study investigator to review their medical records. Nonfatal myocardial infarctions were considered confirmed by hospital records if they met the World Health Organization criteria[7] (i.e., symptoms plus either cardiac-enzyme elevations or diagnostic electrocardiographic changes). Myocardial infarctions that required hospitalization and for which confirmatory information was obtained by interview or letter, but for which no medical records were obtainable, were designated as probable. Thus, infarc-

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tions of indeter... were not includ... participants' re... Nonfatal stro... cal records if th... rapid in onset ... criteria of the N... ischemic stroke... artery), subarac... rhages. We excl... infection or neo... required hospita... letter or telephc... unavailable, wer... Most deaths... used the Natior... nonrespondents... follow-up was m... sibly attributabl... sion from the ne... the medical rec... nary disease if t... that a fatal myo... coronary death a... listed on the de... another, more pl... (e.g., on the basi... next of kin) to ha... was the cause lis... terion for a deten... as fatal if they w... records or if stro... on the death certi...

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**Population for A**

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tions of indeterminate duration discovered on routine examination were not included. Coronary-artery surgery was ascertained by the participants' reports alone.

Nonfatal strokes were considered confirmed by a review of medical records if they were characterized by a typical neurologic deficit, in onset and lasting at least 24 hours, and if they met the criteria of the National Survey of Stroke.[8] We classified strokes as ischemic strokes (thrombotic or embolic occlusion of a cerebral artery), subarachnoid hemorrhages, or intraparenchymal hemorrhages. We excluded subdural hematomas and strokes caused by infection or neoplasia. Strokes reported on the questionnaires that required hospitalization and were confirmed by information from a letter or telephone call, but for which the medical records were unavailable, were designated as probable.

Most deaths were reported by the participants' families. We used the National Death Index[9] to identify deaths among the nonrespondents to each two-year questionnaire; the mortality follow-up was more than 98 percent complete. For all deaths possibly attributable to cardiovascular causes, we requested permission from the next of kin (subject to state regulations) to review the medical records. Deaths were considered to be due to coronary disease if the medical records or autopsy findings confirmed that a fatal myocardial infarction had occurred. The category of coronary death also included cases in which coronary disease was listed on the death certificate as the underlying cause without another, more plausible cause and in which the nurse was known (e.g., on the basis of the hospital record or an interview with her next of kin) to have had coronary disease before death. In no case was the cause listed on the death certificate used as the sole criterion for a determination of coronary death. We classified strokes as fatal if they were documented by autopsy findings or hospital records or if stroke was listed as the underlying cause of death on the death certificate.

The category of cardiovascular mortality included deaths from stroke, deaths from coronary disease, sudden deaths (death within one hour of the onset of symptoms in an apparently healthy woman), and deaths for which coronary disease was listed as the underlying cause and no more plausible cause could be assigned, but for which confirmation was lacking. Major cardiovascular disease was defined to include both death from cardiovascular disease and nonfatal myocardial infarction and stroke. All the interviews and reviews of medical records were conducted without the investigators' knowledge of the category of estrogen use.

## Population for Analysis

Women for whom information on hormone use was missing (3.6 percent of all respondents) were excluded from the analysis. Because women with diagnosed cardiovascular disease may alter their hormone use and are also at increased risk for progression of the disease, their inclusion could distort the results. We therefore excluded from the analysis all women who reported a diagnosis of any cardiovascular disease or cancer (except skin cancer other than melanoma) on the 1976 questionnaire. Similarly, women who reported such a diagnosis on a subsequent questionnaire were excluded from further analysis. Thus, at the start of each two-year interval, the base population included no women reporting these diagnoses. For the analyses of mortality from all causes, however, these women were included, so that deaths due to illnesses lasting more than two years could be considered.

We classified women as postmenopausal from the time they reported having a natural menopause or undergoing hysterectomy with bilateral oophorectomy. Women who underwent hysterectomy without bilateral oophorectomy were considered postmenopausal when they reached the age at which natural menopause had occurred in 90 percent of the cohort (54 years for smokers and 56 for nonsmokers). The women's reports of reaching menopause were highly accurate in this cohort.[10]

In 1976, a total of 22,950 postmenopausal women entered the analysis for the 1976–1978 period. The population was expanded to include women who became postmenopausal subsequently and were free of cancer and cardiovascular disease. During the 10-year period from 1976 through June 1, 1986, we accrued 337,854 person-years of follow-up among 48,470 women. The follow-up of the cohort, calculated as a percentage of the total potential person-years

of follow-up, was 88.4 percent complete for nonfatal outcomes; for mortality, it was more than 98 percent complete. Follow-up rates were quite similar within the different categories of hormone use.

## Statistical Analysis

For each participant, person-months were allocated to the categories of hormone use according to the data reported in 1976 and updated at each two-year interval according to information obtained subsequently. Follow-up for a participant ended with a diagnosis of cardiovascular disease or death. If no questionnaire was returned for a two-year follow-up period, the most recent data were applied to the subsequent follow-up interval. If a woman's previous status had been current hormone use, however, she was classified in the update as having used hormones at some time, but current or former use was not specified.

We calculated the relative risk associated with hormone use, defined as the incidence rate of cardiovascular disease among hormone users (estimated as the number of events divided by the person-time of follow-up for the hormone users) divided by the corresponding rate among women who had never used hormones. Age-specific rates of cardiovascular disease for users and nonusers were calculated in five-year categories and used to compute age-adjusted relative risks with 95 percent confidence intervals.[11] To adjust for a number of risk factors simultaneously, we used proportional-hazards models.[12] All P values are two-tailed.

## RESULTS

Women currently using postmenopausal hormones accounted for 21.8 percent of the total follow-up time of 337,854 person-years. Former hormone users accounted for 25.2 percent of the time, and women who had never used hormones 53 percent. In all three groups, potential risk factors for cardiovascular disease were distributed in generally similar patterns. Table 1 shows the age-standardized proportions of

Table 1. Distribution of Characteristics and Coronary Risk Factors Reported by the Women in the Cohort, According to Postmenopausal Hormone Use, with Standardization for Age.*

| VARIABLE | HORMONE USE | | |
| --- | --- | --- | --- |
| | CURRENT | FORMER | NONE |
| | *percent of subjects* | | |
| Parental MI before the age of 60 | 10.6 | 10.0 | 9.3 |
| Hypertension | 23.2 | 25.0 | 21.8 |
| Diabetes mellitus | 2.7 | 3.8 | 3.5 |
| High serum cholesterol | 9.9 | 11.2 | 7.6 |
| Current smoker (15–24 cigarettes/day) | 11.2 | 14.7 | 14.5 |
| Quetelet index ≥29† | 9.8 | 13.3 | 15.0 |
| Bilateral oophorectomy | 50.3 | 39.3 | 9.3 |
| Past use of oral contraceptives | 34.0 | 27.6 | 23.9 |
| Vigorous physical activity ≥1 time/week‡ | 48.2 | 43.1 | 42.4 |
| | *grams per day* | | |
| Mean dietary intake‡§ | | | |
| Saturated fat | 27.6 | 26.2 | 26.7 |
| Cholesterol | 0.32 | 0.32 | 0.32 |
| Polyunsaturated fat | 8.9 | 8.7 | 8.7 |
| Dietary fiber | 17.3 | 17.2 | 16.8 |
| Alcohol | 7.9 | 7.5 | 7.3 |

*Data are standardized to the age distribution of the person-years of follow-up for the cohort, from 1976 through 1986. MI denotes myocardial infarction.

†The Quetelet index was calculated by dividing the weight in kilograms by the square of the height in meters.

‡As assessed in 1980 and standardized to the age distribution of the cohort at that time.

§Adjusted for energy intake.

Table 2. Relative Risk of Cardiovascular Disease among Current and Former Postmenopausal Hormone Users, as Compared with Those Who Never Used Postmenopausal Hormones, after Adjustment for Age and Multiple Risk Factors.*

| Group† | No. of Person-Years | Major Coronary Disease | | Fatal Cardiovascular Disease | | Total Stroke | | Ischemic Stroke | | Subarachnoid Hemorrhage | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of Cases | RR (95% CI) | No. of Cases | RR (95% CI) | No. of Cases | RR (95% CI) | No. of Cases | RR (95% CI) | No. of Cases | RR (95% CI) |
| No hormone use | 179,194 | 250 | 1.0 | 129 | 1.0 | 123 | 1.0 | 56 | 1.0 | 19 | 1.0 |
| Current hormone use | 73,532 | | | | | | | | | | |
| Adjusted for age | — | 45 | 0.51 (0.37–0.70) | 21 | 0.48 (0.31–0.74) | 39 | 0.96 (0.67–1.37) | 23 | 1.26 (0.78–2.02) | 5 | 0.80 (0.30–2.10) |
| Adjusted for age and risk factors | — | | 0.56 (0.40–0.80) | | 0.61 (0.37–1.00) | | 0.97 (0.65–1.45) | | 1.46 (0.85–2.51) | | 0.53 (0.18–1.57) |
| Former hormone use | 85,128 | | | | | | | | | | |
| Adjusted for age | — | 110 | 0.91 (0.73–1.14) | 55 | 0.84 (0.61–1.15) | 62 | 1.00 (0.74–1.36) | 34 | 1.14 (0.75–1.74) | 12 | 1.42 (0.70–2.90) |
| Adjusted for age and risk factors | — | | 0.83 (0.65–1.05) | | 0.79 (0.56–1.10) | | 0.99 (0.72–1.36) | | 1.19 (0.77–1.86) | | 1.03 (0.47–2.25) |

*RR denotes relative risk, and CI confidence interval.

†Women with no hormone use served as the reference category in this analysis. The risk factors included in the multivariate models were age (in five-year categories), cigarette smoking (none, former, current [1 to 14, 15 to 24, and ≥25 cigarettes per day]), hypertension (yes, no), diabetes (yes, no), high serum cholesterol level (yes, no), parental myocardial infarction before the age of 60 (yes, no), Quetelet index (in five categories), past use of oral contraceptives (yes, no), and time period (in five two-year periods).

women who reported various characteristics and coronary risk factors according to their estrogen-use status, on the basis of cumulative person-years from 1976 through 1986. Table 1 also shows the mean intake of various nutrients, with adjustment for energy intake,[13] and the proportion of women reporting a period of vigorous exercise at least once per week, both of which were ascertained in 1980. Estrogen users were less likely to have diabetes and more likely to be lean, to engage in regular, vigorous physical activity, to have had a surgical menopause, and to have used oral contraceptives in the past.

Among the postmenopausal women who reported no previous cardiovascular disease, we documented 293 nonfatal myocardial infarctions (228 confirmed and 65 probable), 112 confirmed deaths from coronary disease, and 224 strokes (52 fatal and 172 nonfatal; 177 confirmed and 47 probable) during the 10 years of follow-up. Of the strokes, 113 were ischemic strokes and 36 were subarachnoid hemorrhages; the remaining strokes were of other or unknown types. There were 41 other deaths from cardiovascular causes, for a total of 205 cardiovascular deaths. Coronary-artery surgery or angioplasty was reported by 185 women. In the analyses of total mortality, which included women in whom illnesses developed during follow-up, there were 1263 deaths from all causes. No material differences were observed in any of the analyses between the confirmed and the probable categories of myocardial infarction and stroke or between the fatal and the nonfatal categories of coronary disease or stroke; we therefore merged these categories into two larger categories: major coronary disease (nonfatal myocardial infarction and death from coronary causes) and total stroke.

Overall, the age-adjusted risk of major coronary disease among current estrogen users was about half that of women who had never used estrogen, with tive risk of 0.51 (95 percent confidence interval, .37 to 0.70; P<0.0001) (Table 2). For former users, the age-adjusted relative risk was 0.91 (95 per-

cent confidence interval, 0.73 to 1.14; P = 0.42). In contrast, we observed no association between current estrogen use and total stroke. The age-adjusted relative risk was 0.96 (95 percent confidence interval, 0.67 to 1.37) and was virtually unchanged after further adjustment for other cardiovascular risk factors. No material associations were observed for ischemic stroke or subarachnoid hemorrhage; there were too few cases of intraparenchymal hemorrhage for analysis.

We observed no apparent association between estrogen use and the incidence of coronary-artery surgery. Among the current users, the age-adjusted relative risk was 1.21 (95 percent confidence interval, 0.84 to 1.73), and for former users it was 0.86 (95 percent confidence interval, 0.60 to 1.22). Among the former users, there were no notable trends with regard to duration of use or time since most recent use. Simultaneous adjustment for other risk factors in multivariate analyses had virtually no effect on these estimates. We found no evidence to suggest that the degree of protection associated with current estrogen use was related to the duration of use, independent of age, for any of the end points; among the former users, the period of time since the cessation of estrogen use was not consistently related to the risk of cardiovascular outcomes (data available elsewhere*).

The study had insufficient statistical power to determine the effects of specific forms of hormone therapy other than unopposed oral conjugated estrogen. Of the 57,570 person-years of follow-up for current hormone users from 1978 through 1986, 71.5 percent involved the use of unopposed oral conjugated estrogen, 11.5 percent other estrogens, 2.7 percent estrogens with progestin, 2.2 percent other hormones, and 12

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percent hormones of unknown type (or information was missing). The age-adjusted relative risk of major coronary disease with current use of unopposed oral conjugated estrogen was 0.40 (95 percent confidence interval, 0.26 to 0.62).

Information about the dose of conjugated estrogen was available for the period from 1980 through 1986. The only marked difference in the association observed with different dose levels was an apparent increase in the risk of coronary disease among women taking more than 1.25 mg per day (relative risk, 2.8; 95 percent confidence interval, 0.9 to 8.2), as compared with the substantial decrease in risk among those taking lower doses. The use of estrogen at doses of more than 1.25 mg per day was very uncommon (4 percent of the cohort), however, and the relative risk is based on only three cases.

We assessed whether the inverse association of estrogen use with the risk of coronary disease differed for women with different characteristics. We observed few marked differences in the associations. The age-specific relative risk appeared to show a nonsignificant trend (P = 0.19) toward more protection from coronary disease among younger postmenopausal hormone users. For the oldest age group, women 60 to 64 years of age, the relative risk was 1.35 (95 percent confidence interval, 0.65 to 2.82). We noted possible tendencies toward more protection among smokers than among nonsmokers, among women without a parental history of myocardial infarction before the age of 60, and among the leanest women, but these differences in relative risks were not statistically significant.* Among the women who had a natural menopause, the age-adjusted relative risk of major coronary disease for current estrogen users was 0.62 (95 percent confidence interval, 0.39 to 0.97), not as low as the risk for women who underwent bilateral oophorectomy (relative risk, 0.40; 95 percent confidence interval, 0.22 to 0.73).

To evaluate the effect of estrogen use among women at low risk, we defined a subgroup of women who were not current smokers; had no hypertension, diabetes, or high serum cholesterol level; and had a Quetelet index below 32, the 90th percentile for this cohort. For this group, the age-adjusted relative risk of major coronary disease among current hormone users was 0.53 (95 percent confidence interval, 0.31 to 0.91).

To adjust for the effects of several potential risk factors simultaneously, we used proportional-hazards models to estimate the relative risks associated with current and former use of estrogens, controlling for age, follow-up period, and the characteristics listed in Table 1. Because the current estrogen users were slightly healthier, this adjustment attenuated the apparent benefit slightly. The results (shown as adjusted for age and risk factors) were similar to those obtained after adjustment for age alone; for major coronary disease, the relative risk among current users was 0.56 (95 percent confidence interval, 0.40 to 0.80) (Table 2). A model that also included age at menopause as a continuous variable yielded virtually the

same estimates. Similar models that included the data on dietary intake and physical activity yielded similar findings, although the estimates were less precise because only data for 1980 through 1986 could be included.

To assess whether receiving more medical care might account for the benefit in postmenopausal estrogen users, we repeated the analysis, limiting it to women who reported having visited a physician in 1978 (65 percent of the cohort). The results were similar to those for the population as a whole: the age-adjusted relative risks of major coronary heart disease were 0.45 (95 percent confidence interval, 0.31 to 0.66) for current estrogen users and 0.79 (95 percent confidence interval, 0.60 to 1.05) for former users. For cardiovascular mortality, the age-adjusted relative risks were 0.52 (95 percent confidence interval, 0.40 to 0.69) for current users and 0.77 (95 percent confidence interval, 0.62 to 0.95) for former users.

In analyzing mortality from all causes, we focused primarily on women who had used estrogen at any time, in order to avoid the potential problem created by shifts in status from current to former use as a result of a diagnosis of disease. We also eliminated the requirement that the cohort be free of diagnosed cancer and heart disease at the beginning of each two-year period; this allowed us to include deaths due to illnesses lasting more than two years. Thus, in this analysis, the cohort was free from diagnosed cancer and heart disease at base line in 1976 (or at entry into the analysis, for those who became postmenopausal later) and was followed until death or the cutoff date of May 31, 1986. For women who had used estrogens at any time, the age-adjusted relative risk of mortality from all causes was 0.81 (95 percent confidence interval, 0.72 to 0.91; P = 0.0004); for cardiovascular mortality, it was 0.68 (95 percent confidence interval, 0.52 to 0.90). After adjustment for other risk factors, the relative risks were slightly attenuated, but they remained statistically significant; for total mortality, the risk was 0.89 (95 percent confidence interval, 0.78 to 1.00), and for cardiovascular mortality it was 0.72 (95 percent confidence interval, 0.55 to 0.95; P = 0.02). Because in the earlier analyses benefits had been found to be attributable to current estrogen use, this analysis underestimated the benefit of estrogen by including former users with current users. To remove this bias in part, we excluded women who had already discontinued estrogen use at base line but not those who used estrogen at base line and discontinued it later. The exclusion of the latter group would have led to an overestimate of the benefit, because estrogen therapy is often discontinued in women who have potentially fatal illnesses, such as breast cancer.

## DISCUSSION

In this prospective study of 48,470 women, we observed that when current postmenopausal estrogen users were compared with women who had never used estrogen, they had about half the risk of major coronary disease or fatal cardiovascular disease and no

increase in the risk of stroke. The prospective study design virtually eliminated the biases in recall and ⟩ction that can affect case–control studies. The fol-low-up rate was high, particularly for fatal outcomes, reducing the likelihood that differential follow-up could have affected the results.

Information on exposure to estrogen and other potential risk factors was derived from reports by the women themselves, but we believe them to be reliable. The reports have been validated by a review of the medical records and by direct measurement with respect to several conditions.[6,14] Also, the risk factors reported by the subjects were strong predictors of subsequent cardiovascular disease,[2,5,15,16] and the subjects were all registered nurses with a demonstrated interest in medical research.

The most plausible alternative to a cause–effect relation between estrogen use and the reduced risk of coronary disease is that healthier women are selected for such therapy. In this cohort, however, the estrogen users appeared only slightly healthier than the nonusers and were generally similar to them with respect to most cardiovascular risk factors. The estrogen users had a much higher incidence of bilateral oophorectomy, a coronary risk factor only for women not receiving estrogen-replacement therapy.[17,18] The estrogen users also tended to be leaner, which may result in lower levels of estrogen from adipose tissue.[19] The likelihood of lower levels of endogenous estrogen in thinner women is consistent with the trend toward ⟩eater benefit from postmenopausal estrogen with ⟩spect to coronary disease in that group, but the protection associated with estrogen use was present in women in all categories of the Quetelet index. The stratified and multivariate proportional-hazards models indicated only minor overall confounding, as judged by the similarity of the relative risks after adjustment for age alone with those that took account of other risk factors. The similar benefit in the analysis limited to women who reported a recent visit to a physician suggests that access to medical care appeared to have little effect on estimates of the effect of estrogen on the risk of cardiovascular disease.

The apparent marked benefit of estrogen in reducing the risk of coronary disease is consistent with previous evidence. Of 15 other prospective studies, 14 found decreased risks among estrogen users.[1] The Framingham Study alone found an elevated risk,[3] which was not statistically significant when women with angina were omitted. A subsequent reanalysis of the Framingham data showed a nonsignificant protective effect among younger women but a nonsignificant adverse effect among older women.[20] Similarly, all three cross-sectional studies of coronary angiography showed substantially less atherosclerosis among estrogen users.[21-23] A quantitative overview of previous ⟩ies taken together yielded a relative risk of 0.56 ⟩ercent confidence interval, 0.50 to 0.61); when only the analytic prospective and angiographic studies

were considered, the relative risk was 0.50 (95 percent confidence interval, 0.43 to 0.56).[1]

The nonsignificant trend in our data toward a decreasing benefit of estrogen with increasing age is consistent with the Framingham data,[3,20] but Henderson et al. found a substantial reduction in risk among women in their 70s.[28] Future follow-up will clarify this issue, but the weight of the evidence suggests a protective effect among postmenopausal women of all ages. In the analysis of women with a favorable risk-factor profile, the observed age-adjusted relative risk of major coronary disease, 0.53, was virtually identical to that for the whole cohort. This implies that women at lower risk enjoy the same relative benefit from estrogen as women in general. Because rates of coronary disease were lower among the low-risk women, however, the same relative decrease corresponded to a smaller reduction in the number of events.

As in other studies,[1] we found that the benefit of therapy was evident primarily among current estrogen users, and there was no indication of an effect of the duration of use independent of age. The best-supported mechanism is the markedly favorable effect of estrogen on serum lipids: estrogens raise the level of high-density lipoprotein cholesterol and lower that of low-density lipoprotein cholesterol. Although estrogen-induced changes in lipid metabolism are sufficient to explain a large reduction in the risk of coronary disease,[24] other plausible mechanisms have been proposed.[25] We observed less benefit, and perhaps an adverse effect, among women taking more than 1.25 mg of estrogen daily. Such high doses were common in the Framingham cohort, which may partly explain their discrepant results.

The absence of an association between estrogen use and the incidence of coronary-artery surgery was unexpected, particularly in view of evidence from cross-sectional angiographic studies showing a strong association of estrogen use with a reduction in atherosclerosis.[21-23] Perhaps women taking estrogens under closer medical supervision are more likely to undergo coronary surgery when they have a given level of symptoms than women not taking estrogens.

We found no effect of estrogens on the incidence of total stroke or that of ischemic stroke and subarachnoid hemorrhage. In the Leisure World Study, Paganini-Hill et al.[26] did find a decrease in risk, but the benefit may have been overestimated because patients with previous cardiovascular disease, who may be more prone to strokes and less likely to have estrogen prescribed, were not excluded. However, this can explain only part of the observed benefit. The Framingham Study[3] found an adverse effect of using estrogen at any time on the risk of stroke, whereas the large, prospective Copenhagen Study[27] found little effect either way. Both the Copenhagen Study and our own study included mostly middle-aged women, as compared with the Leisure World Study,[26] in which the median age was 73; perhaps the protective effect is limited to older women.

In analyses of total mortality, it is important to exclude subjects at the start of follow-up who have life-threatening diseases. Because women with such diseases (e.g., breast cancer) are both less likely to be prescribed estrogen and more likely to die within a given period, their inclusion in an analysis would exaggerate any benefit of estrogen. Similarly, an analysis restricted to women who continue to use estrogen would have the same effect, because women who acquire certain life-threatening conditions may be advised to cease hormone use. In our analysis, which took those considerations into account, we observed an age-adjusted relative risk of 0.81 (95 percent confidence interval, 0.72 to 0.91) and a multivariate relative risk of 0.89 (95 percent confidence interval, 0.78 to 1.00). The relative risk of cardiovascular mortality in women with any estrogen use, after adjustment for other risk factors, was 0.72 (95 percent confidence interval, 0.55 to 0.95). The benefit with respect to mortality from all causes is likely to be an underestimate, because the effects of estrogen-induced protection from hip fracture and its associated mortality would be more pronounced at an older age. Indeed, in the Leisure World Study, a relative risk of 0.64 (95 percent confidence interval, 0.52 to 0.78) was found for total mortality among current estrogen users,[28] but this was probably an overestimate of the true benefit, because women with prevalent disease were not omitted at base line. Bush et al. reported a relative risk of 0.54 among estrogen users for mortality from all causes,[29] but their result may also have overestimated the benefit, for the same reason. Petitti et al. reported a relative risk of total mortality of 0.8 (95 percent confidence interval, 0.6 to 1.1) in a follow-up study of healthy women.[30]

The consistency of the epidemiologic data, the apparent absence of important confounding or selection bias, and biologic plausibility[24,25] all suggest a causal association between estrogen use and a reduced risk of coronary disease. Further work is needed to identify the women most likely to benefit from hormone therapy, as well as the effect of added progestins. Proposed clinical trials among women with established coronary disease will be useful. The findings regarding mortality from all causes as well as risk–benefit analyses[31-33] suggest that, overall, the benefits of postmenopausal estrogen therapy outweigh the risks,[34] even apart from the substantial benefits in alleviating menopausal symptoms. These risks include an increase in the rate of endometrial cancer, which can be completely or largely blocked by the addition of a progestin, and possibly some increase in the incidence of breast cancer.

The risk–benefit assessment will differ according to a given woman's medical condition and nonmedical characteristics (including the fear of cancer), so we make no global recommendations. The decision must be made by the individual woman and her physician after they evaluate all the relevant benefits and risks.

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# Hormone replacement therapy

*Findings of women's health initiative trial need not alarm users*

Observational studies have suggested a major health benefit of postmenopausal hormone replacement therapy, including reductions in coronary heart disease, osteoporotic fractures, and colorectal cancer. Such studies have also suggested an increased risk for breast cancer and possibly stroke. Critics have said that the benefits, but not the risks, may simply reflect a healthy user bias and have demanded randomised trials. The women's health initiative is a randomised trial of these health outcomes to assess risks and benefits of intervention strategies in a postmenopausal population. The trial has shown harm for cardiovascular diseases, including coronary heart disease (the primary outcome) and stroke, although it showed benefits for hip fractures and bowel cancer. The relative risks for invasive breast cancer, coronary heart disease, and stroke were increased, although the absolute risks were very small. The findings may not be the same for types of hormone replacement therapy other than those used in this trial, or for lower doses of the regimen that was used—a point that is acknowledged by the authors of the study.

One treatment arm of the trial included over 16 000 postmenopausal women who were taking continuous combined oestrogen-progestogen hormone replacement therapy, using conjugated equine oestrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg daily, tested against placebo.[1] This primary prevention study was due to run for 8.5 years but was halted at just over 5 years because the number of cases of breast cancer had reached a prespecified safety limit. For 10 000 women taking hormone replacement therapy each year, compared with those not taking it, there would be an additional eight cases of invasive breast cancer, seven heart attacks, eight strokes, and eight pulmonary embolisms. However, there would also be six fewer bowel cancers and five fewer hip fractures. Overall mortality was not increased with therapy.

Survival of the human species over two million years implies that female sex hormones by themselves are not dangerous to health. If harm is established, we must therefore examine the types of substitutes that we use and their means of delivery. The small increase in the number of patients with breast cancer accords with previous population studies,[2] as are the increases in venous thromboembolism and the decreases in fractures and in bowel cancer. Given the biological effects of oestrogen on the cardiovascular system, the lack of benefit on coronary heart disease is surprising—but these findings apply only to this

particular hormone replacement therapy regimen, and other coronary heart disease studies of this hormone replacement therapy have not shown benefit.[3-5]

Hormone replacement therapy regimens using different oestrogens and progestogens, and different routes of administration, may be similar in their effects on the breast, bowel, and skeleton. But the metabolic effects of different regimens are clearly different,[6] and this is most likely to have an impact on their cardiovascular effects. Indeed, the women's health initiative trial also has an oestrogen-alone arm for women with hysterectomies, which has not been stopped. We need to see these findings to know whether the medroxyprogesterone acetate is causing the harm. It is most unhelpful that this point about different oestrogens and progestogens was not appreciated by the recent recommendations of the Committee for Safety of Medicines and the Medicines Control Agency,[7] which were inappropriate with respect to cardiovascular disease. Particularly for coronary heart disease, the dose (and possibly type) of oestrogen and the type of progestogen may be crucial. Similar studies using different types of hormone replacement therapy than the one used in this trial must be carried out.

Women who are currently taking continuous combined oestrogen-progestogen should not panic, as it is most unlikely to have caused considerable harm. Certainly the risk of breast cancer is not appreciably increased during the first four years, so women wishing to take this therapy for the short term relief of menopausal symptoms should be reassured. However, they need to discuss with their doctor whether they should shift to a different preparation, which could theoretically have a more beneficial effect on the cardiovascular system.

There is no right or wrong hormone replacement therapy to use in the short term, but in the light of the findings of this trial the use of hormone replacement therapy regimens containing conjugated oestrogens 0.625 mg together with medroxyprogesterone acetate (at any dose) should be avoided in the long term. The findings of this trial may not apply to lower doses of conjugated equine oestrogens, given with or without other progestogens. The long term effects of alternative hormone replacement therapy preparations have not yet been tested in large randomised trials, and this must become a research priority.

At present, long term hormone replacement therapy should be given only on an individual basis, depending on the needs and risk factors of the patient.

Long term therapy could still be considered for prevention of osteoporosis, used as part of the management of women with particular cardiovascular risk factors, and used for better quality of life. We do not yet know the effects, if any, for the prevention of dementia, although preliminary evidence is encouraging. Women who are already taking long term hormone replacement therapy should be reviewed and counselled. If they need further treatment, consideration should be given to switching them to another form of hormone replacement therapy if they are taking a regimen of conjugated equine oestrogen and medroxyprogesterone acetate.

For women starting hormone replacement therapy, we continue to recommend that the starting dose of oestrogen is kept low in women over the age of 60. For example, this would be 1 mg for oral, or 50 $\mu$g for transdermal, oestradiol 17$\beta$—the 0.3 mg dose of conjugated equine oestrogens is not currently available in the United Kingdom. The risks and benefits of alter-

natives to hormone replacement therapy (such as tibolone and raloxifene) are still to be determined, but they are unlikely to be the same as the regimen used in the women's health initiative trial.

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# An ethically defensible market in organs

## *A single buyer like the NHS is an answer*

The American Medical Association has just voted to encourage studies that would determine whether financial incentives would increase the pool of donor organs from cadavers.[1] The association is only eight years behind a proposal that we made, outlining probably the only circumstances in which a market in donor organs could be achieved ethically and in a way that minimised the dangers of such a scheme. This is how an ethical market in live organs would work.

To meet legitimate ethical and regulatory concerns any such scheme must have built into it safeguards against wrongful exploitation and show concern for vulnerable people, as well as taking into account considerations of justice and equity. If all this can be done then a market in human body products will be shown to be, at the very least, not prima facie unethical.[2]

One way of attending to this need for prudent regulation would be to establish a monopsony, a situation where only one buyer exists for the products of several sellers.[3] The one legitimate purchaser in the marketplace would be required to take on responsibility for ensuring equitable distribution of all organs and tissues purchased. This would prevent the rich using their purchasing power to exploit the market at the expense of the poor. The monopsonist would also have other obligations, such as ensuring correct tissue typing to maximise histocompatibility and so minimise graft rejection, and screening for diseased or otherwise

hazardous organs and tissues (for example, blood infected with HIV).

In the United Kingdom, the NHS would be ideally suited for this role. The NHS or a comparable monopsonistic purchaser would purchase live organs and tissues just as it does other goods such as dialysis machines or drugs. It would then make them available as needed on the basis of urgency or some other fair principle of distribution at no cost to the recipient.

In effect, the monopsonist is responsible for the running of the scheme. Should it also be permitted to set the prices of various organs and tissues that it is interested in purchasing? Leaving the pricing of organs to the judgment of the purchaser in a particular marketplace introduces the possibility of a conflict of interests. If the monopsonist was not only to act as purchaser, but also held responsibility for setting the price of what it purchases, it is not unlikely that it would attempt to set prices as low as possible so as to conserve its resources. This would, however, be counterbalanced by the need to provide sufficient incentives to attract would be organ vendors.

It might be thought that in a monopsonistic market there is no possibility for a pricing mechanism as in the free market. But the monopsonist is under pressure to purchase, this pressure resulting from the need for organs: if the purchaser is responsible for supplying patients with organs, and if demand from the public for

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# Hormone Replacement Therapy Containing Progestins and Given Continuously Increases Breast Carcinoma Risk in Sweden

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**BACKGROUND.** The authors previously reported an increased risk of breast carcinoma with longer duration of hormone replacement therapy (HRT) use. It is unclear if different types of HRT confer different risks.

**METHODS.** In this study, a population-based cohort of 29,508 women were interviewed during 1990–1992 to determine whether there are any differences in breast carcinoma risk according to different types and duration of HRT use.

**RESULTS.** At the end of the follow-up period in December 2001, the cohort constituted 298,649 person-years. Slightly more breast carcinoma cases were seen (n = 556) than expected (n = 508.37; standardized morbidity ratio = 1.09, 95% confidence interval [CI] = 1.00–1.19). Approximately 3663 women had ever used HRT. In Cox regression models, time to breast carcinoma in relation to duration and type of HRT use was analyzed, adjusting for age at menarche, age at first full-term pregnancy, parity, age at menopause, family history of breast carcinoma, and age at interview. In women with a natural menopause, a significantly higher risk was observed for longer duration of combined continuous HRT use compared with never users (hazard ratio [HR] = 4.60, 95% CI = 2.39–8.84). Nonsignificant elevated risks also were observed for longer combined sequential (HR = 2.23, 95% CI = 0.90–5.56), gestagen only (HR = 3.74,9 5% CI = 0.94–14.97), and estriol use (HR = 1.89, 95% CI = 0.81–4.39). No increased risk was seen in women after 5 years of nonuse. When studying women who ever used only one type of HRT, even more elevated HRs for gestagen-containing preparations were seen. The highest risks were associated with the combined continuous and gestagen-only therapy in women with ≥ 48 months of use. Use of estradiol without progestins did not increase breast carcinoma risk significantly. The authors estimated the cumulative risk of breast carcinoma in a 50-year-old woman with gestagen-containing therapies for ≥ 48 months, with a follow-up of 10 years, to be 7% (95% CI = 5.4–11.4%) compared with 2% (95% CI = 1.6%–2.9%) for never-users of HRT.

**CONCLUSIONS.** Longer use of HRT containing progestins significantly elevates breast carcinoma risk whereas estradiol use does not. Continued use of progestins rendered the highest risks. The yearly risk of breast carcinoma for long-term users of progestins is of the magnitude of 50% the risk of a BRCA1 mutation carrier. *Cancer* 2003;97:1387–92. © 2003 American Cancer Society.

An increasing number of women will use hormone replacement therapy (HRT) at and after menopause. The overall long-term health consequences of HRT use are not fully known. Positive effects could be counterbalanced by more negative effects. One such nega-

tive factor is the increased risk for breast carcinoma seen especially after longer HRT use. However, a metaanalysis and our previous study have indicated that the risk for breast carcinoma disappears after 5 years of nonuse.[1,2]

There are indications that the tumor biology and prognosis of patients who develop breast carcinoma after HRT use are more favorable compared with other age-matched breast carcinoma patients.[3–12] However, it is unclear if certain preparations are more hazardous than others. Some studies have suggested that preparations containing estrogen alone do not increase the breast carcinoma risk substantially whereas preparations containing both estrogens and progestins do increase the risk.[13–16] Because conflicting data are reported for the combined continuous and combined sequential HRT therapy, it is not known which is more strongly associated with breast carcinoma risk.[13,14,16]

There is a need to further study the risk relationship through prospective studies. In the current cohort investigations, the risk for breast carcinoma has been studied in relation to the type of HRT, exposure time, and reproductive risk factors (i.e., age at menarche, parity, age at first full-term pregnancy, and family history of breast carcinoma). The difference between combined and continuous administration of estrogens and progestins compared with sequential administration could have a biologic significance.

## MATERIALS AND METHODS

Forty thousand women ages 25–65 years were randomly selected from the general population of the South Swedish Health Care Region. They were invited to take part in a standardized written interview of risk factors of malignant melanoma and breast carcinoma. No woman had a past history of malignancy. The interviews were performed between 1990 and 1992. Approximately 74% of all women ($n = 29,508$) agreed to participate.

The questionnaire inquired about age at menarche, parity, age at first full-term pregnancy, age at menopause, type of menopause, oral contraceptive use (starting age, duration of use, brand use, and age at last use), HRT use (starting age, duration of use, brand use, and age at last use), family history of cancer/breast carcinoma, sun bathing habits, constitutional factors, and alcohol and smoking habits.

Using a unique identification number, the vital status and the cancer incidence up to age 75 years of these referents then were followed from the time of interview onward in the population-based Census Registry, Cause of Death Registry, and the Swedish Cancer Registry (South Swedish Regional and National

Swedish Tumour Registry). Each individual could have had more than one tumor registered. The vital status was determined up to January 1, 2002. None of the subjects were lost to follow-up. The type and duration of HRT were studied within the cohort using the Cox regression model.[17] Adjustments were made for age at interview, age at menarche, parity, age at first full-term pregnancy, and a first-degree relative with breast carcinoma. Women who did not have information concerning all studied variables were excluded from the analysis. The covariates were evaluated by likelihood ratio tests and the assumptions for the Cox model were investigated.[17] A $P$ value $< 0.05$ was considered significant.

When estimating cumulative risks for different exposure groups, we used the life table actuarial method.[17] Using the Cox regression model, the risk for different HRTs was modeled while adjusting for possible confounding factors both for all women and for women with a natural menopause. Analyses were presented both for women using only one brand and for women using more than one brand. Individuals were followed from the time of interview to the first event of breast carcinoma, death, or the end of follow-up (January 1, 2002).

The HRT exposure was divided into combined exposures (combined and sequential) and single exposures with estradiol, estriol, and gestagens using the Swedish pharmacopoeia available. Individuals who did not know the brand name were grouped into a separate entity.

## RESULTS

At the end of the follow-up in December 2001, the cohort constituted 298,649 person-years. A total of 556 malignant breast tumors developed (508.37 were expected; standardized morbidity ratio [SMR] = 1.09, 95% confidence interval [CI] = 1.00–1.19). Approximately 3600 women had ever used HRT.

Table 1 shows the number of women exposed for each category of HRT use and the number of each exposure group, as well as the number of diagnosed breast carcinoma cases. Table 2 presents a Cox regression analysis of the time to breast carcinoma in relation to the type of HRT use and ever-use of HRT among all women ($n = 28,378$) and among women with a natural menopause ($n = 8442$). Hazard ratios are adjusted simultaneously for the other types of HRT exposures and for year of interview. Among women with a natural menopause, significantly increased risks were associated with the combined continuous and combined sequential use of HRT. Of all the data gathered, combined continuous use of HRT showed the highest risks.

TABLE 1
Number of Women Exposed for Each Category of HRT Use and the Number of Women with Different Base Characteristics Used as Covariates (First-Degree Relatives with Breast Carcinoma, Age at First Full-Term Pregnancy, Nulliparity, Age at Menarche)[a]

| Characteristics | Women with a natural menopause (n = 8357) | All women (n = 28378) |
|---|---|---|
| HRT use (combined sequential therapy) | | |
| 1–48 mos | 184 (13) | 410 (16) |
| 48+ mos | 136 (6) | 245 (11) |
| HRT use (combined continuous therapy) | | |
| 1–48 mos | 272 (15) | 377 (23) |
| 48+ mos | 173 (16) | 245 (19) |
| HRT use (gestagens only) | | |
| 1–48 mos | 178 (4) | 429 (13) |
| 48+ mos | 86 (3) | 136 (6) |
| HRT use (estradiol only) | | |
| 1–48 mos | 245 (8) | 526 (13) |
| 48+ mos | 137 (2) | 300 (8) |
| HRT use (estriol) | | |
| 1–48 mos | 290 (8) | 409 (9) |
| 48+ mos | 185 (7) | 256 (11) |
| HRT use (unknown) | | |
| 1–48 mos | 211 (2) | 328 (4) |
| 48+ mos | 65 (3) | 110 (3) |
| Never users of HRT | 6707 (153) | 25,515 (429) |
| First-degree relative with breast carcinoma | | |
| Yes | 589 (26) | 1574 (55) |
| No | 7830 (196) | 26,981 (483) |
| Age at first full-term pregnancy | | |
| < 35 yrs | 7139 (181) | 22,939 (430) |
| ≥ 35 yrs | 241 (11) | 615 (21) |
| Age at menarche | | |
| < 14 | 1765 (46) | 8410 (136) |
| ≥ 14 | 6529 (171) | 19,662 (394) |
| Nulliparous | 963 (30) | 4717 (83) |

HRT: hormone replacement therapy.

[a] The number of breast carcinomas that developed during the follow-up time is shown in parentheses. The median age at interview was 45 years of age (range, 25–65) for all women and 56 years (range, 35–65 years) for women who underwent a natural menopause.

In Table 3, stratified Cox regression analyses of time to breast carcinoma in relation to the type of HRT use and duration of use among women with a natural menopause are shown both for women using only one type of HRT and for women using different types. Hazard ratios are adjusted for year of interview. Among women using only one brand and among women using different brands, the highest risks were seen for combined continuous and gestagen-only therapy. Significantly elevated risks were also associated with combined sequential therapy and there was a suggestion that the risk appeared earlier compared with other exposures. Although there were little data to indicate a risk with estradiol use, the risk was non-

TABLE 2
Cox Regression Analysis of Time to Breast Carcinoma in Relation to Type of HRT Use and Ever Use among All Women (n = 28,378) and among Women with a Natural Menopause (n = 8442)[a]

| Characteristics | Women with a natural menopause (n = 8357) Hazard ratio 95% CI | All women (n = 28,378) Hazard ratio 95% CI |
|---|---|---|
| HRT use (combined sequential therapy) | 2.27 (1.26–4.10) | 1.22 (0.74–2.00) |
| HRT use (combined continuous therapy) | 2.33 (1.38–3.93) | 2.45 (1.61–3.71) |
| HRT use (gestagens only) | 1.05 (0.37–2.96) | 1.41 (0.79–2.53) |
| HRT use (estradiol only) | 0.81 (0.34–1.96) | 0.71 (0.40–1.26) |
| HRT use (estriol) | 1.45 (0.80–2.63) | 1.29 (0.79–2.13) |
| HRT use (unknown type) | 0.57 (0.18–1.80) | 0.41 (0.15–1.10) |

CI: confidence interval; HRT: hormone replacement therapy.

[a] Hazard ratios are adjusted simultaneously for the other types of HRT exposures and for year of interview.

significantly elevated after estriol use. Use of HRT of unknown type was not associated with a significantly increased risk.

Table 4 presents a Cox regression analysis of time to breast carcinoma in relation to type and duration of HRT use, family history, age at first full-term pregnancy, nulliparity, and age at menarche among all women (n = 28,378). Adjusting for each factor simultaneously, hazard ratios also are adjusted for types of HRT and year of interview. Again, the highest risk is associated with the longer use of combined continuous HRT use and gestagen-only use. In addition, longer use of estriol is associated with a significantly increased risk.

Table 5 shows a Cox regression analysis of time to breast carcinoma in relation to type and duration of HRT use, family history, age at first full-term pregnancy, nulliparity, and age at menarche among women experiencing a natural menopause (n = 8357). Adjusting for each factor simultaneously, hazard ratios also are adjusted for types of HRT, menopausal age, and year of interview. The highest risk is associated with the longer use of combined continuous HRT use and gestagen-only use. Longer use of combined sequential therapy and estriol use are associated with a nonsignificantly increased risk. No increased risk was noted among women after 5 years of nonuse.

We estimated the cumulative risk of breast carcinoma in a 50-year-old woman with gestagen-containing therapies for 48 months or more, with a follow-up of 10 years, to be 7% (95% CI = 5.4–11.4%) compared with 2% (95% CI = 1.6%–2.9%) for never-users of HRT.

TABLE 3
Stratified Cox Regression Analyses of Time to Breast Carcinoma in Relation to Type of HRT Use and Duration of Use among Women with a Natural Menopause[a]

| Characteristics | Women who ever used only one type of HRT HR 95% CI | Women who used different types of HRT HR 95% CI |
| --- | --- | --- |
| HRT use (combined sequential therapy) | | |
| Never users of HRT | 1.00 | 1.00 |
| 1–48 mos | 2.98 (1.29–6.90) | 2.94 (1.41–6.12) |
| 48+ mos | 3.11 (0.99–9.83) | 2.97 (1.21–7.28) |
| HRT use (combined continuous therapy) | | |
| Never users of HRT | 1.00 | 1.00 |
| 1–48 mos | 1.45 (0.52–3.99) | 1.74 (0.80–3.78) |
| 48+ mos | 6.28 (3.17–12.41) | 5.03 (2.63–9.62) |
| HRT use (gestagens only) | | |
| Never users of HRT | 1.00 | 1.00 |
| 1–48 mos | 1.44 (0.20–10.38) | 0.78 (0.19–3.19) |
| 48+ mos | 6.30 (0.88–45.29) | 3.14 (1.00–9.94) |
| HRT use (estradiol only) | | |
| Never users of HRT | 1.00 | 1.00 |
| 1–48 mos | 1.56 (0.38–6.38) | 1.40 (0.56–3.48) |
| 48+ mos | — | 1.05 (0.25–4.26) |
| HRT use (estriol) | | |
| Never users of HRT | 1.00 | |
| 1–48 mos | 1.44 (0.63–3.28) | 1.44 (0.59–3.53) |
| 48+ mos | 2.29 (0.93–5.68) | 2.27 (0.99–5.20) |
| HRT use (unknown) | | |
| Never users of HRT | 1.00 | 1.00 |
| 1–48 mos | 0.35 (0.05–2.52) | 0.31 (0.04–2.22) |
| 48+ mos | 1.10 (0.15–7.95) | 1.76 (0.43–7.18) |

HRT: hormone replacement therapy; CI: confidence interval; HR: hazard ratio.
[a] Hazard ratios are shown both for women using only one type of HRT and for women using different types. Hazard ratios are adjusted for year of interview.

## DISCUSSION

Using the same cohort of women in South Sweden, we reported previously that the risk of breast carcinoma in relation to HRT use after > 4 years of exposure was approximately doubled (SMR = 1.92) compared with never-users.[2] In the previous publication, we did not analyze the impact of different types of HRT. In the current study, we added another year of follow-up and analyzed whether the risk differed according to the different brands of HRT used. We divided the exposures into combined exposures (combined and sequential) and single exposures with estradiol, estriol, and gestagens.

The current results support the hypothesis that progestin-containing brands are associated with the highest risks. After > 4 years of exposure, hazard ratios more than doubled for combined exposures (combined and sequential) and for gestagen-only therapy whereas exposure to estriol and estradiol provided

TABLE 4
Cox Regression Analysis of Time to Breast Carcinoma in Relation to Type and Duration of HRT Use, Family History, Age at First Full-Term Pregnancy, Nulliparity, and Age at Menarche among All Women ($n = 28,378$)[a]

| Characteristics | HR | 95% CI | P value |
| --- | --- | --- | --- |
| HRT use (combined sequential therapy) | | | |
| Never use | 1.00 | | |
| 1–48 mos | 1.18 | 0.62–2.23 | 0.606 |
| 48+ mos | 1.44 | 0.67–3.08 | 0.347 |
| HRT use (combined continuous therapy) | | | |
| Never use | 1.00 | | |
| 1–48 mos | 2.01 | 1.14–3.55 | 0.015 |
| 48+ mos | 3.13 | 1.70–5.75 | 0.000 |
| HRT use (gestagens only) | | | |
| Never use | 1.00 | | |
| 1–48 mos | 1.14 | 0.56–2.32 | 0.724 |
| 48+ mos | 2.53 | 0.94–6.80 | 0.065 |
| HRT use (estradiol only) | | | |
| Never use | 1.00 | | |
| 1–48 mos | 0.77 | 0.38–1.57 | 0.478 |
| 48+ mos | 0.58 | 0.22–1.55 | 0.280 |
| HRT use (estriol) | | | |
| Never use | 1.00 | | |
| 1–48 mos | 0.87 | 0.41–1.85 | 0.723 |
| 48+ mos | 1.98 | 1.04–3.79 | 0.038 |
| HRT use (unknown) | | | |
| Never use | 1.00 | | |
| 1–48 mos | 0.30 | 0.07–1.20 | 0.09 |
| 48+ mos | 0.73 | 0.18–2.93 | 0.654 |
| Family history of breast carcinoma | 1.76 | 1.34–2.38 | 0.000 |
| Age at first full-term pregnancy > 35 yrs | 1.60 | 1.03–2.48 | 0.036 |
| Nulliparity | 1.36 | 1.07–1.73 | 0.012 |
| Age at menarche > 13 yrs of age | 1.02 | 0.85–1.25 | 0.781 |

CI: confidence interval; HRT: hormone replacement therapy; HR: hazard ratio.
[a] Hazard ratios are adjusted for each factor simultaneously, year of interview menopause age.

lower hazard ratios and insignificant for estradiol. The data suggest that continuous administration of progestins is more hazardous than sequential administration, supporting the findings in a previous published Swedish case–control study.[13] This interpretation is supported in our study both by findings among women using only one brand and among women using different HRT types. A smaller risk may be associated with sequential therapy, which mimics the natural cycle, compared with combined continuous therapy. Reports in the literature are inconsistent regarding the use of sequential versus continuous administration of HRT.[13,14] Therefore, there is a need for more information, especially from prospective cohort investigations and randomized trials. We estimated

**TABLE 5**
Cox Regression Analysis of Time to Breast Carcinoma in Relation to Type and Duration of HRT Use, Family History, Age at First Full-Term Pregnancy, Nulliparity, and Age at Menarche among Women Experiencing a Natural Menopause ($n = 8357$)[a]

| Characteristics | HR | 95% CI | P value |
|---|---|---|---|
| HRT use (combined sequential therapy) | | | |
| Never use of | 1.00 | | |
| 1–48 mos | 2.53 | 1.21–5.28 | 0.013 |
| 48+ mos | 2.23 | 0.90–5.56 | 0.084 |
| HRT use (combined continuous therapy) | | | |
| Never use of | 1.00 | | |
| 1–48 mos | 1.37 | 0.63–3.01 | 0.43 |
| 48+ mos | 4.60 | 2.39–8.84 | 0.000 |
| HRT use (gestagens only) | | | |
| Never use of | 1.00 | | |
| 1–48 mos | 0.52 | 0.11–2.39 | 0.403 |
| 48+ mos | 3.74 | 0.94–14.97 | 0.062 |
| HRT use (estradiol only) | | | |
| Never use of | 1.00 | | |
| 1–48 mos | 1.11 | 0.41–2.98 | 0.834 |
| 48+ mos | 0.35 | 0.07–1.86 | 0.219 |
| HRT use (estriol) | | | |
| Never use of | 1.00 | | |
| 1–48 mos | 1.26 | 0.56–2.86 | 0.58 |
| 48+ mos | 1.89 | 0.81–4.39 | 0.14 |
| HRT use (unknown) | | | |
| Never use of | 1.00 | | |
| 1–48 mos | 0.29 | 0.04–2.07 | 0.22 |
| 48+ mos | 1.31 | 0.32–5.34 | 0.702 |
| Family history of breast carcinoma | 1.68 | 1.10–2.55 | 0.016 |
| Age at first full-term pregnancy | | | |
| > 35 yrs | 1.92 | 1.04–3.54 | 0.04 |
| Nulliparity | 1.20 | 0.81–1.79 | 0.36 |
| Age at menarche | | | |
| > 13 yrs of age | 0.99 | 0.72–1.37 | 0.96 |

HRT: hormone replacement therapy; CI: confidence interval; HR: hazard ratio.
[a] Hazard ratios are adjusted for each factor simultaneously, year of interview, and menopausal age.

that the cumulative risk for a 50-year-old women in the highest risk group (combined continuous therapy and duration of $\geq$ 48 months) was 7% and that the corresponding risk for never users was 2%. Although studies have suggested a better survival rate for HRT users who develop breast carcinoma,[3–12] we believe that the increased incidence is remarkably high. For example, the risk associated with a first-degree relative with breast carcinoma is about 1.5–2.0. A first-degree relative with breast carcinoma is one of the strongest risk factors for breast carcainoma.

A percentage (12.5%) of the respondents could not name the type of HRT given. The analyses in that group suggest that the majority were estrogen preparations or were not HRT at all. Because the women

selected for interview had no previous cancer history, there should be no recall bias between the type of HRT and outcome (breast carcinoma).

A recent trial found a high incidence of breast carcinoma, stroke, and cardiovascular events among women followed up to 5 years, which led to the termination of the trial.[16] Therefore, there is a need for further prospective studies with longer follow-up to investigate the various modes of therapy.

Progestin-containing preparations used continuously are the most hazardous to women. We cannot yet address whether $\geq$ 10 years of HRT use confers an even higher breast carcinoma risk for women taking progestin-containing brands because too few women in this cohort have been exposed to HRT for such a duration.

There is a possibility that the effect of HRT is underestimated because during the follow-up, women assigned as unexposed may have started to use HRT. The cohort is currently being reinterviewed and future studies will be able to look at this potential bias.

Compared with another Swedish cohort investigation of HRT use, the current investigation has the advantage of retrieving the HRT information by direct interviews and not by prescriptions filled at pharmacies.[18] The recall of the exposure was further aided by time calendar and charts of brands prescribed in Sweden. Furthermore, the current cohort is population based and is not limited to the use of certain pharmacies, hospitals, or attending mammography units.

A small percentage of the women (12.5%) could not name the brand of HRT that they had been given. The hazard ratios in this group of women who were exposed to an unknown type of HRT did not reveal a very high risk, suggesting that the majority of the exposure in the unknown group was due to estradiol-only brands or to drugs that were not part of HRT. A possible shortcoming in the design of our investigation is that we did not confirm the HRT exposure by comparing it with the prescribing physicians' records. However, not all records would be available due to clearing of records after 5 years by some physicians. In addition, prescriptions are not always taken by the patients. By relying on information provided by the patient, such bias is reduced. Conversely, previous studies have confirmed a satisfactory aggreement between patient recall and records regarding brand and type of HRT exposure.[19,20]

All risk and prognostic studies concerning HRT so far have had limited follow-up time. There is a need to follow women with HRT exposure for a longer period of time as a recent U.S. investigation has suggested that survival after > 10 years is worse for HRT-exposed women compared with never-users.[21]

These data suggest that estrogen-only therapy is a rather safe therapy with little breast carcinoma risk. If there is a need for HRT containing progestins, as in women with intact uterine tissue, an attractive alternative would be to use a more androgenic progestin combination (e.g., tibolone). This type of therapy would not render the breast tissue as dense as most other progestin-containing preparations would. It is not known if this would transfer to a lower breast carcinoma risk. Therefore, risk studies should be initiated.

The results of the current investigation confirm a high risk for breast carcinoma after at least 4 years of HRT use, especially for progestin-containing preparations. We found a 7% cumulative risk for breast carcinoma patients after $\geq$ 48 months of combined estrogen and progestin use with a follow-up of 10 years compared with a 2% risk among never users.

The greatest hazard appears to be for continuous combined therapy, whereas combined sequential therapy shows an intermediate risk and estradiol-only preparations are not associated with a significantly increased risk. These results may help physicians to better tailor therapy to avoid breast carcinoma.

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# Warning: the estrogen product you are about to prescribe...

**Robert L. Barbieri, mD Editor-in-Chief**

The status of hormone replacement therapy (HRT) changed forever in July 2002, when the estrogen-progestin arm of the Women's Health Initiative (WHI) was halted. As you undoubtedly recall, that trial concluded that, among postmenopausal women, the risks of HRT-most notably heart disease, stroke, and breast cancer-exceed the benefits.1

## The agency's position that the findings of the WHI should be extended to all estrogen preparations is shaky scientifically

Under instruction from the US Food and Drug Administration (FDA), Wyeth Pharma-ceuticals (Collegeville, Pa)-the manufacturer of the estrogen-progestin formulation used in the WHI trial-changed its labeling in August to reflect these findings. But now, thanks to new labeling requirements unveiled by the FDA last month, all menopausal medications that contain estrogen (alone or in combination with a progestin) will have to include a boxed warning-the highest level of warning information-to highlight the increased risk for heart attack, stroke, and breast cancer.

## A valid decision?

According to an FDA press release, the new labeling was mandated to "emphasize individualized decisions that appropriately balance the benefits and the potential risks of these products."2 But the agency's position that the findings of the WHI should be extended to all estrogen preparations-whether or not they contain a progestin-is shaky scientifically. After all, the mere fact that the estrogen-only arm of the WHI continues implies that it is associated with a pattern of benefits and risks superior to that of the estrogen-progestin arm.

Based on multiple clinical trials, including the WHI, most experts agree that for menopausal women, oral estrogen-alone or combined with a progestin-should not be used for the primary or secondary prevention of heart disease.

However, there is greater complexity and a broader range of opinions concerning the use of estrogen-progestin for the treatment of vasomotor symptoms, vaginal and vulvar atrophy, and osteoporosis. One reason for the complexity is the fact that clinicians and menopausal patients inevitably vary in the values they place on the intricate pattern of benefits and risks associated with HRT.

## New treatment recommendations

Operating from a risk-averse viewpoint, the FDA advises the following:

- For menopausal women, when oral estrogen-progestin has been prescribed solely for the prevention of osteoporosis, alternatives such as exercise, vitamin D and calcium, bisphosphonates, raloxifene, and calcitonin should be considered. "Estrogens and combined estrogen-progestin products should only be considered for women with significant risk of osteoporosis that outweighs the risks of the drug," the FDA notes.[2]
- When estrogen-progestins are prescribed solely for the treatment of vulvar and vaginal atrophy, topical vaginal products should be considered.
- Estrogens and estrogen-progestins are the best pharmacologic treatments available for vasomotor symptoms and insomnia associated with hypoestrogenism. However, for this indication, clinicians should use the "lowest dose" for the "shortest duration for the individual woman" to reach treatment goals.[2] Prescribers are left to deduce the meaning of "lowest dose" and "shortest duration." Whatever the interpretation, changes in current practice will be required.

## Applying the guidelines

For menopausal women with vasomotor symptoms, many clinicians will initiate a standard dose of estrogen, such as conjugated equine estrogen (CEE) 0.625 mg. Let's assume that the dose is effective in relieving vasomotor symptoms. How will the physician know whether it is the lowest effective dose? He or she may need to consider titrating the dose downward-until vasomotor symptoms begin to recur. Alternatively, some clinicians may start with a very low dose (CEE 0.3 mg or less) and titrate upward until sufficient relief from vasomotor symptoms is obtained. These doses are likely to vary considerably among individual patients.

Patient characteristics also will influence the lowest possible dose effective for the treatment of hot flashes. For example, women who drink significant quantities of alcohol can probably adjust their estrogen dose downward by as much as 50%, because ethanol alters the metabolism of oral estrogen. If clinicians and patients widely accept the concept of "lowest possible dose," we are likely to see an increase in the number of women using minimal daily doses of estrogen, such as CEE

(0.3 mg), transdermal patches (25 µg), and oral estradiol (0.5 mg).

In the short term, the relabeling of all estrogen and estrogen-progestin hormone replacement regimens is likely to increase the frequency and intensity of patient consultations concerning proper management of the menopause. Individualizing treatment to the unique needs of each woman will continue to be the cornerstone of that management. n

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Back to top

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*Vasodilation*

In animal studies, cyclic high-dose MPA (equivalent to 10 mg/day in humans) and continuous low-dose MPA (equivalent to 2.5 mg/day in humans) diminished the beneficial effect of CEE on acetylcholine-induced coronary vascular dilation.[87,91] However, the addition of nomegestrol acetate to ET did not reverse the beneficial effects of 17β-estradiol on vascular dilation,[92] indicating that different progestins exert different effects. In another study, coronary artery vasospasm was avoided with the combination of 17β-estradiol plus progesterone but not with 17β-estradiol plus MPA.[93]

In women, both acute and long-term use of ET produces dilation of coronary arteries.[94,95] Some studies have found that use of CEE with either oral micronized progesterone or MPA improves flow-mediated dilation,[96] whereas others have found that MPA impairs flow-mediated dilation in a dose-dependent manner.[97] The combination of NETA and 17β-estradiol did not improve flow-mediated dilation.[98] In another study,[99] 17β-estradiol increased nitrous oxide levels, but the addition of NETA did not significantly increase these levels. Two studies assessing flow-mediated dilation in either older women ($\geq$ 80 years) using mostly unopposed ET[100] or women with established angina pectoris using ethinyl estradiol and NETA[101] found no vasodilatory benefit from ET or EPT. Some have postulated that both MPA and NETA may exert some androgenic action that partially reverses the benefit of estrogen effects on vasomotion in women,[102] although the addition of methyltestosterone to ET does not diminish vascular reactivity in monkeys.[103]

*Other cardiovascular risk factors*

A number of cardiovascular risk factors are improved with both ET and EPT, which could be expected to reduce CHD. Oral ET improves low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and lipoprotein(a) [Lp(a)]. The addition of progestogen may or may not affect lipid concentrations, depending on the type of progestogen used. Some progestogens can modify the estrogen-induced increase in triglycerides.[21,104,105] Although the effects of ET/EPT on lipids and lipoproteins are considered to be important, they have not been found to modify risk factors in clinical trials. In HERS and WHI, the beneficial changes with EPT, especially in HDL-C, did not protect against an increase in CHD events.[75,77]

In the PEPI trial,[106] the most favorable effect on HDL-C concentrations was observed in women taking unopposed estrogen (CEE). Adding MPA (2.5 or 10 mg/day for 12 days/month) blunted much of estrogen's benefit, although oral micronized progesterone (200 mg/day) still resulted in beneficial changes in HDL-C. In another study,[105] combining norgestimate with 17β-estradiol resulted in HDL-C improvement similar to CEE plus micronized progesterone but caused less of an increase in triglyceride levels. Another EPT combination, ethinyl estradiol and NETA, lowered HDL-C but had little effect on triglyceride levels.[21] Concentrations of LDL-C have been lowered with both ET and EPT,[106-110] although higher doses of NETA (0.5 mg) enhanced LDL-C reductions.[107] Levels of Lp(a) are decreased with both ET and EPT.[108,110]

The beneficial effects of ET on other cardiovascular risk factors, including a number of atherogenic and inflammation markers, do not seem to be blunted by the addition of progestogen.[96] Whereas a number of inflammation markers associated with increased CVD risk are decreased with ET/EPT, C-reactive protein (CRP) levels are increased with both ET and EPT.[111,112] However, the combination of transdermal 17β-estradiol and oral NETA decreased CRP levels in women with diabetes mellitus (DM),[113] suggesting that hepatic metabolism associated with oral therapies may be involved with the increase.

The effects of ET/EPT on hemostasis and fibrinolysis have been mixed. In addition to lowering Lp(a) with ET/EPT, both CEE and oral 17β-estradiol reduce fibrinogen and type-1 plasminogen activator inhibitor (PAI-1) levels, beneficial changes that are not affected by the addition of MPA[114] or NETA.[107] There is evidence that oral ET is associated with a procoagulant state with adverse changes in antithrombin III and protein C.[115] In vitro evidence suggests that some progestogens with glucocorticoid activity (eg, MPA) may potentiate the procoagulant effects of thrombin by increasing the availability of thrombin receptors in smooth muscle cells.[116] Some have proposed that there may be susceptible subgroups of women who are more prone to thrombotic events, such as those with low baseline Lp(a) levels[110] or prothrombotic genetic variants.[117]

ET/EPT has been shown to lower fasting glucose and insulin concentrations and improve insulin sensitivity in some studies,[118,119] but not in others.[120,121] One study reported improvement in women using transdermal NETA but deterioration in women using oral LNG,[121] a difference attributed to the strong androgenicity of LNG. However, in women with type-2 DM, both ET and EPT have improved a number of CHD risk factors, including lipid and lipoprotein parameters, glycemic control, and thrombotic indices,[122-124] as well as

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# Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial

OBJECTIVE--To assess pairwise differences between placebo, unopposed estrogen, and each of three estrogen/progestin regimens on selected heart disease risk factors in healthy postmenopausal women. DESIGN--A 3-year, multicenter, randomized, double-blind, placebo-controlled trial. PARTICIPANTS-- A total of 875 healthy postmenopausal women aged 45 to 64 years who had no known contraindication to mone therapy. INTERVENTION--Participants were randomly assigned in equal numbers to the following groups: (1) placebo; (2) conjugated equine estrogen (CEE), 0.625 mg/d; (3) CEE, 0.625 mg/d plus cyclic medroxyprogesterone acetate (MPA), 10 mg/d for 12 d/mo; (4) CEE, 0.625 mg/d plus consecutive MPA, 2.5 mg/d; or (5) CEE, 0.625 mg/d plus cyclic micronized progesterone (MP), 200 mg/d for 12 d/mo. PRIMARY ENDPOINTS--Four endpoints were chosen to represent four biological systems related to the risk of cardiovascular disease: (1) high-density lipoprotein cholesterol (HDL-C), (2) systolic blood pressure, (3) serum insulin, and (4) fibrinogen. ANALYSIS--Analyses presented are by intention to treat. P values for primary endpoints are adjusted for multiple comparisons; 95% confidence intervals around estimated effects were calculated without this adjustment. RESULTS--Mean changes in HDL-C segregated treatment regimens into three statistically distinct groups: (1) placebo (decrease of 0.03 mmol/L [1.2 mg/dL]); (2) MPA regimens (increases of 0.03 to 0.04 mmol/L [1.2 to 1.6 mg/dL]); and (3) CEE with cyclic MP (increase of 0.11 mmol/L [4.1 mg/dL]) and CEE alone (increase of 0.14 mmol/L [5.6 mg/dL]). Active treatments decreased mean low-density lipoprotein cholesterol (0.37 to 0.46 mmol/L [14.5 to 17.7 mg/dL]) and increased mean triglyceride (0.13 to 0.15 mmol/L [11.4 to 13.7 mg/dL]) compared with placebo. Placebo was associated with a significantly greater increase in mean fibrinogen than any active treatment (0.10 g/L compared with -0.02 to 0.06 g/L); differences among active treatments were not significant. Systolic blood pressure increased and postchallenge insulin levels decreased during the trial, but neither varied significantly by treatment assignment. Compared with other active treatments, unopposed estrogen was associated with a significantly increased risk of adenomatous or atypical hyperplasia (34% vs 1%) and of hysterectomy (6% vs 1%). No other adverse effect differed by treatment assignment or hysterectomy status. CONCLUSIONS-- Estrogen alone or in combination with a progestin improves lipoproteins and lowers fibrinogen levels without detectable effects on postchallenge insulin or blood pressure. Unopposed estrogen is the optimal regimen for ation of HDL-C, but the high rate of endometrial hyperplasia restricts use to women without a uterus. In women with a uterus, CEE with cyclic MP has the most favorable effect on HDL-C and no excess risk of endometrial hyperplasia.

# Combined hormone replacement therapy and risk of breast cancer in a French cohort study of 3175 women

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## ABSTRACT

The largest-to-date randomized trial (Women's Health Initiative) comparing the effects of hormone replacement therapy (HRT) and a placebo concluded that the continuous use of an oral combination of conjugated equine estrogens (CEE) and medroxy-progesterone acetate (MPA) increases the risk of breast cancer. This conclusion may not apply to women taking other estrogen and progestin formulations, as suggested by discrepancies in the findings of *in vitro* studies, epidemiological surveys and, mostly, *in vivo* studies of human breast epithelial cell proliferation showing opposite effects of HRT combining CEE plus MPA or estradiol plus progesterone. To evaluate the risk of breast cancer associated with the use of the latter combination, commonly prescribed in France, a cohort including 3175 postmenopausal women was followed for a mean of 8.9 years (28 367 woman-years). In total, 1739 (55%) of these women were users of one type of estrogen replacement with systemic effect during at least 12 months, any time after the menopause, and were classified as HRT users. Among them, 83% were receiving exclusively or mostly a combination of a transdermal estradiol gel and a progestin other than MPA. Some 105 cases of breast cancer occurred during the follow-up period, corresponding to a mean of 37 new cases per 10 000 women/year. Using multivariate analysis adjusted for the calendar period of treatment, date of birth and age at menopause, we were unable to detect an increase in the relative risk (RR) of breast cancer (RR 0.98, 95% confidence interval (CI): 0.65–1.5) in the HRT users. The RR of breast cancer per year of use of HRT was 1.005 (95% CI 0.97–1.05). These results do not justify early interruption of such a type of HRT, which is beneficial for quality of life, prevention of bone loss and cardiovascular risk profile, without the activation of coagulation and inflammatory protein synthesis measured in users of oral estrogens.

## INTRODUCTION

Despite the large number of epidemiological studies analyzing the risk of breast cancer during hormone replacement therapy (HRT), the specific influence of combined estrogen plus progestin treatments is still the subject of debate[1–9]. In most of these studies, the combined HRT users account for a small minority, selected according to unspecified and probably variable criteria, among a majority of unopposed estrogen users, thus weakening the power of statistical analysis and

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ORIGINAL ARTICLE

introducing potential biases. Following two recent randomized trials, the Heart and Estrogen/progestin Replacement Study (HERS)[10] and the Women's Health Initiative (WHI)[11], the larger concluded that the continuous use, with a duration of 5 or more years, of an oral combination of conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) increased the risk of breast cancer. This conclusion may not apply to women taking other estrogen and progestogen formulations because differences in routes of administration, doses and sequences of HRT may variously alter the risk. For example, the daily urinary excretion of 16-hydroxyestrone, a potentially genotoxic metabolite[12], is quite different in users of oral and transdermal estrogens[13], and the assumption of a difference in risk level depending on the route of estrogen administration is not unrealistic. Moreover, the consequence of stimulation of 17β-hydroxysteroid dehydrogenase activity by the progestin may be reversed if the main estrogen accumulated in breast tissue is estrone instead of estradiol[14,15]. Oral CEE increase estrone and estrone sulfate far more than estradiol plasma and breast tissue levels[16], and MPA is a synthetic progestin that may be different from progesterone or other progestins in its effects on breast tissues[2]. According to surgical breast biopsies performed in postmenopausal women, the breast epithelial cell mitotic activity increases during treatment with oral CEE, and even more so during HRT combining oral CEE and MPA[17]. Some of the epidemiological surveys and the largest randomized trial suggest that this HRT regimen is not optimal for breast tissues and should be stopped as soon as possible[5-7,11].

In France, the most widely prescribed HRT for the unselected majority of postmenopausal women combines transdermal estradiol with oral progesterone or closely related progestins[18,19]. The use of transdermal estradiol leads to a plasma and breast tissue estradiol/estrone ratio close to one[20,21]. According to surgical breast biopsies, this HRT regimen induces better control of mitogenic activity, and should be more favorable for the breast epithelium[22].

The present cohort study aimed to evaluate the long-term influence of such combined HRT on breast cancer incidence in a French population.

## SUBJECTS AND METHODS

### Study population

All women who had consulted at least once between January 1975 and December 1987 at the department of Endocrinology and Reproductive Medicine, Necker Hospital, Paris (ERN), and who were postmenopausal or had reached the age of 50 years between these two dates, were eligible for inclusion in the cohort. Their main reasons for consulting were climacteric symptoms, benign breast symptoms, uterine symptoms, nongynecological symptoms or routine check-up.

To eliminate non-informative cases, women with less than 1 year of follow-up were excluded. Women who had developed breast cancer or a cancer at another site, before the beginning of the follow-up, were also excluded. Using these criteria, a total of 3175 women were included in the study.

### Data collection

The main sources of data were ERN medical records. In the case of missing information, patients were questioned by mail, and, if they did not respond, they were contacted by telephone. Demographic data, menopausal status, HRT use, type and duration of use, and breast cancer occurrence were collected.

Additionally, a more detailed questionnaire was sent by post to a subcohort of 2069 women who attended ERN for the first time between 1979 and 1984, the mid-period of recruitment. The additional information concerned socioeconomic status, reproductive factors and family history of breast cancer. The questionnaire also included the main reason for the first visit to ERN.

### HRT use analysis

Users of any type of estrogen replacement with systemic effect for at least 12 months, any time after the menopause, were classified as HRT users. To eliminate non-causal exposure, women who had used estrogens for less than 12 months, or who used only vaginal formulations, were classified as HRT non-users. Many of the HRT users had received several different types of HRT. Treatments had been changed because of either side-effects or the development of new formulations. To analyze the specific effect of one type of HRT, we selected the women who had used this type of HRT for the longest time.

### Statistical methods

Both internal and external analyses were performed. Women were analyzed for their risk of

breast cancer over the period starting on the date of their first visit to ERN for menopausal women, or at the time of the menopause for women still premenopausal at the date of their first visit. The end of follow-up was defined as the first of the following four events:

(1) Data collection cut-off on 1 December 1995;

(2) The last information, obtained from ERN medical record, telephone interview or mail questionnaire;

(3) Occurrence of breast cancer;

(4) The date of death.

For external comparison, the expected number of breast cancers during the follow-up period was estimated using the rates by 5-year calendar period, and 5-year age class, estimated by the FRANCIM (Reseau des Registres des Cancers, France) Group for France for the period from 1975 to 1995. This estimation was performed using data from all local cancer registries in France and national mortality data[23]. The standardized incidence ratio (SIR) was defined as the ratio of observed to expected number of breast cancers. The SIR of breast cancer was modelled assuming that the number of breast cancers followed a Poisson distribution. Statistical tests were carried out using the deviance of nested models[24]. These analyses were done using AMFIT software[25] and Statistical Analysis System (SAS) software. As the confidence interval of an SIR ratio cannot be calculated analytically, we performed simulations. For each SIR ratio (study population/general French population), 100 000 pairs of values were simulated and their ratios were calculated. The 2500th and the 97 500th of these ratios, classified in ascending order, were retained as the lower and upper limits of the 95% confidence interval of the SIR ratio.

Internal statistical analysis was performed using (time) Cox's proportional hazards regression[26]. Because breast cancer incidence increased in France between 1975 and 1995[23,27], and was also strongly related to age at menopause, all analyses were adjusted for calendar period, date of birth and age at menopause. In the subcohort of 1918 women with more complete information, the analysis was additionally adjusted on the main risk factors for breast cancer. Analysis of the role of 'duration of HRT use' and of 'time since last use of HRT' was performed using these variables as time-dependent variables in a Cox's proportional hazards model.

## RESULTS

The median year of inclusion of the 3175 women was 1982, and their mean age at inclusion was 50 years (range 20–59 years). Among these 3175 women, 1739 (55%) were defined as users of HRT. The median date of the first visit to ERN was 1980 for both HRT users and non-users, and the median date of start of follow-up was 1982 for HRT users and 1981 for non-users. During the follow-up period, a mean 3% of patients were lost each year. The mean follow-up was 8.9 years (ranging from 1 to 24 years), collecting a total of 28 367 woman-years.

The main characteristics of HRT users and non-users are given in Table 1. In the whole cohort, age at menopause was similar between the two groups of women. The duration of follow-up was slightly longer (9.3 years) in HRT users than in non-users (8.6 years). As expected, the main reason for the first consultation was significantly related to the use of HRT: among the HRT users, 74% of women gave climacteric symptoms as the main reason for the first visit, while this percentage fell to 26% in non-users. Women with a surgical menopause were also more frequently HRT users than those with a natural menopause. HRT users had fewer children than non-users. Last, among HRT users, fewer were retired at the time of inclusion than among HRT non-users ($p < 0.0001$).

## Use of HRT and breast cancer risk

In the total cohort, 105 women developed breast cancer during the follow-up period. Among the 105 women with breast cancer, 43 were classified as HRT non-users and 62 as HRT users (Table 2).

From external comparison, the expected number of breast cancers from the general French population of the same age during the same calendar period was 65.6. Thus, our total cohort had an excess of risk of 60%. This excess of risk was similar among the HRT users (62 observed vs. 37.1 expected) and among the HRT non-users (43 observed vs. 28.5 expected) (Table 2). The ratio of the SIRs was 1.11 (95% confidence interval (CI) 0.75–1.66).

From internal comparison, the unadjusted relative risk of breast cancer associated with HRT use was 1.12 (CI 0.73–1.75, $p = 0.6$), compared with the non-users. When adjusting for calendar period of treatment, date of birth and age at menopause (Table 2), the risk of breast cancer was 0.98 (CI 0.65–1.5).

**Table 1** Characteristics of cohort according to hormone replacement therapy (HRT) use. Values are expressed as mean (SD) unless otherwise specified

| Characteristics | Use of HRT | | |
| --- | --- | --- | --- |
| | No (n = 1436) | Yes (n = 1739) | p Value* |
| *Whole cohort* | | | |
| Age at menopause in years | 50 (4.6) | 50 (4.7) | NS |
| Follow-up in years | 8.6 (5.7) | 9.3 (5.2) | < 0.001 |
| *Additional questionnaire (1979–84)* | | | |
| Menopausal symptoms as reason for first visit | 26% | 74% | < 0.0001 |
| Surgical menopause | 16% | 22% | < 0.005 |
| Age at natural menopause (years) | 52 (3.8) | 51 (3.5) | NS |
| Age at surgical menopause (years) | 46 (6.7) | 47 (6.1) | NS |
| Number of children | 2.2 (2.0) | 1.9 (1.5) | 0.02 |
| Age at first full-term pregnancy (years) | 26 (5.0) | 26 (4.8) | NS |
| Breast cancer in first- and second-degree relatives | 11% | 12% | NS |
| History of benign breast symptoms | 35% | 40% | NS |
| Professional status | | | |
| executive | 21% | 26% | NS |
| retired | 12% | 6% | 0.0001 |

*Wilcoxon rank test for continuous variable and Fisher exact test for proportion; NS, not significant

**Table 2** Standardized incidence ratio (SIR) and relative risk (RR) of breast cancer (BC) according to hormone replacement therapy (HRT) use

| HRT use | Number of women | Observed number of BC (O) | Expected number of BC (E)[†] | Ratio of SIRs[‡] | RR of BC (95% CI)[††] |
| --- | --- | --- | --- | --- | --- |
| Non-users | 1436 | 43 | 28.5 | 1* | 1** |
| Any HRT | 1739 | 62 | 37.1 | 1.11 (0.75–1.66) | 0.98 (0.65–1.48) |
| Estrogen + progestin[‡‡] | 1545 | 59 | 32.8 | 1.19 (0.81–1.79) | 1.10 (0.73–1.66) |

*External reference category; **internal reference category; [†]expected number of breast cancers from general French population rates; [‡]ratio between standardized incidence ratio (SIR = O/E) in category and that among patients who did not receive any HRT; [††]adjusted to period of treatment, date of birth and age at menopause; [‡‡]type of HRT used for longest time; CI, confidence interval

In the subcohort of the 1918 women who responded to the additional questionnaire (92.7% response rate), 64 breast cancers occurred during follow-up, and a similar relative risk of breast cancer in HRT users was observed (RR = 0.92, CI 0.55–1.5) as compared with the risk in the total cohort of HRT users, when adjusting for date of birth and age at menopause. Further adjustments on the number of children, age at birth of first child, family history of breast cancer and professional status did not significantly modify this risk.

## Hormonal constituents and breast cancer risk

Among the 1739 HRT users in the total cohort, 1545 women (89% of HRT users) used mostly or exclusively combined HRT, and 59 developed breast cancer during the follow-up. The number of expected breast cancer was 32.8. From external comparison, the risk of breast cancers was 1.19 (CI 0.81–1.79). From internal comparison, the relative risk adjusted for the calendar period of treatment, date of birth and age at menopause was 1.10 (CI 0.73–1.66), compared with the risk among HRT non-users (Table 2).

In combined HRT users, estrogens were mainly transdermal estradiol gel formulation (83%), and, less often, transdermal estradiol patches, oral estradiol or oral CEE; progestins were mainly oral micronized progesterone (58%) or dydrogesterone (10%). Other progestins used were promegestone, lynestrenol, chlormadinone acetate and nomegestrol acetate. Fewer than 3% used MPA. All progestins were prescribed for at least 10 days per month, but inter- and intraindividual variations were too great (10, 12, 14, 25 or 30 days) to allow reliable estimation of the potential influence of these criteria.

## Subgroup analyses

Among the women who had no family history of breast cancer, the risk associated with HRT use was 0.72 (CI 0.38–1.4), whereas it was 2.6 (CI 0.54–13) among those who reported a family history of breast cancer. These results were based on only ten breast cancers, and the interaction test was not statistically significant. Of the other factors registered in the questionnaire (number of children, age at birth of first child, professional status, main reason for the first consultation, surgical menopause), none appeared to modify

the risk of breast cancer associated with the use of HRT. Body mass index (BMI) was recorded only for women with breast cancer: among these women, BMI was not significantly different in HRT users (23 kg/m$^2$) and non-users (24 kg/m$^2$).

## Duration and timing of exposure

No significant increase in the risk of breast cancer was associated with the duration of HRT use (Table 3). The relative risk per year of HRT use was estimated to be 1.005 (CI 0.97–1.05, $p = 0.8$). Similarly, the risks among current, former and past HRT users were shown to be entirely comparable (Table 4). When both duration of use and the last period of use were analyzed together, no significant increase in breast cancer incidence was observed in any of the four subgroups considered (Table 5).

## DISCUSSION

The present cohort study, based on 28 367 woman-years, analyzed the risk of breast cancer in 3175 women who consulted at ERN for the first time between 1975 and 1987. This risk was assessed in 1739 (55%) women who had used

**Table 3**   Relative risk (RR) of breast cancer (BC) according to duration of hormone replacement therapy (HRT) use

| Duration of HRT use (years) | Number of women | Average follow-up (years) | Number of BC | RR[†] (95% CI) | p Value |
|---|---|---|---|---|---|
| None or < 1 | 1436 | 9 | 43 | 1* | |
| 1–4 | 600 | 8 | 20 | 0.86 (0.49–1.49) | 0.6 |
| 5–9 | 437 | 9 | 24 | 1.03 (0.61–1.75) | 0.9 |
| ≥ 10 | 702 | 12 | 18 | 1.15 (0.64–2.05) | 0.6 |
| Per year | | | | 1.005 (0.97–1.05) | 0.8 |

*Reference category; [†]Cox's proportional hazards risk model, using duration of HRT use as time-dependent variable, stratified on period of treatment, date of birth and age at menopause; CI, confidence interval

**Table 4**   Relative risk (RR) of breast cancer (BC) according to last period of hormone replacement therapy (HRT) use

| Last use of HRT[†] | Number of women | Number of BC | RR[‡] (95% CI) | p Value |
|---|---|---|---|---|
| Non-users | 1436 | 43 | 1* | |
| Current users | 845 | 30 | 0.83 (0.51–1.34) | 0.4 |
| Former users[††] | 215 | 11 | 1.42 (0.76–2.64) | 0.3 |
| Past users[‡‡] | 674 | 21 | 1.12 (0.63–1.98) | 0.7 |

*Reference category; [†]information missing for five women; [‡]Cox's proportional hazards risk model, with time since last use of HRT as time-dependent variable, stratified on period of treatment, date of birth and age at menopause; [††]stopped during past 4 years; [‡‡]stopped 5 years ago or more; CI, confidence interval

Table 5 Relative risk (RR) of breast cancer (BC) associated with hormone replacement therapy (HRT) use according to both last period of use and duration of use

| | Duration of use (years) | | | |
| | ≤ 5 | | 5 or more | |
| Last period of use[†] (years) | BC/n[‡] | RR[††] (95% CI) | BC/n[‡] | RR[††] (95% CI) |
| --- | --- | --- | --- | --- |
| < 5 | 7/268 | 0.59 (0.26–1.34) | 34/792 | 1.08 (0.68–1.72) |
| 5 or more | 13/331 | 1.13 (0.58–2.19) | 8/343 | 1.23 (0.51–2.97) |

[†]Information missing for five women; [‡]total number of patients; [††]relative risk of BC estimated by Cox's proportional hazards model, using duration of HRT use and time since last use of HRT as time-dependent variables, and adjusted on period of treatment, date of birth and age at menopause (reference category is subgroup of non-users of HRT); CI, confidence interval

HRT compared with 1436 (45%) women who had not. During a mean follow-up of 8.9 years (ranging from 1 to 24 years), 105 women developed invasive breast cancer, 62 of them being HRT users. Both external and internal comparisons of risk associated with the use of HRT were performed. The incidence of breast cancer measured in both HRT users and non-users consulting at ERN was higher than the incidence estimated for the general French population of the same age during the same historical period. This first suggests that breast cancer cases were not underdiagnosed in the study cohort, but also that the study population consulting at ERN may have been at higher risk than the general population. Within the French population, large variations in the incidence of breast cancer, related to geographical area and urban versus country residency, have already been reported[23]. This relative excess may be due in part to the urban and socioeconomic status of women consulting for any reason at ERN, and also to their general acceptance of regular mammograms. The 105 cases of breast cancer occurring during the follow-up period correspond to a mean of 37 new cases per 10 000 women/year, and is quite similar to the incidence (35 new cases per 10 000 women/year) measured in the US multicentric randomized trial requiring annual mammograms and clinical breast examinations[11].

HRT users and non-users were slightly different with respect to some of the potential risk factors analyzed (professional activity, incidence of surgical menopause, duration of follow-up, number of children). The greatest difference between groups was found for the main reason for the first visit to ERN: 74% of those consulting mainly for menopausal symptoms received a HRT prescription, while only 26% of women of the

same age consulting for another main reason were given the same prescription (Table 1). A personal history of benign breast symptoms, such as diagnosis of 'fibrocystic breast disease', or cyclic breast tenderness with or without dense mammograms, had no apparent influence on prescription. Family history of breast cancer was not different in users (12%) and non-users (11%), and apparently was not a reason to discourage women from using HRT.

From internal analysis, there was no significant increase in the risk of breast cancer related to use of the specific type of HRT most prescribed in France. In a univariate analysis, the relative risk of breast cancer was 1.12 (CI 0.73–1.75, $p = 0.6$). After adjustment for the calendar period of treatment, date of birth and age at menopause, the relative risk was 0.98 (CI 0.65–1.5). This relative risk was similar in the women whose follow-up was based on their medical file at ERN, completed by mail or telephone interview, and in the women having replied to an additional questionnaire. As in the WHI trial[11], the relative risk of breast cancer in HRT users was not significantly affected by their family history or other risk factors.

In an analysis limited to the 59 breast cancer patients who received mostly or exclusively estrogen combined with a progestin, 10–30 days each month, the adjusted relative risk was 1.10 (CI 0.73–1.66). This relative risk was similar in the women whose follow-up was based on their medical file at ERN, completed by mail or telephone interview, and in the women having replied to an additional questionnaire. Based on a mean follow-up of 8.9 years and a duration of HRT > 5 years for 47% of the treated population, the relative risk of breast cancer per year of exposure to HRT was 1.005 (CI 0.97–1.05). Therefore, in contrast with some recent US cohort studies and

one randomized trial, no increase in breast cancer risk was detected in combined HRT users, neither in the mid- nor in the long-term.

The first specificity of the French cohort is that the standard prescription for unselected average postmenopausal women was combined HRT, actually used by 89% of the treated group. By contrast, only 4–12% of the treated populations included in cohorts in the 1970s, 1980s and 1990s used a progestin combined with estrogens, while the majority received unopposed estrogens[1,5–9]. The various criteria for selecting this minority are largely unknown, and may have introduced unidentified biases[4]. For example, among 2082 postmenopausal breast cancer patients analyzed in a recent US cohort study[5], only 101 (4.8%) used MPA added for ± 10 days per month to CEE. A harmful effect associated with duration of estrogen–progestin use was reported (RR 1.08 per year of treatment, CI 1.02–1.16), based on only 18 cases (0.8% of the total) of invasive breast cancer diagnosed in recent users of combined HRT for > 4 years with a BMI index < 24.4 kg/m² (RR 1.9, CI 1.1–3.3). Multiplying small selected subgroups increases the risk of results being simply due to chance distribution of collected or uncollected subject characteristics, and, hence, is misleading[4]. In one study, only the sequential use of a progesterone-derived progestin (5.3% of cases) appeared to be associated with a significantly increased risk[5]. Another study showed that only the continuous combined use of testosterone-derived progestins (1.9% of cases) was associated with an increased risk[8], and, in a third, the risk was similar for use of oral estrogens alone and for sequential or continuous combined HRT (11.2% of cases)[9]. The present French cohort study, in which combined HRT is prescribed to an unselected majority of the treated population, avoids this major methodological bias.

The WHI randomized trial concluded that the continuous use of an oral combination of CEE and MPA increases the risk of breast cancer. Thirty-eight new cases per 10 000 women/year, as a mean, were diagnosed in this HRT group, while 30 new cases per 10 000 women/year were diagnosed in the placebo group. The power of our study to detect an excess of eight cases per 10 000 women/year, corresponding to a relative risk of 1.23, is 62%. Therefore, we may have missed such a relatively small increase. However, in the WHI trial, even if the previous use of HRT by 30% of the study population is quite confusing, the most impressive result is the rapid increase during the follow-up period in breast cancer incidence ratio

between HRT and placebo groups. This ratio rose from 0.62 after the first year to 2.64 by the fifth year. Based on an analysis of the effect of HRT duration, a trend of this magnitude is highly improbable in our study, which has a power higher than 95% to detect such a time-related change between the 1–4-year use group and the 5–9-year group.

Then, the main specificity of the French cohort is that 83% of the combined HRT users were receiving mostly or exclusively a transdermal estradiol gel formulation, and the progestin was oral micronized progesterone in 58%, while MPA users were less than 3%. It is plausible that various combinations of estrogens and progestins may differently influence the relative risk of breast cancer. The serum and breast tissue levels of estrone and estrone sulfate and the estrone/estradiol ratio are far higher following oral estrogens than following transdermal estradiol[16,20,21]. The first consequence may be a difference in progestin-stimulated 17β-hydroxysteroid dehydrogenase activities[14]. The balance between 17β-hydroxysteroid dehydrogenase activities of the first reducing estrone to estradiol and second, oxidizing estradiol to estrone may favor the synthesis of estradiol if the estrone/estradiol ratio is high in the epithelial cell environment. For estrogen-dependent breast cancer cells, almost exclusively equipped with the first isoform of the enzyme, estrone will become almost as active as estradiol[15]. Furthermore, MPA has been described to stimulate the reducing rather than the oxidizing activity in human breast cells[14]. Accordingly, the addition of MPA to oral CEE, which provides predominantly estrone, has been shown to increase the mitogenic activity of breast epithelial cells *in vivo*[17]. Conversely, in one *in vitro* study, MPA reduced the mitogenic effect of estradiol on MCF-7 cells, supporting the concept of a pivotal influence of the baseline estrone/estradiol ratio on the results[28]. When this ratio is close to or lower than 1, the main effect of progesterone in normal human breast cells *in vitro* is to down-regulate the estradiol receptor and to decrease proliferation[29]. Additionally, the endogenous surge of progesterone during the luteal phase stimulates more the oxidation of estradiol into estrone than the reduction of estrone into estradiol[30,31]. *In vivo*, the addition of progesterone to transdermal estradiol has been shown to decrease the mitogenic activity of breast epithelial cells[20,22,32].

Another consequence of high levels of estrone is that the daily urinary excretion of 16OH-estrone, a metabolite expected to be genotoxic[12],

has been shown to be four-fold higher in users of oral estradiol than in users of transdermal estradiol[13].

The potential increase in the risk of breast cancer linked to the use of oral estrogens combined with synthetic progestins is one of the reasons for discouraging postmenopausal women from using any type of HRT for more than a few years[11,33]. The results of the present study, in long-term users of a combination of transdermal estradiol and a progestin closer to progesterone than MPA, do not show any increase in breast cancer risk. The power required to detect a time-related change in the relative risk of breast cancer similar to that measured in the WHI is higher than 95%. Also, analysis of the clinical and biological characteristics of breast tumors diagnosed in French HRT users does not suggest

that prognosis is worse than in untreated post-menopausal women[34]. We conclude that, at present, there is no evidence to recommend early interruption of this type of HRT, which is beneficial for quality of life and prevention of bone loss, and is associated with an improved cardiovascular risk profile without the activation of coagulation measured in oral estrogen users[18,19,35,36].

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# Differing effects of low-dose estrogen–progestin therapy and pravastatin in postmenopausal hypercholesterolemic women

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## ABSTRACT

*Background* Most studies examining the potential cardioprotective effects of post-menopausal estrogen have been undertaken in healthy women, with doses that may not be appropriate for long-term intervention. New low-dose estrogen–progestin regimens alleviate postmenopausal symptoms with a favorable side-effect profile; however, little is known of the impact of such regimens in women at increased risk of cardiovascular disease. Hence, we have evaluated the effects of low-dose oral estrogen–progestin therapy on serum lipoprotein lipids, brachial artery reactivity and fibrinogen in hyper-cholesterolemic postmenopausal women in direct comparison with the effects of pravastatin, a lipid-lowering agent known to reduce cardiovascular events in women.

*Methods* In a randomized, double-blind, double-dummy, parallel trial, we studied the effects of continuous combined estrogen–progestin therapy (1 mg 17β-estradiol with 500 μg norethisterone acetate daily) or pravastatin (20 mg daily) in 72 postmenopausal women with fasting serum low-density lipoprotein (LDL) cholesterol levels greater than 124 mg/dl after an 8-week run-in diet, over a 24-week period. The primary end-point was percentage change in LDL cholesterol from baseline.

*Results* The intention-to-treat population comprised 65 women, mean age $59 \pm 6.3$ years, and 29 in each group completed the trial. Diet alone reduced LDL cholesterol significantly in both treatment groups, in association with a reduction in weight during this period. Compared with respective baseline values, pravastatin decreased LDL cholesterol and total cholesterol to a greater extent than hormone therapy ($p = 0.0001$ and 0.003 for difference between treatments, respectively). High-density lipoprotein (HDL) cholesterol levels decreased with hormone therapy, but did not change with pravastatin ($p = 0.01$). Lipoprotein(a) decreased significantly with hormone therapy only (–14%, 95% confidence interval (CI) –21 to –6%, $p = 0.01$ for difference between groups). Brachial artery flow-mediated dilatation (FMD) was impaired at baseline, and this increased with hormone therapy (absolute mean change in artery diameter as percentage units 2.07, 95% CI 0.57–3.57, $p = 0.009$) versus no change with pravastatin (0.19, 95% CI –1.1 to 1.5, $p = 0.78$), with a near-significant difference between the two groups ($p = 0.058$). A significant correlation between improved brachial artery FMD

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and reduction in LDL cholesterol was not observed. Fibrinogen decreased significantly in both treatment groups with no difference between treatments.

*Conclusions* In postmenopausal hypercholesterolemic women, pravastatin and hormone therapy exhibited divergent effects. The former lowered total and LDL cholesterol more effectively, whereas hormone therapy lowered lipoprotein(a) significantly and improved brachial artery endothelium-dependent dilatation, independent of the reduction in LDL cholesterol. The modest increase in brachial artery FMD seen is consistent with hypercholesterolemia compromising endothelial integrity, and suggests that the important effect of estrogen on the endothelial microenvironment may be attenuated in women with endothelial dysfunction.

## INTRODUCTION

Recent epidemiological data indicate that the cardiovascular benefits of standard-dose hormone therapy[1,2] are seen with low-dose estrogen use, that is, less than 0.625 mg conjugated equine estrogens or equivalent, particularly among current users and in the first year of use[1,3]. Low-dose estrogen alleviates vasomotor symptoms[4], protects against bone loss[5] and is associated with fewer side-effects such as mastalgia and irregular bleeding[4]. Hence, the prescription of low-dose therapy is increasing. Several intervention studies have shown reductions in cardiac events with 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors in women with low-density lipoprotein (LDL) cholesterol levels greater than 124 mg/dl[6-8], and we have shown comparable improvements in lipoprotein lipids, specifically LDL cholesterol, high-density lipoprotein (HDL) cholesterol and lipoprotein(a), with high-dose oral hormone therapy in otherwise healthy hypercholesterolemic postmenopausal women[9]. Estrogen also influences the endothelial microenvironment by enhancing endothelium nitric oxide production, and thus improves peripheral and coronary endothelium-dependent vasodilatation[10,11]. A close correlation between the effects of estrogen on endothelium-dependent vasomotor responses in the coronary circulation and flow-mediated vasodilatation in the brachial artery has been demonstrated, making the latter a useful surrogate marker for assessing risk[12]. However, the effects of low-dose continuous combined estrogen–progestin therapy on lipoprotein lipids and endothelium-dependent vasodilatation in hypercholesterolemic women are not known. Fibrinogen, a marker of cardiac event risk[13,14], is also modified by standard-dose estrogen therapy[15]. The average dose of pravastatin used for lipid-lowering in Australia is 24.9 mg/day[16].

The effects of this dose of pravastatin on endothelial function, and fibrinogen, and the relationships between these parameters and changes in lipids in postmenopausal women have not been extensively studied. To characterize further and elucidate the effects of low-dose hormone and pravastatin therapies in hypercholesterolemic postmenopausal women, we have directly compared the effects of a dose of continuous combined oral estrogen–progestin, suitable for older postmenopausal women, with those of pravastatin, given at the average dose used in the community, on lipids, brachial artery vasomotor responsiveness and fibrinogen levels.

## METHODS

### Subjects

Women who were postmenopausal (defined as greater than 12 months amenorrhea and serum follicle stimulating hormone level above 25 IU/ml), 45–75 years of age, who had a fasting serum LDL cholesterol level > 124 mg/dl at screen and after 8 weeks on the standard Australian National Heart Foundation diet, who had a normal mammogram within the previous 2 years, a normal cervical smear within the past year and who had not taken postmenopausal hormone therapy or lipid-lowering therapy (including soluble fiber, vitamin E and fish oil supplements) in the 12 weeks before enrolment were eligible for the study. Women with a history of estrogen-related cancer, confirmed thromboembolic disease, a previous cerebrovascular accident, uncontrolled hypertension (blood pressure > 160/95 mmHg), unstable cardiovascular disease (i.e. a myocardial infarction, or coronary or peripheral angioplasty within the preceding 3 months), genital bleeding of unknown cause, alcohol intake > 30 g/day, severe obesity (body mass index > 35 kg/m$^2$), insulin-dependent diabetes mellitus or unstable non-insulin-dependent diabetes mellitus, homozygous familial hypercholesterolemia or abnormal liver function tests

were excluded from the study. Women who were receiving anticonvulsant or anticoagulant therapy were also excluded, but the use of diuretic agents, beta blockers and thyroid hormone was acceptable if the dose was expected to remain stable throughout the study.

Subjects were recruited from the Jean Hailes Centre, Clayton, and from the general population via television and radio announcements over a 6-month period. This study was approved by the Human Research and Ethics Committee, Monash Medical Centre, Clayton, Victoria, and all participants gave written informed consent.

## Protocol

The trial was a single-center, randomized, double-blind, double-dummy, parallel-group comparative trial. There was a 9–10-week run-in/screening phase, which included a minimum 8 weeks of diet to ensure a stable lipid baseline (two LDL cholesterol values, 1 week apart, that did not differ by more than 12%), and to enable exclusion of women achieving normalization of their lipid profile on diet alone. The randomized treatment phase commenced at week 0 and was 24 weeks in duration. Treatment was with either 17β-estradiol 1 mg plus 500 μg norethisterone acetate (Activelle®; Novo Nordisk, A/S, Denmark) or pravastatin 20 mg (Pravachol®, Bristol-Myers Squibb, Australia) daily. The randomization code was generated by Almedica US (New Jersey, USA), using the system ADLS 5.13. Blood was sampled after a 12-h fast at screening, at randomization, and every 8 weeks during the treatment phase. Height and weight were measured at screening, and weight at each subsequent visit. Body mass index was calculated as weight in kilograms divided by the square of the height in meters. Brachial artery studies were undertaken, and lipoprotein(a) and fibrinogen levels were measured at 0 and 24 weeks.

## Measurement of lipids, lipoproteins and fibrinogen

Lipid analysis was performed at a central laboratory, Dorevitch Laboratory, Fairfield, Victoria. LDL cholesterol and very-low-density lipoprotein (VLDL) were calculated using Friedewald's formula[17]. Total cholesterol was determined by the CHOD-PAP method and triglycerides by the GPO-PAP method using a Boehringer Mannheim Systems (Indianapolis, IN, USA), Hitachi 747 machine. HDL cholesterol was also measured by

an enzymatic colorimetric test using a Boehringer Mannheim/Hitachi 747 machine. Lipoprotein(a) was determined by a rate nephelometry method with a kit from Beckman Immage™ Immunochemistry Systems (Beckman Instruments, Inc., NSW, Australia). Fibrinogen was determined using the Von Clauss method[18], with reagents from Behring Diagnostics, GmbH (Germany).

## Endothelium-dependent arterial function

These studies were conducted in the Cardiovascular Centre, Monash Medical Centre, Clayton, Victoria. All studies were performed and results read by a single vascular technician, blinded to the treatments, under uniform conditions using methodology described previously[19]. Brachial artery diameter was measured at rest, after reactive hyperemia (endothelium-dependent flow-mediated dilatation (FMD)) and following the sublingual administration of glyceryl trinitrate (GTN) (endothelium-independent dilatation) at 0 and 24 weeks, using a high-resolution ultrasound machine (ATL, HDI Ultramark 9, Seattle, WA, USA) with a 7–10 MHz linear array transducer. The transducer angle was noted to remain consistent between studies. The flow-mediated vasodilator response to reactive hyperemia, induced by deflation of a blood pressure cuff previously inflated to suprasystolic pressure for 5 min, was continuously recorded from 30 s before until 5 min after cuff deflation. After return to baseline, GTN (0.6 mg) was administered sublingually, and brachial artery images were recorded before and until 5 min post-GTN. Change in arterial diameter (percentage dilatation) was calculated for each individual as artery diameter pre-intervention – post-intervention/ pre-intervention × 100.

## Other measures

Three quality-of-life questionnaires were used: the Australian Quality of Life instrument[20], the European Quality of Life (EuroQoL-EQ-5D Australian–English version) instrument[21] and the Women's Health Questionnaire[22].

## Statistical analysis

A reduction in LDL cholesterol from baseline to end of treatment was the primary clinical outcome. The sample size calculated for a power of 90% and a significance level of 0.05, assuming an intrasubject standard deviation of 15%, was

14. To perform a between-group comparison that might be based on non-parametric analysis, a minimum of 32 women were to be recruited to each group, with the number randomized greater, to allow for discontinuation.

Data on the intent-to-treat population, defined as all women who were randomized and who received at least one dose of treatment, are presented for all parameters except vasomotor responses. The latter analysis was done per protocol, as an individual percentage change could be calculated only for those who underwent evaluation at both time-points. The numbers of women excluded from the per-protocol analysis were equivalent for each treatment group. Baseline data were summarized as means, standard deviations, ranges and medians, to describe the study subjects. Descriptive statistics and 95% confidence intervals (CIs) of the mean or median percentage change between baseline and the last available measurement after randomization were produced. Whether conditions for a valid application of analysis of variance were satisfied (comparability of variance within treatment groups and normality of the residuals) was evaluated. If substantial deviation from these conditions was observed, non-parametric techniques were applied: within each treatment group, 95% CIs for median percentages from baseline were calculated. This was done using the bootstrap method, sampling 10% of the data repeatedly, each time calculating the median, thus obtaining a representation for a distribution of the true median. The comparison of treatment groups on the basis of the mean percentage change from baseline to 24 weeks was performed using a $t$ test. For parameters measured at several time-points, a longitudinal analysis of variance capable of handling missing observations was performed, to evaluate efficacy over time within treatments as well as differences between treatments. Furthermore, a regular analysis of variance, applying the last observation carried forward, was used in the case of drop-outs or missing observations. For all parameters, the baseline values represent the entire intent-to-treat population, whereas the values at 24 weeks are calculated only from those for whom data were available. Hence, for all non-lipid variables, the percentage change is calculated only from those that had paired data, i.e. at baseline and 24 weeks. All statistical analyses were undertaken with Statistical Analysis System (SAS) software (release 6.12) in a UNIX environment (SAS Institute Inc., USA). The quality-of-life instruments were evaluated using the Wilcoxon rank-sum test.

## RESULTS

In total, 107 women were screened, and 72 were randomized and underwent evaluation of baseline characteristics. One subject was excluded as she did not take any dispensed medication. In each group, seven discontinued prematurely (Table 1). Four in the hormone therapy group withdrew because of adverse events that included mastalgia and abdominal enlargement, and one woman with a 10-year history of hypertension suffered a myocardial infarction 3 weeks after randomization, and also withdrew from this group. Two discontinued in the pravastatin group owing to abdominal enlargement and gastrointestinal symptoms. Sixty-five women constituted the final intention-to-treat population. The treatment groups did not differ in any variable at baseline (Tables 2–4). During the 8-week run-in diet period, LDL cholesterol levels decreased significantly in both treatment groups (mean decrease –7%, 95% CI –11 to –4%), and reached a nadir with the combination of diet and both interventions at 8 weeks, after which time there were no further dietician contacts until the study end. Weight decreased marginally in both groups up to 8 weeks, after

**Table 1** Summary of retention of patients during trial

|  | 1 mg 17β-estradiol + 0.5 mg norethisterone acetate | Pravastatin |
|---|---|---|
| Randomized | 36 (100.0) | 36 (100.0) |
| Withdrawals | 7 (19.4) | 7 (19.4) |
| adverse events | 4 (11.1) | 2 (5.6) |
| non-compliance | 2 (5.6) | 4 (11.1) |
| ineffective therapy | 0 (0.0) | 0 (0.0) |
| other | 1 (2.8) | 1 (2.8) |
| Completed trial | 29 (80.6) | 29 (80.6) |

**Table 2**  Clinical characteristics of randomized population ($n = 72$) at baseline

| Characteristic | Hormone therapy ($n = 36$) | Pravastatin ($n = 36$) |
|---|---|---|
| *Age* (years) | | |
| Mean (SD) | 59.0 (6.3) | 59.0 (6.4) |
| Range | 50.1–74.7 | 45.5–73.1 |
| *Height* (cm) | | |
| Mean (SD) | 162.1 (5.5) | 161.2 (5.9) |
| *Weight* (kg) | | |
| Mean (SD) | 72.1 (10.8) | 72.3 (11) |
| Range | 50.0–97.5 | 47.0–95.0 |
| *Body mass index* (kg/m$^2$) | | |
| Mean (SD) | 27.5 (4.0) | 27.7 (4.1) |
| Range | 20.6–34.7 | 17.5–36.5 |
| *Blood pressure* (mmHg) | | |
| Systolic mean (SD) | 134.8 (147) | 134.6 (16.5) |
| Diastolic mean (SD) | 83.5 (7.7) | 82.8 (7.5) |
| *Heart rate* (beats/min) | | |
| Mean (SD) | 73.7 (5.0) | 73.8 (5.6) |
| *Tobacco use* ($n$ (%)) | | |
| Non-smoker | 35 (97.2) | 35 (97.2) |
| 1–5 cigarettes/day | 1 (2.8) | 0 (0.0) |
| > 5 cigarettes/day | 0 (0.0) | 1 (2.8) |

SD, standard deviation

which weight increased in the hormone therapy group but continued to decline in the pravastatin arm until 16 weeks. By week 24, weight did not vary from baseline in either group. The effects of the two treatments over the entire study period are summarized in Table 3.

Pravastatin more effectively lowered LDL cholesterol, the primary end-point ($p = 0.0001$), and total cholesterol ($p = 0.003$). Hormone therapy caused a significant reduction in HDL cholesterol (–6%), but pravastatin had no effect ($p = 0.01$ for difference between therapies). The ratio of HDL cholesterol/LDL cholesterol was not modified by hormone therapy, but increased with pravastatin ($p = 0.0001$ for difference between groups). Neither triglycerides nor VLDL cholesterol changed significantly in either treatment group. Lipoprotein(a) decreased significantly by 14% with hormone therapy, and was unaltered by pravastatin ($p = 0.01$ for difference between treatments). A higher baseline level of lipoprotein(a) was correlated with a greater reduction in this parameter in women treated with hormone therapy ($r = 0.399$, $p = 0.04$), with no significant correlation for pravastatin therapy.

The effects of each therapy on vascular parameters are indicated in Table 4. FMD was poor at baseline, compared with a robust response to GTN in both groups. Hormone therapy was associated with an increase in brachial artery FMD from baseline (absolute change in FMD from baseline as percentage units of 2.07, 95% CI 0.57–3.57, $p = 0.009$) versus no change with pravastatin (0.19, 95% CI –1.1 to 1.5, $p = 0.78$), with a near-significant difference between the two groups ($p = 0.058$). The increase in brachial artery FMD was not correlated with the reduction in LDL cholesterol in either the hormone group ($r = 0.21$, 95% CI –0.19 to 0.16) or the pravastatin group ($r = 0.12$, 95% CI –0.28 to 0.52). The increase in FMD was not correlated with a change in any other biochemical parameter. Neither therapy improved non-endothelium-dependent brachial artery dilatation induced by GTN administration.

Fibrinogen decreased significantly from baseline to the trial end in both treatment groups, based on 95% CIs, with no difference between the groups (Table 3).

**Table 3** Effects of postmenopausal hormone therapy and pravastatin on weight and on serum lipid and lipoprotein concentrations in intention-to-treat population (58 women who completed trial and additional seven women). Values are expressed as mean (SD) unless indicated otherwise

| Variable | At screen* | At randomization† | At 24 weeks | Mean percentage change‡ (95% CI) | p Values |
|---|---|---|---|---|---|
| *Weight* (kg) | | | | | |
| Hormone therapy | 72.9 (10.7) | 72.3 (10.9) | 72.2 (10.9) | −0.2 (−1.2 to +0.8) | 0.72 |
| Pravastatin | 72.4 (10.8) | 72.3 (10.9) | 72.2 (11.2) | 0.04 (−1.1 to +1.2) | |
| *LDL cholesterol* (mmol/l)** | | | | | |
| Hormone therapy | 4.5 (0.62) | 4.2 (0.7) | 4.1 (0.73) | −3 (−7 to +1.0) | 0.0001 |
| Pravastatin | 4.6 (0.6) | 4.2 (0.57) | 3.4 (0.62) | −17 (−23 to −11) | |
| (Normal < 3.4) | | | | | |
| *Total cholesterol* (mmol/l)** | | | | | |
| Hormone therapy | 6.9 (0.73) | 6.6 (34) | 6.2 (33) | −4 (−7 to −1.0) | 0.003 |
| Pravastatin | 6.9 (0.73) | 6.5 (26) | 5.7 (31) | −12 (−16 to −7) | |
| (Normal < 5.5) | | | | | |
| *HDL cholesterol* (mmol/l)** | | | | | |
| Hormone therapy | 1.67 (0.4) | 1.63 (0.4) | 1.50 (0.3) | −6 (−10 to −3) | 0.013 |
| Pravastatin | 1.53 (0.3) | 1.53 (0.3) | 1.53 (0.3) | 1 (−4 to +6) | |
| (Normal 0.9–2.2) | | | | | |
| *Triglycerides* (mmol/l)†† | | | | | |
| Hormone therapy | 1.58 (0.76) | 1.82 (1.24) | 1.67 (0.88) | +2 (−8 to +13) | 0.3 |
| Pravastatin | 1.70 (0.76) | 1.70 (0.7) | 1.54 (0.76) | −4 (−14 to +5) | |
| (Normal 0.5–2.0) | | | | | |
| *VLDL cholesterol* (mmol/l)** | | | | | |
| Hormone therapy | 0.70 (0.3) | 0.75 (0.3) | 0.73 (0.3) | −1 (−12 to +13) | 0.69 |
| Pravastatin | 0.78 (0.4) | 0.73 (0.3) | 0.73 (0.3) | −4 (−16 to +5) | |
| *HDL : LDL cholesterol ratio* | | | | | |
| Hormone therapy | 0.38 (0.11) | 0.4 (1.12) | 0.38 (0.1) | −2 (−7 to +3) | 0.0001 |
| Pravastatin | 0.34 (0.09) | 0.4 (0.09) | 0.46 (0.1) | +27 (+15 to +39) | |
| *Lipoprotein(a)* (mg/dl) | | | | | |
| Mean | | | | | |
| hormone therapy | | 43.4 (50.7) | 32.1 (36.0) | −14 (−21 to −6) | 0.01 |
| pravastatin | | 37.9 (39.5) | 40.7 (44.0) | −1 (−8 to +6) | |
| Median | | | | | |
| hormone therapy | | 21.3 | 19.0 | −19 (−21 to −6.5) | 0.01 |
| pravastatin | | 18.0 | 21.6 | −0.91 (−8.0 to +5.6) | |
| *Fibrinogen* (g/l) | | | | | |
| Hormone therapy | | 3.0 (0.73) | 2.7 (0.4) | −8.6 (−0.6 to −0.10) | 0.80 |
| Pravastatin | | 2.9 (0.45) | 2.7 (0.5) | −0.3 (−0.5 to −0.07) | |

*Values at screening are those measured before dietary intervention; †values measured at randomization are mean of two measures 1 week apart for which low-density lipoprotein (LDL) cholesterol did not vary by more than 12%; ‡mean percentage change was calculated for individual subjects from pretreatment baseline value to value at completion of treatment; p values are for difference between two treatment groups by analysis of covariance; **to convert values for cholesterol to mg/dl, divide by 0.0259; ††to convert values for triglycerides to mg/dl, divide by 0.0113; CI, confidence interval; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein

## QUALITY OF LIFE

The Australian Quality of Life instrument score and the European Quality of Life score did not change from baseline to 24 weeks, and there was no difference between the two groups. The nine-dimensional Women's Health Questionnaire

**Table 4** Effects of postmenopausal hormone therapy and pravastatin on brachial artery diameter and blood flow following hyperemia or administration of glyceryl trinitrate (GTN). Values are expressed as mean (SD) unless indicated otherwise

| Brachial artery changes | Prehyperemia/ pre-GTN | Post-hyperemia/ post-GTN | FMD/GTN-induced dilatation* | Absolute change FMD/GTN-induced dilatation 0 vs. 24 weeks, mean (95% CI) | p Value[†] |
|---|---|---|---|---|---|
| *Flow-mediated* | | | | | |
| Brachial artery diameter (mm) | | | | | |
| hormone therapy | | | | | |
| week 0 | 4.07 (0.45) | 4.08 (0.43) | 0.41 (2.9) | +2.07 (+0.57 to +3.57) | 0.058 |
| week 24 | 4.12 (0.52) | 4.23 (0.56) | 2.48 (3.7)[‡] | | |
| pravastatin | | | | | |
| week 0 | 4.02 (0.40) | 4.10 (0.43) | 1.9 (2.4) | +0.19 (−1.14 to +1.52) | |
| week 24 | 4.09 (0.38) | 4.17 (0.38) | 2.1 (2.1) | | |
| Blood flow (ml/min) | | | | | |
| hormone therapy | | | | | |
| week 0 | 171.3 (74.1) | 626.3 (260.4) | | | 0.49 |
| week 24 | 228.3 (152.7) | 890.0 (401.1) | | | |
| pravastatin | | | | | |
| week 0 | 186.4 (97.6) | 610.5 (277.4) | | | |
| week 24 | 216.6 (124.7) | 890.2 (355.4) | | | |
| *GTN-mediated* | | | | | |
| Brachial artery diameter (mm) | | | | | |
| hormone therapy | | | | | |
| week 0 | 4.1 (0.39) | 4.75 (0.50) | 15.8 (6.0) | −2.01 (−4.9 to +0.9) | 0.69 |
| week 24 | 4.26 (0.48) | 4.89 (0.54) | 13.5 (3.9) | | |
| pravastatin | | | | | |
| week 0 | 4.04 (0.46) | 4.63 (0.47) | 15.0 (5.0) | −1.37 (−3.42 to +0.67) | |
| week 24 | 4.13 (0.41) | 4.68 (0.43) | 13.3 (4.6) | | |
| Blood flow (ml/min) | | | | | |
| hormone therapy | | | | | |
| week 0 | 161.7 (61.1) | 206.6 (70.4) | | | 0.21 |
| week 24 | 187.1 (70.6) | 254.6 (98.8) | | | |
| pravastatin | | | | | |
| week 0 | 155.5 (82.9) | 204.8 (73.9) | | | |
| week 24 | 236.5 (111.8) | 277.3 (124.4) | | | |

*Flow-mediated dilatation (FMD) and GTN-induced dilatation calculated as artery diameter pre-intervention − post/pre-intervention × 100; [†]p values are for difference between two treatment groups by analysis of covariance; [‡]p = 0.009 for difference from baseline; CI, confidence interval

recorded at screening, randomization and 24 weeks revealed reduced vasomotor symptoms and increased sense of attractiveness with hormone therapy ($p$ = 0.0004 and 0.04 for difference from pravastatin for each, respectively).

## TOLERANCE

Among the women treated with hormone therapy, 13 reported mastalgia at some stage and three reported bleeding; however, only four withdrew because of adverse events. One woman randomized to hormone therapy experienced an acute myocardial infarction 3 weeks into the study. Whether this was precipitated by the intervention cannot be determined. Among the women using pravastatin, two discontinued because of gastrointestinal symptoms. Levels of fasting glucose and insulin did not change with either treatment, and alkaline phosphatase fell with hormone therapy (−20.7%, 95% CI −24 to −17%). These were included as safety parameters, not study end-points.

## DISCUSSION

This study of estrogen–progestin therapy was conducted according to the rigorous Guidelines for the Clinical Evaluation of Lipid-Lowering Agents in Adults and Children[23]. Our data demonstrate that the changes induced by low-dose continuous combined oral estrogen–progestin therapy and pravastatin in lipids, endothelial function and fibrinogen, in hypercholesterolemic postmenopausal women, differ substantially with respect to the effects on total and LDL cholesterol, HDL cholesterol, lipoprotein(a) and brachial artery FMD. Importantly, our findings corroborate with those of some and contrast with those of other studies employing different hormone therapy regimens. Significant reductions in LDL cholesterol have been seen with higher-dose oral estrogen therapy[24–26], particularly in hypercholesterolemic women[9,27]. In the present study, only a modest lowering of LDL cholesterol occurred with the low dose of estrogen used. This may be in part due to our study design, including a rigorous dietary intervention period and the benefits of dietary change carrying over into the initial treatment phase. Other smaller studies that have not included rigorous LDL inclusion criteria and have been undertaken over shorter intervention periods[27–29] are likely to have overestimated the cholesterol-lowering effects of estrogen in women.

Our findings are consistent with our earlier observations that the reduction in cholesterol achieved with estrogen is proportional to the dose administered and to the baseline value[9]. Norethisterone acetate ameliorated the increase in triglycerides that occurs when oral estrogen is given alone or with medroxyprogesterone acetate[9,24–27]. However, this probable benefit contrasts with the potentially deleterious impact that this more androgenic progestin has on HDL cholesterol, even at the low dose given. Pravastatin therapy resulted in sustained reductions in total and LDL cholesterol, but was not associated with an increase in HDL cholesterol. The latter finding contrasts with those from studies of pravastatin and simvastatin in women with similar lipid profiles, but which both terminated after a shorter intervention period[9,27].

The importance of lipoprotein(a) as an independent risk factor for cardiovascular events has been reaffirmed in findings of the Heart and Estrogen/progestin Replacement Study[30]. As with different and higher-dose hormone therapy regimens[9,27], the hormone therapy used in the present study significantly lowered lipoprotein(a), with an inverse correlation between baseline value and change, as recently described[30]. Both the estradiol and norethisterone components are likely to have contributed to this reduction[31]. In line with our findings, other studies have shown that HMG CoA reductase inhibitors do not significantly lower lipoprotein(a) levels[8,9,26].

The participants in this study had very poor baseline post-hyperemia brachial artery reactivity, consistent with their age and hypercholesterolemia[32]. Brachial artery FMD increased with the low-dose hormone regimen, but to a lesser degree than that seen in normolipemic postmenopausal women[26]. Our findings indicate that pravastatin has no clinically significant endothelial function effects in this population of women, at the dose administered. In addition, the lack of an inverse relationship between LDL cholesterol and endothelial function in this study reinforces the findings of independent and differing effects of statins and estrogen. These results contrast with those of earlier studies conducted under differing circumstances[33,34].

In older, higher-risk women, increased rates of cardiac events and thromboembolic events have been reported in the first year of oral estrogen use[25,35]. It is known that oral conjugated estrogen acutely lowers levels of fibrinogen, an effect that is usually considered favorable[15]. We observed a reduction at 24 weeks with half of the above dose in terms of bioequivalence. Pravastatin also lowered fibrinogen.

Our data indicate that low-dose continuous combined estrogen–progestin therapy significantly improves endothelium-dependent brachial artery FMD, independent of change in LDL cholesterol, and lowers lipoprotein(a), effects not seen with pravastatin, in hypercholesterolemic postmenopausal women. However, these women exhibited impaired endothelial function at baseline, and, despite a marked improvement, this was not restored to a level seen in normolipemic women[26]. This would suggest that, if modification of endothelial function plays a major role in the cardioprotection afforded by estrogen, this is attenuated in women with pre-existing endothelial dysfunction, and this, in turn, may in part explain the disappointing results of prospective estrogen intervention studies in women at high cardiovascular risk.

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PERSPECTIVE

# Postmenopausal Hormones — Therapy for Symptoms Only

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Over the past two decades, multiple observational studies have suggested that postmenopausal hormone therapy reduces the risks of osteoporotic fractures and coronary heart disease. On the basis of this evidence, hormone therapy was often recommended for women who were at high risk for fractures and coronary disease. But these recommendations were based entirely on observational evidence, which can sometimes be misleading if the groups being compared have different risk patterns and lifestyle. In the early-to-mid-1990s, several large, randomized trials were initiated to provide definitive evidence concerning the risks and benefits of hormone therapy for the prevention of disease. The largest of these trials, the Women's Health Initiative (WHI), included more than 27,000 older, generally healthy postmenopausal women; those with an intact uterus were randomly assigned to receive estrogen plus progestin or placebo, and those without an intact uterus were randomly assigned to receive estrogen alone or placebo. The estrogen-plus-progestin segment was stopped last summer when results showed that hormone therapy caused small increases in the risks of coronary events, stroke, pulmonary embolism, and breast cancer. There were also small decreases in the risks of hip fracture and colon cancer, but the overall harm outweighed these benefits. The investigators examined the net effect on these six potentially deadly conditions and reported that hormone therapy results in two such serious adverse events per 1000 women treated for one year. After five years of treatment, the risk was one serious adverse event per 100 women treated.

Given that hormone therapy was associated with decreased risks of colon cancer and hip fracture, are there women who are at high risk for these conditions who might have a net benefit from treatment with hormones? A woman with a family history of colon cancer has a risk of the disease that is approximately twice that of women with no such family history. According to the rates of disease and the relative risks found in the WHI, the estimated harm is lower among such women, but the net effect is still about 1.4 serious adverse events per 1000 women per year. A woman with osteoporosis (defined by a T score for bone mineral density that is lower than −2.5) has approximately double the risk of hip fracture, but the net effect of hormone therapy is still about 1.5 serious adverse events per 1000 women per year. What about women at very high risk for hip fracture, such as those who have already had a vertebral fracture and have low bone mineral density? Assuming that the risk of hip fracture is increased by about a factor of five among such women, the decreases in the risks of hip fracture and colon cancer will just about balance the increased risks of coronary events, stroke, pulmonary embolism, and breast cancer. Given the availability of other effective agents, the use of hormone therapy for the treatment or prevention of osteoporosis is not appropriate for most women.

The annual increase in the risk of serious adverse events associated with postmenopausal hormone therapy is relatively small, but why should women take any risk? Until recently, it has been argued that many women — even older women who do not have vasomotor or urogenital symptoms — feel better when they take hormones. This claim has now been laid to rest by new results from the WHI. In this issue of the Journal, Hays et al. provide clear evidence that hormone therapy does not result in better quality of life among older women without menopausal symptoms. After one year, there was a statistically significant difference favoring the hormone group in three of nine measures of quality of life, but these differences were not clinically important, representing an improvement of only 1 to 4 percent over baseline scores. Two previous randomized trials in

women without vasomotor symptoms also found no improvement in quality of life associated with postmenopausal hormone therapy.[1,2]

The WHI also found that hormone therapy had no effect on measures of depression, insomnia, sexual function, or cognition. Cognitive function was measured with the Modified Mini–Mental State Examination. This measure is not very sensitive for detecting subtle beneficial effects, but the findings make it unlikely that hormone therapy improves cognition. These negative results are supported by findings from the Heart and Estrogen/Progestin Replacement Study (HERS) among older women with coronary disease.[3] WHI investigators are also conducting an ancillary study, the Women's Health Initiative Memory Study, that will more completely assess cognitive function and dementia during five years of follow-up.

It is important to note that the WHI was not designed to test the effect of hormone therapy on vasomotor or other menopausal symptoms. The majority of women enrolled in the WHI did not have menopausal symptoms. Among the 12 percent of women who did report moderate-to-severe vasomotor symptoms at base line, the symptoms were unlikely to be very bothersome, since the women were willing to be randomly assigned to placebo. In this subgroup, hormone therapy improved vasomotor symptoms and reduced sleep disturbance. Multiple other randomized trials among younger women with hot flashes have shown that systemic estrogen therapy is highly effective in relieving vasomotor symptoms, reducing both the severity and the frequency of hot flashes by about 80 percent[4] and thereby improving the quality of life.[5]

The benefit of relief of vasomotor symptoms needs to be balanced against the risks associated with hormone use. As noted above, among women in the WHI, there was one serious adverse event for every 100 women treated for five years. Most women with vasomotor symptoms require treatment for a much shorter duration than five years, and therefore the risk will be smaller. Furthermore, the average age of women enrolled in the WHI was 63 years. Most women with vasomotor symptoms are at least a decade younger than this, and the rates of underlying diseases among younger women are lower. Thus, the absolute risk associated with hormone therapy will be lower among younger women who choose to use it for the relief of symptoms. If the rates of diseases among 50-year-old women are estimated to be about half of those reported for older



Number of Adverse Events per 1000 Women Treated with Postmenopausal Hormone Therapy.
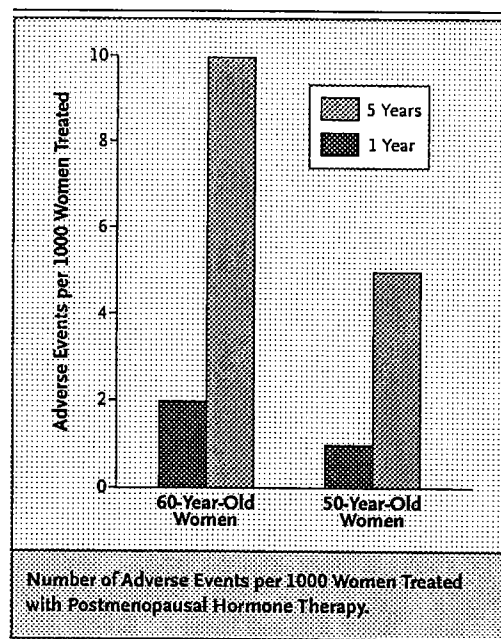
women in the WHI, the net effect of hormone therapy in this age group will be about one serious adverse event per 1000 women treated for one year (see Figure). Is this risk worth the relief of vasomotor symptoms provided by hormone therapy? Other treatments, including megestrol, selective serotonin-reuptake inhibitors and other antidepressants, and clonidine, provide some relief of vasomotor symptoms, but systemic hormone therapy is the most effective treatment. Hot flashes are not deadly, but they can be very disabling. Some women may choose to try other remedies or to live with their symptoms, whereas others will find the relief of symptoms afforded by hormone therapy worth the risk.

Are there some perimenopausal women who should be more concerned about adverse effects of hormone therapy for the treatment of menopausal symptoms? Since hormone therapy increases the risk of coronary events, stroke, breast cancer, and venous thromboembolic events, women at increased risk for these conditions will incur a higher absolute risk while taking hormones. All women, but particularly those at higher risk for the adverse effects of hormone therapy, should consider alternative therapies. Women who choose to take estrogen should start with a low dose and gradually increase it until symptoms are adequately controlled. Vasomotor symptoms resolve within sever-

al months in many women and within a few years in most women, so an attempt should be made at least every six months to taper the dose of hormones and to discontinue therapy.

Postmenopausal therapy with estrogen and progestin results in increased risks of disease, does not make asymptomatic women feel better, and does not improve cognition. There is no role for hormone therapy in the treatment of women without menopausal symptoms. Women with vasomotor symptoms must weigh the risks associated with treatment against the benefit of symptom relief. Vasomotor symptoms occur in about two thirds of women and are very distressing in 10 to 20 percent. We clearly need to identify new treatments that are highly effective and safe.

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