

# Cause-Specific Mortality in Women Receiving Hormone Replacement Therapy

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To assess the risks and benefits of menopausal hormone replacement therapy, we followed a 23,246-member, population-based cohort of Swedish women who were prescribed menopausal estrogens for an average of 8.6 years for mortality. Compared with the general population, the standardized mortality ratio for all-cause mortality in this cohort was 0.77 (95% confidence limits = 0.73, 0.81). Deaths in each of the 12 major categories of causes of death except for injuries occurred 12% to 86% less frequently than expected. We examined in detail four specific causes of death according to the type of hormone prescribed, namely weak estrogens (primarily estriol), more potent estrogens (primarily estradiol and conjugated estrogens) in combination with a progestin, and more potent estrogens without a progestin. Mortality from endometrial cancer was not related to the prescription of weak estrogens or an estrogen-progestin combination, but mortality was 40% higher in women prescribed more potent estrogens without a proges-

tin. Women prescribed weak estrogens, more potent estrogens, and the combined estrogen-progestin regimen were at reduced risk of death from ischemic heart disease (standardized mortality ratios of 0.7, 0.6, and 0.4, respectively). The more potent estrogens and the estrogen-progestin combination were associated with a marked reduction in risk of intracerebral hemorrhage (standardized mortality ratios of 0.4 and 0.6, respectively) and "other" cerebrovascular disease, but not other types of stroke. The concern that use of progestins would lead to psychic disorders related to suicide received no support from our results. Breast cancer results are described elsewhere. These data provide little evidence of an adverse effect of the combined estrogen-progestin regimen as compared with estrogens alone on mortality. They do indicate, however, that both selection factors and biology may contribute to the almost across-the-board reduction in mortality associated with hormone replacement therapy. (Epidemiology 1997;8:59-65)

**Keywords:** all-cause and specific-cause mortality, hormone replacement therapy, cohort study.

Estrogen replacement therapy in the postmenopause involves a variety of biological effects. Important benefits include alleviation of vasomotor symptoms and urogenital atrophic conditions<sup>1</sup> and, in the long run, prevention of osteoporotic fractures<sup>2</sup> and possibly cardiovascular disease.<sup>3</sup> Among harmful effects associated with long-term therapy are an established increased incidence of endometrial cancer<sup>4</sup> and a suspected increased risk of breast cancer.<sup>5</sup> Recently, an increasingly large proportion of women treated with hormones have been receiving estrogen with progestins added cyclically to prevent the development of endometrial hyperplasia and neoplasia.<sup>4</sup> This regimen has become controversial because of

claims that progestins may not protect against the development of breast cancer<sup>5,6</sup> and fears that they could reduce the cardioprotective effect of estrogens.<sup>7</sup>

One method to assess overall risks and benefits of exogenous hormone use is the analysis of mortality. Several studies have reported lowered all-cause mortality in women using estrogens,<sup>8-12</sup> and particularly reduced risk of deaths due to cardiovascular disease<sup>8,9,11-14,15</sup> and stroke.<sup>8,9,16</sup> There is little epidemiologic evidence, however, regarding mortality among women using the combined estrogen-progestin regimen.

Using data from a population-based cohort of 23,246 Swedish women who were prescribed replacement hormones, we have previously reported on incidence of all cancers,<sup>17</sup> endometrial cancer,<sup>4</sup> breast cancer,<sup>5,18</sup> hip fracture,<sup>19</sup> acute myocardial infarction,<sup>20</sup> and stroke,<sup>21</sup> and on relative survival.<sup>22</sup> In addition, a detailed evaluation of breast cancer mortality has been published.<sup>23</sup> The aim of the present analysis is to present the relation between hormonal exposure and overall and cause-specific mortality, based on all 1,472 deaths that occurred in this cohort during a follow-up period of nearly 10 years. A particular advantage in studying this cohort is the widespread use of the combined estrogen-progestin regimen and the use of estrogen compounds of markedly different potencies.

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## Subjects and Methods

### THE COHORT

All women who were prescribed oral hormone replacement therapy within the Uppsala Health Care Region of Sweden were identified from all prescription forms for estrogen tablets reported from the pharmacies within the region during a 3-year period from April 1977 through March 1980. Data on the women's identity (the National Registration Number, a 10-digit number which provides exclusive identification of an individual and a means for record linkage), compound type, dose, regimen, and date of purchase were computerized. Some 23,246 such women over age 35 years were identified, constituting virtually all those prescribed estrogens within this defined population during the period of ascertainment. The mean age at time of recruitment was 54.5 years. All of the drugs prescribed were used solely for hormone replacement therapy and not contraception in Sweden. The methods involved in the design of this population-based cohort study are described in detail elsewhere.<sup>24</sup>

### GENERAL EXPOSURE CHARACTERISTICS

To characterize the cohort with respect to total hormone exposure before and after prescription recording and to assess confounding by factors pertinent to the risks of malignant and cardiovascular diseases, a questionnaire was sent on two occasions, 1980 and 1984, to a randomly selected subset of the entire cohort, constituting 753 women, of whom 653 (89%) responded on the first occasion and 84% on the second.<sup>25,26</sup>

These questionnaire data from the cohort sample provided a means to evaluate concordance between the prescription-based data and those given in the questionnaire among the sampled women, and to describe the characteristics of women allocated to various exposure groups, as specified below. The same questionnaire was sent to a sample of 1,325 women from the general population of the region, age matched to the distribution of the cohort. We compared data from the 1,034 respondents (79%) with data from the cohort questionnaire for a variety of potentially confounding variables.

### EXPOSURE GROUPS

We defined three prescription-based exposure groups. We grouped women who were prescribed estradiol compounds or conjugated estrogens during the 3-year period separately from those prescribed "other" estrogens only. We used this classification to characterize the strength of estrogen used. Estradiol compounds and conjugated estrogens are considered to be relatively potent estrogenic compounds that are equally efficient at ordinary doses in treating vasomotor symptoms. They yield similar plasma concentrations of estradiol and estrone.<sup>27</sup> "Other" estrogens were predominantly (83%) estriol compounds, biologically weak estrogens used in the Scandinavian countries to treat urogenital atrophic conditions.<sup>25,28</sup> This distinction defines a difference in aver-

age estrogen dose that is substantially greater than any of the dosage differences within a single compound.

We further divided women prescribed estradiol compounds or conjugated estrogens into those prescribed a brand containing estradiol valerate (2 mg), combined for 10 days of each 21-day cycle with the progestin levonorgestrel (250  $\mu$ g), and those who were prescribed estradiol compounds or conjugated estrogens but not this particular combined brand. We used the terms "combined regimen" and "more potent estrogens" throughout to designate these two exposure groups.

Based on questionnaire data from the random sample of the cohort, 56% of all treatments were with estradiol compounds (predominantly estradiol valerate, with a small proportion prescribed ethinyl estradiol), 22% with conjugated estrogens, and 22% "other" estrogens (estriol, estrone sulfate, methallenestrol, methallenestril). The questionnaire data from the random sample also indicated that 95% of women who were prescribed the orally administered estradiol compounds or conjugated estrogens, according to the prescription database, had actually used these brands. Among those for whom the prescription database indicated prescriptions for only the "other" estrogens, the questionnaires revealed that 81% had used only these agents (19% had used more potent estrogens either before or after the study intake period).

The estradiol valerate-levonorgestrel combination was registered for 32% of the women who had ever been prescribed estradiol compounds or conjugated estrogens and accounted for 65% of all combined treatments reported in the random sample. Other progestins used were medroxyprogesterone acetate, norethindrone acetate, and lynestrenol (accounting for 18%, 15%, and 2% of combined treatment episodes, respectively). These, however, could not be identified through the prescription records. Among respondents to the questionnaire to the random sample of the cohort, 11% of women who had no prescription record of the fixed combination of estradiol valerate-levonorgestrel reported use of a combined regimen at some time during their postmenopause.

### FOLLOW-UP

All 23,246 cohort women were followed up for deaths through linkage to the National Causes of Death Registry by means of the National Registration Number.<sup>29</sup> This registry holds codified data on specific causes of death classified according to the *International Classification of Diseases, Injuries, and Causes of Death*, 8th revision (ICD).

The present results are based on a follow-up period from March 1977 through the end of 1986, during which period 1,472 deaths occurred. We grouped the observed deaths into 30 main diagnostic categories, according to underlying causes of death defined by the ICD codes, as specified in Table 2.

Analyses of death from cerebrovascular disease included codes 430-438 (cerebrovascular diseases) and 344 (cerebral paralysis), consistent with analyses for stroke incidence from this cohort.<sup>21</sup> Separate analyses

**TABLE 1.** Distribution of Specified Risk Factors among the Background Population and Cohort by Prescription Group

Factor	Percentages*			
	Background Population	"Other" Estrogens	More Potent Estrogens	Combined Regimen
Community code				
Missing	10.5	0	0	0
Rural	43.3	52.0	35.7	38.4
Urban	46.2	48.0	64.3	61.6
History of diabetes mellitus	2.3	2.9	1.6	1.6
History of hypertension	17.2	18.7	17.8	12.6
Hysterectomy	7.3	19.4	26.6	6.3
Bilateral oophorectomy	2.9	7.1	16.1	2.7
Quetelet index†				
Missing	2.9	1.2	0	0
≤19	6.3	6.4	5.1	6.4
20–24	47.0	46.3	57.9	55.6
≥25	43.7	46.1	37.0	38.0
Educational level				
<8 years	70.8	74.7	63.9	64.1
8–10 years	6.7	14.3	20.6	19.3
High school	2.0	4.1	2.7	4.1
Vocational	16.6	1.5	5.2	4.3
University	3.8	5.5	7.7	8.2

\* Age adjusted to the age distribution of the background population and cohort sample combined.

† Weight (kg)/height (m)<sup>2</sup>.

were also made for the following subtypes of stroke: code 430 (subarachnoid hemorrhage), 431 (intracerebral hemorrhage), 432–435 (cerebral infarction, cerebral embolism, and transient ischemic attack, hereafter called thromboembolic stroke), 431–436 (composite category of all acute stroke diagnoses except subarachnoid hemorrhage, hereafter referred to as acute stroke), and 344 and 437–438 ("other" cerebrovascular disease).

#### STATISTICAL METHODS

We compared risk of death in the cohort with that in the population of the Uppsala health care region. We calculated the standardized mortality ratio (SMR) as the ratio of the number of observed deaths divided by the number expected. We computed the expected values from the person-years of observation in the cohort, counted from the date of the first recorded prescription until the date of death or end of the observation period, and multiplied by sex-, cause-, age-, and calendar-year-specific death rates in the general population of the region. The women in the cohort constituted about 5% of the total female population in this age range in the region, 92% of whom were naturally or surgically menopausal (based on information from the questionnaire to a sample of the background population). Thus, the rates used for deriving expected values essentially reflect those in menopausal women unexposed to exogenous menopausal hormones. Confidence limits (CL) of 95% around the relative risks (RR) were based on the Poisson variability of the observed counts.<sup>30</sup>

When calculating SMRs for cancers of the endometrium, cervix, and ovary, we adjusted for unequal proportions of women at risk in the background population and cohort (or specific prescription group) owing to removal of the uterus or ovaries. We adjusted by reducing the number of person-years at risk in the cohort (or prescription group) by the ratio of [1 – the proportion having the operation in the cohort (or prescription group)] to (1 – the proportion having the operation in the background population).

#### Results

##### CHARACTERISTICS OF THE COHORT

The comparison of risk factor data for the background population and the prescription-based exposure groups in the cohort revealed some differences (Table 1). Women in the background population and "other" estrogen group differed from women prescribed more potent estrogens and the combined regimen with regard to urban or rural residence, history of diabetes mellitus, Quetelet index, and education. The prevalence of hysterectomy and bilat-

eral oophorectomy in the background population was similar to that in women prescribed the combined regimen and was considerably lower than that in the other two groups. There was no notable difference among the background population and prescription groups, with the exception of women prescribed the combined regimen, with respect to prevalence of hypertension. According to previous analyses, cohort women were more likely to practice regular physical exercise than were women in the background population (37% and 22%, respectively).<sup>20</sup> The percentage of current smokers was also higher in the cohort than the background population (26% vs 20%).<sup>20</sup>

##### MORTALITY ANALYSES

A total of 199,810 person-years of observation were accumulated for an average observation period of 8.6 years. In all, 1,472 deaths occurred vs 1,922.6 expected, yielding a 23% reduction in mortality among the cohort women (SMR = 0.77; 95% CL = 0.73, 0.81) (Table 2). For 20 of the 30 main diagnostic categories investigated, SMRs were more than 10% below unity. The categories with SMRs not below unity were lung cancer, melanoma, cervical cancer, endometrial cancer, venous thromboembolism, injuries, and suicide.

All-cause mortality did not differ materially among the various prescription-based exposure groups; the SMRs for women prescribed "other" estrogens (26% of the cohort), more potent estrogens (50% of the cohort), and the combined regimen (24% of the cohort) were

TABLE 2. Number of Observed (O) and Expected (E) Deaths, Relative Risk Estimates (RR), and 95% Confidence Limits (CL), According to Underlying Causes of Death (ICD Numbers)

Diagnostic Group	ICD Numbers	O	E	RR	95% CL
Infectious diseases	000-136	2	14.78	0.14	0.02, 0.49
Malignancies	140-239	547	646.24	0.85	0.78, 0.92
Large intestine	153	40	46.19	0.87	0.62, 1.18
Pancreas	157	32	43.92	0.73	0.50, 1.03
Trachea, bronchus, lung	162	49	45.04	1.09	0.80, 1.44
Melanoma of the skin	172	9	7.10	1.27	0.58, 2.41
Breast	174	85	117.69	0.72	0.58, 0.89
Cervix uteri	180	23	18.73	1.23	0.81, 1.73
Endometrium	182	20	19.91	1.00	0.66, 1.47
Ovary, fallopian tube	183	52	52.73	0.99	0.76, 1.27
Kidney and other urinary organs	189	26	26.36	0.99	0.64, 1.45
Brain	191	15	15.95	0.94	0.53, 1.55
Endocrine, nutritional, and metabolic diseases	240-279	27	39.65	0.68	0.45, 0.99
Hematologic diseases	280-289	1	3.40	0.29	0.00, 1.64
Mental diseases	290-315	10	13.94	0.72	0.34, 1.32
Neurologic diseases	320-343, 345-389	18	25.13	0.72	0.42, 1.13
Circulatory system diseases	344, 390-458	611	882.80	0.69	0.64, 0.75
Hypertension	400-404	4	8.17	0.49	0.13, 1.25
Ischemic heart disease	410-414	304	494.35	0.61	0.55, 0.69
Other heart diseases	420-429	59	71.48	0.83	0.63, 1.06
Cerebrovascular diseases	344, 430-438	172	218.37	0.79	0.67, 0.91
Arterial diseases	440-448	37	51.77	0.71	0.50, 0.99
Venous thromboembolism	450-453	30	29.64	1.01	0.68, 1.45
Other cardiovascular diseases	390-398, 454-458	5	9.02	0.55	0.18, 1.29
Respiratory diseases	460-519	69	97.83	0.71	0.55, 0.89
Gastrointestinal diseases	520-577	42	56.01	0.75	0.54, 1.01
Urogenital diseases	580-629	11	21.45	0.51	0.26, 0.92
Injuries	800-999	107	90.76	1.18	0.97, 1.42
Suicides	950-958	60	33.98	1.77	1.35, 2.27
Remainder	464-466, 630-799	27	30.63	0.88	0.58, 1.28
All causes of death		1,472	1,922.61	0.77	0.73, 0.81

0.8, 0.8, and 0.7, respectively (Table 3). The SMRs for the "other" estrogens were below unity for all broad categories of death except endocrine, metabolic, and nutritional diseases, neurologic diseases, gastrointestinal diseases, and remaining causes of death not otherwise specified. The SMRs for the more potent estrogens were below 1.0 for all major categories of death except injuries, whereas the SMRs for the combined regimen were below unity for all major categories of death except mental diseases, injuries, and remaining causes of death not otherwise listed in Table 3.

An examination of data for specific causes of death previously associated with use of hormone replacement is also given in Table 3. Based on a total of 20 deaths from endometrial cancer, women prescribed "other" estrogens or the combined regimen were at lower risk than the background population (SMRs of 0.8 and 0.6, respectively), whereas those prescribed more potent estrogens alone were at increased risk (SMR = 1.4).

There were substantial reductions in risk of ischemic heart disease associated with "other" estrogens (SMR =

0.7), more potent estrogens (SMR = 0.6), and the combined regimen (SMR = 0.4).

The 172 deaths from cerebrovascular diseases were chiefly cases of subarachnoid hemorrhage (N = 30), intracerebral hemorrhage (N = 34), thromboembolic stroke (N = 31), and acute ill-defined cerebrovascular disease (N = 37). The RR of death from subarachnoid hemorrhage ranged from 1.7 in women prescribed "other" estrogens to 0.5 in those prescribed the combined regimen. For the broad category of death from acute stroke, each prescription group was associated with a 20% reduction in risk. An examination of subtypes of acute stroke revealed no major change in risk of death from intracerebral hemorrhage associated with "other" estrogens (RR = 0.9), but a marked reduction in risk associated with more potent estrogens alone (RR = 0.4) and the combined regimen (RR = 0.6). There were slight reductions in risk of death from thromboembolic and ill-defined acute stroke associated with "other" estrogens, but not with the more potent estrogens alone. Numbers of deaths from thromboembolic stroke or acute

TABLE 3. Relative Risk (RR) of Death and 95% Confidence Limits (CL) for Selected Disease Groups by Hormone Regimen Using the General Population as the Referent

	"Other" Estrogens		More Potent Estrogens		Combined Regimen	
	RR (No. of Deaths)	95% CL	RR (No. of Deaths)	95% CL	RR (No. of Deaths)	95% CL
Infectious diseases	0.0 (0)	0.0, 0.5	0.2 (1)	0.0, 0.9	0.6 (1)	0.0, 3.3
Malignancies	0.8 (193)	0.7, 1.0	0.9 (285)	0.8, 1.0	0.7 (69)	0.5, 0.9
Endometrial cancer	0.8 (6)	0.4, 1.7	1.4 (12)	0.9, 2.2	0.6 (2)	0.1, 2.1
Endocrine, nutritional, and metabolic diseases	1.0 (19)	0.6, 1.5	0.4 (6)	0.1, 0.8	0.5 (2)	0.1, 1.8
Hematologic diseases	0.7 (1)	0.0, 3.7	0.0 (0)		0.0 (0)	
Mental diseases	0.7 (5)	0.2, 1.7	0.2 (1)	0.0, 1.0	2.8 (4)	0.8, 7.3
Neurologic diseases	1.3 (12)	0.7, 2.3	0.3 (4)	0.1, 0.9	0.5 (2)	0.1, 1.8
Circulatory system diseases	0.7 (368)	0.7, 0.8	0.7 (213)	0.6, 0.8	0.5 (30)	0.3, 0.7
Ischemic heart disease	0.7 (187)	0.6, 0.8	0.6 (106)	0.5, 0.7	0.4 (11)	0.2, 0.6
Cerebrovascular diseases	0.9 (102)	0.7, 1.0	0.7 (59)	0.6, 0.9	0.6 (11)	0.3, 1.1
Subarachnoid hemorrhage (430)	1.7 (14)	0.9, 2.9	0.9 (13)	0.5, 1.5	0.5 (3)	0.1, 1.4
Acute stroke (431-436)	0.8 (57)	0.6, 1.0	0.8 (38)	0.6, 1.1	0.8 (7)	0.3, 1.6
Intracerebral hemorrhage (431)	0.9 (23)	0.6, 1.3	0.4 (8)	0.2, 0.7	0.6 (3)	0.1, 1.7
Thromboembolic stroke (432-435)	0.8 (15)	0.5, 1.3	1.1 (14)	0.6, 1.8	0.8 (2)	0.1, 2.8
Acute ill-defined (436)	0.7 (19)	0.4, 1.1	1.2 (16)	0.7, 1.9	1.2 (2)	0.1, 4.4
Other (344, 437-438)	0.8 (31)	0.5, 1.1	0.4 (8)	0.2, 0.9	0.5 (1)	0.0, 3.0
Respiratory diseases	0.8 (41)	0.6, 1.1	0.6 (21)	0.4, 0.9	0.8 (7)	0.3, 1.7
Gastrointestinal diseases	1.0 (26)	0.7, 1.5	0.6 (13)	0.3, 1.0	0.4 (3)	0.1, 1.2
Urogenital diseases	0.7 (8)	0.3, 1.4	0.4 (3)	0.1, 1.1	0.0 (0)	
Injuries	0.7 (24)	0.5, 1.1	1.3 (56)	1.0, 1.7	1.6 (27)	1.1, 2.4
Suicides	1.2 (10)	0.6, 2.3	1.8 (32)	1.2, 2.6	2.1 (18)	1.3, 3.4
Remainder	1.3 (18)	0.8, 2.0	0.3 (4)	0.1, 0.8	1.4 (5)	0.4, 3.2
All causes of death	0.8 (715)	0.7, 0.8	0.8 (607)	0.7, 0.8	0.7 (150)	0.6, 0.8

ill-defined stroke among women prescribed the combined regimen were small, but there was no indication that this regimen had a more adverse effect upon mortality than the more potent estrogens alone. All of the prescription groups were associated with some reduction in the risk of death from "other" cerebrovascular disease.

Suicides accounted for the majority (60 deaths, 56%) of all 107 deaths and all of the excess risk attributed to injuries. "Other" estrogens were not associated with a substantial increase in the risk of suicide compared with the background population (SMR = 1.2; 95% CL = 0.6, 2.3), whereas more potent estrogens and the combined regimen were associated with SMRs of 1.8 and 2.1, respectively. There were no observed or expected deaths due to fractures among the deaths from injuries.

## Discussion

The 23% reduction in overall mortality in this group of women is consistent with the improved relative survival already reported,<sup>22</sup> as well as with reductions of 20-66% reported for women receiving hormone replacement therapy in several other investigations.<sup>8-12,31</sup> Although plausible biological mechanisms have been proposed to explain the apparent protective effect of exogenous estrogens, particularly in regard to cardiovascular disease,<sup>7</sup>

there has been concern over how much of this effect might be a biological result of the hormones and how much might be an artifact of the selective prescribing of hormones to women without obvious signs of disease or risk factors for death.<sup>23,32-34</sup> In our study, the lack of specificity of the protective effect, particularly with regard to the more potent estrogens, and the different risk factor profiles for the "other" and more potent estrogen groups indicate that selection factors may be more strongly related to estrogen type than to the decision to initiate estrogen treatment.

With these factors in mind, a more detailed discussion of the four specific causes of death related to hormone use in other investigations is instructive. The patterns of mortality from endometrial cancer by estrogen dose reflect those for incidence in this cohort<sup>4</sup> and dozens of other investigations over the last 15 years. Similarly, results for mortality in relation to the combined regimen are consistent with those for incidence in this cohort.<sup>4</sup> Removal of prevalent cases from the background population rates to account for the selective prescription of hormones to women without disease would most likely accentuate the adverse effects of the more potent estrogens alone and attenuate the reduction in risk associated with the other prescription groups.

In regard to mortality from ischemic heart disease, the "other" and more potent estrogens were associated with RRs of 0.7 and 0.6, respectively. The corresponding incidence estimates in this cohort, based on data through 1983, were 0.9 and 0.7.<sup>20</sup> The lower estimates for mortality than incidence may reflect, at least in part, the selective prescription of hormones to women without ischemic heart disease. The remaining reduction in risk could reflect confounding by cardiovascular risk factors, chance, or a true biological effect. Because risk factor information was not available for the entire cohort, we were unable to quantify the extent of confounding. It is unlikely, however, that a history of diabetes mellitus or hypertension seriously confounds our results, given their low prevalence. Control for smoking, on the other hand, would, if anything, further reduce the estimates, whereas control for physical activity, body mass index, and education would most likely attenuate the protective effect of the more potent estrogens. It is also possible that other relevant factors that are difficult to quantify may confound the estimates.<sup>33</sup> Urban residence and a generally more health-oriented behavior, control for which would likely attenuate the protective effect of estrogens, may be such factors. Thus, our data indicate a somewhat smaller protective effect of estrogens on ischemic heart disease than the 50% reduction suggested by Stampfer and Colditz<sup>35</sup> in a recent quantitative assessment of the literature.

Our data indicate that the addition of progestins to estrogen replacement therapy does not counteract whatever beneficial effect estrogens may have on ischemic heart disease mortality. Because the main selection factor for the combined regimen as opposed to more potent estrogens alone appeared to be the presence of a uterus, confounding is not a major concern in assessing differences in these two regimens. Other studies also suggest that the addition of progestins to estrogen replacement therapy does not have a markedly adverse effect, at least on risk factors for cardiovascular disease.<sup>36</sup>

The reduced risk of death from cerebrovascular disease associated with the more potent estrogens alone was largely confined to intracerebral hemorrhage and "other" cerebrovascular disease. Deaths from intracerebral hemorrhage and "other" cerebrovascular disease among women prescribed the combined estrogen-progestin regimen were few, but there was no marked evidence of an adverse effect. As for ischemic heart disease, confounding by quantifiable risk factors for stroke, particularly hypertension, is unlikely to account for all of the reduction in risk of death from intracerebral hemorrhage and "other" cerebrovascular disease. The concern remains, however, that differences in other variables, such as urban or rural residence, might attenuate the effect of the more potent estrogens. Reductions in incidence in this cohort associated with the more potent estrogens were evident for both intracerebral hemorrhage and thromboembolic stroke, but not for subarachnoid hemorrhage (which is unrelated to atherosclerosis).<sup>21</sup> Thus, our results support the possibility of a biological effect of hormonal replacement on mortality from intracerebral

hemorrhage and the lack of an effect on subarachnoid hemorrhage. We are more hesitant in interpreting the results for thromboembolic stroke in view of the discrepancy between our results for incidence and mortality. As Paganini-Hill<sup>37</sup> showed in a recent review, the bulk of the epidemiologic evidence indicated that women taking estrogen replacement therapy are at decreased risk for stroke incidence and mortality. On the other hand, few studies have examined risk in relation to type of stroke. The results from studies that have examined subarachnoid hemorrhage separately are inconsistent.<sup>37</sup>

Finally, risk of suicide was assessed in detail because of conflicting reports of a relation between this cause of death and hormone replacement therapy in other studies.<sup>8,9</sup> Users of more potent compounds were at higher risk compared with both the background population and users of "other" estrogens. Once again, selection bias is a possible explanation for these results, since it has been suggested that persons with psychiatric illness might be more likely to have been prescribed hormonal therapy.<sup>9</sup> It is also possible that our results are confounded by other variables, such as education. Nevertheless, concern that added progestins would lead to psychiatric disorders related to suicide received no support from our results.<sup>7</sup>

These data indicate that both selection factors and biology may contribute to the almost across-the-board reduction in mortality associated with menopausal hormone replacement therapy. More clearly, these data offer little support for the concern that the combined estrogen-progestin regimen has a more adverse effect on mortality than estrogens alone.

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