Estimated Gains in Life Expectancy with Use of Postmenopausal Estrogen Therapy: A Decision Analysis

John P. Zubialde, MD; Frank Lawler, MD, MSPH; and Neal Clemenson, MD
Oklahoma City, Oklahoma

Background. Epidemiologic data are accumulating that suggest that postmenopausal estrogen therapy reduces the risk of developing coronary artery disease (CAD). Computer simulation by Markov analysis can be applied to current data to estimate the increase in life expectancy obtained from postmenopausal estrogen use and compare them with benefits from other therapies for CAD risk reduction. Decision-analysis techniques can also examine whether the benefits of unopposed estrogen regimens ever exceed those of combination therapy.

Methods. In our analysis, hypothetical cohorts of postmenopausal women age 50 and 65 years with intact uteri were assigned either to estrogen and progesterone therapy or unopposed estrogens. The subjects were also defined by risk category for CAD. Outcomes were measured in terms of life expectancy for treatment cohorts compared with identical untreated cohorts.

Results. Life expectancy benefits in combined therapy groups were found to be very substantial for all CAD risk categories. Cohorts who began therapy at age 50 years showed benefits ranging from 0.3 years of additional life for those at low risk of developing CAD to 2.3 years for those at high risk. Even though the addition of progestins may theoretically result in reduction of overall CAD benefits, impressive gains in life expectancy were still found even when a 40% reduction in estrogenic effect was considered. Overall, benefits were very favorable when compared with other accepted strategies for CAD risk reduction. Little additional benefit was found to justify use of unopposed estrogens given the potential added mortality from endometrial cancer.

Conclusions. Substantial increases in life expectancy may result from postmenopausal estrogen therapy. These may be equal to or possibly greater than benefits from other well-recognized risk-reduction strategies. Little advantage in additional life expectancy is found to justify use of unopposed estrogens.

Key words. Estrogen replacement therapy; coronary disease; life expectancy; decision analysis. *J Fam Pract 1993; 36:271-280.*

Convincing data continue to emerge about the beneficial effects of postmenopausal estrogen therapy on the reduction of cardiovascular disease mortality. While an excellent job has been done of discussing the evidence for coronary artery disease (CAD) risk reduction,[1–5] little information has been presented about the potential magnitude of this impact on overall life expectancy and how estrogen therapy compares with benefits obtained from using other well-accepted risk-reduction strategies. Analysis of existing epidemiologic information using decision-analysis techniques can provide a better overall picture of this potential and allow for more critical evaluation of the risks and benefits of postmenopausal estrogen therapy. Also, in the absence of well-defined information from clinical trials (which at this time appear to be years from completion), this information will be important in guiding the emphasis placed on estrogen replacement therapy.

Coronary artery disease is a major source of morbidity for postmenopausal women and the number 1 cause of death. Nevertheless, the current emphasis seems to be on awaiting the outcomes of clinical trials before making formal recommendations for the general use of estrogens. This means that some patients may miss the potential benefits of estrogen therapy while clinicians await formal recommendations. From a clinical research standpoint, the question of the ethics of assigning patients to a placebo group in randomized trials also re-

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From the Department of Family Medicine, Program in Clinical Decision Making, University of Oklahoma Health Sciences Center, Oklahoma City. Requests for reprints should be addressed to John P. Zubialde, MD, Department of Family Medicine, Room 223, Rogers Building, 800 NE 15th St, Oklahoma City, OK 73104.

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mains. Although we understand that decision analyses do not generate the kind of definitive information that comes from clinical trials, they are widely accepted in many fields as a means of critically assessing risks and benefits. Furthermore, the current body of epidemiologic data on estrogen replacement therapy is certainly large enough to obtain good insight into the answers to these questions.

In the case of postmenopausal estrogen use, several areas of potential risks and benefits must be considered. Evidence strongly indicates that there are definite benefits to be gained from the use of estrogens in terms of osteoporosis prevention and symptom relief.[6–8] These benefits in terms of added life expectancy have also been well established[7,9] and are thus not reevaluated in our model. However, with mounting evidence pointing to significant reductions in CAD risk, we believed that it was important to evaluate the impact that this would have on the potential for additional life-expectancy benefits. Any benefits gained from estrogen therapy must be carefully weighed against the increased risk for endometrial cancer and the potential reduction of estrogen's benefits when progestins are added to counter this risk. In addition, any potential for added risk of breast cancer must also be considered.

Given this complicated picture of risks and benefits, evaluation of the epidemiologic data becomes a complex process. However, use of a tool known as Markov modeling,[10] designed specifically for this kind of analysis, provides the ability to estimate both life expectancy and changes in health status over many years. A more realistic model of health states is obtained because rates of disease incidence and mortality that are age specific and dependent on prior states of illness or disease can be included. Using this type of model, one can thus compare benefits to cohorts using no estrogen with those using either unopposed estrogen or combined estrogen and progesterone regimens. Differences in projected life expectancy for each strategy can then be compared to determine where or if a substantial advantage exists.

Thus, in this analysis, we will address the following questions related to three theoretical cohorts who are given no replacement estrogen, unopposed estrogen, or combined estrogen and progesterone: (1) Is there a significant advantage in terms of life-expectancy benefit for women using postmenopausal estrogens? (2) Is there ever an advantage in using unopposed estrogen regimens in women with intact uteri given the added risks of endometrial cancer? (3) What is the degree of expected benefits of estrogen therapy compared with other well-recognized CAD risk-reduction strategies?

Methods

For this analysis we created a discrete time, nonstationary Markov cycle tree.[11] In this type of model, potential states of health are listed initially with potential subsequent health states listed thereafter. The probability of changes in the state of health as well as the probability of mortality associated with each state of health are not static and change with time as a cohort ages and actual disease processes occur. Each cycle represents a single year in time, with a utility value of 1 year. Thus, if a person remains in a given state of health or changes (transitions) to another other than death, a utility of 1 year is assigned. Eventually, all members of each study cohort will die, and the total utility accumulated will represent the average life expectancy of the cohort. The probabilities of dying are represented by the total associated mortality rates for a given state of health. Probabilities of transitioning to a different state of health are represented by the age-specific incidence of disease for the cohort taking into consideration any increased relative risk caused by the therapeutic strategy employed. Probability of dying from the "no disease" state incorporates the chance of dying from any disease process other than the three evaluated.

Commercially available decision analysis software was used to create our model (*SMLTREE*, J. Hollenberg, New York, 1991). Years of life expectancy were not adjusted for quality of life. The model was "run" until 99.9% of all patients in each cohort had died. The average life expectancy was then assessed by the sum of the total utilities for the cohort modeled. Thus, the net difference between life expectancies for each cohort represents the net benefit or liability of one strategy compared with another.

Population

The population samples for this study consisted of hypothetical cohorts of menopausal women age 50 or 65 years with intact uteri. Age 50 years was chosen because the average age at which menopause occurs is generally considered to be between 47 and 52 years of age, and age-specific epidemiologic information fitting well with our modeling efforts began at age 50 years. Age 65 years was also chosen to determine if significant life-expectancy gains might still occur for populations starting therapy later than usual. This also tends to be an age where initiation of therapy is not stressed because of a reduced impact of estrogen on bone preservation.

Given these populations, the Markov model was then constructed to analyze the three therapeutic strategies for postmenopausal therapy. Details of the construc-

tion of this model and information used are presented later in this section.

Three therapeutic strategies were considered. The first therapeutic strategy was administration of estrogen and progestin combined. A particular regimen was not defined by our model, but when this could influence the epidemiologic data used, we made note of this under the appropriate section. The second therapeutic strategy was administration of unopposed estrogen. The third strategy, with which the previous two were compared, was no administration of estrogen.

States of Health, Data, and Assumptions

For each of the cohorts, the initial state of health was defined as no disease. Nine possible transition states were then allowed. The five main outcome states were defined as death (absorbing state), endometrial cancer, coronary artery disease, breast cancer, and no disease. Four additional states were also included that would not be initially significant but would be necessary for later transitions. These included CAD and uterine cancer, CAD and breast cancer, uterine cancer and breast cancer, and all three diseases. A total of 29 possible outcome states were then created based on the possible sequences of disease states entered. Incidence, mortality rates, and relative risks used for calculations in each state are listed in Table 1 and discussed individually below.

Table 1. Sources and Values of Data

	Source	Value
Mortality rates (annual rate per person-year)		
Endometrial cancer	Malkasian[12]	2.23%
Coronary artery disease	Proudfit et al[13]	6.1%
	CASS[14]	1.6%
	European collaborative study[15]	3.3%
	Veterans Administration study[16]	4.3%
Breast cancer	Adami et al[17]	5.2%
Incidence		
Endometrial cancer	Devesa et al[18]	
Coronary artery disease	Framingham study[19]	
Breast cancer	Costanza, NCI/SEER[20]	
Relative risk		
Endometrial cancer		
Unopposed estrogens	Voigt et al[21]	5.7
Combined therapy	Voigt et al[21]	1.6
Breast cancer	Dupont and Page[22]	1.08
	Steinberg et al[23]	1.3
Coronary artery disease		
Estrogen therapy	Stampfer et al[1]	0.56
	Stampfer et al[2]	0.5
	Barrett-Connor and Bush[4]	0.5
	Ettinger[5]	0.5

**Data sets may be found in the documents referenced as follows: reference 18, Appendix 2; reference 19, Table 1-1; reference 20, Table 1.*

DEATH

Death is defined as the ultimate absorbing state with no further transitions possible. The probability of entering this state in any given cycle is defined by the age and sex-specific mortality rates for the population being evaluated. In the first distribution, the probability of dying is simply the average mortality rate for women age 50 years. The source of information for age-specific mortality rates was the US Life Tables,[24] with mortality rates generated from using survival by year. This allowed us to assess mortality rates on a yearly basis rather than project 5- to 10-year averages, and thus enhanced the overall accuracy of our results.

The software used allowed for the mortality rate to change with each cycle (or year), thus more accurately reflecting the true mortality rate among the cohort as they aged. As the Life Tables could not give age-specific mortality rates by year above age 85 years, a curve was plotted based on the mortality data of the previous 20 years and extrapolated to age 100 years. Mortality rates for this group were then estimated, ensuring that the overall mortality was the same as that listed in the Life Tables for the group over 85 years of age. All mortality rates were then reduced by the age- and sex-specific mortality rates from ischemic heart disease, cancer of the corpus uteri, and breast cancer.[24] This was done because we later added this mortality back in on the Markov model. Mortality rates for each subsequent state of disease were represented by this general mortality rate plus the additional mortality rate for the disease state entered. If published age-specific mortality rates were available, these were used and referenced. Where only disease-specific survival rates were available, the DEALE (declining exponential approximation of life expectancy) method of estimating mortality rates from survival data was used.[25] All attempts were made to use only age-specific data to avoid underestimating mortality rates. Where there was uncertainty as to which data to use, the highest mortality rate was chosen, thus biasing against estrogen, if at all.

ENDOMETRIAL CANCER

It is recognized that both combined therapy and unopposed therapy increase the risk of developing endometrial cancer. The exact magnitude of the relative risk is still debated, with estimations varying widely between published studies.[26] The best recent information was published in 1991 and consisted of a population-based, case-control study.[21] Relative risks were reported as 5.7 for unopposed estrogen used longer than 3 years, and 1.6 for use of combined therapy for at least 6 months. These estimates appear to be consistent with a generally ac-

cepted sixfold relative risk of developing endometrial cancer. In actuality, these numbers should more correctly be termed *relative risk estimates* derived from odds ratios because of the case-control nature of this study. We believe, however, that these are accurate representations of the added risk. These data were incorporated into the model, gradually introducing the relative risks from minimum to maximum over the first 4 cycles (4 years) to more accurately reflect the increasing risk of developing the disease with time.[26] Age-specific incidence of uterine cancer has been reported by Devesa et al.[18] Incidence of cancer of the corpus uteri was used because of our inability to get more specific information on endometrial cancer alone. In addition, it is generally believed that over 94% of all uterine cancers are endometrial, with sarcomas being rare.[27,28] Mortality for endometrial cancer induced by use of unopposed estrogens is widely held to be less prevalent than that of non–estrogen-induced cancer because of the preponderance of stage I, grade 1 tumors. Our calculations led to a 2.2% increase in annual mortality rate based on an 80% relative survival rate at 10 years, which is reflective of the average survival rate for grade 1 tumors.[12,29] A mortality rate of 2% is noted in a similar study by Hillner and co-workers.[9]

CORONARY ARTERY DISEASE

The most widely debated and potentially significant effect of postmenopausal estrogen replacement is its effect of reducing the risk for CAD. A number of excellent reviews and studies have made it very clear that use of estrogens significantly decreases a woman's chance of developing coronary disease, with risk reduction in the range of 40% to 50%.[1–4] It also appears that women at lower risk enjoy the same relative benefit from estrogen as women in general.[1] The main issue yet to be settled is the impact that the addition of progestins has on this reduction of risk.

Many studies have looked at the effect of various regimens of combined estrogen and progestin therapy on lipid profiles. There now seems to be emerging evidence that regimens of equine estrogen with medroxyprogesterone acetate may have only minimal effect on lipids over longer periods of use.[30–32] It is also generally believed that only 25% to 50% of the effect of estrogen is a result of improvement in lipid profiles.[4,32,33] We adjusted our model to accommodate this uncertainty by placing a modifying variable into it that allowed us to reduce the beneficial effect of estrogen when progestins are added.

Incidence of CAD was best represented by the age-specific incidence of coronary heart disease among women in the Framingham study.[19] These rates were then correlated with risk status for CAD using information presented by Wilson[34] on coronary risk prediction in adults. In this study, average incidence of CAD increases with age (Framingham data) and the range of values occurring between low-risk and high-risk groups narrows. Low-risk populations are defined in this study as being normotensive, cholesterol levels <185 mg/dL (4.78 mmol/L), no left ventricular hypertrophy, no glucose intolerance, and nonsmoking. Average risk represents the general population risk for an individual of a given age and sex. High risk is defined as the presence of a blood pressure of 180 mm Hg systolic, cholesterol level of 310 mg/dL (8.02 mmol/L), cigarette smoking, left ventricular hypertrophy, and glucose intolerance. We then added to our model an intermediate category labeled "moderate risk," corresponding to an incidence rate midway between that of the high- and average-risk categories. For women in the age range of 50 to 60 years, high-risk populations show an average of five times the incidence of disease compared with the incidence among the general population. Incidence in low-risk groups is 40% of that of the general population. In the age range of 60 years and older, incidence of CAD in high-risk groups falls to three times the average incidence, and incidence in low-risk groups decreases slightly to only 30% of the average incidence. We accordingly modified our incidence data to reflect this age-specific correlation with risk category.

In published studies looking at mortality estimates in patients with CAD of varying severity and comparing medical with surgical therapy, a wide range of values was reported. Estimates ranged from as low as 1.6% annually for those treated medically in the CASS study,[14] to as high as 9% (6.1% when adjusted for mortality from other diseases) in the 15-year survival study done by Proudfit and colleagues.[13] This latter study may be more representative of our cohorts because it specifically identified survival rates for patient subgroups over 50 years of age where the others did not. Although this was not sex-specific, it was stated that no difference was found in survival rates between the sexes. Authors of the CASS study indicated a prestudy estimation of a 3.5% mortality rate based on their review of the literature.[14] Computer simulation using the incidence data described in the Framingham study for women over 50 years of age would require a 5% annual mortality rate to explain the overall mortality ascribed to the ischemic heart disease category of the Life Tables. This would suggest that the more likely actual value for the general population of women over 50 years of age may be closer to the values reported by Proudfit and colleagues for the subgroup over 50 years of age. However, as there was no general consensus in the literature on the average rate of CAD mortality, we chose to use 3.8% (mid-range of published

values), and do a sensitivity analysis on the range of values. Results of life-expectancy benefits are thus reported as the value obtained using the mid-range value, as well as the complete range of values calculated using both the lowest and highest reported CAD mortality rates.

BREAST CANCER

The question of whether postmenopausal estrogen therapy increases the risk for breast cancer remains unanswered. Two recent meta-analyses of existing literature have yielded conflicting results, with one showing little to no increased risk,[22] and the second suggesting as much as a 30% increased risk for women treated with estrogen therapy for more than 15 years.[23] Review of the methodologies used, however, suggests that much of the added risk found in the second study may reflect the inclusion of premenopausal women on estradiol. Given this conflict in information, we believe that evaluation using no added risk as well as a worst-case scenario (relative risk 1.3) would be important to determine the potential effect on overall outcome.

As for age-specific incidence rates, excellent information was available, and varied little between studies. We believed the most accurate information was that from the National Cancer Institute's Surveillance, Epidemiology and End Results study conducted from 1984 through 1988.[20] Mortality rates, however, varied greatly between studies, with average values ranging from 2.5% per year[35] to 8% per year[17] depending on the age of the cohort followed and the average severity of disease at diagnosis. For our study we chose 5.2% per year representing an average mortality rate for women over 50 years based on 15-year follow-up.[17]

Decision Analysis Between Strategies

The first part of the analysis examined the estimated life expectancy in women using estrogen and progestin combination therapy and then compared it with the life expectancy of women of the same age who did not receive therapy. In the second part of the analysis, the estimated life-expectancy benefits generated by the use of combination therapy or unopposed estrogens were compared using decision analysis techniques. This comparison was done only for the 50-year-old cohort. It is felt that the addition of progestins to the regimen may reduce the CAD protective effect seen when estrogen alone is administered and thereby reduce the life expectancy benefit. On the other hand, use of unopposed estrogens increases the risk of endometrial cancer. The question then becomes whether an advantage in terms of additional years of life might occur by using unopposed estrogens even considering the added risk of cancer. Because of the limitation of the model in making these comparisons, it was necessary to assume a uniform incidence of CAD for all those over 50 years of age in each risk category. These were estimated by calculating an average incidence that would give the same overall life expectancy generated by the age-specific information. Using this assumption, our model allowed us to find the percentage reduction in estrogen's protective effect that would produce a set difference in life-expectancy benefit between the two therapeutic strategies. Differences of 0, 0.25, and 0.5 years were examined. This was done so that the reader might decide at what point the potential improvement in life expectancy might justify the additional expense and attention required in monitoring and follow-up of the patient on unopposed estrogen therapy. Additionally, patient input would be required regarding the psychological impact of anticipating the additional risk of cancer incurred using this strategy.

Testing of the Model for Accuracy

Before beginning the overall analysis, we determined how well the model performed in estimating life expectancy for the general population. The first test was run using the mortality rates for the general population and no increased incidence of CAD or endometrial cancer. This allowed for the calculation of general life expectancy for 50- and 65-year-old women. The calculated life expectancies were 30.6 and 18.4 years, respectively, which compared favorably with the 31.0 and 18.6 years listed in the Life Tables.[24]

Results

The first part of our analysis examined cohorts of women aged 50 and 65 years with intact uteri using combined estrogen and progesterone therapy compared with identical untreated cohorts. Additional life-expectancy benefits obtained for treatment groups are listed in Table 2 with benefits noted by risk category for CAD. Numbers in parentheses represent the range of values possible based on a sensitivity analysis of the available data reported in the literature. Figure 1 represents these results graphically. All numbers reported are based on no added risk of breast cancer, as careful review of the current literature has led us to believe that this more likely represents the actual risk status. However, a worst-case scenario, with a 30% increased risk of breast cancer, was also analyzed as described in the Methods section, and was found to reduce the reported values as follows:

Table 2. Estimated Life Expectancy Benefit of Combined Estrogen and Progesterone Therapy in Years, by CAD Risk Status

CAD Risk Category†	Theoretical Reduction in Benefit by Adding Progestin to Estrogen, %	Estimated Life-Expectancy Benefit, y (range)*	
		Therapy Initiated at Age 50 Years	Therapy Initiated at Age 65 Years
Low	0	0.31 (0.12 – 0.44)	0.14 (0.06 – 0.21)
	20	0.23 (0.08 – 0.34)	0.11 (0.04 – 0.16)
	40	0.16 (0.05 – 0.23)	0.07 (0.02 – 0.11)
Average	0	0.86 (0.40 – 1.19)	0.47 (0.21 – 0.66)
	20	0.67 (0.30 – 0.93)	0.37 (0.16 – 0.52)
	40	0.48 (0.21 – 0.67)	0.27 (0.11 – 0.38)
Moderate	0	1.73 (0.85 – 2.33)	0.81 (0.38 – 1.13)
	20	1.34 (0.65 – 1.80)	0.63 (0.29 – 0.88)
	40	0.96 (0.46 – 1.30)	0.46 (0.21 – 0.64)
High	0	2.25 (1.13 – 3.00)	1.07 (0.52 – 1.47)
	20	1.71 (0.85 – 2.29)	0.83 (0.41 – 1.14)
	40	1.22 (0.60 – 1.63)	0.60 (0.29 – 0.82)

**Range of increased life expectancy based on sensitivity analysis of data from the literature.*
†Risk categories are defined in Methods section under "Coronary Artery Disease."
CAD denotes coronary artery disease.

low-risk cohorts lost an impressive 70% of the net added benefit because of smaller overall benefits from reduced CAD. The remaining cohorts had much less impact, with average-risk groups losing only 20% of the benefit, and moderate and high-risk groups losing only 10% and 7% of the benefit, respectively.

The most striking information obtained from this analysis was the degree of impact that the addition of estrogens had on life expectancy even among those at

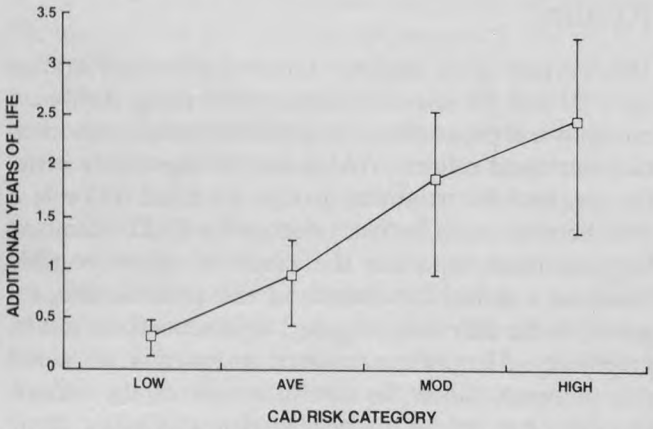

Figure 1. Years of life gained with estrogen and progestin therapy in women 50 years of age. The line plotted assumes a CAD annual mortality rate of 3.8%. Range of values (as indicated by lines with crossbars) represents potential outcomes based on sensitivity analysis.

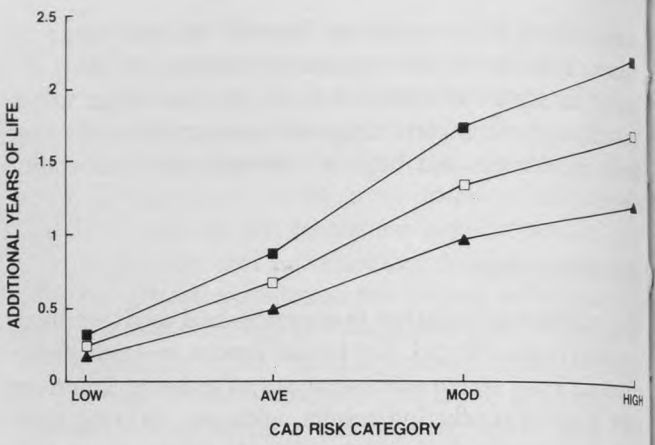

Figure 2. Years of life gained with estrogen and progestin therapy in women 50 years of age assuming a CAD annual mortality of 3.8%. Symbol ■ = no reduction of beneficial effect of estrogen when progestin is added; □ and ▲ = 20% and 40% assumed reduction in effect, respectively (ie, if progestin is assumed to reduce the CAD benefit of estrogen by 20% to 40%).

low-risk of developing CAD. Life expectancy benefits were substantial in all risk categories. In the low-risk cohort of women age 50 years, benefit varied from 0.12 years (1.6% CAD mortality)[14] to 0.44 years (6.1% CAD mortality).[13] In the high-risk cohort, life expectancy benefits increased sharply, ranging from 1.13 years (1.6% CAD mortality)[14] to 3.0 years (6.1% CAD mortality).[13]

For women beginning estrogen with progestin therapy at age 65 years, benefits ranged from an additional 0.06 to 0.21 years in the low-risk category. For high-risk groups, benefits ranged from 0.52 years to 1.47 years across the same range of CAD mortality estimates. Based on these data, it appears that postmenopausal therapy may be of benefit even in older patients for whom provider emphasis on therapy has been low because the benefit to life expectancy was thought to be small.

As anticipated, reduction in the beneficial effect of estrogens by the addition of a progestin occurred in all risk categories. These reductions are represented graphically in Figures 2 and 3. It should be noted, however, that despite a 40% reduction of benefit, which could theoretically be the case in the event of complete reversal of estrogen's lipid benefits, very impressive improvements in life expectancy are still achieved. In the worst-case scenario in which breast cancer develops, and progestins reduce estrogenic protection by 40%, benefits are further reduced by 45% for those in the average-risk cohorts. Moderate-risk and high-risk groups lose only 20% and 15%, respectively. Again, benefits decrease the most in the low-risk groups to the extent that a net loss actually occurs among those 50 and 65 years old. This

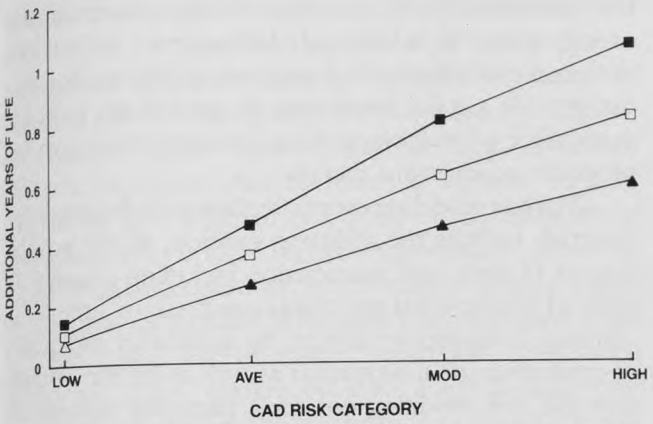

Figure 3. Years of life gained with estrogen and progestin therapy in women age 65 years of age assuming a CAD annual mortality of 3.8%. Symbol ■ = no reduction of beneficial effect of estrogen when progestin is added; □ and ▲ = 20% and 40% reduction, respectively.

again emphasizes the need for better information on the true degree of impact of progestins.

Combined vs Unopposed Estrogen Use

In the second part of our analysis, we evaluated when life-expectancy benefits from the use of unopposed estrogen therapy might be significantly greater than the use of combined estrogen and progesterone. As mentioned before, there is about a sixfold increased risk of endometrial cancer in patients using unopposed estrogens.[21] However, there is also thought to be a potential reduction in the CAD protective effect of estrogen when combined therapy is used to reduce the risk of endometrial carcinoma. By varying the level of progestin interference (reduction in benefit) in each cohort from 0% to 100%, we were able to establish a threshold level of interference that was used to generate a set minimum life-expectancy difference between treatment strategies. Results of threshold values are listed in Table 3 along with the range of values based on sensitivity analysis.

It can be seen from our results that in a person of average risk for CAD, unopposed and combination therapies could be considered equally beneficial if greater than a 41% reduction in the CAD protective effect occurred with the addition of progesterone. One would be 0.25 years better off by using unopposed estrogen if greater than 66% reduction occurred with the addition of a progestin. A 0.5 year advantage would require more than 92% reduction of benefit by the addition of progestin. For low-risk cohorts, however, there is never any advantage, as unopposed regimens always have a poorer outcome than combined regimens.

Numbers underlined in Table 3 show where a realistic amount of reduction could possibly occur, based on the fact that 25% to 50% of estrogen's beneficial effects are probably caused by changes in lipids and thus may be partially or completely affected when a progestin is added.[4,32,33] As more data become available on this subject, a clearer picture may emerge. If we assume that a reasonable overall estimate of the reduction is 30% or less, however, only the moderate- to high-risk groups for CAD might benefit to any significant degree from the use of unopposed estrogens, but then only if a maximum of 0 to 0.5 years is considered acceptable additional life-expectancy benefits for the patient. No attempt was made to state where benefits are significant enough to justify use of unopposed estrogens. Considerations not included in our analyses were the additional time, effort, and cost of monitoring that is required in patients taking unopposed estrogens as well as the psychological effects of a known increase in the risk of cancer. These consider-

Table 3. Reduction in Estrogen Protective Effect Required to Show a Set Life-Expectancy Advantage with Use of Unopposed Estrogens

CAD Risk Status	Life Expectancy Advantage of Unopposed Therapy		
	Equivalent, % (range)	0.25 years, % (range)	0.5 years, % (range)
Low	Never achieved	Never achieved	Never achieved
Average	41 (31-82)	66 (51-100)	92 (72-100)
Moderate	17 (13-38)	30 (24-64)	43 (34-89)
High	11 (8-24)	21 (16-45)	32 (22-64)

NOTE: Numbers in parentheses represent range of potential thresholds based on sensitivity analysis. Underlined numbers indicate where reasonable levels of interference may occur.

Example 1. No additional life-expectancy benefit ever occurs with use of unopposed estrogens in women at low risk for CAD. The risk of endometrial cancer mortality always outweighs the benefits of unopposed estrogen regimens in this group.

Example 2. For women at average risk for CAD, the additional life expectancy benefits of both unopposed estrogen and combined estrogen and progestin regimens are equivalent if the addition of progestins reduces the protective effect of estrogen by 41%. If less reduction actually occurs, combined estrogen and progestin regimens are always more favorable than unopposed estrogen regimens. However, if a more than 41% reduction in benefits occurs with added progestins, then unopposed regimens are more favorable. A reduction of 66% in estrogenic protective effect when using combined regimens is required to show a 0.25 year advantage in life-expectancy benefits for the unopposed regimen. Similarly a near total reduction (92%) is required to show an advantage of 0.5 years.

CAD denotes coronary artery disease.

Table 4. Comparison of Life-Expectancy Gains for Various Therapeutic Interventions for Reducing the Incidence of Coronary Disease

Intervention	Life Expectancy Gain* y (range)
Combined estrogen and progestin intervention in women aged 50 years	0.86(0.40 – 1.19)
Other therapeutic interventions in women aged 35 years†	
Cholesterol reduction to 200 mg/dL (5.2 mm/L) if over	0.8(0.4 – 1.4)
Smoking elimination	0.7(0.4 – 0.8)
Blood pressure reduction to 88 mm Hg, diastolic	0.4(0.3 – 0.6)
Reduction of weight to ideal body weight	0.4(0.3 – 0.4)

NOTE: All comparisons are for the population-wide average of women at the stated age.
**If all risks for coronary artery disease could be eliminated, the life-expectancy gain for a 35-year-old woman would be 3.2 years[36] and for a 50-year-old woman, 2.2 years.*
†Based on a study by Tsevat et al.[36]

ations remain essential in the clinician's overall assessment of risk and benefit.

Discussion

Evidence continues to mount about the potential benefits of estrogen replacement therapy, with convincing data now available on its ability to reduce risk for CAD. As we have seen from our analysis of the available epidemiologic data, significant increases in life expectancy can be anticipated, which is desirable given the fact that cardiovascular disease remains the most common cause of death in adult women. By comparison, a previous study by Tsevat and Weinstein[36] examined the potential gains in life expectancy from other widely accepted therapeutic interventions modifying cardiovascular risk factors (Table 4). For women at age 35 years, population-wide gains in life expectancy were estimated to be 0.8 years for strict cholesterol reduction to < 200 mg/dL (5.2 mmol/L), 0.7 years for smoking cessation, 0.4 years for strict blood pressure control to <88 mm Hg diastolic, and 0.4 years from weight reduction to ideal body weight. When comparing our data with these, it appears that the benefit from postmenopausal estrogen therapy is at least as important as the other well-accepted interventions listed here. Also, when considering the cost of estrogen therapy, the infrequency of monitoring, and little or no induced costs, the benefits are even more dramatic. Additionally, we looked only at the potential impact of this effect on life expectancy and not at the other potential benefits to society as a whole that may stem from the additional decrease in overall morbidity, quality of life, and cost savings. Considering that estimates of the total cost of cardiovascular disease are approaching $109 billion annually,[37] even a fraction of this amount in cost savings would be substantial. Although we did not look at formal cost-effectiveness analyses, simple mathematics can provide a quick assessment of the benefits gained in years of life when looking at the low cost of estrogen and progestin replacement therapy.

Markov modeling cannot replace well-designed clinical trials because the ability to consider all the possible sources of error and interference, including practical aspects of therapy, patient compliance, etc, is limited. In addition, outcomes are affected by availability and quality of epidemiologic information as well as by the assumption that risk modifications for a particular strategy are applied immediately. In reality there may be a lag time of several years. Fortunately for us, however, there has been a convergence of much of the estrogen-related data presented here, allowing for more reassurance of the accuracy of the output from this analysis. Thus, the importance of models such as this stems from their ability to generate an overall picture of what the potential impact may be using the best available information and decision-analytic methods to date and providing important insights into the potential benefits for our patients while we await further information.

Ultimately, proof of estrogen's effect on CAD risk would require a randomized prospective trial of healthy postmenopausal women. Estimates by Barrett-Connor and Bush[4] indicate that a long-term study of as many as 50,000 women would be required to validate the effects. As this type of undertaking is unlikely in the immediate future, the balance of current evidence points to emphasis on the use of postmenopausal estrogens for prevention of CAD in postmenopausal women. As for current recommendations, the vast experience we have with the use of estrogens over many years should help to validate their use. Similarly, some of the previous barriers to their use (eg, patient dissatisfaction caused by withdrawal bleeding) are being removed as new regimens of continuous combined therapy are developed and proven in clinical trials.

As for the concern over risk of breast cancer, we have shown that even in a worst-case scenario with a 30% increased risk of breast cancer, all patient cohorts evaluated still showed significant benefit from estrogen therapy in terms of added life expectancy. Patients at low risk for CAD benefited the least, but never showed a net loss of life-expectancy benefits when compared with untreated cohorts, unless it can be shown that progestins significantly reduce the effect of estrogens on CAD risk. Clearly, further clarification of progestin's effect on CAD risk will be essential.

In the case of unopposed estrogen use, however, our data indicate that a reasonable degree of benefit (com-

pared with combined estrogen and progestin therapy) is not as likely, except perhaps for some moderate- to high-risk groups, and then only if progestins reduce the beneficial effect of estrogen by 20% or more. In addition, the costs of regular endometrial sampling, combined with the likelihood that as many as 12% to 44% of women on this regimen will progress to endometrial hyperplasia after 6 to 12 months[26] (potentially requiring the addition of progestins), would suggest that the added benefits may be negated. The added psychological effect of an increased risk of cancer would also need to be considered. Thus, current evidence suggests that combined estrogen and progesterone therapy should be recommended even for women at high-risk for CAD unless future studies show more interference from progestins than is anticipated. Obviously, unopposed estrogen therapy is preferred for women who have had hysterectomies, regardless of their CAD risk status.

In women who have had hysterectomies the added risk of endometrial cancer is removed. Thus, the risk of adding a progestin that could reduce cardiovascular benefits would have to be weighed against any added benefit to the individual from reduction of other potential complications. It therefore seems preferable for these women to continue with estrogen alone.

We agree with the statement of Goldman and Tosteson[38] in *The New England Journal of Medicine* in September 1991 that the time has come for action and not just debate on this issue. If information from clinical trials is what is needed to solidify the formal recommendation of this therapy, then they should begin immediately. In the meantime, however, evidence from this analysis certainly suggests that benefits from CAD risk reduction are as important as if not more important than other currently recognized therapies including cholesterol reduction, hypertension control, smoking cessation, and weight reduction. Immense resources are currently being spent for each of these risk-reduction strategies, and for many, cost of pharmacologic agents alone (without considering induced costs) outweighs the cost of estrogen and progesterone therapy by several fold. The cost-effectiveness of this strategy is obvious.

In conclusion, significant potential benefits in life expectancy from CAD risk reduction combined with the already proven benefits from osteoporosis prevention and symptom relief would seem to point to a greater emphasis on postmenopausal estrogen use in appropriate patients. As for the design of clinical trials, the potential for such substantial benefits makes room for debate on the ethics of randomizing patients (even low-risk patients) to a placebo in such trials.

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