EDITORIALS

The Current State of Hormonal Prevention of Coronary Heart Disease in Menopausal Women

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The increased incidence and prevalence of coronary heart disease among older women, coupled with the less favorable prognosis for women who sustain coronary events than for men, has resulted in the medical community's attention to the potential beneficial effects of hormone therapy in menopausal women. Much biological evidence supports a protective mechanism of estrogen; nevertheless, some aspects are contradictory. Although observational studies have shown a clear cardiovascular benefit associated with hormone therapy, the significant skew inherent in these data has resulted in overestimation of benefits and underestimation of risks. Recent reanalysis of these observational data controlling for confounding variables failed to show cardiovascular benefit. Several randomized, double-blind, placebo-controlled studies have failed to show improvement in clinical cardiovascular outcomes with menopausal hormone therapy both in healthy women and in women with established coronary heart disease. Current research has also focused on pharmacologic agents that selectively modulate estrogen receptors, such as raloxifene, which are useful for the prevention and treatment of osteoporosis without increasing the risk of breast cancer. A clinical trial is now underway to evaluate the effects of raloxifene on coronary events and on the incidence of invasive breast cancer in menopausal women both with established coronary heart disease and at increased risk for coronary events. Current recommendations do not advocate the initiation of menopausal hormone therapy for the primary or secondary prevention of coronary events. The proven lifestyle interventions of smoking cessation, heart healthy diet, weight control, and physical activity should be undertaken, with statin use for control of elevated LDL cholesterol levels and pharmacologic blood pressure control when appropriate.

Key words: Estrogen. Coronary heart disease. Thromboembolism. Breast cancer. Raloxifene.

Situación actual de la prevención hormonal de la enfermedad coronaria en la menopausia

El aumento de la incidencia de cardiopatía isquémica entre mujeres mayores, unido a que su pronóstico es peor que el de los varones, ha centrado la atención de la comunidad médica en el posible efecto beneficioso de la terapia hormonal sustitutoria para el tratamiento de la enfermedad coronaria de las mujeres menopáusicas. La mayoría de las evidencias biológicas confirma el mecanismo protector de los estrógenos. Sin embargo, algunos aspectos son contradictorios y, aunque los datos observacionales han apuntado un claro beneficio asociado a la hormonoterapia, el importante sesgo derivado de este tipo de estudios ha sobrevalorado los beneficios y subestimado los riesgos. Análisis recientes de estos datos observacionales, tras corregir por las posibles variables de confusión, no han demostrado ningún beneficio cardiovascular. En varios ensayos clínicos aleatorizados, a doble ciego y controlados con placebo, no se ha apreciado ninguna mejoría en los resultados clínicos asociados a la hormonoterapia, tanto en mujeres sanas como en mujeres con historia de enfermedad coronaria. La investigación actual se ha centrado en el estudio de los fármacos moduladores de los receptores de los estrógenos, como el raloxifeno, que son útiles para la prevención y el tratamiento de la osteoporosis, sin incrementar el riesgo de cáncer de mama. Está en marcha un ensayo clínico para evaluar los efectos del raloxifeno en los episodios coronarios y en la incidencia de cáncer de mama, tanto en mujeres menopáusicas con enfermedad coronaria establecida como en aquellas con alto riesgo de sufrir episodios coronarios. Las recomendaciones actuales no abogan por la iniciación del tratamiento hormonal en la prevención primaria o secundaria de la cardiopatía isquémica. Se aconseja, en su lugar, adoptar estilos de vida saludables, como dejar de fumar, seguir una dieta cardiosaludable, controlar el peso y practicar alguna actividad física. Cuando se considere apropiado, se debe utilizar estatinas para regular los valores elevados de colesterol de los LDL así como controlar la presión arterial.

Palabras clave: Estrógenos. Enfermedad coronaria. Tromboembolia. Cáncer de mama. Raloxifeno.

Heart disease is a significant cause of mortality in women (it is the leading cause of death in women in the United States); in addition, the prognosis after a myocardial infarction or coronary artery bypass surgery is significantly worse for women than for men. Thus there was considerable interest in any intervention that might provide cardioprotection and menopausal hormone therapy was explored in this regard.

BIOLOGIC PLAUSIBILITY

Biologic mechanisms suggesting benefit for estrogen are persuasive but at times contradictory. For example, estrogen has favorable effects on some lipid and lipoprotein concentrations, causing a 10% to 15% decrease in LDL cholesterol and a similar increase in HDL cholesterol levels. Nevertheless, oral estrogen therapy has a deleterious effect on triglyceride concentration. Estrogen also has a beneficial effect on many measures of coagulation and fibrinolysis, but paradoxically is uniformly associated with an increase in deep vein thrombosis and pulmonary embolism. In addition, although estrogen decreases homocysteine concentration, it elevates levels of the inflammatory marker C-reactive protein. Estrogen diminishes the inflammatory response to atherosclerosis, reduces the proliferation of vascular smooth muscle cells, and facilitates endothelial vasodilation; additionally, there is recent evidence that estrogens may enhance angiogenesis. However, biologic plausibility alone is only hypothesis – generating and is not evidence for cardiac protection.

OBSERVATIONAL STUDIES

Reports from observational studies almost uniformly identified that estrogen had a cardioprotective effect. A meta-analysis of these studies showed a 35% to 50% reduction in coronary risk associated with estrogen therapy; although there are fewer studies of the response to combination therapy using estrogen and progestin, these studies also suggest a beneficial effect.[1] Observational data must be considered with caution, owing to factors that may distort the results of such studies.[2]

Among these factors is the bias associated with the selection process. Women who smoke, are hypertensive, diabetic, obese, have angina, have heart failure, claudication, or those who have had a myocardial infarction or cerebrovascular accident were traditionally not considered candidates for menopausal hormone therapy. It is difficult to know to what degree the favorable results obtained are due to hormone therapy when the study population is selected for having few coronary risk factors or prior cardiovascular events. Another factor that influences

results is treatment compliance. In several cardiovascular clinical trials, examination of both men and women in the placebo group showed that those adherent to placebo had a 40% to 60% lower occurrence of coronary events than those not adherent to placebo, obviously suggesting that adherence is a surrogate for other health-related behaviors. A third element that must be considered when interpreting the results of observational studies is the effect of early adverse effects. In a cross-sectional study, women who discontinued hormone use due to early the occurrence of adverse effects are not captured in the group of hormone users. Taking all these factors into account, observational data tend to overestimate benefits and underestimate risks.

A recent metaanalysis of the observational study data cited above that adjusted for socioeconomic status, education, and major coronary risk factors failed to demonstrate cardiac protection, with a relative risk of 1.07 for hormone users.[3] This obviously reflects the fact that women who use hormone therapy differ from nonusers in many aspects including general health status, health consciousness, socioeconomic status, coronary risk attributes and the like. Additionally, a recently published scientific review for the U.S. Preventive Services Task Force examined both published observational and clinical trial data and summarized the effects of hormone therapy as follows:[4] benefits included prevention of osteoporotic fractures and colorectal cancer; there was uncertainty as to the prevention of dementia; and harms included an increased risk of coronary heart disease, stroke, venous thromboembolism, cholecystitis, and breast cancer (with five or more years of hormone use).

## OUTCOMES FROM RANDOMIZED CLINICAL TRIALS

The PEPI (Post-menopausal Estrogen Progestin Intervention) clinical trial was designed to study the effect of therapy with estrogen and progestin on cardiovascular risk factors in healthy menopausal women. The study hypothesis was that the administration of estrogen decreases the risk of coronary heart disease because of the favorable effect on cardiac risk factors. Healthy menopausal women were randomized to receive one of the following treatments: *a)* 0.625 mg daily of conjugated equine estrogen; *b)* the same estrogen dose combined with medroxyprogesterone acetate administered cyclically; *c)* the same dose of estrogen with medroxyprogesterone acetate administered continuously, and *d)* the same estrogen dose combined with micronized progesterone administered cyclically. These treatment groups were compared with a placebo group. The study showed a beneficial effect of all

hormone regimens on HDL cholesterol, LDL cholesterol, and fibrinogen concentrations, but an increase in triglyceride concentrations. The most favorable effect on HDL concentration was obtained with the administration of estrogen alone or with the combination of estrogen and micronized progesterone. The use of medroxyprogesterone acetate was associated with an increase in blood glucose levels, but none of the treatments had an effect on arterial blood pressure or insulin concentration. Similarly, none of the treatment regimens resulted in an increase in body weight compared with placebo. Significant adverse effects of estrogen were observed: in women who had a uterus and received unopposed estrogen, adenomatous or atypical endometrial hyperplasia (an unequivocal precursor of endometrial cancer) occurred at a rate of 10% annually. These data appropriately changed clinical practice, in that currently women with a uterus should receive estrogen associated with a progestin. The findings of the PEPI study show that estrogen administered in association with micronized progesterone is the best combination of the regimens studied for achieving a favorable coronary risk profile in women with an intact uterus; for women who have undergone hysterectomy, administration of estrogen alone is recommended.

Evidence has concomitantly mounted of the non-cardiac risks associated with menopausal hormone therapy. The available data indicate that, in addition to the adenomatous or atypical endometrial hyperplasia associated unopposed with estrogen treatment, hormone therapy increases the relative risk of venous thromboembolism by a factor of 2 to 4, increases the risk of surgical biliary tract disease by 40%, and (with treatment lasting 5 to 10 years or more) increases the risk of breast cancer by a factor of 4 to 5.

It was not until 1998, with the publication of the findings of HERS (the Heart and Estrogen/Progestin Replacement Study), that data from the first large randomized, double-blind, placebo-controlled clinical trial displayed effects of estrogen/progestin therapy in menopausal women with pre-existing coronary heart disease.

HERS enrolled 2763 menopausal women up to the age of 80 years with an intact uterus who had documented coronary heart disease (previous myocardial infarction, coronary artery bypass graft surgery, coronary angioplasty, or more than 50% narrowing of 1 or more major coronary arteries if the sole presentation was angina pectoris). The women were randomized to receive 1 capsule daily that contained 0.625 mg of conjugated estrogen and 2.5 mg of medroxyprogesterone acetate or 1 capsule containing a placebo. The primary planned study outcome was the combination of non-fatal myocardial infarction and coronary death, and various secondary outcomes were also examined (coronary
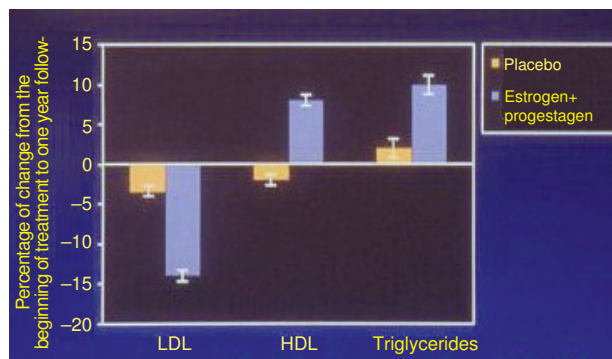
Fig. 1. Changes in the lipoprotein profile produced in the post-menopausal women included in the HERS study. As predicted, after 1 year of oral hormone therapy treatment there was a significant reduction in LDL concentration and an increase in HDL and blood triglyceride concentrations.

revascularization, hospitalization due to unstable angina, hospitalization due to congestive heart failure, peripheral arterial disease, etc.).

During follow-up, the changes in the lipoprotein profile occurred as anticipated; one year data showed a greater lowering of LDL cholesterol with estrogen/progestin than with placebo and concomitantly a greater increase in HDL cholesterol. The anticipated but unwanted increase in triglyceride concentration with hormone therapy was also documented (Figure 1).

Nevertheless, at the end of the trial, there was no significant difference in the primary outcome of non-fatal myocardial infarction or coronary death. A post hoc analysis of time-trend was of concern in that hormone use in the first year was associated with a relative risk of 1.52 for coronary events; this risk was neutral by year two and hormone therapy appeared to demonstrate a beneficial trend in years 3-5. The researchers concluded that 4 years of this hormone regimen failed to decrease the overall risk of coronary heart disease. There was a tendency to an early increase in coronary events and a later decrease. The risk of venous thromboembolism tripled, and the risk of surgical biliary disease was increased by 40%. Nevertheless, this clinical trial did not address treatment with estrogen alone nor the effect of other estrogen/progestin regimens; further, women without heart disease were not studied. The recommendations deriving from HERS are: *a)* that this hormone regimen should not be initiated for the secondary prevention of coronary heart disease, and *b)* for women who have received such hormone treatment for several years, it may be appropriate to continue therapy for potential late benefit.

What about clinical trial data subsequent to HERS? A small randomized study PHASE (the Papworth Hormone-replacement therapy Survival Enquiry) in

the United Kingdom used transdermal hormone therapy compared with placebo in 255 menopausal women with coronary heart disease. The study was complicated by considerable therapeutic dropouts and drop-ins. At 4-year follow-up, a non-significant increase in cardiovascular risk, mostly early in the trial, and in venous thromboembolism was observed.[5]

Early warning data were of concern in predominantly healthy menopausal women in the U.S. Women´s Health Initiative (WHI). This large study included more than 160 000 such women aged 50 to 79 years and explored various aspects of menopausal health, mainly in an observational cohort. In a subgroup of about 27 000 women, the researchers analyzed in a randomized, placebo-controlled trial, the effect of hormone therapy (estrogen alone in women who had undergone hysterectomy or estrogen with progesterone in women with an intact uterus) compared with placebo. In 2000, the Data Safety and Monitoring Board recommended that the investigators write each of the 27 000 women in the randomized trial informing them of an unexpected early increase in cardiovascular events (myocardial infarction and stroke) in both hormone groups compared with placebo; this was an unanticipated occurrence and the information was not included in the informed consent documents. This involved fewer than 1% of the women and, because of the possibility of late benefit, the Data Safety and Monitoring Board recommended continuation of the study. These events occurred in addition to the anticipated increase in venous thromboembolism. Again in 2001, the women were notified, at the behest of the Data Safety and Monitoring Board, that the small increased cardiovascular risk persisted in the year 3-4 data; again trial continuation was recommended.[6]

The ERA (Estrogen Replacement and Atherosclerosis) study was an angiographic trial designed to investigate if hormone therapy (estrogen or estrogen plus progestin) was beneficial for the angiographic progression or regression of disease in women with documented coronary heart disease, as had been suggested by observational studies. An angiogram was performed at the initiation of the trial and at the end of an average of 3.1 years of follow-up. There were no differences in progression or regression of angiographic coronary heart disease. Once again, a hormone study was negative for benefit.

Two other intermediate outcome studies present contradictory data with regard to the benefit of hormone therapy on the progression of subclinical atherosclerosis. The German PHOREA (Postmenopausal HOrmone REplacement against Atherosclerosis) study analyzed the effect of estradiol combined with gestodene in women with an increased carotid artery intimal medial thickness by ultrasound examination. Although hormone treatment was associated with a significant decrease in LDL cholesterol, fibrinogen and FSH, there was no difference in the progression of subclinical atherosclerosis by carotid ultrasound at the conclusion of the study.[7] On the other hand, the United States EPAT (Estrogen in the Prevention of Atherosclerosis Trial) study focused on the role of estradiol in healthy menopausal women with an LDL concentration >130 mg/dL. When the LDL value was >160 mg/dL, lipid lowering treatment was given. Women were followed by serial carotid ultrasound examination. At the end of this study, and in contrast to the results of the European study, there was a decrease in the progression of subclinical carotid atherosclerosis, but only in the women who did not receive statin therapy. Once statins were given, hormone therapy provided no additional benefit.[8]

WEST (the Women´s Estrogen for Stroke Trial) investigated the role of 17-beta-estradiol in the prognosis of menopausal women (mean age, 71 years) who had a recent transient ischemic attack or ischemic stroke. Estrogen did not reduce the risk of death or non-fatal recurrent cerebrovascular accident, but increased the risk of fatal cerebrovascular accident and worsened the neurological signs and functional deficits that were a result of non-fatal stroke. The researchers concluded that estradiol is contraindicated for the secondary prevention of cerebrovascular disease.[9]

Figures 2a and 2b, prepared in the spring of 2002, summarize the recent menopausal hormone secondary and primary prevention clinical trials, respectively, and the benefits and risks obtained from each. Both clinical outcome and intermediate outcome trials are presented.

NEWLY REPORTED CLINICAL TRIALS: SUMMER OF 2002

HERS II (the Heart and Estrogen/progestin Study follow-up)[10] was an open label observational study that followed the majority of HERS participants for an additional 2.7 years, with women encouraged to remain on their original drug assignment. The question addressed was whether the trend toward a reduced risk of coronary events with hormone use in the later years of HERS would persist with additional follow-up. HERS II enrolled 93% of surviving HERS participants and about half of the women continued to adhere to their original study drug assignment. Nonetheless, with an average of 6.8 years of total follow-up, this estrogen/progestin regimen did not reduce the risk of cardiovascular events in women with established coronary heart disease. Even after adjustment for potential confounders, and other factors including statin use, there was no difference in outcome. Nor were outcomes altered when the analysis was performed

a) Secondary prevention (clinical results)

Study	Treatment	Observation	Benefit	Risk
HERS	CEE + MPA	CHD	–	±
PHASE	Transdermic E+P	CHD	–	±
WEST	17-β estriadol	Ictus	–	+

Intermediate results

Study	Treatment	Determination	Benefit
ERA	CEE CEE+MPA	Coronary angiography	–

b) Primary prevention (clinical results)

Study	Treatment	Observation	Benefit	Risk
WHI	CEE CEE+MPA	Cardiovascular	–	±

Intermediate results

Study	Treatment	Determination	Benefit
PHOREA	17-β estriadol	Carotid IMT	–
EPAT	17-β estriadol	Carotid IMT	+

(– with liporeducer therapy)

Fig. 2. Summary of the risks and benefits obtained in the principal clinical trials of secondary prevention *(a)* and primary prevention *(b)* that analyzed the effect of oral or transdermal hormone therapy on the incidence of cardiovascular disease and ictus.

on an «as treated» rather than the «intention-to-treat» basis. Given this null outcome, the concomitant risks deserve emphasis. There was a two-fold increase in the occurrence of venous thromboembolism, which predominated in the initial years; and a nearly 50% increase in the rate of gallbladder disease requiring surgery. Thus the investigators concluded that this estrogen/progestin regimen did not provide cardiovascular benefit for older women with established coronary heart disease and had the potential to cause harm.

The Women´s Health Initiative (WHI), on the advice of the Data Safety and Monitoring Board, terminated the estrogen/progestin therapy arm of the randomized hormone trial in July 2002, after an average follow-up of 5.2 years.[11] The therapy was terminated both because of an increased risk of invasive breast cancer that exceeded the preset trial stopping boundaries and because the global risk score showed an excess of

harm over benefit. These women will continue to be followed on an observational basis. The estrogen-only arm of the randomized trial is continuing.

Because the overall benefit to risk ratio of estrogen/progestin for predominantly healthy menopausal women is unfavorable on a population basis, it cannot be recommended for health promotion and disease prevention. However, it is important to emphasize that the majority of women in WHI did not experience any adverse events, i.e., the individual risk of harm is small. For example, treatment of 2000 such women for 5 years with this combined hormone regimen would result in an excess of 7 coronary events, 8 strokes, 8 cases of invasive breast cancer, and 8 cases of pulmonary embolism; in contrast, there would be 6 fewer cases of colorectal cancer and 5 fewer hip fractures. It is worthy of note that coronary events, stroke, breast cancer, and pulmonary emboli contributed equally to harm.

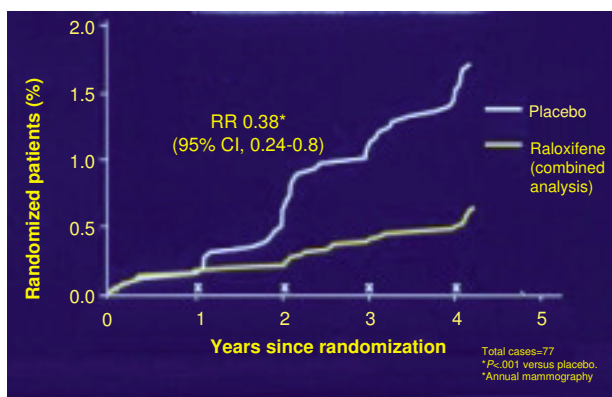| Intermediate study variables	Changes at 6 months followup
Decrease in total cholesterol	−6.6%*
Decrease in HDL-C	−10.9%*
Decrease in fibrinogen	−12.2%*
Decrease in Lp(a)	−4.1%
Absence of increase in triglycerides	−4.1%
Absence of effect on total HDL-C	+0.7%
PAI-1	−2.1%
HDL$_2$	+15.4%
	*P<.05 versus placebo

Fig. 3. The effect of treatment with raloxifene, an estrogen-receptor modulator, on the lipoprotein profile in post-menopausal women at 6-month follow-up. Note that in this case an increase in the concentration of triglycerides was not produced by the treatment, as occurred with classic hormone treatment, but it also did not have an effect on HDL concentrations (Taken from Walsh BW et al.[12])


Fig. 4. The effect of raloxifene on the incidence of invasive breast cancer in post-menopausal women after 4 years of treatment, according to the results of the MORE study. Contrary to previously published findings concerning classic hormone therapy, raloxifene not only did not increase the rate of breast cancer but drastically reduced it (Taken from Cauley JA et al.[13]).

Mention must be made of the group of women not included either in HERS or in WHI, and that is the group of highly symptomatic menopausal women. They would be unlikely to volunteer to participate, given the 50% likelihood of randomization to placebo. In these predominantly younger women, the symptomatic, quality of life, and potential other benefits of hormone therapy may well exceed harm – although this has not been proven in a rigid scientific evaluation.

POTENTIAL ALTERNATIVES TO «CLASSIC» MENOPAUSAL HORMONE THERAPY FOR CARDIOPROTECTION: SELECTIVE ESTROGEN RECEPTOR MODULATORS

Recent attention has focused on the selective estrogen receptor modulators, non-hormonal preparations that have estrogen antagonist effects in the breast and uterus and estrogen agonist effects on bone and on cardiovascular risk factors. Raloxifene, the only agent currently involved in large clinical trials, is licensed in the U.S. for the prevention and treatment of osteoporosis and may have favorable effects on the breast and the cardiovascular system. Its effect on the lipoprotein profile is summarized in Figure 3.[12] Available data show considerable clinical safety. Although the risk of venous thromboembolism is similar to that associated with menopausal hormone therapy, raloxifene does not result in endometrial stimulation as measured by transvaginal ultrasound or endometrial biopsy and is not associated with vaginal bleeding. It is not associated with increased breast pain or tenderness and does not increase the risk of breast cancer. The major symptomatic side-effect is the occurence of hot flashes and leg cramps, that did not differ in the intervention and placebo groups.

The MORE (Multiple Outcomes of Raloxifene Eva-

luation) trial randomized osteoporotic women at risk for fracture, but not selected for risk for either breast cancer or coronary heart disease. Analysis of the trial data showed a reduction in invasive breast cancer in the raloxifene compared with the placebo group; the magnitude of potential benefit was such that the U.S. National Institutes of Health has undertaken a comparative study of raloxifene and tamoxifen for the prevention of breast cancer in women at increased risk for breast cancer. Figure 4 shows the reduction in the incidence of invasive breast cancer associated with the use of raloxifene among women who received this drug during 4 years of follow-up.[13]

Given these encouraging features, we decided to undertake the RUTH (Raloxifene Use for The Heart) study, which randomized more than 10 000 menopausal women in 26 countries, with the aim of evaluating the effect of raloxifene on the heart. The principal study outcomes are the combined endpoint of death due to coronary heart disease, non-fatal myocardial infarction, and hospitalization for acute coronary syndromes; and a co-primary endpoint of invasive breast cancer. RUTH was designed to enroll women both with documented coronary heart disease and those at increased risk for coronary events. The RUTH enrolment scoring system assigned a specific number to the existence of prior coronary events and certain coronary risk factors.[14] The score increased as the risk increased; thus, for example, having had a previous myocardial infarction conferred 4 points, while having diabetes was equal to 3 points. Other coronary risk factors addressed were age, smoking, hypertension, hyperlipidemia, etc. Women had to have a minimum rating of 4 points to be included in RUTH. The baseline characteristics of RUTH participants are described in a manuscript in press.[15]

Fig. 5. The incidence of cardiovascular events during follow-up of post-menopausal patients randomized to receive raloxifene or placebo, according to the results from the MORE study. When the subgroup of women without cardiovascular risk factors (chart on the left) is considered, no protective treatment effect is seen. On the other hand, among patients with cardiovascular risk factors (chart on the right), treatment with raloxifene was seen to significantly reduce the rate of cardiovascular events during the follow-up period (Taken from Barrett-Connor E et al.[16]).
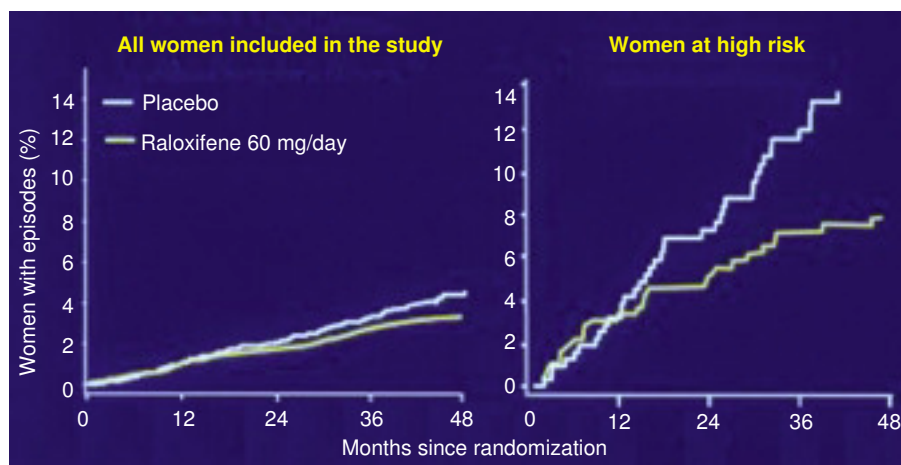
The scoring system used in RUTH was applied to analyze the osteoporotic women in the MORE study, to retrospectively identify those at increased risk of coronary events. Women at increased cardiovascular risk benefited significantly from raloxifene treatment with regard to the percentage of cardiovascular events that occurred during follow-up (Figure 5), which was not observed when the entire study population was analysed.[16] Significantly, there was no early increase in cardiovascular events in increased cardiovascular risk MORE women treated with raloxifene.

RECOMMENDATONS CONCERNING MENOPAUSAL HORMONE THERAPY FOR THE PREVENTION OF CARDIOVASCULAR DISEASE

The 2001 recommendations of the American Heart Association (AHA)[17] with regard to menopausal hormone therapy reflect the results obtained from recent clinical trials. Although prior coronary disease clinical practice guidelines of American College of Cardiology and the American Heart Association recommended hormone therapy as the preferred lipid reduction treatment for menopausal women with coronary heart disease, and these recommendations were also made by the National Cholesterol Education Program Adult Treatment Panel II (NCEP II), current guidelines advise administration of statins, which have been shown to provide a clear outcome advantage in clinical trials in women, without the risks association with hormone therapy. Current AHA recommendations are that initiation of hormone therapy is not indicated for the secondary prevention of coronary heart disease. In the 2001 AHA Scientific Advisory,in women with cardiovascular disease who had received hormone treatment for a prolonged period, the decision about whether to continue or interrupt therapy should be based on the established non-coronary benefits and risks of hormone therapy and patient preference. On the other hand, if a woman is hospitalized for an acute coronary event or other illness or surgery associated with immobilization while receiving hormone therapy, the risk of venous thromboembolism warrants interruption of treatment or venous thromboembolism prophylaxis is recommended.[17]

AHA clinical recommendations for use of hormone therapy for the primary prevention of coronary heart disease will derive from the results of clinical trials that are currently in progress. At present, there is insufficient evidence to recommend hormone therapy solely for the primary prevention of coronary heart disease; initiation and continuation of hormone therapy should be based, in healthy women, on the established non-coronary risks and benefits, on possible non-coronary risks and benefits, and on individual patient preference.

2002 AHA recommendations will be forthcoming. A recent U.S. National Institutes of Health publication[18] presents a comprehensive evidence-based review of women´s health and menopause.

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