

How *HRT* Hurts the Heart

Coronary artery disease (CAD) is a killer and recent studies have come up with evidence that HRT might have a role in increasing CAD among women. Why?

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For many years, specialists have recommended hormone replacement therapy (HRT) as an appropriate adjunct in managing the postmenopausal woman concerned about reducing the risk for cardiac disease. The recent turnaround in general medical opinion has left all of us a little perplexed as we now try to understand how we could possibly have been so misleading to our patients.

The connection between CAD and HRT

Coronary artery disease (CAD) remains the leading cause of death among women in this country. While premenopausal women are relatively protected from cardiac events, there is an exponential rise in cardiovascular events after menopause. Coupled with this observation is the basic scientific support for the potential role of hormones in providing vascular protection. Indeed, we have animal studies from the 50's showing that exogenous estrogen can inhibit coronary atherosclerosis although this effect may be modified by the addition of specific progestins. While exogenous hormones affect lipoprotein levels in a seemingly advantageous manner, studies in monkeys also show that estrogens favourably modulate, on an acute basis, the vasomotor response of atherosclerotic arteries, suggesting a direct vascular effect. In human subjects infusion of physiologic doses

of 17 β -estradiol in women with CAD increases acetylcholine induced coronary blood flow, suggesting normalization of endothelial function. Studies are available demonstrating significant increase in exercise duration in patients with CAD following the application of transdermal estradiol. Finally, apart from lowering low density lipoprotein (LDL), lipoprotein(a), and increasing high density lipoprotein (HDL) cholesterol, there is data suggesting that exogenous estrogens reduce circulating levels of fibrinogen and plasminogen activator inhibitor 1 (PAI 1) thereby promoting antithrombotic and pro-fibrinolytic effects.

The medical profession's enthusiasm for HRT, gradually fuelled by inferences from studies—similar to those summarized above seemed to be justified by observational studies, the largest and perhaps most influential one being the Nurses' Health Study (NHS).

What does the NHS tell us?

In that study over 120,000 registered nurses aged 30 to 55 were followed for two years. They were sent questionnaires to get updated information on hormone use and other factors. Some 70,000 participants free of cardiac problems at recruitment sustained 1,131 cardiac events in this cohort. Analysis suggested that there was a substantial reduction in events in current hormone users as compared to those who had never taken hormones

Frequently Asked Questions: **HRT and Coronary Artery Disease**

Questions

What have the results of the recent studies demonstrated?

In which specific cases should HRT be used?

What should now be used as a secondary prevention of CAD in menopausal and post-menopausal women?

Answers

The Women's Health Initiative study confirms the adverse effects of combined HRT if used for the primary prevention of CAD, at a cost of the following per 10,000 healthy post-menopausal women on combination therapy for one year:

- 7 additional CV events
- 8 more strokes
- 8 more pulmonary emboli
- 8 more invasive breast cancers

HRT should only be recommended for intractable post menopausal symptoms and even then, for the shortest duration.

HERS and ERA trials have raised concern about use of HRT in secondary prevention of CAD. The emphasis should now be on the use of proven therapies for hypertension, hyperlipidemias, hyperglycemia, and obesity as indicated.

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with a relative risk ratio of 0.6. These benefits seemed to hold regardless of the dose of oral conjugated estrogens, or whether there was co-administration of progestogens. This often quoted observational study has been the impetus for HRT recommendation and likely contributed significantly to the increased use of HRT in North America.

Significantly however, further analysis has indicated that there were, within this large cohort of patients nearly, 2,500 post-menopausal women

To read more on HRT and CAD:

1. Hormone Replacement Therapy and the Pathophysiology of Cardiovascular Disease: A Symposium (Editors: Karas, RH and Mosca, L)
2. Risk and Benefits of Hormone Replacement Therapy: The evidence speaks. CMAJ. 2003 Apr 15;168(8):1001-10.

with previous CAD. In this group of women, those who used hormones under 12 months multivariate analysis showed an increase of 25% in vascular events when compared to those women who never used hormones. It was only after two years that this group of hormone users, began to show a benefit.

What did early HRT enthusiasts have to say?

Between 1980 and 1992, the enthusiasm for HRT by the health-care profession led to a tripling in the use of HRT by post-menopausal women in the U.S., from 16% to 44%. Lending further credence to this practice were “surrogate end point” studies including the Estrogen in the prevention of Atherosclerosis Trial (EPAT). The subjects were healthy post-menopausal women free of overt coronary disease with an average age of 61. Carotid ultrasounds were done at baseline and six per month thereafter. After two years, the group treated with 17 β -estradiol showed a significant decrease in progression of carotid intimal thickening compared to the placebo treated group.

Why is HRT suddenly risky?

Not all studies were supportive of HRT. Heart and Estrogen/Progesterone Replacement Study (HERS) and Estrogen Replacement and Atherosclerosis trial (ERA) are two studies that gave seemingly contrary results. In HERS, 4.1 years of steady conjugated equine estrogen (CEE) and medroxyprogesterone acetate were administered to 2,763 post-menopausal women with established CAD. At the end of the first year, there was a 52% increase in cardiac events in the treated group. However, by the fourth year there was a 33% decline in events in this group, suggesting that benefits would accrue but only after time.

In ERA 309 post-menopausal women with CAD received CEE combined with progestogen placebo. No effect seemed evident after three years by serial quantitative angiography. Both these studies contributed to the tampering of earlier enthusiasm for HRT in secondary prevention of CAD.

What did the WHI discover?

The most definitive study we have to date regarding the value of HRT in primary prevention that has conclusively addressed our concerns is the now much publicized Women’s Health Initiative (WHI) study. This study is a randomized primary prevention trial of post-menopausal hormones in over 16,000 women. The data safety monitoring board suggested



Table 1

HRT Studies

Study Name	NHI	HERS	ERA	WHI
Size	≥120,000	2,763	309	160,000
Patients	30-55 years 70, 000 free of cardiac problems	post-menopausal women with CAD	post-menopausal women with CAD	randomized, post-menopausal women
Duration	2 years followup since 1976	4.1 years	3 years	5.2 years
End points	Analysis suggested that there was a substantial reduction in events in current hormone users compared to those who had never taken hormones.	By the fourth year there was a 33% decline in events after a 52% increase in the first year.	No effect seemed evident after 3 years by serial quantitative angiography.	The active treatment group had a greater risk of breast cancer, as well as increased coronary events, stroke and pulmonary embolism.
Comments	This often quoted observational study has been the driving impetus for HRT and likely contributed to the increased use of HRT in North America	This suggested that the benefits would accrue, but only after time.	Both this study and HERS contributed to the tampering of earlier enthusiasm for HRT.	The study comparing estrogen/progestin combination was terminated early because the group met prespecified levels of increased risk.

- **CAD** Coronary Artery Disease
- **ERA** Estrogen Replacement and Atherosclerosis Trial
- **HERS** Heart and Estrogen/Progesterone Replacement Study
- **HRT** Hormone Replacement Therapy
- **NHS** Nurses' Health Study
- **WHI** Women's Health Initiative

early termination of the arm (over three years sooner than planned) comparing estrogen/progestin combination with placebo at 5.2 years, because the active treatment group met prespecified levels of increased harm. Specifically, the active treatment group had a greater risk of invasive breast cancer with a hazard ratio of 1.26, as well as increased coronary events, stroke, and pulmonary embolism. Of note, however, there were some benefits, including an over 30% decrease in hip fractures and colorectal cancer. Most adverse outcomes began to appear within the first two years, although the increased risk of breast cancer only became apparent in the third year. The portion of the trial comparing estrogen alone to placebo in patients who have had hysterectomies still continues.

Meanwhile as analysis of the data proceeds, we continue to be inundated with additional disturbing reports suggesting higher risk of strokes as well as risk of dementia in the treated sector. The question of genetic predisposition to thrombotic complications of atherosclerosis upon exposure to HRT will prove of interest to researchers in the field of pharmacogenetics.

Where do we go from here?


To be objective, the WHI study has demonstrated that a specific dose of estrogen combined with a specific dose of progestin in women without prior documented CAD over one year will result in seven more cardiac events, eight more strokes, eight more invasive breast cancers, eight more pulmonary emboli, but five fewer hip fractures and six fewer colorectal cancers. Over five years, this works out at one woman in a hundred succumbing as a result of excess events. This number is a significant number in the context of millions of women who have relied on this therapy worldwide.

Based on this study, we can only recommend the use of this combination of HRT for intractable

Take-home message

- Women already on HRT for more than two years run the increased risk of breast cancer.
- HRT is only recommended for intractable post-menopausal symptoms and even then for the shortest duration.
- Other treatment to consider are soy products, clonidine and topical vaginal estrogens.

post-menopausal symptoms and even then for the shortest duration.

For women already on HRT for more than two years, the increased risk of breast cancer at this stage is an issue that looms increasingly. For women who have had a hysterectomy and are on estrogens alone, the WHI study has no conclusive suggestions, at the time of going to print. These women continue to participate in the trial. Women with severe post-menopausal symptoms unable to discontinue the treatment should have the benefit of having the increased risk put into proper perspective while other measures like soy products, clonidine and topical vaginal estrogen preparations for premenstrual syndrome symptomatology should be considered. 

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