**ESTROGEN, PART I: HEART DISEASE AND THE WOMEN'S HEALTH INITIATIVE (08/2007)**

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**Bottom Line at the Top:** The 2002 Women's Health Initiative study of post-menopausal hormone therapy panicked 1000's of doctors and millions of women into discontinuing hormones. Problem is, the conclusions ONLY apply to healthy white women, an average of 15 years into their menopause, who are willing to be randomly assigned to take Premarin with Provera or not.

In 2002, the Women's Health Initiative (WHI) proved that reams of scientific evidence can be tossed into irrelevancy by one study. Until 2002, most data pointed to the conclusion that hormone replacement therapy (HRT), or at least estrogen, reduces risk for heart disease. Then the New England Journal of Medicine published the WHI, evaluating the health effects of the hormones Premarin and Provera in 16,608 post-menopausal women. The safety monitoring board stopped the trial early, after women took their study pill an average of 5.2 years. They had noticed higher rates per year of breast cancer (8 more cancers per 10,000 women) and heart attack (7 more events per 10,000 women).

U.S. women suffered a collective hot flash, as doctors rushed to stop HRT, to prevent heart attacks and law suits. Some doctors were kind enough to have women taper off their hormones, to make the hot flashes less devastating. HRT prescriptions plummeted from 22.8 million in 2001 to 12.7 million in 2003. Standard dose Premarin use dropped 80%, while other hormone formulations declined at a lower rate and low dose Premarin use slightly increased.

The lynch mob that followed WHI proclaimed that estrogen increases cardiovascular disease, clots, dementia, and breast cancer with no net clinical benefits. If the mob were politicians, I'd understand. But these people were doctors and scientists who should have known that a study of Premarin and Provera in mostly white women 15 years after menopause applies only to those drugs (not all hormones) and those women.

Postmenopausal women lack the hormones estrogen and progesterone. Losing these sex hormones leads to hot flashes and genital and breast atrophy. Because heart, blood vessels, joints, bone, brain, liver also have estrogen receptors, women lose estrogen's effect on those organs also. We know much less about those consequences.

**WHI cardiovascular disease study results**
16,608 women with an intact uterus, aged 50 – 79
Received Premarin/Provera or placebo daily for an average of 5.2 yr

Relative risk* starting with conditions made worse by HRT, and ending with conditions it seems to prevent

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| pulmonary embolism | 2.13 |
| stroke | 1.41 |
| heart disease | 1.29 |
| breast cancer | 1.26 |
| overall death rate | 1.00 |
| uterine cancer | 0.83 |
| hip fracture | 0.66 |
| colon cancer | 0.63 |

* A relative risk of 2 = twice the rate, 1 = the same, and a number less than one is a low risk (0.5 would be half the risk), compared to placebo.

(JAMA 2002;288:321)

To make the life of hot flashes less miserable and to prevent osteoporosis, doctors prescribe HRT. In women without a uterus, HRT equals estrogen in one form or another. If a woman has not had a hysterectomy, we add progesterone to prevent estrogen-induced uterine cancer.

For years we also thought that HRT prevented heart disease, because pre-menopausal women suffer fewer heart attacks than do men of similar ages. After

menopause, women catch up, making heart disease the primary cause of death in women.

Animal experiments in the 1950's demonstrated that estrogen administered to animals on a high-fat diet prevented coronary heart disease. Retrospective, case-control studies in women supported the cardio-protective effect of estrogen. A variety of observational studies, with various types of subjects, hormones, parameters and end-points, were all mostly positive.

Even though numerous observational studies of estrogen showed reduced risk of heart disease, the significance of the association was questioned. Women who took estrogen were more likely to be lean and practice healthful behavior. A randomized trial had to be done for proof, as is necessary for any medication.

**To whom do the WHI results apply?** Every study involves a group of subjects and an intervention, and the **results apply only to similar people undergoing taking the same medication.** To understand the implications of WHI, we must know its specifics.

From 373,092 women contacted, the WHI study group recruited 27,347 (16,608 with uteri and 10,739 who had had a hysterectomy) healthy women, 50 to 79 years of age (average 63.3) from 40 U.S. clinical centers. The women who were screened but did not participate were either disinterested in participating, unwilling to sign a consent, deemed unreliable for medication adherence (dementia or substance abuse), likely to move out of the area in 3 years or saddled with a current or history of disease that might recur in 3 years.

Less than 10% of the women contacted made up the study group of 27,347. **That means that 345,745 women, representing a huge segment of the female population, were excluded or chose not to participate for whatever reason.**

WHI included mostly white (83%), healthy women, an average of 15 years into their menopause, who were willing let someone randomly decide whether or not they took hormones. It does not apply to women who knew that they would hate their sleepless, sweating lives if they went off hormones and on placebo. WHI studied illness only in people with no life-threatening illness. Those who are black, Hispanic, drunk or forgetful can forget thinking the results apply to them.

**About which drugs can we draw conclusions? Only Premarin and Provera.** Calling Premarin and Provera 'estrogen' and 'progesterone,' as most authors do so loosely, ignores the fact that neither is equivalent to normal human hormones. This misleading simplification is unconscionable. **Premarin (CEE) is a mixture of 6 conjugated estrogens from horses, only two of which are native to humans.** Their estrogenic activity varies, with some being more active and others less. Their effect on the liver and blood vessels are for the most part unknown. Provera, or medroxyprogesterone acetate (MPA), is a derivative of human progesterone, with weaker progesterone and more androgenic (male hormone) activity.

Estrogens and progestins other than Premarin and Provera are available, including the 'natural' hormone, 17β-estradiol. 'Natural' progesterone must be taken in a large dose of a micronized form (200 mg) because of poor absorption. Synthetic hormones are used primarily in oral contraceptives.

No existing HRT (including 'bioequivalent' hormones) perfectly mimics normal human hormone physiology. Most women take hormones orally, while natural estrogen is released directly into the circulation. After absorption by the gut, *any* estrogen taken by mouth must pass through the liver, at levels 4-5 times that of normally circulating hormones. Those high levels stimulate the liver's production of proteins involved in clotting, blood pressure (renin substrate) and cholesterol (apolipoproteins).

A skin patch slowly delivers estrogen through the skin into the blood. This transdermal estrogen bypasses the liver activating, it far less. Both Premarin and 17β-estradiol come in patch form. No one has studied the long-term cardiac or health outcomes of any transdermal estrogen.

In spite of these differences, authors and doctors lump all types of hormonal treatments under the moniker HRT. They persist in drawing conclusions for all estrogens and progestins based on data with Premarin and Provera. This condemns all hormone replacement by association and is scientifically irresponsible. As we have found with innumerable other medications, drugs of a similar type often differ in their activity and side effects. HRT is no different.

**How can we reconcile WHI results with past studies?** More than 40 studies over three decades, with several hundred thousand woman-years of follow-up, pointed to beneficial effects of HRT for preventing heart disease. Those studies suggested that estrogen, usually Premarin, reduced coronary disease by 35-50%. Most were observational studies, not placebo-controlled, randomized, blinded or prospective trials, but they most agreed that estrogen confers at least some benefit.

The key to the difference between WHI outcomes and that of past studies might partly lie in timing. **Blood vessels lose their estrogen receptors with old age or disease.** Early in menopause, if a woman does not already have vascular disease, estrogen may work the magic that keeps pre-menopausal women from having so many heart attacks. Later on, when estrogen can't bind to blood vessels because the receptors are gone, it's impotent.

In monkeys, estrogen delays artery clogging if given early, but not late in menopause. The Estrogen in the Prevention of Atherosclerosis Trial (EPAT) of women treated with 17β-estradiol showed the same thing: In the first year angiograms showed no extra clot and there was a normal risk of heart attacks.

A younger woman who smokes or has diabetes might have damaged her blood vessels sufficiently that estrogen receptors disappear even before menopause, so estrogen won't have an effect. Similarly, once atherosclerosis diseases blood vessels to the point that estrogen receptors are obliterated, it's useless to try to reverse that disease with estrogen.

Even WHI investigators draw different conclusions when considering only women soon after menopause. After sending women into hot flash devastation, they published data in June 2007 of the effect of Premarin on 1064 younger women, 50-59 years of age and starting Premarin early in their menopause. They measured the level of calcium build-up in arteries, which is somewhat proportional to coronary disease. Those who had taken estrogen were 30 to 40 percent less likely to have measurable levels of coronary artery calcium compared to those on placebo.

We think we know one thing for sure: **In women who already have heart disease, long (15-23 years) after onset of menopause, Prempro does not 'fix' their heart problem.** This was proved convincingly by three large studies. In the Heart and Estrogen/Progestin Replacement Study (HERS), the heart attack and death rates did not budge in 2763 female cardiac patients taking Prempro for an average of 4 years. Two other studies used angiograms before and after three years of HRT (Premarin or Prempro in one and 17β-estradiol ± micronized progesterone in the other) to show that narrowed coronary arteries were no different with or without hormones.

HERS found that hormones escalated heart attack risk in the first year after starting HRT. Oral estrogen does make some women more susceptible to clotting, so HRT probably tipped the balance towards clot in those women most at risk.

After 5 years, the cardiac event rate matched that of placebo, with no further benefit or harm. Throughout the whole time period, the overall death rate was the same on or off hormones.

In the middle 3-5 years, HRT reduced risk, possibly because these women were not as susceptible to the clotting effects of HRT, and able to experience the benefits of estrogens. Estrogen dilates non-diseased coronary artery walls, so they can carry more blood. Estrogen raises the good HDL-cholesterol and reduces bad LDL-cholesterol, while Provera raises LDL-cholesterol. Estrogen reduces some aspects of inflammation and clotting, but increases others.

The recommendations that followed these studies advised against starting or continuing HRT long after the onset of menopause for the purpose of preventing heart disease. That conclusion does not cover all scenarios, however. It does not apply to women early in menopause, women with exceptional risk for osteoporosis (which estrogen guards against), women with severe hot flashes or black women. More than 80% of the subjects in two of those studies were Caucasian and the third studied mostly Hispanics.

Many doctors have switched their patients to 'natural' hormones, assuming their safety and beneficence. These assumptions are premature, since 'natural' hormones given orally might activate the liver and induce clotting similarly to Premarin. Perhaps the delivery route (pill vs patch vs cream) is more important than the type. 'Natural' hormones need their own studies to determine their worth and dnagers. It's going to be hard to address all different variables,

when such studies take years, thousands of women and millions of dollars.

In the meantime women and their doctors must make decisions based on limited data, involving a flawed combination of Premarin and Provera.