NEW HOT PAPERS - 2008

November 2008

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JoAnn Manson talks with *ScienceWatch.com* and answers a few questions about this month's New Hot Paper in the field of Clinical Medicine.

Article Title: Estrogen therapy and coronary-artery calcification
Authors: Manson, JE, et al.
Journal: N ENGL J MED
Volume: 356
Issue: 25
Page: 2591-2602
Year: JUN 21 2007
* Harvard Univ, Sch Med, Brigham & Womens Hosp, Div Prevent Med, 900 Commonwealth Ave E,3rd Fl, Boston, MA 02215 USA.
(addresses have been truncated)

SW: Why do you think your paper is highly cited?

There's enormous interest in the role of estrogen in the development of coronary heart disease (CHD) and in understanding the basis for the glaring discrepancies between observational studies and randomized trials of estrogen and CHD. An emerging body of evidence supports the theory that age or time since menopause influence the relationship between menopausal estrogen therapy and CHD outcomes.

The results suggest that estrogen may have a beneficial effect on the heart if started in early menopause, when a woman's arteries and endothelium are still likely to be relatively healthy, but a harmful effect if started in late menopause, when advanced atherosclerosis and unstable plaques may be present. The Women's Health Initiative Coronary Artery Calcium Study (WHI-CACS) was designed to assess subclinical coronary disease among younger women in the WHI trial, to see if estrogen treatment was associated with a reduced burden of calcified plaque in the coronary arteries at the completion of the randomized trial.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

The study describes a new discovery that estrogen treatment was associated with lower levels of subclinical coronary artery disease (coronary artery calcium by noninvasive CT imaging) in women aged 50-59 in the WHI estrogen-alone trial. The key findings are summarized in the table below. Higher levels of coronary artery calcium are a strong marker for future risk of cardiovascular events and younger women treated with estrogen were less likely to have severe calcification. To our knowledge, the study is the first to assess the association between estrogen and coronary artery calcification in a clinical trial setting.

Table: Extent of Coronary Artery Calcium in Women Randomized to Conjugated Equine Estrogens (CEE) vs Placebo in the WHI CEE Trial.

Coronary Artery Calcium Score	Intention-to-Treat Analyses	Analyses Restricted to Adherent Participants*

<10 (ref)	1.00 (ref)	1.00 (ref)
10-100	0.82 (0.57-1.18)	0.67 (0.44-1.02)
>100-300	0.72 (0.44-1.17)	0.43 (0.23-0.80)
>300	0.58 (0.35-0.95)†	0.39 (0.21-0.73)‡

- Participants adherent to ≥80% of study pills for at least 5 years.*
- † p-value=0.03
- ‡ p-value=0.004

Data from Manson JE, *et al. NEJM,* 2007

SW: Would you summarize the significance of your paper in layman's terms?

The results suggest that estrogen may slow plaque build-up in the coronary arteries and have a beneficial effect on the heart if started in early menopause, when a woman's arteries are likely to be relatively healthy. However, we know from the WHI and other studies that hormone therapy can have a harmful effect on the heart (including plaque rupture) if started in late menopause, when advanced stages of atherosclerosis may be present.

The implication of the "timing hypothesis" is not that recently menopausal women should be given estrogen for CHD prevention but rather that younger women can be reassured about cardiac risks when considering short-term use of estrogen therapy for relief of hot flashes, night sweats, and other menopausal symptoms. The reduction in menopausal symptoms must be weighed against other risks and benefits of treatment, but heart disease is typically not a major factor in the equation for women who are recently menopausal.

SW: How did you become involved in this research, and were there any problems along the way?

I'm one of the Principal Investigators of the Women's Health Initiative and have been involved in this large-scale randomized trial since 1993. I'm also one of the lead investigators on the Nurses' Health Study, a large observational study that has been assessing the benefits and risk of hormone therapy for more than 20 years.

"An emerging body of evidence supports the theory that age or time since menopause influence the relationship between menopausal estrogen therapy and CHD outcomes."

The Nurses' Health Study and several other observational studies had suggested a 40-50% lower risk of CHD among women who were current users of hormone therapy compared with nonusers, with nearly 80% of hormone therapy users initiating treatment within 2-3 years of menopause onset (as compared with an average of >12 years past menopause in the clinical trials).

After the initial reports from the WHI estrogen + progestin trial, as well as the estrogen-alone trial (age range of participants 50-79 yrs, mean age 63), we took a closer look at the data, focusing on the timing of initiation of hormone therapy. Not only were absolute rates of adverse outcomes attributable to estrogen considerably lower in younger than in older women, but the hazard ratios also appeared more favorable in recently menopausal women than in those distant from menopause onset. (Related information: 1¦2)

SW: Where do you see your research leading in the future?

We're interested in assessing the role of other clinical characteristics, as well as the role of genetic factors and other biomarkers, in predicting which women will have favorable outcomes on hormone therapy and which women should avoid treatment. Such findings will help women and their clinicians make more informed decisions about the use of hormone therapy.

For example, another factor that appeared to influence coronary outcomes on hormone therapy in the WHI was the participant's lipid profile at baseline. In a recently published analysis, women with an LDL/HDL cholesterol ratio <2.5 had more favorable CHD outcomes on hormone therapy than women with a ratio >2.5 (odds ratio 0.60 [95% CI, 0.34-1.06] vs. 1.73 [1.18-2.53], respectively, p for interaction = 0.02).

We're also interested in evaluating the role of different formulations of hormones, dosages, and routes of administration (such as transdermal vs oral) in relation to health outcomes and quality of life.

SW: Do you foresee any social or political implications for your research?

We hope that our findings will help to inform decision-making about the use of hormone therapy and help

women and their clinicians make more informed choices. However, it's important to emphasize that the implication of the "timing hypothesis" is not that recently menopausal women should be given estrogen for CHD prevention (or other chronic disease prevention) but rather that it may be possible to reassure younger women about cardiac risks when considering short-term use of estrogen therapy for relief of menopausal symptoms (such as moderate-to-severe hot flashes and night sweats that can interrupt sleep and impair quality of life).

The reduction in menopausal symptoms must be weighed against other risks and benefits of treatment, but younger women tend to have lower absolute rates of adverse events on hormone therapy than older women more distant from menopause onset.

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•>See also a Fast Breaking Paper comment by JoAnn Manson from June 2004.

Keywords: estrogen, coronary heart disease, menopause, menopausal estrogen therapy, early menopause, arteries and endothelium, late menopause, advanced atherosclerosis, unstable plaques, women's health initiative coronary artery calcium study, calcified plaque, coronary arteries, coronary artery calcium, relief of hot flashes, night sweats, menopausal symptoms, nurses' health study.

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