

NEWS Commentary

The following news items are reviews of important scientific articles with commentary that address clinical relevance. This material comes from the First to Know® program of The North American Menopause Society (NAMS), offered to its members via broadcast e-mail. You can receive the complete program by joining the Society (www.menopause.org). Please note that the opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS.

Lower incidence of diabetes seen among hormone therapy users in Women's Health Initiative

Margolis KL, Bonds DE, Rodabough RJ, et al, for the Women's Health Initiative Investigators. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: Results from the Women's Health Initiative Hormone Trial. *Diabetologia* 2004; 47:1175-87.

Combined estrogen plus progestogen therapy (EPT) may reduce the incidence of diabetes mellitus (DM), possibly by mediating a decrease in insulin resistance, according to data from the Women's Health Initiative (WHI), a randomized, double-blind, placebo-controlled clinical trial. A total of 15,641 postmenopausal women aged 50 to 79 were assigned to either placebo or continuous-combined EPT consisting of 0.625 mg/day conjugated equine estrogens plus 2.5 mg/day medroxyprogesterone acetate (Prempro). For this study, the investigators determined the incidence of DM based on self-reports of treatment with insulin or oral DM medications. Fasting glucose, insulin, and lipoproteins were measured at 1 and 3 years.

After 5.6 years of follow-up, the cumulative incidence of treated DM was 3.5% in the hormone therapy (HT) group and 4.2% in the placebo group (hazard ratio, 0.79; 95% CI, 0.67-0.93; $P = 0.004$). When the results were adjusted for changes in body mass index and waist circumference, there were no significant changes in the hazard ratios. Investigators also found significant 1-year decreases among EPT users when compared with placebo recipients in levels of fasting glucose and fasting insulin resulting in decreased insulin resistance. The authors conclude that these results indicate that EPT reduces the incidence of DM, possibly through a decrease in insulin resistance.

Comment. This WHI publication reports that HT, when compared with placebo, reduces the incidence of DM by 15 cases per 10,000 women per year. Fasting glucose and insulin were decreased in HT users compared with placebo, suggesting improved insulin resistance. Although others have reported similar results, it is unlikely that HT will be prescribed to prevent DM, given the greater risk than benefit of this regimen for other outcomes, as previously reported in other WHI articles.

To study new incidence of DM, the authors correctly excluded all women (6%) who had self-reported DM at baseline. About half of U.S. adults with DM have not been diagnosed, and this 6% is half the expected 12% prevalence (based on glucose tolerance testing) among older overweight women in the U.S. (In the WHI, women had an average age of 63 years and an average body mass index of 28.) Thus, it is not clear that the reduced risk occurred in women without DM at baseline.

Fasting glucose was reduced in the WHI, as it was in the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial. However, 2-hour glucose levels, which were elevated by hormone treatment in PEPI, were not measured in the

WHI. Many studies have shown that this postchallenge glucose test is a stronger risk indicator for cardiovascular disease than fasting hyperglycemia. Could this elevated postchallenge glucose have played a role in the unexpected excess of cardiovascular disease observed with HT in healthy women in WHI, and with HT in women with documented coronary heart disease in the Heart and Estrogen/progestin Replacement Study (HERS)? If nonoral estrogen reduces both fasting and postchallenge glucose, it might be preferred for women with and without DM, but studies with clinical outcomes are needed.

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Comment. In this secondary analysis from the WHI, postmenopausal women randomized to EPT had a lower incidence of treated DM (as identified by self-report) than women assigned to placebo (21% relative risk reduction over 3 years). At 1 year, a comparison of changes from baseline in estimated insulin resistance (HOMA model) among a subgroup of the women indicated a significant reduction in this measure in the combined HT group as compared with the placebo group, although the groups were not significantly different at 3 years.

Type 2 DM is associated with substantial morbidity and mortality, particularly from cardiovascular disease. Thus, effective approaches to prevent the development of DM would have substantial benefits. Although this report by Margolis et al raises the intriguing possibility that combined EPT might reduce the risk of DM, these findings, as the authors

acknowledge, cannot be used as justification to prescribe this therapy, given the associated hazards previously reported in the WHI.

While the availability of glucose and insulin levels in only a subset of women limits conclusions regarding mechanisms whereby EPT may reduce DM risk, these findings should encourage further mechanistic investigations, with the goals of developing newer agents that may confer similar benefit without the risks. At the same time, clinicians should bear in mind other established means of reducing the risk for DM. In the Diabetes Prevention Program [Knowler, *N Engl J Med* 2002] the use of metformin reduced type 2 DM risk by 31%, and a diet-plus-exercise program reduced it even more substantially (by 58%) over approximately 3 years of follow-up in high-risk individuals. People at risk for DM should be counseled to make lifestyle changes that can reduce this risk far more, and more safely, than might EPT.

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Comment. Results from observational studies, [Manson, *Ann Epidemiol* 1992] from HERS, [Kanaya, *Ann Intern Med* 2003] and now the WHI strongly indicate that EPT reduces the incidence of DM in postmenopausal women. It is noteworthy that both HERS and WHI results were with continuous-combined estrogen with progestin, as the latter is often viewed as antagonistic to the bene-

ficial effects of estrogen on carbohydrate metabolism. Growing evidence indicates that reducing insulin resistance in women can prevent the onset of DM [Buchanan, *Diabetes* 2002] and that improvement in insulin resistance can reduce the progression of atherosclerosis [Xiang, *Diabetes* 2002].

Diabetes is a much more devastating disease in women than in men, and it is more likely to occur in women. The risk for DM (3,000 in 10,000) is comparable to or greater than that of other chronic diseases in women, such as hip fracture, coronary heart disease, and breast cancer. Because DM is a rapidly growing disease associated with extensive health-care costs as well as significant morbidity and mortality (cardiovascular disease is the primary cause of diabetic deaths), the health and economic benefits from reducing the incidence of DM should have a highly significant beneficial impact on women's health. The WHI data translate into an approximate reduction with EPT of 600 new cases of DM per 10,000 women aged 50 years and older. It is clear that EPT can reduce the incidence of DM to the same degree as medications used in the prevention of cardiovascular disease [Pepine, *J Am Coll Cardiol* 2004]. Physicians should consider the reduction of DM and the resulting health and economic implications when prescribing long-term HT, especially in women with characteristics associated with an increased risk for new-onset DM—Hispanic or African-American ethnicity, increased age, elevated systolic blood pressure, history of antihypertensive medication use, elevated nonfasting serum glucose, low plasma HDL-cholesterol, and increased body mass index.

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Younger postmenopausal women may receive mortality benefit from hormone therapy

Salpeter SR, Walsh JME, Greyber E, et al. Mortality associated with hormone replacement therapy in younger and older women. *J Gen Intern Med* 2004;19:791-804.

In postmenopausal women younger than 60 years of age, estrogen-containing hormone therapy (HT) has significantly reduced total mortality by 39% in clinical trials, while in women older than 60 HT has had no significant effect on total mortality, according to this meta-analysis of 30 randomized, controlled clinical trials published between 1966 and 2002. Data from 30 trials, which included 26,708 women using either estrogen therapy (ET) or estrogen plus progestogen therapy (EPT), were pooled to determine total mortality as well as mortality due to specific causes such as cardiovascular disease (CVD) and cancer. The mean trial duration was 4.5 years, and the mean age of participants was 62.2 years.

Overall, total mortality associated with ET/EPT was lower than that for the control group; the odds ratio (OR) was 0.98 (95% CI, 0.87-1.18). When divided into younger and older age groups based on mean ages, those under age 60 (mean age, 53.9) had a significantly reduced OR for total mortality of 0.61 (95% CI, 0.39-0.95) and those older than age 60 (mean age, 64.6) had an OR of 1.03 (95% CI, 0.90-1.18).

For specific causes, the overall OR for CVD mortality associated with ET/EPT was 1.10 (95% CI, 0.90-1.34). For cancer mortality, the OR was 1.03 (95% CI,

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0.82-1.29), and for breast cancer mortality specifically, the OR was 1.03 (95% CI, 0.29-3.67). For mortality from causes other than CVD or cancer, ET/EPT was associated with a significantly reduced OR of 0.67 (95% CI, 0.51-0.88). When divided into younger and older age groups, ET/EPT was not associated with a significant change in mortality, with the exception of reduced mortality from causes other than CVD and cancer in the older age group (OR, 0.68; 95% CI, 0.56-0.91).

Comment. This systematic review attempted to answer the question of whether the age of the woman using postmenopausal HT has an effect on mortality. Investigators performed a meta-analysis of clinical trials that reported mortality rates associated with the use of postmenopausal

HT and analyzed the results based on mean ages. They reported a significant trend between increasing risk of mortality and increasing mean age of the women using HT, raising the possibility of a health benefit for younger postmenopausal women.

The studies included in this meta-analysis by Salpeter and colleagues varied substantially with respect to entry criteria and primary outcomes being assessed, study size, and type/dose of HT. Furthermore, because age groups were defined according to mean age of participants in each trial rather than the actual age of the pooled participants, some overlap in ages likely occurred between the analyses of younger and older women. Although the findings of this meta-analysis are sure to incite yet another round of controversy regarding risks and benefits of postmenopausal HT, they suggest that clinicians can provide a substantial amount of

reassurance regarding safety to younger women considering use of ET/EPT to treat menopause-related symptoms.

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