



FIRST TO KNOW®

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This special issue of *First to Know* evolved from the lively discussion following NAMS coverage of Dr. Philip Sarrel et al's article "The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years" from the *American Journal of Public Health* in our July issue. Included in this special issue are commentaries from current and past NAMS Board Members, well-known experts in the field of menopause. The original summary of the article and the original commentary are included.

Margery L.S. Gass, MD, NCMP—*Executive Director*

Is ET avoidance associated with early death in women with hysterectomy?

Study covers decline in estrogen use, 2002-2011

Sarrel PM, Njike VY, Vinante V, Katz DL. The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. *Am J Public Health*. 2013 Jul 18. [Epub ahead of print] **Level of evidence: II-3.**

Summary. Over a 10-year period, researchers examined how estrogen therapy (ET) avoidance affected mortality rates among hysterectomized women aged 50 to 59 years. They applied a formula relating mortality in hysterectomized women assigned to placebo in the Women's Health Initiative (WHI) and the entire population of comparable US women, finding that a minimum of 18,601 and a maximum of 91,610 postmenopausal women died prematurely because of ET avoidance. Study authors concluded that for young postmenopausal women with hysterectomy an informed conversation with their healthcare provider about ET effects is of vital importance.

Comment #1. In 2011, LaCroix et al¹ analyzed health outcomes among women who had undergone hysterectomy in the WHI clinical trial of conjugated equine estrogens (CEE) versus placebo. Analyses, which were stratified

by age at randomization, were based on therapy during the trial (~6 y) and follow-up after the trial (~5 additional y). All-cause mortality was reduced among women aged 50 to 59 years assigned to CEE (hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.53-1.00) and was relatively unchanged among CEE users aged 60 to 69 years (HR, 1.04; 95% CI, 0.88-1.24) and women aged 70 to 79 years (HR, 1.12; 95% CI, 0.94-1.33). In the youngest age stratum, the estimate was 13 fewer deaths per 10,000 person-years for women assigned to CEE; in the oldest age stratum, the estimate was 19 additional deaths.

Based on these estimates and estimates of the number of US women undergoing surgical menopause, Sarrel et al examined excess mortality that might be attributed to declining rates of estrogen therapy in the wake of early WHI publications. Their calculations—based on reasonable but inherently messy assumptions—suggested about 1,900 to 9,200 "excess deaths" annually within the 50- to 59-year-old age group.

Although subgroup analyses must always be interpreted cautiously, findings from WHI indicate that age modifies the risks and benefits of hormone therapy. For women who have undergone hysterectomy, the point estimates of LaCroix et al imply reduced mortality among women aged 50 to 59 years using CEE and

increased mortality among women aged 70 to 79 years using CEE. This is useful information. As Manson points out in her *First to Know* commentary,² (reprinted on page 6 of this issue) WHI findings have undoubtedly saved lives. In an era of personalized medicine, decisions about estrogen therapy should be tailored to evidence-based risks and benefits for the individual woman. As Sarrel et al point out, the WHI data suggest that more lives may be saved by rational distinctions among age-defined subgroups of postmenopausal women who have undergone hysterectomy.

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2. Manson JE. Commentary. Is ET avoidance associated with early death in women with hysterectomy? *First To Know*. July 23, 2013:1.

Comment #2. Sarrel's application of the WHI data is unique, but the results are described as "not unexpected." The implications of the findings to women's health are clear and consistent with the totality of the literature. Observational studies consistently show that women who select menopausal hormone therapy (HT) have reduced total mortality relative to women who do not use HT. Just as consistent as these long-term observational studies have been randomized trials in which women younger than 60 years and/or less than 10 years past menopause (similar to the observational populations) when randomized to HT versus placebo show a reduction in total mortality.¹ In a meta-analysis of 30 randomized controlled trials with 119,118 women-years of follow-up, a significant reduction in total

mortality of 39% (HR, 0.61; 95% CI, 0.30-0.95) was shown in women who were on average aged 54 years when randomized to HT relative to placebo.²

Consistent with these results are data from three important trials, the WHI trials of HT and the Danish Osteoporosis Prevention Study (DOPS) of HT in which women who were on average aged 50 years and were 7 months postmenopausal were randomized to HT versus placebo for 10 years.³ Both the WHI-CEE+MPA trial (HR, 0.69; 95% CI, 0.44-1.07) and the WHI-CEE trial (HR, 0.71; 95% CI, 0.46-1.11) showed a 30% reduction in total mortality in the women younger than 60 years and/or less than 10 years past menopause when randomized to HT relative to placebo.⁴

When the data from both WHI trials are combined, the reduction in total mortality in those women randomized to HT relative to placebo is significantly reduced 30% (HR, 0.70; 95% CI, 0.51-0.96).⁴ After 10 years of randomized HT, women had a 43% (HR, 0.57; 95% CI, 0.30-1.08) reduction in total mortality relative to a control group in DOPS with a persistent reduction in total mortality of 34% (HR, 0.66; 95% CI, 0.41-1.08) after 16 years of total follow-up.³ In the 11-year WHI-CEE trial follow-up (7 years of randomized treatment and 4 years of postrandomization follow-up), reduction in total mortality in the women aged 50 to 59 years who were originally randomized to CEE was 27% (HR, 0.73; 95% CI, 0.53-1.00) lower relative to placebo.⁵

Convergence of evidence that HT reduces total mortality derives from a Bayesian analysis of eight prospective observational studies (212,717 women followed for 2,935,495 women-years over a range of 6-22 y) and 19 randomized controlled trials (mean age of women, 54.5 y randomized for 1-6.8 y and followed for 83,043 woman-years).⁶ Total mortality was 22% (HR, 0.78; 95% CI, 0.69-0.90), significantly lower in HT users than nonusers in the observational studies and significantly reduced 27% (HR,

0.73; 95% CI, 0.52-0.96) in the randomized controlled trials; with observational studies and randomized controlled trials combined, total mortality was significantly reduced 28% (HR, 0.72; 95% CI, 0.62-0.82).⁶

To place HT data into perspective, it is noteworthy that lipid-lowering randomized controlled trials have failed to show a reduction in total mortality in women in primary prevention.¹ As a consequence to stopping HT, several studies have shown increases in health hazards that have substantial mortality outcomes such as hip fractures.⁷ Sarrel's application of the WHI data to the projections of increased mortality in women in the general population raises the specter of whether lack of appropriate use of HT is a contributing factor to the rise in female mortality rates in 42.8% of US counties (vs male mortality that rose in only 3% of US counties over the same period of time) despite increasing healthcare expenditures.⁸

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Comment #3. By pointing out the negative health consequences resulting from the profound declines in estrogen use among US menopausal women who have had undergone prior hysterectomy, Sarrel et al have performed a valuable service to women's health clinicians and our patients. As with all medications, ET is associated with risks as well as benefits. Confusion surrounding the findings of the WHI HT clinical trials and, in particular, a failure to distinguish between the safety profiles of ET and estrogen-progestogen therapy, as well as lack of recognition that the risk-benefit profile of HT changes with a woman's age, have led many clinicians and women to fear and avoid HT. I see the results of this unwarranted fear every day in my practice here in Jacksonville, with highly symptomatic, recently menopausal women refusing to consider the most effective therapy for menopausal vasomotor and related symptoms—namely HT.

I am not prepared to make a public health case for increasing estrogen use in menopausal women after hysterectomy. However, the current overblown fear regarding HT and avoidance of HT has meant that many appropriate candidates are missing out on the symptom relief, prevention of osteoporosis, and treatment of symptomatic genital atrophy HT can offer. Sarrel et al appropriately point out

that wholesale avoidance of HT can have negative health consequences.

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Comment #4. The Sarrel article certainly has an interesting perspective but uses a truly impossible calculation that assumes women in one group should receive ET. Menopause practitioners, who deal with hormonal issues several times per day, would recommend individualization instead. Decisions about ET need to include each woman's complicated issues and combination of risks. However, the WHI study of ET given to hysterectomized women aged 50 to 59 years led to a better understanding of these risks and to the realization that for most women in that cohort, the benefits of estrogen outweigh the risks. The informed discussion with a healthcare provider about this issue, recommended by Sarrel et al, is indeed of vital importance. Of even more importance is the need for that healthcare provider to be up-to-date on evidence-based information.

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Comment #5. This paper is provocative for those of us taking care of menopausal women. The EPT results of the large, randomized WHI were first published in 2002, with data from the ET-only arm in hysterectomized women appearing in 2007. Unlike the findings for EPT, the ET arm showed a decrease in heart disease and breast cancer. Also in 2007, Rousseau et al re-evaluated WHI data by years since menopause with findings of less risk and potential heart protection for women under age 60 and within 10 years of menopause. However, the findings of trend of harm by age were weighted by the findings in the older group of

increased heart disease, stroke, venous thromboembolism, and breast cancer. The number of lives saved in Sarrel's article comes from a mathematical model based on a preliminary subgroup analysis from the WHI-ET trial published in 2011,¹ which estimated 13 excess deaths per 10,000 women among posthysterectomy women on placebo compared to ET.

In the midst of the current and ongoing controversy about the timing hypothesis of benefit for early users of HT and harm for older women, there are several key points to remember.

1. There was a trend for harm as women aged, particularly for those women 70 years and older. There are no randomized controlled trial data for long-term users of ET or EPT beyond the increased risks seen in WHI.
2. Neither the WHI re-analysis nor the early trial results of KEEPS presented at the NAMS 2012 Annual Meeting (which showed no harm but no proof of benefit) have confirmed the timing hypothesis that ET (with or without progesterone) given at menopause prevents heart disease.
3. The hysterectomized population in the WHI was a different population than the natural or surgical menopausal groups without hysterectomy. The differences in populations could have led to some of the differences in findings between EPT and ET and might be important in clinical practice.
4. Early surgical menopausal women have an increased risk of heart disease that is decreased with ET, and those women should be considered candidates for estrogen at least until the natural age of menopause.
5. The WHI evaluated only one type of estrogen: conjugated equine estrogen alone or combined with medroxyacetate (Provera). Findings cannot be extrapolated to other types

or formulations of ET or EPT. Growing evidence suggests less stroke and venous thromboembolism with transdermal therapy than oral.

6. Although a decrease in breast cancer was seen at 6.7 years in the WHI ET arm, an increased risk of breast cancer was seen with the EPT WHI arm, and the Nurses' Health Study has suggested increased risk of breast cancer with longer duration of ET.

Treatment of moderate to severe vasomotor symptoms remains the primary indication for HT. There continues to be evidence that the initiation of ET in early postmenopause may reduce coronary artery disease and coronary heart disease risk. Although most observational studies^{2,3} and Sarrel's mathematical modeling study support the potential benefits of systemic ET for prevention of coronary heart disease, most randomized clinical trials have not.⁴

The NAMS 2012 HT position statement⁵ reminds us that decisions about the use of HT depend on each individual situation, severity of menopausal symptoms, and effect on quality of life. The absolute risks of HT use in healthy women under age 60 years or within 10 years of menopause are low, with increasing risks found with increasing age.

As practitioners who counsel menopausal women of all ages on pros and cons, we need to identify individual risks and benefits of HT. We can tolerate more risk when we are treating an illness or bothersome moderate to severe hot flashes than when we offer medication to prevent illness. My hope is that this paper by Sarrel et al will increase the discussion about benefits and risks for symptomatic menopausal women in their 50s, those without a uterus, and those with a uterus.

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Comment #6. The conclusions of this study are based on complex mathematical modeling and assumptions, including interpretation of the WHI ET-alone data that the coronary heart disease and mortality benefits of ET to women in their 50s are absolutely definitive. The WHI findings arise from post hoc subgroup analyses, potentially subject to methodologic concerns. As stated in the NAMS HT Position Statement,¹ the decision for a woman to use HT must be individualized. There are many reasons for hysterectomy, and some indications might render a woman a poor candidate for ET. Associated risks (venous thromboembolism, stroke, gallbladder disease, and incontinence) also need to be factored into the decision to use ET. Similarly, each woman's medical history and ongoing medical conditions must be considered, so it is not reasonable at this time to recommend that all women after a hysterectomy should take ET.

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The commentary below was originally published in First to Know on July 23, 2013.

Comment. This study presents an oversimplified interpretation of the WHI estrogen-alone study. The decision about the use of hormone therapy is complex, and there are both risks and benefits of estrogen for women in all age groups. For example, the risks of stroke and deep vein thrombosis were increased in women taking oral estrogen in the WHI, even among younger women close to the onset of menopause. Although a suggestion of reduced risk of heart disease and all-cause mortality was found with estrogen in younger women (aged 50-59 y), these findings were of only borderline

statistical significance. Moreover, decision-making about ET must be individualized because the balance of risks and benefits is heavily dependent on the personal risk factor profile of the woman and her underlying health risks. Estrogen is appropriate for some, but not all, women. The WHI contributed enormously important information by clarifying the benefits and risks of hormone therapy and identifying high-risk groups who should avoid treatment. The findings have undoubtedly saved countless lives and have been linked to a reduced risk of breast cancer in the population.

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The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented below.

Level I	Properly randomized, controlled trial.
Level II-1	Well-designed controlled trial but without randomization.
Level II-2	Well-designed cohort or case-control analytic study.
Level II-3	Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies).
Level III	Meta-analyses; reports from expert committees; descriptive studies and case reports.

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