

From the EDITOR



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A pioneer in women's health issues and menopause research, in 1967 he established the Groote Schuur Menopause Research Clinic in Cape Town, the world's first such clinic. He was one of the three original founders of the International Menopause Society in 1976, of which he is Honorary Past President, and founded The North American Menopause Society in 1989.

He is the recipient of numerous national and international awards and research grants, and is still an active investigator with multiple grants. Dr. Utian has written over 200 papers related to the reproductive system in women and has authored five books on menopause and its effects on women. He is editor of *Menopause: The Journal of The North American Menopause Society*.

If Only WHI had Kept to its Premise— But Now it's Time for their Mea Culpa

Background

In July 2002 the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) started a firestorm in women's health with the premature termination of the estrogen and progestin (EPT) arm of the Women's Health Initiative (WHI) study. The announcement—at a hastily convened and highly exaggerated press conference—was immediately followed by an early publication in *JAMA*; namely, “Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women. Principal Results from the Women's Health Initiative Randomized Controlled Trial.” (Rossouw et al, for the the Women's Health Initiative Investigators.)¹

The authors concluded that: “*Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.*”¹

My first response was in a *Menopause Management* editorial entitled “Managing Menopause After HERS II and WHI: Coping With the Aftermath,”² of which the following excerpt essentially summarizes my take: “*While the merits and demerits of the data and the wisdom of the decision to terminate this arm of the WHI study will be debated for years, the manner in which*

the study was terminated was poorly planned, abrupt, and inhumane. Predictably, the media response was enormous, ranging from thoughtful to sensational. Panic was caused, numerous women discontinued therapy, and women and their health providers alike have been thrown into a state of confusion, distrust, and quandary of what to do next.”²

The WHI conclusion that harm was greater than benefit was clearly magnified by its concentration on percentiles of relative risk, rather than the pertinent issue to women of absolute risk, and by the use of a new concept called the “global health index” (GHI).

As the WHI study had progressed, the investigators had pondered how to balance risk and benefit, and created a non-validated instrument they termed the GHI. They then relied on their non-validated information to draw absolute conclusions.

I refer to abstracted comments on this in my *Menopause Management* editorial of March/April 2004, entitled “Thoughts on Suffering and Dying—Or, is “Disease A” Really Equivalent to “Disease B”?”³

“The ideal measure of healthcare effectiveness of a particular clinical practice has to be outcome-oriented, and the ultimate measures are length and quality of life (QOL). The latter clearly involves subjective values, but can be measured as a ‘trade-off’ between longevity and quality, the basic concept of the Quality Adjusted Life Year (QALY). Postmenopausal hormone therapy (HT) lends itself well to this type of analysis.

“This entire concept has been largely ignored in the current debate over the use of postmenopausal pharmacotherapy. Any clinician who has spent time with patients suffering with various chronic diseases realizes that one disease is not equivalent to another. In this day and age, for example, it is far easier—medically and emotionally—on the majority of women to be treated for early-stage breast cancer than to be immobilized by severe backache following osteoporotic vertebral crush fractures. Were you to ask the woman with early-stage breast cancer how much life expectancy she would be prepared to trade in order to feel ‘well and active,’ she would likely be prepared to relinquish little, saying that she feels perfectly well. In contrast, the woman with debilitating backache is likely to be willing to trade 5 years of life

expectancy just to be mobile and independent again. Similarly, it is patently absurd to equate a non-fatal heart attack with the stark reality of the irreversible and inexorable descent into the mental oblivion of Alzheimer’s disease.

“Each disease has outcomes that can be measured by subjective and objective values. Therefore, it is totally unacceptable in this day and age to report the outcome of any specific therapy with multiple potential positive and negative endpoints, such as heart attack, thrombosis, dementia, and fracture, as if each of these were equivalent events. Yet, that is precisely how the Global Health Index has been utilized in the reports from the Women’s Health Initiative (WHI). This non-validated index, based on the first occurrence of one of several predefined events, has been

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used by WHI investigators as the defining mechanism to balance the risks and benefits of HT, and to develop conclusions and recommendations for public health policy and clinical practice.”³

Fast-Forward Five Years

There has been a plethora of comment locally and internationally in the general and scientific press, with opinions running for and against the WHI statements. Moreover, the WHI has continued to present new data, and a surfeit of analysis, subanalysis and re-analysis. But has all this fuss really been necessary? I would argue a resounding “No.”

Most recently, two new papers from the WHI clearly demonstrate no increase in cardiovascular risk in women ages 50-59. Indeed, for the first time ever, an intervention (namely, estrogen) has been demonstrated to actually reduce calcified plaque burden in the coronary arteries of these women.^{4,5} Even

statins have not been demonstrated to be this effective in women.

The reduction of coronary artery calcium, an accurate marker of susceptibility to heart attack, was 30% to 40% lower in intent-to-treat analyses, and 60% lower among women with at least 80% adherence to the study medication for at

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least 5 years.⁵ This is a remarkable response. Given that almost 50% of women will die from cardiovascular disease, the public health impact of this response could be enormous.

If only the WHI had limited its reporting to its specific study objectives, parameters and results without the embellishments of their discussion and conclusion sections of their reports, there would be little cause for argument. It seems that defending their misinterpretation of the 2002 data is more important than accepting the scientific facts revealed by their own data. Instead, the WHI investigators and their supporters have continued with their pseudo-scientific dogma and extrapolations, cloaked in the protective guise of “interest in public health,” which is out of synchrony with the continuous flow of data being presented.

An illustrative example of the disconnect between their data and their conclusions, which always look to the downside, was their publication on the effects of EPT on gynecologic cancers; despite the data clearly demonstrating no significant differences, they concluded that *“this randomized trial suggests that continuous combined EPT may increase the risk of ovarian cancer while producing endometrial cancer rates similar to placebo.”*⁶ When challenged that the results were statistically insignificant and that the authors were willing to claim that the non-significant difference in ovarian cancer suggests increased risk, but did not con-

clude that a non-significant reduction in endometrial cancer suggested a decreased risk, the WHI response was surprising.⁷ Although the authors stated that their conclusions were justified *“because we believe that when introducing interventions to prevent chronic diseases, one must be particularly careful not to cause harm,”* they went on to conclude that *“we agree with Utian about these data and their clinical application.”*⁸

So, What was the WHI all About?

The truth is that the WHI was a study designed by the NHLBI of the NIH, largely by cardiologists and epidemiologists, initially without accurate input from reproductive endocrinologists or menopause experts. The prime objective was to determine the balance of risk and benefit when older women were given estrogen therapy or EPT for potential prevention of coronary heart disease. This was never a study about menopause.

The title of the very first report defines their misinterpretation of the results from the outset: *“Risks and Benefits of Estrogen plus Progestin in Healthy Postmenopausal Women.”*¹ The population was neither completely healthy, nor simply postmenopausal. Women up to 79 years of age were started on hormones. Even at that time it would have been unusual clinical practice to start hormones in women over 70, and certainly in doses that would not have been considered appropriate for their age. Had the title been something like *“Risks and Benefits of Initiation of Estrogen plus Progestin by Decade of Age and Time since Menopause in Women Ages 50 to 79,”* and the authors strictly interpreted and discussed their results and conclusions, the WHI investigators would not be playing on the defensive as they are at this time.

Hoisted on their own Petard

Recently, the WHI writing groups have become inexplicably reserved in utilizing the GHI. Why? Have they accepted that one case of breast cancer is not equal to one heart attack, or one stroke, or one fracture? Or have their latest results actually shown that, in specific populations, notably younger women, the

GHI actually demonstrates a potentially favorable outcome?

If we look at their most recent data on absolute risk in the populations studied, broken down into age groups and, as far as possible, into time of onset of drug therapy since age of menopause, what do the numbers look like?

The data for the estrogen-only groups are revealing. In the women younger than age 60, estrogen, compared to placebo, showed a reduction in major adverse effects annually per 10,000 treated women, with 11 fewer cases of coronary heart disease, 2 fewer strokes, 14 fewer cases of diabetes, 8 fewer breast cancers, 56 fewer fractures and 10 fewer deaths. The only adverse event to demonstrate an increase with estrogen over placebo was deep vein thrombosis/pulmonary embolus, with an additional 4 cases, occurring largely in the earlier years of use.^{4,5,9,10} Perhaps even more striking are the 2007 data that show a clear, statistically significant reduction of coronary heart disease risk for women in the WHI who were on EPT and were less than 10 years from menopause, as compared to women who were more than 20 years from menopause.⁴

These results make eminently clear why the GHI is less emphasized. The WHI investigators conclude that these results actually do converge with information from observational studies, animal studies and laboratory studies, and that their results support that the health consequences of HT may vary by duration from menopause. However, they do not conclude that benefit might outweigh risk in this younger group. Why? Could it be that this would make necessary the obvious next step needed from the NIH and the WHI?

The Necessary Next Steps

The medical community has moved too far from scientific objectivity in debating the use of estrogens and progestogens after menopause. Literally millions of women discontinued hormone use after the dramatic announcement by the NIH in 2002. The real story of the WHI may turn out to be incalculable damage wrought on younger peri- and early postmenopausal women who discontinued their

therapy and who are now several years beyond menopause and off hormones. They have suffered menopause-related symptoms. They might even have been protected from heart disease and osteoporosis. Instead, they probably should not now contemplate starting therapy again because they are in the older age group at higher risk. “The last nail in the coffin of hormone therapy,” the mantra often repeated by WHI supporters, might actually have caused the exact opposite outcome of what they had originally hoped and anticipated.

Certain questions need to be raised about the behavior of the WHI investigators and writing groups. Why did the WHI investigators not present the July 2002 data in 10-year subsets? They clearly already had those results, as demonstrated by the demographic details presented in that paper.¹ Was it perhaps because the subsets demonstrated different outcomes, and the only way the WHI results

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could claim a difference on their “GHI” was to present the merged data? Moreover, why were not all the WHI investigators involved in interpreting and reporting on the data?² As recently reported in the *Wall Street Journal*,¹¹ “[Lead author] Jacques Rossouw, a physician with the NHLBI who has overseen the WHI since its inception, confirms that some investigators were upset when they weren’t included in writing the first WHI report. ‘That was an NIH decision supported by the WHI executive committee to keep it to a small group because we realized it was a sensitive paper,’ he says. He is further quoted as saying, ‘Our main job at the time was to turn around the prevailing notion that hormones would be useful for long-term prevention of heart disease. That was our objective. This was a worthy objective which we achieved.’”¹¹ Really?

The response from WHI to the *Wall Street*

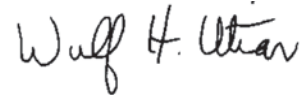
Journal article highlights their insistence on extrapolating their narrow results to broader populations, although this is scientifically unacceptable. They state: “*The younger women who took estrogen-alone had less coronary calcium than the women who didn’t take the drug, suggesting that estrogen-alone might offer some benefit for heart disease in the short term. But since there was no reduction in clinical heart disease in older women (WU: the extrapolation!), it would be unwise to presume that any benefit in younger women would persist into older ages if women continued to use estrogen. There is no evidence that estrogen-alone will continue to protect against the foreseeable, age-related deterioration of the arteries. Potential benefit may thus revert to potential harm, as seen in older women.*”¹²

This is ridiculous. Observational data from large studies like the Nurses’ Health Study have shown a protective effect when women starting at a younger age are followed over time, and such evidence was the catalyst to the initiation of the WHI study itself. The whole premise of contemporary research is that the early initiation of estrogen directly retards atherogenesis. Clearly, the younger women starting hormones in close proximity to menopause need to be followed up and, as the WHI was prematurely terminated, there is unlikely to be any answer to this vexing question forthcoming from the WHI. They simply failed to initially recognize the variance of effect on the younger women.

At the expense of repetition, had the WHI kept to its original study objectives and reported the results impartially and by decade of chronological age and time from menopause there would not be the international disapproval that the study is now receiving. This is unfortunate because there are reams of important and pertinent data coming out of all the substudies of the WHI. For these to be accepted with confidence, it is well time for the NIH to bring all their WHI investigators together to develop a transparent and comprehensive summary of their results. It is also time for the WHI investigators to cease their stubborn defense and misrepresentation of their 2002 data, and to return to scientific integrity.

Do they owe a mea culpa? In my opinion,

“yes.” But there are important and relevant data in the WHI study that need to be clearly and honestly placed in perspective, and the NIH have the ball in their court for taking the first step toward an unbiased review.



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