EDITORIAL

The Impact of the Women's Health Initiative on Clinical Practice

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There is no doubt that the recently published decision and results from the Women's Health Initiative (WHI) will have an impact on postmenopausal women, their interactions with their clinicians, and the thinking of clinicians with regard to postmenopausal hormone therapy. As many of you know, the Drug Monitoring and Safety Board of the WHI made the following two public recommendations after the tenth interim review of the data collected by this American randomized clinical trial: (1) to discontinue the trial arm administering daily 0.625 mg of conjugated estrogens combined with 2.5 mg of medroxyprogesterone acetate or placebo, and (2) to continue the trial arm comparing daily unopposed estrogen (0.625 mg conjugated estrogens) with placebo in hysterectomized women.[1]

The combined estrogen and progestin arm was discontinued after an average of 5.2 years (range 3.5–8.5 years) of follow-up because of an increase in invasive breast cancer tending toward, although not achieving, statistical significance. Because this was combined with a small but statistically significant increase in cardiovascular events in the treated group, the WHI concluded that this combination of estrogen and progestin should not be initiated or continued for the primary prevention of coronary heart disease and that there is a substantial risk of breast cancer.

Adjectives applied by the media to these results and conclusions include "solid, definitive, unequivocal." Careful review of the publication suggests otherwise. This is not just my opinion. The steering committee of the other large randomized, clinical trial, the WISDOM trial (Women's International Study of Long Duration Oestrogen After Menopause), headquartered in England, concluded that the WHI evidence is "not convincing" and that the WISDOM trial should proceed.[2]

The late Trudy Bush stated that the objective of both basic and clinical science is to know the truth.[3] And every epidemiologic study, no matter how good or how large, gives only one view of the truth. She always cautioned that it takes many views to come close to seeing the truth. The Women's Health Initiative is only one view of the truth. Contrary to the impressions reported in the media, the statistical calculations for coronary artery disease, stroke, and breast cancer are not overwhelming in their strength, and there are alternative explanations for the WHI results.

The WHI is heralded as a primary prevention clinical trial of postmenopausal healthy women. The average age of the participants is 63 years, and the age range is 50–79 years (45% were in their 60s and 21% in their 70s). Although only 7.7% of the women reported cardiovascular disease upon entry, a significant number of the participants, because of their age, already had existing atherosclerosis. Does the increase in cardiovascular events in the treated group reflect an effect concentrated in older patients with significant atherosclerosis? The WHI answers this criticism by pointing out a lack of interaction with age, ie, a similar difference between the treated and placebo groups in participants in their 50s, 60s, and 70s. However, the critical factor (results according to duration from menopause) has yet to be analyzed. Women with significant menopausal symptoms (especially hot flushing) were excluded from the WHI, which means that the number of women close to menopause had to be relatively small. There remains, therefore, an important issue with regard to cardiovascular disease: this may not be a pure primary prevention trial.

It seems to me that the cardiovascular results over the last few years are supporting an emerging theme, that you need healthy endothelium to respond to estrogen. Experimental evidence in the monkey indicates that the beneficial effects of hormonal treatment diminish progressively with increasing atherosclerosis.[4] In postmenopausal women, the vasodilatory effects of estrogen dissipate with increasing age.[5] By the time the endothelium is involved with atherosclerosis, it is too late for estrogen to exert a beneficial effect. Therefore the recent results are not so surprising.

The information provided by the WHI does not indicate the prevalence of new statin and aspirin use in the participants. A greater prevalence of new statin-aspirin treatment in the placebo group could lower the event rate, providing a falsely high rate in the treated group. It is well recognized that the beneficial effects of statins occur rapidly, acting to stabilize plaques within a few months. Although statin use and aspirin use at baseline were comparable in the treated and placebo groups, no information is provided regarding new treatment during the follow-up. There is good evidence that the beneficial effect of estrogen on the cardiovascular system is lost in women already being treated with statins.[6] The cardiovascular events did not cross the predetermined boundaries set by the WHI requiring cancellation of the study. With the small numbers involved, a shift of a few cases would have a major impact on the conclusion.

The WHI identified 400 women with established coronary artery disease upon entry. Among these women, the hazard

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risk for cardiac events was 1.28, a risk that did not reach statistical significance with a confidence interval of 0.64, 2.56 (19 versus 16 events). When the remaining women were analyzed separately, the hazard risk was also 1.28, and again the confidence interval was not statistically significant (1.00, 1.65; 146 versus 106 events). These numbers emphasize how small the observed cardiac effect was and how easily a shift of a few cases could change the result.

When are the results of a randomized, double-blind trial compromised by the clinical behavior of the patients? In the WHI, 42% of the treated group stopped their hormone therapy, and 38% in the placebo group stopped medication. This drop out rate exceeded design projections. Women in both groups began hormone treatment provided by their primary clinicians sometime after the study began, 6.2% in the treated group and 10.7% in the placebo group. This drop in rate was also higher than design projections. Of the treated group 40.5% (3444 women) and 6.8% of the placebo group were unmasked, mainly because of vaginal bleeding. When is intent-to-treat analysis inadequate in the face of unmasking, drop outs, and drop ins, especially when duration of exposure is a critical factor?

Intention-to-treat analysis compares all individuals in the treated group with all in the placebo group, regardless of drop outs or drop ins. This is said to be the best method of analysis for clinical trials because it accurately reflects the randomization. One cannot help but wonder how the long-term benefit of a treatment can be assessed if subjects receiving treatment for only a short period of time are included. A high drop-out rate affects the numbers remaining and available for an as-treated analysis. The WHI performed an as-treated analysis, and this produced "more modest changes." The numbers and confidence intervals were not provided.

It seems that the breast cancer results are heavily influenced by years 4 and 5. Remember that the growth of breast tumors is slow (it takes 10 years for a malignant cell to become clinically detectable at 1 cm diameter). The WHI breast cancer results are consistent with hormonal stimulation of preexisting tumors. The hazard risk returned almost to 1.0 in year 6. Case-control and cohort studies have uniformly observed a reduced risk of dying of breast cancer in women whose cancer was diagnosed during their use of hormone therapy. This is not only due to greater use of mammography, but it also reflects lower grade and stage disease in hormone users, a finding that is consistent with accelerated growth of preexisting tumors. In the WHI results, there were only three deaths from breast cancer in the treated group and two in the placebo group. The follow-up was not long enough to provide the outcome of the breast cancers in the participants. The health of the participants is supposed to be monitored until 2005, so hopefully we will learn more about breast cancer mortality.

In summary, the WHI agrees with some case-control and cohort studies indicating that long-term current use of combined estrogen and progestin has a slightly increased risk of breast cancer. It is still not clear whether this finding is due to an effect of hormonal therapy on preexisting tumors. The epidemiologic data indicate that a positive family history of breast cancer should not be a contraindication to the use of postmenopausal hormone therapy. Women who develop breast cancer while using postmenopausal hormone therapy have a reduced risk of dying from breast cancer. This is probably because of increased surveillance and early detection and acceleration of tumor growth so that tumors appear at a less virulent and aggressive stage.

WHAT SHOULD WE TELL PATIENTS?

We must recognize the WHI results and their importance. They will change clinical practice, but I have tried to highlight some meaningful observations that will provide clinical perspective. It is appropriate to point out that the adverse effects reported by the WHI are small and not the dramatic, definitive results portrayed in the media. Remember that 97.5% of the participants in the WHI never experienced an adverse clinical event. However, I recognize that even a small risk frightens patients. It is important to emphasize that there are alternative explanations for the results. With regard to coronary artery disease, I do not believe we should discard a large body of biologic (including the monkey experiments of Tom Clarkson's group) and epidemiologic evidence and make decisions based solely upon the WHI. The recent trial results are reasons to be conservative regarding hormone therapy for older women with evidence of coronary artery disease. Certainly we should not promote estrogen as a first-line drug to prevent further clinical events in women with coronary artery disease, especially in women who have had a recent myocardial infarction. Multiple clinical trials have established that treatment with statins is very effective in preventing clinical cardiac events. The recent reports make an argument that the optimal approach to postmenopausal hormone therapy is to start treatment close to menopause, avoiding a significant period of exposure to low estrogen levels before beginning therapy. And there continues to be good reason (a combination of biologic data and uniform agreement in a large number of observational studies) to believe that hormone therapy has a beneficial role in the primary prevention of coronary artery disease, a beneficial cardiovascular effect in younger postmenopausal women without apparent atherosclerosis.

The results of the Heart and Estrogen/progestin Replacement Study II indicate that the increased risk of venous thromboembolism associated with hormone therapy is concentrated in the first two years of use (in fact, the increase was statistically significant only in the first year). They also support the conclusion that low-dose aspirin and statin treatment protect against this risk.[7] Thus there is little reason to be concerned over this infrequent side effect in long-term users.

There continue to be good reasons to expect beneficial effects of hormone therapy on menopausal symptoms, brain function, and the skin. The WHI provides strong support for a reduction in osteoporotic fractures and colorectal cancer. The reduction in osteoporotic fractures answers those who emphasize the lack of randomized trial data for the effect of estrogen on osteoporosis and fractures. The size of fracture

reduction in the WHI is substantial because this population was at low risk for osteoporotic fractures (for example, women with previous fractures were excluded). The reduction in colorectal cancer is consistent with a uniform story in a large number of case-control studies. It is important to emphasize that the trial arm with unopposed estrogen is continuing because no increase in breast cancer has been found. It should be emphasized that despite the reported increases in clinical events in the WHI, there was no difference in the death rates between the treated and placebo groups.

Are the WHI results limited to one kind of hormonal formulation? Of course, there is no way to know the answer at the present time. Clinicians and women will react to the WHI results by choosing other progestins, other doses, and other routes of hormonal administration. These are reasonable decisions, but we must be frank in our patient dialogues that there are few, if any, data to guide us.

The confusion and controversy that surround postmenopausal hormone therapy make it all the more important to individualize treatment. The specific objectives for each patient must be identified, and the best treatment option (formulation, dose, and route of administration) that meets the patient's goals must be selected, a process that will require time-consuming patient-clinician dialogue. Because of the astounding rate at which we are accumulating new information, I recommend the following approach for clinicians and patients. Have an agreement with each patient that a treatment decision is for the short-term, for the following year. Each year, review and evaluate the decision incorporating that year's new information, and then together forge a firm commitment to a new decision for the coming year.

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