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WHI Trial Arm With E/P Finds An Increase In Breast Cancer

SPECIAL REPORT

Editor's note: *With the recent lay media attention on the WHI study and the HRT controversy, Dr. Speroff has focused the main part of this issue on the study in question.* OB/GYN Clinical Alert *subscribers receive Dr. Speroff's comment on the matter, as well as additional expert comment from Dr. Sarah Berga.*

ON MAY 31, 2002, THE DATA AND SAFETY MONITORING BOARD (DSMB) made its 10th interim review of the data accumulated by the Women's Health Initiative (WHI). The DSMB made 2 recommendations that were made public on July 9, 2002: 1) To discontinue the trial arm administering daily 0.625 mg conjugated estrogens combined with 2.5 mg 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. The combined estrogen/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 trending toward, although not achieving, statistical significance. The conclusions highlighted by the WHI were derived from an unadjusted intent-to-treat analysis. The released results are shown in Tables 1, 2, and 3.

The WHI enrolled participants between 1993 and 1998 at more than 40 sites and was scheduled to end in 2005. The statistical parameters for benefit or harm were established in 1997 early in the study. When the increase in breast cancer exceeded the predetermined boundary, the DSMB was obligated to recommend discontinuation of this arm of the trial. The WHI concluded that this combination of estrogen/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 (Writing Group for the WHI Investigators. *JAMA*. 2002;288:321-333).

COMMENT BY LEON SPEROFF, MD

The decision to terminate the combined E/P arm of the WHI was disappointing, disturbing, important, and necessary. The initiation and conduct of the first large clinical trial of postmenopausal hor-

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mone therapy generated high expectations, and I shared in the anticipation of solid, strong, and useful information. It is not without some trepidation that I challenge the image of WHI as an unflawed study. I would rather avoid placing myself in a position that can be viewed as defensive, but I cannot shirk my responsibility to formulate a response that hopefully will prove helpful for clinicians and patients in balancing the initial emotional reaction to the WHI.

The National Heart, Lung, and Blood Institute concluded in its press release that combined hormone therapy is unlikely to benefit the heart. In my view, the results do not justify a definitive conclusion. First of all, the WHI is heralded as a primary prevention clinical trial of postmenopausal healthy women. The average age of the participants is 63, and the age range is 50-79 (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, and we are increasingly aware that the beneficial effects of hormone therapy on the cardiovascular system are progressively diminished with increasing atherosclerosis.[1]

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; at a presentation of the WHI data, the investigator presented a graphic that indicated a similar difference between the treated and placebo groups in participants in their 50s, 60s, and 70s.[2] 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 numbers of women close to menopause had to be relatively small.

There remains, therefore, an important issue in regard to cardiovascular disease: this may not be a pure primary prevention trial. The WHI investigator in his presentation claimed that "unhealthy" women would have been balanced between the treated and placebo groups, but if the cardiovascular effect of estrogen is diminished in the presence of atherosclerosis, this would have an effect on the results.

The information provided from the WHI does not indicate the prevalence of new statin and aspirin use in the participants. A year-by-year analysis of coronary

Table 1

Overall Conclusions from WHI TRIAL

	E/P Treatment	Placebo	Hazard Risk
Total women:	8506	8102	—
Invasive breast cancer	166	124	1.26 (1.00-1.59)
Noninvasive breast cancer	40	33	1.13 (NS)
CHD	164	122	1.29 (1.02-1.63)
CHD deaths	33	26	1.18 (0.70-1.97)
Stroke	127	85	1.41 (1.07-1.85)
Fatal stroke	16	13	1.20 (0.58-2.50)
Nonfatal stroke	94	59	1.50 (1.08-2.08)
Pulmonary embolism	70	31	2.13 (1.39-3.25)
DVT	115	52	2.07 (1.49-2.87)

Table 2

Attributable Risks for Daily 0.625/2.5 Conjugated Estrogens/Medroxyprogesterone Acetate

97.5% of women on treatment had no events.
+7 myocardial infarctions per 10,000 women per year
+8 strokes per 10,000 women per year
+8 breast cancers per 10,000 women per year
+18 cases of PE/DVT per 10,000 women per year

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Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Speroff is involved as a consultant, and does research for Wyeth Ayerst, Pfizer, Ortho, and Novo Nordisk. Dr. Berga is a consultant for Pfizer, Organon, and Women First, Inc., and is involved in research for Berlex and Health Decisions, Inc. Dr. Gershenson is involved in research for Pharmacia-Upjohn, Oncotech, Genetech, SmithKline Beecham, Atairigen, and the National Cancer Institute. Dr. Noller and Dr. Hobbins report no relationships related to this field of study.

Table 3

Other Results Recorded in the Discontinued WHI Arm with Daily E/P

	E/P Treatment	Placebo	Hazard Risk
Total women:	8506	8102	—
Hip fracture	44	62	0.66 (0.45-0.98)
Vertebral fracture	41	60	0.66 (0.44-0.98)
Other fractures	579	701	0.77 (0.69-0.86)
Endometrial cancer	22	25	0.83 (0.47-1.47)
Colorectal cancer	45	67	0.63 (0.43-0.92)

heart disease is of interest and importance. (*See Table 4*.)

It is easy to see that the coronary heart disease results are influenced by the events in year 5. What happened in year 5? Does this reflect new statin/aspirin treatment in the placebo group, lowering the event rate and providing a falsely high rate in the treated group? Did a similar experience take place in years 1 and 2? 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.[3] Keep in mind that 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 effect on the conclusion.

The WHI identified 400 women with established coronary heart disease upon entry. Among these women, the hazard 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 vs 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; 145 vs 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. At a presentation of the WHI data, the investigator revealed that the released results were based upon diagnoses in the field, and that central adjudication of the cardiac diagnoses was revealing what seems to me as an important level of disagreement in 16% of the cases.[2] It will be important to keep an eye on the final calculations.

Table 4

Year-by-Year Analysis of CHD

	E/P Treatment	Placebo	Participants
Year 1	43 (0.51%)	23 (0.29%)	8435/8050
Year 2	36 (0.43%)	30 (0.38%)	8353/7980
Year 3	20 (0.24%)	18 (0.23%)	8268/7888
Year 4	25 (0.32%)	24 (0.32%)	7926/7562
Year 5	23 (0.39%)	9 (0.16%)	5964/5566
Year 6+	17 (0.33%)	18 (0.42%)	5129/4243

When is the effect 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% stopped medication in the placebo group. 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. Also, 40.5% of the treated group (3444 women) and 6.8% of the placebo group were unblinded, mainly because of vaginal bleeding. When is intent-to-treat analysis inadequate in the face of unblinding 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 can't 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. The WHI performed an "as treated" analysis, and this produced "more modest changes." The numbers and confidence intervals are not provided. A high drop out rate affects the numbers remaining and available for an as treated analysis.

For several years, I have argued that the lack of agreement, uniformity, and consistency among more than 60 case-control and cohort studies is a strong reason that the risk of breast cancer associated with hormone therapy cannot be a large one. The WHI results support that conclusion, amounting to a 26% increase, 8 cases per 10,000 women per year, and even this conclusion had a marginal level of confidence. I have further argued that those studies reporting an increase in risk could be reflecting hormonal acceleration of growth in pre-existing tumors. Is that a possibility in the WHI results? Here again, analysis by year is helpful. (*See Table 5*.)

It is apparent 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 diame-

Table 5

Year by Year Analysis of Breast Cancer

	E/P Treatment	Placebo	Participants
Year 1	11 (0.13%)	17 (0.21%)	8435/8050
Year 2	26 (0.31%)	30 (0.38%)	8353/7980
Year 3	28 (0.34%)	23 (0.29%)	8268/7888
Year 4	40 (0.50%)	22 (0.29%)	7926/7562
Year 5	34 (0.57%)	12 (0.22%)	5964/5566
Year 6+	27 (0.53%)	20 (0.47%)	5129/4243

ter). The WHI breast cancer results are consistent with hormonal stimulation of pre-existing tumors. Notice that the hazard risk returned almost to 1.0 in year 6!

It is important to emphasize that a positive family history of breast cancer did not affect the results.

Case-control and cohort studies have uniformly observed a reduced risk of dying of breast cancer in women diagnosed during the use of hormone therapy. This is not only due to greater use of mammography, but it reflects lower grade and stage disease in hormone users, a finding that is consistent with accelerated growth of pre-existing tumors. In the WHI results, there were only 3 deaths due to breast cancer in the treated group and 2 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.

There is some good news. 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 recorded. Also keep in mind that the risk of venous thrombosis is concentrated in the first two years of use,[4] and thus there is no reason to be concerned over this infrequent side effect in long-term users.

This will be an on-going story. We can expect periodic publications from the WHI as the data are analyzed in greater depth according to specific diseases and risk factors.

What Are We To Tell Patients?

Almost every patient will already have learned the facts, heavily and prominently reported by the media. One cannot deny 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 risk of breast cancer is small, and there is no major effect, but of course that is little consolation to patients. Remember that 97.5% of the participants in the WHI never experienced an adverse clinical event. In regard to coronary heart disease, I don't believe we should discard a large body of biologic (including the monkey experiments in Tom Clarkson's group) and epidemiologic evidence and make decisions solely based upon the WHI. I will continue to maintain that there is good reason to expect a beneficial cardiovascular effect in younger postmenopausal women without apparent atherosclerosis. Nevertheless, we should aggressively encourage women at high risk for cardiovascular disease to be treated with statins. There continue to be good reasons to expect beneficial effects of hormone therapy on menopausal symptoms, brain function, the skin, and the WHI provides strong support for a reduction in osteoporotic fractures and colorectal cancer. It should be emphasized that despite the reported increases in clinical events in the WHI, there was no difference in the death rates comparing the treated and placebo groups. Hopefully with time, a more objective and less emotional understanding of postmenopausal hormone therapy will be reached.

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 may 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 little, if any, data to guide us.

The late Trudy Bush always argued that the objective of both basic and clinical science is to know the truth. And every epidemiologic study, no matter how good or how large, gives only one view of the truth.[5] She always cautioned that it takes many views to come close to seeing the truth. The WHI is only one view of the truth. Contrary to the impressions reported in the media, the statistical calculations for coronary heart disease, stroke, and breast cancer are not overwhelming in their strength. The cardiovascular results may reflect new statin/aspirin use and the effect of hormone therapy on pre-existing breast tumors (a so-called promoter effect) may be the reason for the breast cancer results. I think it is appropriate to share with patients these alternative explanations for the WHI results.

COMMENT BY SARAH L. BERGA, MD

Do you have the facts on the recent analysis of the

WHI trial? First, please look at the absolute increases in the key categories. Then look at the hazard ratios, which convey the excess risk in each arm. It is helpful here to refer to Figure 4 in the *JAMA* source document. The hazard ratio was calculated, as were the confidence intervals, for various outcome measures. Notice that there are two columns for the confidence intervals, unadjusted and adjusted. Please look at the column with the adjusted confidence intervals. How many of the ranges cross 1.0? The answer is all. This means that none of the findings met criteria for statistical significance. This is because there are so few cases. Usually when both the adjusted and unadjusted confidence intervals are presented, it is because there is some doubt about the unadjusted ones representing "reality," thus greater weight should be given to the adjusted confidence intervals.

Now, for sake of argument, let's assume that there are actually statistically significant findings. Look at the column with the unadjusted confidence intervals and find the hazard ratio for dementia. Sorry. That is not one of the outcome variables. Why? Because one cannot answer the question as to whether "HRT" reduces the risk of dementia in a study conducted for only 5 years in women younger than 75. If fact, the global index did not include any measures relevant to the effect of sex steroids on brain function.

What do you make of the fact that only the Prempro arm was stopped and that the Premarin arm was allowed to continue? First, it means that the risk of breast cancer was not as high in the Premarin arm as in the Prempro arm. Second, it likely means that there was cardiovascular benefit in the Premarin arm. How much? We have to wait. In the meantime, the media and others would have you believe that all HRT is bad, even though the only arm that was stopped was the Prempro arm. Another, more logical, interpretation is that Provera counteracted the benefits of the Premarin upon the cardiovascular tree. The concurrent use of Provera in a continuous manner may even account for the small, but statistically nonsignificant, increase in the hazard ratio for breast cancer. Remember when it was widely posited that Provera did oppose the beneficial effects of Premarin? Maybe that hypothesis is true. We await the results of the Premarin arm.

Let's get a little more theoretical. The study compared Premarin, Prempro, and placebo. Would you agree with the following interpretation? Premarin is an estrogen and Provera is a progestin, therefore all HRT formulations must be equally risky. In other words, Prempro is a good proxy for all continuous HRT preparations. I have written before about the many reasons that not all estrogens are the same. Certainly, not all progestins are the same. Therefore, although it is indeed tempting, in strict terms, one cannot generalize from this study to all HRT formulations. In other words, there is no scientific basis for collapsing across categories and using the WHI Prempro data to generalize to all other forms of continuous combined HRT—much less other regimens. How do estrogens differ? Let me count the ways: route of delivery, conjugated or not, bioidentical or not, and metabolites. The same holds for progestins. And not all women are the same. And not all tissues within a given woman are the same. Are women to be reduced to the sum of breast, bone, and cardiovascular tree? Hopefully not. Did all women get the same dose regardless of body weight and concurrent conditions? Yes. Would we really give a 100-pound woman the same dose as a 250-pound woman? Would we typically give a woman many years off HRT the same initial dose as a woman who is just having menopausal symptoms? It seems unlikely. Were serum levels of estrogen conjugates or unconjugated estrone measured to see if the women who suffered adverse events had higher or lower serum levels? No. In summary, no one study can arrive at truth and this study provides only partial information. The recent WHI results suggest that the use of Prempro may minimally increase some risks. But it does not suggest that all HRT preparations are dangerous or that long-term HRT is dangerous. The WHI did not address long-term risks.

There is a bright side. Remember the pill scare of the 1970s? As a result of the initial worrisome results, what happened? We got better, lower-dose pills.

My prediction is that the results of the WHI will lead us to the following practices:

1. We will learn to individualize HRT dose and we will develop guidelines for individualizing intelligently;
2. We will discover exactly how estrogen preparations differ from one another so that we can individualize;
3. We will discover whether the transdermal route of delivery gives a better risk/benefit profile;
4. We will determine, which, if any, progestins are safer than Provera. If they all are risky, then we will more widely use progestin IUDs for protecting the uterus or we will develop better intrauterine alternatives.

My predictions are based on the premise that the concept of ameliorating age-related disability has inherent merit and that to do this we need to refine our approach rather than abandon the attempt. In other words, it is the present set of compounds rather than the concept that is lacking. There is nothing wrong with wanting to age gracefully. Sex steroids are likely to play a role in doing so, but we need to refine how we give them in order to minimize risk and maximize benefit. ■

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HERS II: Follow-Up Report of the HERS Trial

ABSTRACTS & COMMENTARY

Synopsis: *There was no cardiovascular benefit associated with hormonal treatment of women with coronary heart disease during 6.8 years of observation, and hormone treatment increases the rates of venous thromboembolism and biliary tract surgery.*

Sources: Grady D, et al, *JAMA*. 2002;288:49-57; Hulley S, et al. *JAMA*. 2002;288:58-66.

Of the 2763 postmenopausal women in the Heart and Estrogen/progestin Replacement Study (HERS), 2321 (93%) agreed to be involved in additional follow-up evaluation. The original study[1] lasted 4.1 years, the average extended follow-up equaled 2.7 years, for a mean total of 6.8 years. At the beginning of the follow-up period, and the average age of the participants was 71 (67 at baseline and 74 at closure). The HERS investigators could detect no significant differences in the rates of coronary events or secondary cardiovascular events comparing the treated group with the placebo group. There was no statistical trend for a beneficial effect of hormone therapy with longer duration of treatment. Because of the absence of a difference, the follow-up period, scheduled to last 4 years, was terminated early.

The original HERS report indicated a 2-3-fold increase in deep vein thrombosis (DVT) and pulmonary embolism in the hormone-treated group. In the follow-up period, there was no longer a statistically significant increase in DVT. There was no reduction in pulmonary embolism, but the number of events was too small to provide accurate assessment. The event rates for venous thrombosis were 5.9 per 1000 women per year of treatment and 2.8 in the placebo group. There were 3 deaths from pulmonary embolism in the treated group. Aspirin attenuated the risk associated with hormone therapy.

Overall, there was a 48% increase in risk for biliary tract surgery in the treated group—6 more cases per 1000 women per year compared to placebo.

There were no statistically significant differences in cancer rates, including breast cancer, comparing the treated and placebo groups. Likewise there was no difference in fractures, but this study was not designed to have sufficient power to study fractures (for example, the treated and placebo groups were not matched for fracture risk factors, bone density, or use of drugs that affect bones), and x-rays were not performed to detect spinal fractures.

The HERS investigators concluded that there was no cardiovascular benefit associated with hormonal treatment of women with coronary heart disease during 6.8 years of observation, and that hormone treatment increases the rates of venous thromboembolism and biliary tract surgery.

COMMENT BY LEON SPEROFF, MD

The original HERS trial was interpreted as demonstrating an early adverse effect of hormonal therapy and an emerging later benefit. This follow-up report emphatically does not support the presence of an emerging benefit with longer duration of treatment.

The additional follow-up period was unblinded; patients and physicians could choose to continue, discontinue, or initiate hormonal or other therapy. Hormone use in the original treated group in HERS declined from 81% after 1 year to 45% during the 6th year (and 11% were using preparations other than the original 0.625 mg conjugated estrogens and 2.5 mg medroxyprogesterone acetate). During the 6th year, 8% of the placebo group were now receiving hormone therapy. Raloxifene or tamoxifen had even been initiated, 3% in the hormone group and 4% in the placebo group. The HERS investigators recognized this problem conceding that their power to detect an increasing benefit was eroded by the changing treatments; however, their analysis indicated an ability to detect at least an 18% reduction in cardiac risk. What about statins?

At baseline, the use of statins (and aspirin) was essentially equally prevalent in the treated and placebo groups (about 40% of the subjects used statins and 80% used aspirin). However, more women in the placebo group began treatment with statins, so that by the end of the follow-up period, the 69% vs. 65% difference-comparing placebo with treatment was statistically significant. The HERS investigators addressed this potential confounder by adjusting for the difference in statin use (as well as other confounders) and concluded that the adjusted analyses were essentially identical to the original analyses. However, no mention is made of the fact

that the percentage use of statin use is impressively high. What if any beneficial effect of estrogen is lost because of the effect of statin therapy? Indeed, in a primary prevention trial, inhibition of atherosclerosis with estrogen treatment was observed only in women *not* receiving statins.[2] The HERS investigators compared coronary heart disease events in the hormone group with the placebo group in women not using statins or aspirin and found no difference. However, this very important possible explanation for the lack of a beneficial effect of estrogen in HERS cannot be answered by the analysis of the HERS data because statin and aspirin treatment were not randomized, and the number of events in women not on statins or aspirin was very small. Statin drug treatment reduces the risk of coronary events by approximately 30% (greater in higher risk individuals) in both men and women, exerting both primary and secondary prevention.[3,4] The increasing use of statins, especially in older women who are not hormone users, makes it difficult to have a true placebo group in studies of coronary heart disease.

Intention-to-treat analysis compares all individuals in the treated group to all in the placebo group, regardless of individual compliance or completion of the study. Proponents argue that this is the best method of analysis for clinical trials because it reflects the full effect of randomization. Opponents contend that this method is intuitively wrong; how can the long-term benefit of a treatment be assessed if subjects receiving treatment for only a short period of time are included? HERS II performed an "as-treated" analysis, focusing on women with 80% or more compliance and found relative hazards (like relative risk) similar to those in the intent-to-treat analysis. However, the relative hazard for primary coronary heart disease events in HERS II was lower, although not statistically significant (RH = 0.81; CI = 0.52-1.32). Events were fewer in the as-treated analyses because only 37% of the events qualified. Adjustment for statin use was performed only in the intent-to-treat analysis ("only a trivial effect on the findings"). Therefore, do the HERS II results reflect intent-to-treat analysis (with a difficulty in detecting a long-term effect) and few events in the as-treated analysis (because of compliance and drop out problems)?

Every effort thus far to find a defining characteristic that would identify susceptible patients for the possibly increased risk of cardiac events in the first year of treatment has failed to identify a high-risk group of women.[5] It remains an unanswered question whether reported increases in cardiovascular events early after the initiation of hormone therapy reflect a true risk of hormone therapy or the effect of reduced events in the placebo groups because of new onset treatment with statins (and aspirin).

It seems to me that the cardiovascular results over the last few years are supporting an emerging theme. The theme is: you need healthy endothelium to respond to estrogen. Experimental evidence in the monkey indicates that the beneficial effects of hormonal treatment are progressively diminished with increasing atherosclerosis.[6] In postmenopausal women, the vasodilatory effects of estrogen dissipate with increasing age.[7] By that time, the endothelium is involved with atherosclerosis, and it is too late for estrogen to exert a beneficial effect. Therefore the recent results are not so surprising.

The results of HERS II indicate that the increased risk of venous thromboembolism associated with hormone therapy is concentrated in the first 2 years of use (in fact, the increase in HERS was statistically significant only in the first year). They also support the conclusion that low-dose aspirin and statin treatment protect against this risk.[8] When considering the venous thromboembolism rates in HERS, remember that these women were at high risk for this complication, reflected by a high event rate in the placebo group.

And let's not ignore the encouraging finding of no significant increase in breast cancer in these older women treated for 6.8 years! In addition nonsignificant (due to small numbers) decreases in colon cancer and endometrial cancer were observed in the hormone-treated group.

The recent trial results are reasons to be conservative regarding hormone therapy for older women with evidence of coronary heart 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 results also indicate that there is no need to avoid the use of medroxyprogesterone acetate, because there has been no difference observed comparing women treated only with estrogen to those treated with estrogen and progestin. The recent reports make an argument that the optimal approach to postmenopausal hormone therapy is to start treatment close to the menopause, avoiding a significant period of exposure to low estrogen levels prior to 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 heart disease. ■

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CME Question

4. The following statements are true regarding the HERS trial *except*:

a. The HERS trial included only women with significant coronary heart disease.

b. According to the HERS trial, women on hormone therapy have an increased risk of venous thromboembolism as long as they are on treatment.

c. The HERS trial is not an accurate assessment of estrogen's effect on bones.

d. With extended follow-up, the HERS trial found that hormone therapy provides no cardiovascular benefit in women who already have atherosclerosis.

Attention Readers

American Health Consultants is happy to announce that we are opening up our *Primary Care Reports* author process to our readers. A biweekly newsletter with approximately 5000 readers, each issue is a fully referenced, peer-reviewed monograph.

Monographs range from 25-35 Microsoft Word document, double-spaced pages. Each article is thoroughly peer reviewed by colleagues and physicians specializing in the topic being covered. Once the idea for an article has been approved, deadlines and other details will be arranged. Authors will be compensated upon publication.

As always, we are eager to hear from our readers about topics they would like to see covered in future issues. Readers who have ideas or proposals for future single-topic monographs can contact Managing Editor Robin Mason at (404) 262-5517 or (800) 688-2421 or by e-mail at robin.mason@ahcpub.com. ■

PHARMACOLOGY WATCH

No Shortage in Sight for Tetanus-Diphtheria Vaccine

The number of vaccine shortages has been unprecedented in the last year, but at least one vaccine, tetanus-diphtheria (Td), is back in full production. The Centers for Disease Control and Prevention (CDC) has announced that they are removing restrictions on the Td booster. Despite the fact that there is only one manufacturer of the vaccine, supplies are large enough to resume routine vaccination. The news is also good for childhood vaccines that have been in short supply, including MMR, varicella, and PCV-7 (pneumococcal) vaccine. All are expected to be in full supply by the end of the year.

Cholesterol-Lowering Therapy OK for Seniors

What to do with the 75-year-old patient with a cholesterol of 300, but no history of heart disease? Primary prevention studies have shown a benefit for treatment of younger patients, but there have been few studies of primary prevention studies in the elderly. Now data from the Cardiovascular Health Study of patients age 65 or older suggest that cholesterol-lowering therapy is useful in older patients as well. After nearly 7.5 years of follow-up, elderly patients with elevated cholesterol levels clearly benefited from cholesterol-lowering treatment. Compared with no drug therapy, statin use was associated with a decreased risk of cardiovascular events (multivariate hazard ratio [HR], 0.44; 95% CI, 0.27-0.71) and all-cause mortality (HR, 0.56; 95% CI, 0.36-0.8). This translates into a relative risk reduction of 56% of incident cardiovascular events and a 44% reduction in all-cause mortality. This was a prospective study, as pointed out in an accompanying editorial; however, it does add to the body of medical literature that suggests that the recent National Cholesterol Education Program (NCEP) guidelines should apply to those aged 65 or older (*Arch Intern Med*. 2002;162:1395-1400; editorial 1329-1331).

Beta-Blockers and CABG Patients

Preoperative beta-blockers have been shown to reduce operative complications and mortality in noncardiac surgery, and now 2 studies confirm the importance of beta blockade in patients undergoing coronary artery bypass grafting (CABG). In a large observational analysis of more than 600,000 patients undergoing CABG, preoperative beta-blocker therapy was associated with a small but consistent survival benefit in all patients except those with a preoperative left ventricular ejection fraction of less than 30% (*JAMA*. 2002;287:2221-2227). The most common postoperative complication of CABG is atrial fibrillation. A recent meta-analysis compares beta-blockers, sotalol, amiodarone, and biatrial pacing to prevent atrial fibrillation after heart surgery. All 4 modalities were effective (odds ratio compared to placebo—beta-blockers 0.39, sotalol 0.35, amiodarone 0.48, biatrial pacing 0.46). Each of the 4 drug modalities also significantly reduced length of stay. Significantly, beta-blockers, which are safe and easily administered were as effective as other treatment modalities (*Circulation*. 2002;106:75-80).

Asthma Sufferers: Use Clarithromycin

Asthmatics with evidence of infection with *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* ben-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5517. E-mail: robin.mason@ahcpub.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

efit from a 6-week course of the macrolide antibiotic clarithromycin, according to a new study. In 55 patients with stable asthma in the Denver community, 31 were found to have evidence of mycoplasma or chlamydia infections by PCR and culture. All 55 patients were randomly assigned to treatment with either placebo or clarithromycin 500 mg p.o. b.i.d. 6 weeks. Patients who were PCR-positive and received clarithromycin were found to have a significant improvement in FEV_1 (2.50 pretreatment, 2.69 post-treatment; $P = 0.05$), while those who were PCR negative and those who did not receive antibiotic showed no change (*Chest*. 2002; 121:1782-1788). In a related study, Turkish researchers administered azithromycin 250 mg twice weekly to a group of 11 asthmatics for 8 weeks. No change in FEV_1 was noted, but patients had a marked reduction in bronchial hyperresponsiveness as measured by histamine challenge tests. These patients were not evaluated for evidence of infection prior to initiating therapy (*J Asthma*. 2002;39:181-185).

Good News: Antibiotic Use in Children Down

Meanwhile, efforts by the CDC and others to curb the use of antibiotics in children seem to have paid off. Researchers compared antibiotic prescription rates from 1999-2000 to data from 1989-1990. The number of prescriptions per 1000 individuals age 15 and younger decreased from 838 to 503 a decade later ($P < 0.001$). Prescriptions per 1000 office visits also fell during the same period of time (*JAMA*. 2002;287:3096-3102).

Linezolid Successful in Treatment of MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA), the bane of hospitals coast-to-coast, is effectively treated with linezolid. Previously vancomycin has been the standard of care for treating MRSA. A new study compares linezolid with vancomycin in 460 patients with known or suspected MRSA infections. Patients were treated with either linezolid 600 mg twice daily (n= 240) or vancomycin 1 g twice daily (n = 220) for 7-28 days. Clinical cure rates and microbiological success rates were similar for both groups, and both regiments were well tolerated with similar rates of adverse events. It is suggestive that linezolid is a reasonable alternative to vancomycin for MRSA infections and adds the additional option of oral therapy (*Clin Infect Dis*. 2002;34:1481-1490). The study is timely, as the CDC has reported the first isolate of fully vancomycin resistant *S aureus* in a Michigan man. Several cases of intermediate vancomycin-resistant staph have been reported, but this represents the first case of full resistance (*Morb Mortal Wkly Rep MMWR*. 2002;51:565-567).

SSRIs Relieve Dizziness in Psychiatric Patients

General internists and family practitioners will be delighted to learn that selective serotonin reuptake inhibitors (SSRIs) have been shown to effectively relieve dizziness in patients with psychiatric symptoms, a common office complaint. A group of 60 patients at University of Pennsylvania with psychogenic dizziness, dizziness due to a neurotologic condition (with psychiatric symptoms), or idiopathic dizziness were treated with an SSRI for at least 20 weeks. Two thirds of patients had been treated previously with either meclizine or a benzodiazepine. Twenty-five percent of the patients did not tolerate SSRIs. Of those who finished at least 20 weeks of therapy, 84% improved substantially with no difference between patients with major psychiatric disorders and those with lesser psychiatric symptoms. Patients with peripheral vestibular conditions and migraine also improved with SSRIs (*Arch Otolaryngol Head Neck Surg*. 2002;128:554-560).

DEET-Based Mosquito Repellents Just in Time for Vacation

Just in time for summer vacation, the *New England Journal of Medicine* has published a report showing that DEET-based mosquito repellents are superior to non-DEET-based repellants. DEET is the most common compound found in commercial insect repellents. Recently, several botanical repellents have come on the market as well as 3 repellant-impregnated wristbands. These were tested against DEET containing repellents as well as one other chemical repellent containing IR3535. The worst performers were the wristbands, which offered no protection. The IR 3535-based repellents offer minimal protection while the soybean oil-based botanical repellents work for an average of 95 minutes. In comparison, the formulation containing 23.8% DEET offers complete protection for more than 300 minutes (*N Engl J Med*. 2002;347:13-18).

FDA Actions

Risedronate (Actonel), P&G Pharmaceuticals' bisphosphonate for the treatment of osteoporosis, has been approved in a 35 mg once-a-week form. The drug has been available as a 5-mg daily tablet. As with other bisphosphonates, the drug needs to be taken 30 minutes before meals, and patients must remain upright for at least 30 minutes following administration. ■