HEARTBEAT

The Healthy Heart Report

WOMEN AT RISK

Recent findings on hormone replacement therapy bring clarity to a long-standing debate, but for the millions of women on hormone therapy, questions remain.

by Patrick Perry

Illustrated by Charles Edward Chambers

For the six million women in the United States on hormone replacement therapy, the news sent a proverbial "hot flash" throughout the country. Last July, researchers released long-awaited results from the federally funded Women's Health Initiative (WHI), after halting the first and largest trial comparing the effects of the most widely used type of hormone replacement therapy (HRT) with placebos in healthy women. Enrolling over 16,000 postmenopausal women aged 50 to 90 years—half were given the combined estrogen-progestin drug and the rest placebo—researchers found that women in the trial on HRT were at increased risk of coronary artery disease, stroke, pulmonary embolism and breast cancer. In light of the new study, millions of women scrambled for answers.

"Women who are currently taking estrogen plus progestin should have a serious talk with their doctor to see if they should continue it," said study author Dr. Jacques Rossouw of the National Heart, Lung, and Blood Institute, which sponsored the WHI. "Not only did this therapy not prevent heart disease, it actually increased the risk of heart disease, strokes, and blood clots."

Women jumped onto the hormone therapy bandwagon in the 1960s to ease the symptoms of menopause, bolstered by the longstanding belief that HRT benefited everything from the heart to bone density, preserving youth in the process. But over time, newer medications, such as the statins to control cholesterol and the bisphosphonates and raloxifene (Evista) to prevent bone loss, emerged that proved more efficient in addressing specific health concerns related to hormones lost at menopause. The WHI sought to answer the widely held belief that long-term use of HRT helped prevent heart disease.

"The whole purpose of healthy women taking long-term estrogen-progestin therapy is to preserve health and prevent disease," said Drs. Suzanne Fletcher and Graham Colditz of Harvard Medical School in an editorial accompanying the study

that appeared in *JAMA*. "The results of this study provide strong evidence that the opposite is happening for important aspects of women's health, even if the absolute risk is low. Given these results, we recommend that clinicians stop prescribing this combination for long-term use."

The American Heart Association now says that HRT should not be recommended solely for the prevention of heart disease and that women with a history of one or more heart attacks should avoid hormone replacement if not already on it.

In our previous issue, Dr. Nanette Wenger discussed long-term hormone replacement therapy. In this issue, Dr. Wenger, professor of medicine at Emory University and well-known advocate for women's health, addresses findings from the recent Women's Health Initiative study, offering suggestions to women concerned about HRT and their health.

Q: *In the Sept./Oct. issue of the* Post, *you mentioned that the results of the Women's Health Initiative would offer answers to longstanding questions regarding hormone replacement therapy when completed in 2005. Were you surprised when the study was halted and results released early?*

A: The WHI study was done to see whether hormone replacement therapy offered cardiovascular benefit, which was considered to be a potential major benefit. If there were cardiovascular benefits to hormone therapy, all of the other risks associated with HRT would be acceptable because coronary artery disease is the leading cause of death among women. The WHI was stopped because of the breast cancer risk.

When a study is initiated, researchers set up stopping boundaries, meaning that once any level of benefit is reached, then you must stop the study and allow all the women in the community to learn about the benefit. If a certain level of risk is reached, you must stop the study, so that the women in the study are not put at risk.

Because it was thought that hormone replacement therapy might have cardiovascular benefit against heart attack and stroke, the boundaries for

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heart attack and stroke were wide. The boundary for breast cancer risk—where you stop because of risk—was very tight, and that is why the study was halted. In 2000, we wrote to women in the study to tell them that there was unanticipated increase in heart attack and stroke, but the increase was not enough to stop the study.

I was not particularly surprised by the findings. I was, however, surprised at the early breast cancer risk, because conventional wisdom had said that perhaps five or ten years of HRT does not put a woman at risk. In this study at an average of 5.2 years' followup, we see a risk of breast cancer. For this estrogen-progestin preparation, the risks outweigh the benefits; therefore, the therapy should not be recommended to the population as a prevention.

Having said that, the study tells us nothing about estrogen because the breast cancer risk was not seen with estrogen, and the estrogen arm of the WHI study is continuing.

The reaction of the medical community has been mixed. With data from the WHI, people are less challenging about data from HERS (the Heart and Estrogen-Progestin Replacement Study), which found that the use of estrogen plus progestin in postmenopausal women with heart disease did not prevent further heart attacks or death from coronary heart disease. When HERS came out, critics said that the women in the study were older and sicker, adding that in healthy women, there may be benefit to hormones. Now we have healthy women in the WHI, and there was no benefit.

"For this estrogen-progestin preparation, the risks outweigh the benefits; therefore, the therapy should not be recommended to the population as a prevention."

Q: Should women discontinue hormone replacement therapy?

A: It really depends upon the reason that hormone therapy is given, because the risk of breast cancer for an individual woman is very low. If we treat 10,000 women for a year with this hormone regimen, only seven or eight of them will develop an event: either breast cancer, heart attack, stroke, or blood clots to the lung. That is a very small individual risk. For the woman who is taking HRT for menopausal symptoms, that is very likely an acceptable risk if she has significant symptoms. If the menopausal symptoms are trivial, she may perceive that to be an excess risk.

Q: What is the average risk for a similar population of 10,000 women who are not taking HRT?

A: For the 17,000 women in the study, in the placebo group there were 30 cases of breast cancer, while in the treatment group there were 38.

Q: Is this considered a significant risk?

A: It is significant if you are doing the study of a population for *benefit*. While there was a small benefit seen in colon cancer and hip fracture, overall the risk outweighed the benefit. But we don't want women to panic and immediately stop therapy. This is a discussion that should be conducted with a treating physician. If patients receive therapy for menopausal symptoms, they will probably do better if they stop HRT very gradually. Often, abrupt stopping of HRT will result in recurrence of symptoms, where gradual stopping may not. There may also be issues of uterine bleeding that need to be taken up with a physician. Again, it depends why the therapy was given.

Exploring the Alternatives

Without hormone replacement therapy, what steps can women take to prevent osteoporosis and other conditions associated with a loss of hormones during menopause?

One option is Evista. Launched in 1998, Evista (raloxifene) is the first and only selective estrogen receptor modulator (SERM) approved for the prevention and treatment of osteoporosis in postmenopausal women. Evista is not an estrogen, estrogen replacement therapy, or hormone replacement therapy, but the medication has demonstrated in large clinical trials the ability to help restore bone metabolism to premenopausal levels and significantly reduce the risk of fractures in postmenopausal women with osteoporosis.

To learn more about Evista, the *Post* spoke with Dr. Leo Plouffe, Jr., U.S. medical director of women's health and medicine at Eli Lilly, manufacturer of the drug, about the Women's Health Initiative (WHI) trial and recent research on Evista.

"The WHI trial is definitely a landmark, not just in postmenopausal health but across the board in medicine," Dr. Plouffe told the *Post*. "Fortunately, many medications developed during the past 10 years using rigorous scientific principles are now available. There are statin drugs for heart disease. For osteoporosis, there are bisphosphonates—Fosamax, Actonel—and Evista. Evista was developed along those very rigorous scientific standards, so women have many other options."

The clinical trials of Evista for prevention of osteoporosis involved over 2,000, while the trial for the treatment of osteoporosis involved over 7,700 women.

"You are looking at over 10,000 women who were studied in the osteoporosis trial that showed Evista helped maintain bone mineral density, which was one measure of bone health," Dr. Plouffe says. "More important, the studies show clearly that Evista is effective in lowering the risk of fracture that is associated with osteoporosis."

As a result of the WHI trial and the news on HRT, many women want to know if a medication, such as Evista, poses an increased risk of breast cancer or heart disease.

"We can state very clearly right now, as compared with HRT, there is no increased risk of breast cancer with Evista," Dr. Plouffe explained. "There is also no evidence of increased risk of either heart attack or stroke with Evista. In the large

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If the woman had menopausal symptoms years ago and her physician said that she should continue HRT for cardiac protection, the cardiac protection is not there, so let's not use it.

As we discussed, there is really not a good alternative for hormone therapy for symptoms of menopause. If all of these so-called natural remedies have the benefits of estrogen, they may also have the risk. That is something that people often don't consider.

Q: What about natural alternatives such as soy proteins and phytoestrogens, for example?

A: They've never been studied. If they are purported to have estrogen benefits, they may also have estrogen risks. We don't know. In the absence of studies, we know neither benefit nor risk.

For example, if the woman is taking hormones for osteoporosis prevention, she and her doctor must consider that hormones are not cardioprotective and that there is a small risk of breast cancer. Hormones for prevention of osteoporosis are essentially for a lifetime. Do I want to try something else? Do I want to try a bisphosphonate or selective estrogen receptor modulator (SERM)? Or if a woman decides that her bone mineral density now is fine and she goes off the estrogen, then she is in the position of having to check the bone mineral density in three to six months because there may be bone loss after the hormones are stopped.

"If the woman had menopausal symptoms years ago and her physician said that she should continue HRT for cardiac protection, the cardiac protection is not there, so let's not use it."

Q: Does Evista have any protective benefits for the heart?

A: We are presently studying Evista. There is a huge study now for which I am the coprincipal investigator, where we are studying 10,000 women in 26 countries [the RUTH (Raloxifene Use for the Heart) trial]. We will have an answer in the middle of this decade.

Q: What is your basic message to women concerned about hormone replacement therapy?

A: Certainly the message is, "Don't panic." But this issue is something that you should discuss with your treating physician, and women are doing this. As I have been giving professional conferences around the country on this topic, all physicians—not only the OB-GYNs but also primary care physicians and internists—are saying that they are receiving many calls from women. The most important thing is, we do not have all the answers. But women likely will want the recommendation based on the best currently available information, and that is the way we behave. Can we automatically extrapolate this information to other hormone preparations or routes of delivery or dosages? No. It really remains for these preparations to be studied.

Q: When will the estrogen-only group in the WHI trial be completed?

A: It is scheduled to go to 2005. Having said that, if there are any problems—and the Data, Safety and Monitoring Board is looking at this very carefully—it may be terminated early. If it is not terminated, that means there is no overwhelming benefit or risk and the study will continue until the anticipated end in 2005.

Q: In the absence of HRT, what other measures can women take to decrease

MORE (Multiple Outcomes of Raloxifene Evaluation) clinical trial, the risk of breast cancer was 50 percent lower in women treated with Evista. The same MORE trial showed that in women at high risk for heart disease, there was a 40 percent lower risk of combined stroke and heart attack.

"Those data are really prompting us to further study that potential. One such study is a large ongoing trial known as the RUTH (Raloxifene Use for the Heart) trial of 10,000 women around the world, looking at both heart disease and breast cancer. The RUTH trial is an extension of the MORE trial to study whether Evista could demonstrate potential heart benefit, as opposed to previous trials where the benefit was suggested."

The osteoporosis drug has also demonstrated a positive effect on lowering certain parameters of cholesterol.

"A number of prior studies have shown the benefits of Evista in terms of lowering total cholesterol and lowering LDL, or bad, cholesterol," Dr. Plouffe says. "HDL cholesterol and triglycerides are not modified by Evista, so they are unaffected. Nonetheless, this is felt to be a favorable profile. The more important area of investigation has really occurred during the past three years. With the understanding first from the Heart and Estrogen-Progestin Replacement Study (HERS) trial and now with the WHI trial, there seems to be an increase in cardiovascular events with preparations like Prempro.

"Some preparations of hormones have potential to stimulate inflammatory markers and substances in the body. One of these is called C-reactive protein, which is markedly increased—about 80 percent—by compounds like Premarin, Prempro, and other estrogen preparations. Other preparations, such as Evista, do not affect these inflammatory markers. That is a possible mechanism in terms of explaining the difference between these factors."

The news to date has been good for Evista, and researchers look forward to further studies of its potential in heart and other diseases that affect postmenopausal women.

"We are totally convinced—and many people agree strongly with us—that in terms of providing osteoporosis treatment and prevention, Evista is as good an agent as any of the top-line agents out there," Dr. Plouffe says. "In addition, we think Evista holds a lot of promise for other dimensions. It clearly does not increase risk of breast cancer or cardiovascular events in terms of coronary or stroke. But we think, in the long term, we will be able to show the benefits in these other areas." ▲

the risk of heart disease?

A: If women are interested in preventing coronary artery disease, I suggest that they prioritize the proven preventive interventions—smoking cessation, physical activity, healthy diet and weight control, controlling blood pressure, and taking statins for controlling cholesterol levels.

Q: *What forms of exercise are recommended?*

A: Exercise certainly does not have to be as intensive as marathoning. Regular, modest-intensity physical activity for one half-hour on most, if not all, days of the week is recommended. It doesn't have to be done in half-hour segments. Ten minutes three times a day can be just as effective. Physical activity has benefit for so many health issues, such as weight control, coronary disease, diabetes, and hypertension. The tragedy is that we are becoming a nation of sedentary and obese individuals. If within the United States population, and specifically among women, we could target weight control, physical activity, and smoking cessation, we would be taking major steps in preventing heart attack and stroke.

Q: *Many* Post *readers participate in clinical trials.*

A: Women who enroll in clinical trials are very special people and deserve commendation. The Society for Women's Health Research has had a motto: "There are some things only a woman can do." One of these things is to participate in clinical trials that will give information for the health of women. The inclusion of women in clinical trials has been so recent that many women did not have a role model; they did not know another woman who had done so, and thus recruitment of women into clinical trials has been difficult. Another difficulty is that many women are involved in caregiver roles, rendering it difficult for them to keep appointments. Fewer women than men drive also, and are dependent on others for transportation. ▲

Losing Weight

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all the vegetables on the sandwich. And the sandwiches tasted good. You have to be willing to sacrifice something. But for me, this particular diet was the least amount of sacrifice of anything I had tried before.

Q: *What was different about the Subway program from what you had previously tried?*

A: I finally liked what I was eating. In my past, whether microwaving frozen dinner entrees, drinking liquid shakes, or cooking my own food, I just couldn't stand it. The food tasted like rubber or the diet plan was too difficult. I always had an excuse for stopping a diet.

Q: *Your father is a doctor, and I'm sure that you were doted upon as a child. So when they saw Junior growing up and getting a little heavy, how did your parents try to intercede?*

A: With a family physician as a father, obviously I was very educated about what I should be eating my whole life. When I was around my parents, I would eat fairly well. They didn't keep much junk food in the house and always encouraged me to get out and be active, whether playing basketball, soccer, or tag. But as I got older, I started to make my own decisions.

Even at school I could make choices, such as buying extra items or going to the vending machine after school to get a candy bar.

My parents couldn't control those choices. As educated as I was about eating junk food and fast food when I got to high school, I chose to eat it, anyway. That was really my downfall.

I just got to the point where food was almost a drug to me. And my tolerance kept getting higher and higher. It was almost like an addiction, where I just kept wanting more and more; food made my life complete at the time.

Q: *Thinking back as far as the food portions, did you get heavy because you ate a lot?*

A: I did, I think, because I started eating massive quantities and moving less and less. That's the key—you can't have both. With more physical activity, I probably could have eaten and gotten away with most of what I was eating.

Q: *When did you cease to be physically active?*

A: It didn't happen overnight. I played tennis until early high school and basketball through middle school. But when it came time to sign up for the next year, I decided that I didn't want to play basketball anymore, or I was sick of tennis. Instead of replacing those sports with another activity, I cut activity out altogether. I don't like to go to the gym. I would rather walk around.

Q: *If you could go back to those days, would you do it differently?*

A: I don't know if I could do it any differently. I wasn't ready to sacrifice at that point. Losing weight and keeping it off was very much a mental game, and I don't think I had the maturity at that point to do it. I hope that I would talk to myself as a younger person and say, "Don't go down the same path. Look at what you're going to do to yourself down the road. Look at these old 60-inch pants you're going to wear someday. Don't do it!"