Complimentary CME

Then and Now: Expert Insights on Understanding the Women's Health Initiative Hormone Therapy Trials

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Program Description

More than a decade after the publication of initial results from the WHI trials in 2002 for hormone therapy, there is a perception that hormone therapy is unsafe for postmenopausal women. Numerous studies subsequently stratify WHI trial data by age and time since menopause, which conclude that benefits outweigh risks for many women.

Today's panel will discuss the interpretation of data from the WHI trials, including the place for newer and emerging hormone therapies in the treatment of postmenopausal women.

Learning Objectives

After completion of this activity, participants will be able to:

- Re-evaluate their knowledge of WHI HT trials, including initial and follow-up results for Estrogen Therapy (ET) and Estrogen + Progestin Therapy (EPT)
- Assess the benefits and risks of current and newer HT options to identify individualized treatment
- Recognize key gaps in current clinical guidelines and the interpretation of WHI data
- Be able to communicate on the appropriate use of HT for postmenopausal women

Target Audience

The target audience for this activity includes primary care physicians, physician assistants, nurse practitioners, obstetricians/gynecologists, and other specialists who manage the health of postmenopausal women (e.g., endocrinologists, psychiatrists, orthopedists, cardiologists).

Disclosure of Conflicts of Interest

The following faculty has reported real or apparent conflicts of interest that have been resolved:

- JoAnn V. Pinkerton, MD has served as a consultant to Pfizer (fees to UVA), and has also received research support (PI multicenter clinical trial; fees to UVA) from Therapeutics MD.
- Andrew M Kaunitz, MD, FACOG has received research support from Bayer and Therapeutics MD. He has received honoraria from Allergan, Bayer, Merck and Pfizer, and has received royalties from UpToDate.
- André B. Lalonde, MD has nothing to disclose.

The planners and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

- Andrea Funk has nothing to disclose
- Amanda Glazar, PhD has nothing to disclose
- Lynn Heywood-McLean has nothing to disclose

Accreditation

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Then and Now: Expert Insights on Understanding the Women's Health Initiative Hormone Therapy Trials

Dr. Setty:
More than a decade after the publication of initial results from the WHI trials for hormone therapy in 2002, there is a perception that hormone therapy is unsafe for postmenopausal women. Numerous studies subsequently stratify WHI trial data by age and time since menopause, and conclude that benefits outweigh risks for many women. Today's panel will discuss the interpretation of data from the WHI trials, including the place for newer and emerging hormone therapies in the treatment of postmenopausal women.

Welcome to the program, Dr. Pinkerton, Dr. Kaunitz and Dr. Lalonde. It's a pleasure to have you here today.

Dr. Pinkerton:
We're really happy to be here. It's a beautiful day in Washington.

Dr. Lalonde:
Thank you for inviting us.

Dr. Kaunitz:
It's a pleasure to be here.

Dr. Setty:
Well, let's quickly start and review the following case. Carol is a 54-year-old teacher who began menopause at age 52. She has been experiencing increasingly bothersome vasomotor symptoms such as hot flashes, night sweats and sleep disturbance, as well as vaginal dryness. She has an intact uterus. However, her clinician is reluctant to prescribe her hormone therapy due to safety concerns. As we go through this program, we will gain a better understanding of the risks and benefits of hormone therapy for Carol. Let's start with an overview of the purpose and design of the Women's Health Initiative hormone therapy trials. Dr. Pinkerton, can you start us off?

Dr. Pinkerton:
I'm going to start, but before we start, I want to make a point about Carol. She's having hot flashes and she's 54, and as you listen to this trial, I want you to come back to think about

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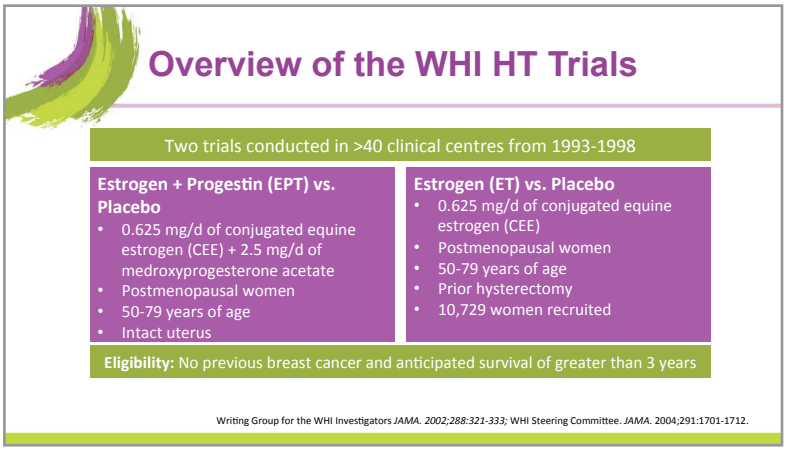
Carole

- Carole is a 54-year old teacher whose last menstrual period was at age 52
- She has been experiencing increasing bothersome vasomotor symptoms including flushes, night sweats and sleep disturbance, as well as vaginal dryness.
- She has an intact uterus
- Her clinician is reluctant to prescribe her hormone therapy due to safety concerns

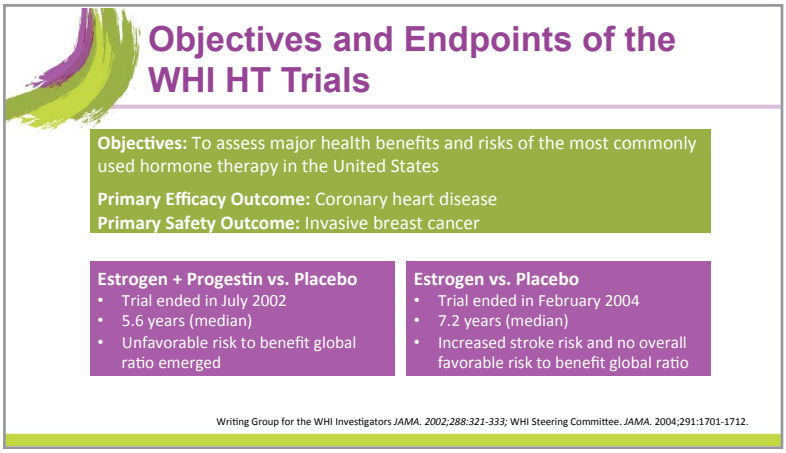
that, because we'll talk about it at the end. But the overview of the WHI, there were two separate trials: One was an estrogen trial using a standard dose of oral 0.625 conjugated equine estrogen combined with a standard dose of progestin, 2.5 milligrams of medroxyprogesterone acetate. They studied about 16,000 women who were between the ages of 50 and 79, and they were all postmenopausal. They had to have no breast cancer and survival anticipated of 3 years. The second trial was estrogen only, the same dose and type of estrogen, oral 0.625 of conjugated equine estrogens, but these women had had a hysterectomy, so without a uterus you didn't need a progestin, and so there were about 10,000 women who were enrolled in that trial.



Dr. Setty:
And what were some of the endpoints that this trial was looking at?

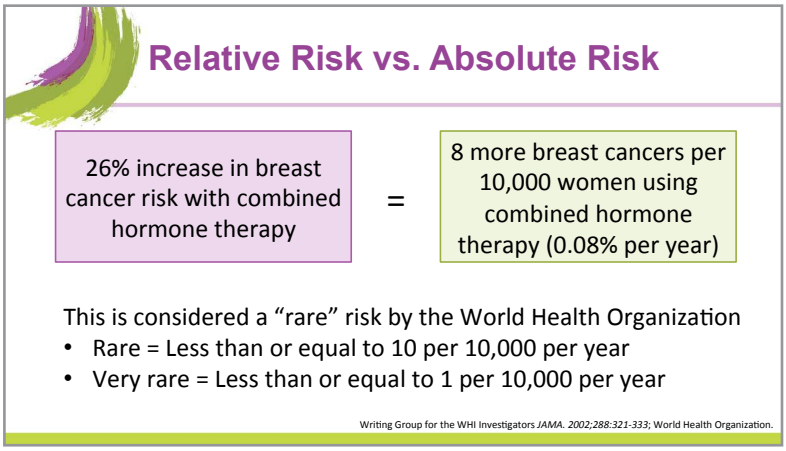
Dr. Pinkerton:
You have to remember that back when this trial was started, we really thought that hormone therapy could prevent heart disease, prevent Alzheimer's disease, decrease the risk of fractures, colon cancer, even breast cancer, so they developed this trial as a prevention trial with a primary outcome to say, "Does it prevent heart disease?" and the primary safety analysis was, "What was the risk on breast cancer?" And so what happened was that unexpectedly in 2002 they ended the estrogen and progestin trial because they found an unfavorable overall global ratio that emerged after 5.6 years, and in the estrogen-only arm, it went 2 years longer—it ended in 2004—so women without a uterus had about an average of 7.2 years in that trial, because again, there was an increased stroke risk and no overall favorable global risk. Again, we weren't looking at specific hot flash treatment. We were looking at prevention of heart disease.

Dr. Setty:
Dr. Lalonde, can you please define for the audience absolute and relative risk, and what does this mean for the patient?



Dr. Lalonde:
This is an extremely important concept, because if it is not properly understood by the clinician, then what he tells the patient is really difficult for them to realize. For example, if you have a 26% increase in risk of breast cancer, this is a relative risk. That means you're comparing a treatment or a medication against a group of people who don't get that same treatment, and that gives you what we call the relative risk, but if you look at absolute risk, then it tells you how many patients per 10,000 cases or patients will get that side effect from that medication. So, it turns out that if you say that you have a 26% risk of breast cancer, in actual fact it's 8 patients per 10,000. This translated at 0.8 patients per thousand. And even more it translates

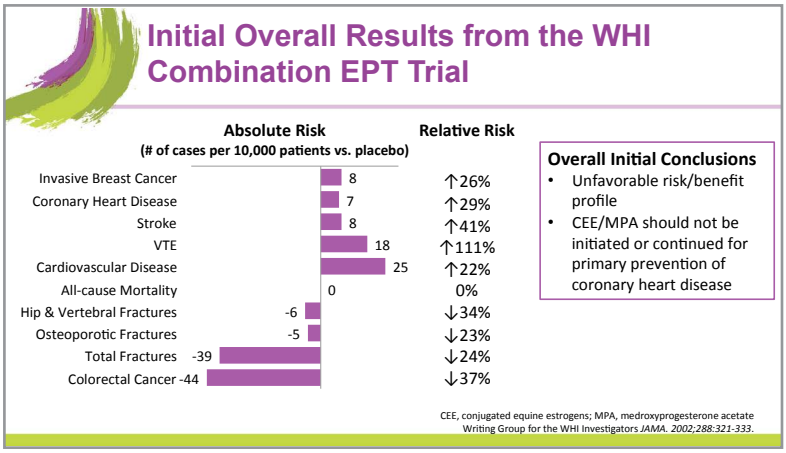
at 0.08 patients per hundred, therefore not even 1 patient, and that is considered a very rare risk by the World Health Organization.



Dr. Setty:
Dr. Kaunitz, can you tell us about the overall initial results from the estrogen-progestin hormone therapy trial?

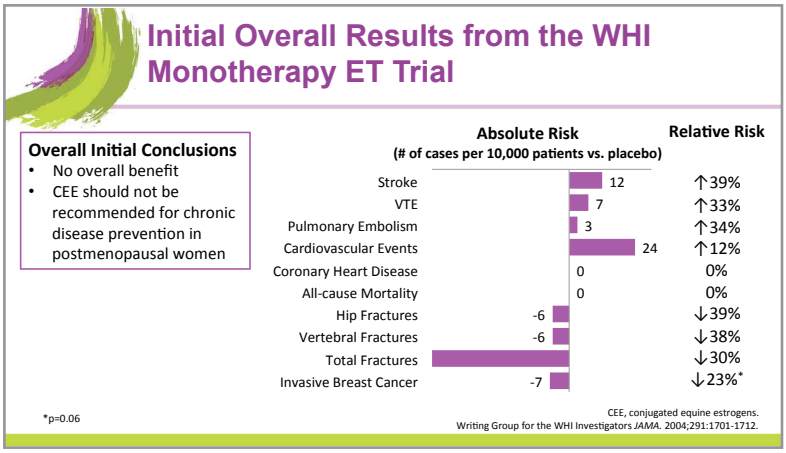
Dr. Kaunitz:
Okay, so in the 2002 headline-generating publication in JAMA, based on the initial findings of women in the larger estrogen-progestin therapy versus placebo group—the group that Dr. Pinkerton explained are women with an intact uterus, like our case—small elevations in risk of invasive breast cancer, coronary heart disease and stroke were noted, so these were small or rare elevations using the WHO criteria that Dr. Lalonde just reviewed with us. It's also important to recognize that in terms of overall mortality, with the initial publication there was no impact: There was no elevation or reduction in risk of overall death. That's an important observation. And then some important protective components of estrogen-progestin therapy were noted. Something that we expected, and this initial analysis confirmed, was a substantial reduction in overall risk of osteoporotic fractures, and we did anticipate this from earlier literature looking at the impact of hormone therapy on skeletal health, but a finding, a protective finding, that we didn't anticipate was a reduced risk of colorectal cancer.

In terms of overall initial conclusions in this 2002 heavily publicized analysis in JAMA—just to summarize what Dr. Pinkerton said earlier—the overall risk-benefit ratio was felt to be unfavorable, and it was on this basis that the estrogen-progestin therapy, as you heard from Dr. Pinkerton, was prematurely discontinued.



Dr. Setty:
Dr. Lalonde, what about the overall results from the initial results of the estrogen-only trial?

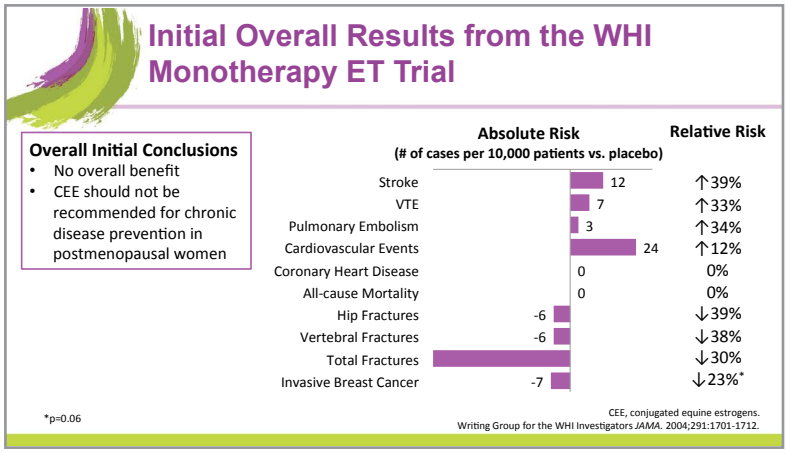
Dr. Lalonde:
Well, there were some substantial differences, and you remember at the beginning we talked that that trial lasted longer, over 2 years longer, and one of the big differences was that there were less complications, such as pulmonary emboli and deep venous thrombosis, but there was a protective effect on breast cancer, which was totally unexpected. Expected was a benefit on reduction of total fractures. So, I



think it's important, although the study stated that it was not recommended for chronic disease prevention, many clinicians felt that the estrogen alone was reassuring.

Dr. Setty:
Dr. Pinkerton, do you have anything to add?

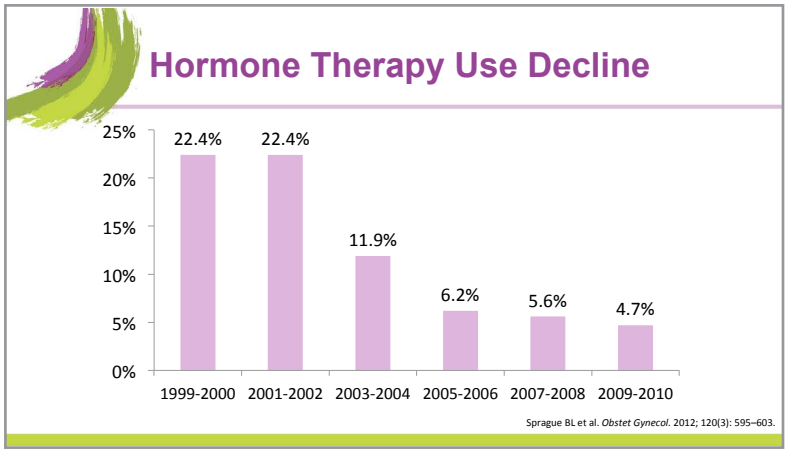
Dr. Pinkerton:
I think that the differences in these trials over time become even more important, that if you have a uterus and we needed to add a progestin, that you saw an increased risk of breast cancer. In the estrogen-only arm we see a decreased risk, and so, therefore, not only do we have to think about the fact that these women were average age 63, so they were older than Carol, but the women who had a uterus who added a synthetic progestin had more risk than those who didn't.



Dr. Kaunitz:
And I'll underscore a point made by Dr. Lalonde. Although the WHI lead investigators concluded, based on all the findings you've just heard, that hormone therapy should not be used to prevent chronic disease—and perhaps that's true for when we are referring to the chronic disease, cardiovascular diseases—in terms of skeletal health, there was a consistent finding, both with the estrogen-progestin arm and the estrogen-only arm, of reduction, an important reduction, of osteoporotic fractures. So, in my mind, prevention of fractures represents an evidence-based, important, consistently-found benefit of hormone therapy for menopausal women.

Dr. Setty:
Yes, that's a very good point. Dr. Pinkerton, what was the unexpected response to the WHI trial?

Dr. Pinkerton:
Fear, fear for women, fear for the practitioners, and what we found was that in 1999, 2000, about 22.4% of women were using hormone therapy. Following the highly publicized release of the estrogen-progestin arm, that number went down to about 11.9%. And then by 2009, 2010, about 4.7% of women had been using hormone therapy. What we found in a consumer survey that was published in Menopause was that the unintended consequences, many women stopped using FDA-approved hormone therapy and may be using non FDA-approved therapy, because symptomatic women still need help.



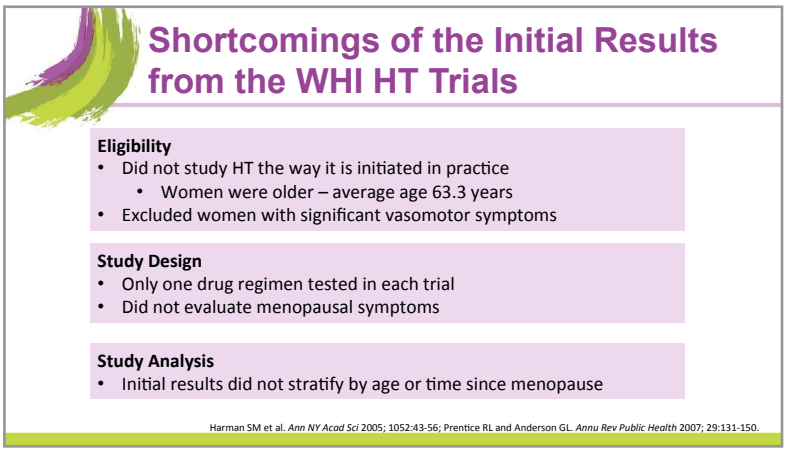
Dr. Kaunitz:
And this explains why our case Carol has found difficulty identifying a provider, a physician, who will treat her bothersome vasomotor symptoms. I know less about what's happening in Canada, but I can say very clearly in the US, this decline that Dr. Pinkerton just referred to in the prevalence of hormone therapy use among US women, it is a radical decline, and it persists to 2016. It has not changed. It remains hard for symptomatic women to find a clinician who would be comfortable, knowledgeable and willing to prescribe hormone therapy.

Dr. Lalonde:
And what's happened, also, we've seen in our country there was a big divide between primary care physicians and specialists, such as an obstetrician-gynecologist, and it got the patient confused, because she would see a primary care physician who'd say, "No, it's too dangerous;" she would see a gynecologist who said, "Wait a minute, let's study your case, let's individualize your treatment." So, that created in the population tremendous confusion. And even to this day it's not resolved as much as we would like to see it.

Dr. Kaunitz:
Yes, and I think we had that same divide in the US with often internists, family physicians, primary care providers being globally reluctant to consider prescription hormone therapy, with specialists being more willing to individualize care and, when appropriate, prescribe. And what happens is that women get caught in the middle. It's not a good situation for them.

Dr. Setty:
Dr. Kaunitz can you talk a little bit about some of the shortcomings of the WHI trials?

Dr. Kaunitz:
One major shortcoming was the age of participants. The median age at which we enrolled women in WHI were women older, actually, than age 63, whereas in clinical practice, as with the case Carol, when women actually present with symptoms, these are young menopausal women who are in general in their late 40's or early 50's. Furthermore, WHI excluded women who had bothersome symptoms at baseline.



Dr. Lalonde:
Also, there was another problem in the study design. For example, they only used one type of hormone, which was oral estrogen and oral progestin, and we know there are many types: vaginal, skin, gels, etc. They also did not evaluate the symptoms that these women have. And further, the biggest problem in the study design was no stratification of age group. In other words, what happened to women who were between 50 and 60, 60 to 70 and over 70?

Dr. Setty:
Since the original publication of the WHI trials, there have been follow-up studies, including stratified analysis of the original results and long-term observational studies. They have given us a lot more information about the use of hormone therapy in women. Dr. Pinkerton, can you comment on some of these studies?

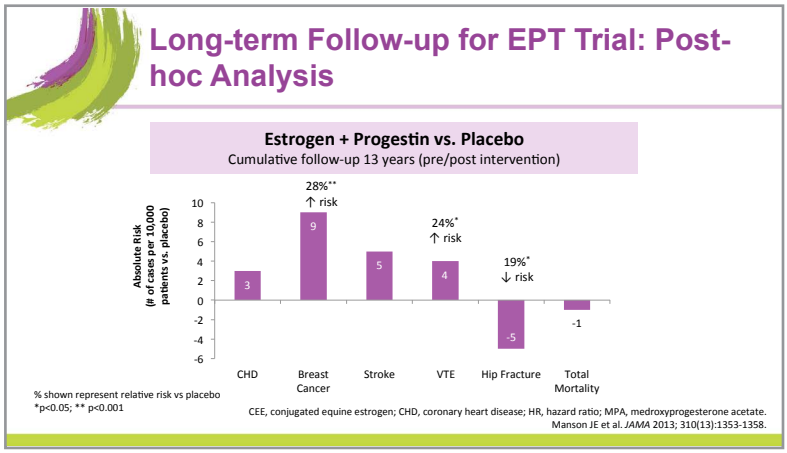
Dr. Pinkerton:
The most important finding came out in 2007 when they stratified by age and time from menopause, and what we found was that in the estrogen and progestin arm, there were fewer heart events and a decrease in all-cause mortality. And then when we look at the estrogen-only arm, the findings were even more robust, that women who took estrogen only had a 44% decrease in heart events and a 23% almost statistically significant decrease in breast cancer. And that means that for women who are symptomatic, who are under 60 or within 10 years of menopause, our patient Carol, she's falling into that benefit group, not just a risk group.

Dr. Setty:
And, Dr. Lalonde, do you have anything to comment on this?

Dr. Lalonde:
Yes, I think the clinicians should look at the woman's age and whether she has symptoms or not. And I think most clinicians used to treat women for menopause when they come in at the age of 45 to 50, 55, if she had symptoms, and what the study has shown us is that you don't start a woman at 65 or 70 years old who has no symptoms on HRT.

Dr. Setty:
So, Dr. Kaunitz, what do some of the long-term follow-up studies to the WHI tell us about the use of hormone therapy in women?

Dr. Kaunitz:
So, in 2013, Dr. JoAnn Manson and colleagues published the long-term follow-up of women in the estrogen-progestin therapy cohort. These were women with an intact uterus at baseline. And the elevated risk of coronary heart events, stroke and blood clot, although was still seen, these elevated risks were substantially attenuated compared with the initial findings. However, the small, as Dr. Lalonde explained, the rare elevated risk of breast cancer did persist. So, when I counsel my patients with an intact uterus regarding initiating or continuing combination estrogen-progestin therapy, I do counsel them that there is a small, but real, elevated risk of breast cancer with ongoing use. However, it's important to recognize that at 13 years follow-up, as with the initial findings, estrogen-progestin therapy clearly did not increase overall mortality. And although attenuated, compared to earlier initial findings, there was some persistent reduction in risk of fractures, including hip fracture.



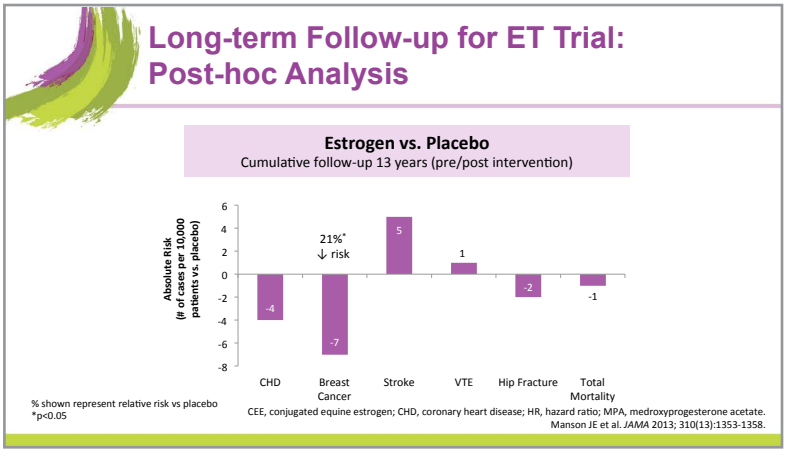
Dr. Setty:
Dr. Lalonde, can you talk to us about the estrogen-only trial?

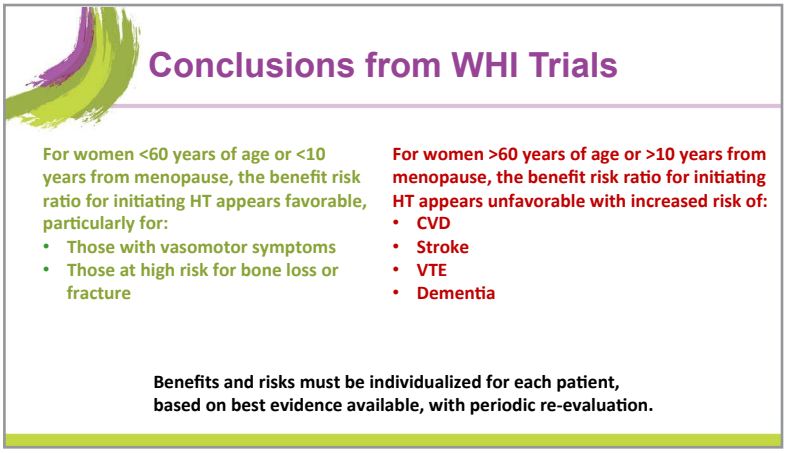
Dr. Lalonde:
Yes, certainly. We anticipated that we would see less side effects with the estrogen-only trial, and that's what we had seen. We'd seen that the cardiovascular and breast cancer risks were very much decreased, and we saw a

small increase in VTE, so really, that was very reassuring for women who did not have a uterus and needed hormone replacement therapy and were of the right age. They had to be close to menopause.

Dr. Setty:
And, Dr. Pinkerton, this is a lot of information. Can you conclude for us?

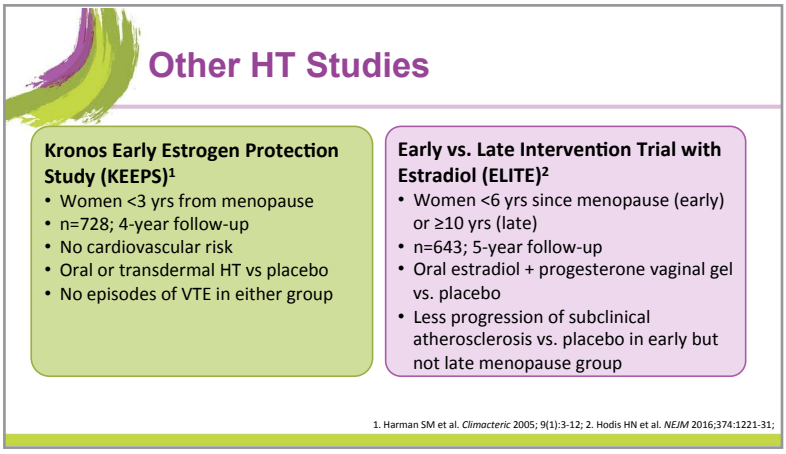
Dr. Pinkerton:
I think it's really important for clinicians to recognize that when you start hormone therapy is the all-important question. So, if you're under 60, if you're within 10 years of menopause, if you're having symptoms, the benefits outweigh the risk for most women. However, if you are over 60, if you are more than 10 years from menopause, the risk outweigh the benefits, and therefore, it's much easier to counsel women to sort of look at how old they are and whether or not they have got symptoms in terms of should we be starting this hormone therapy?





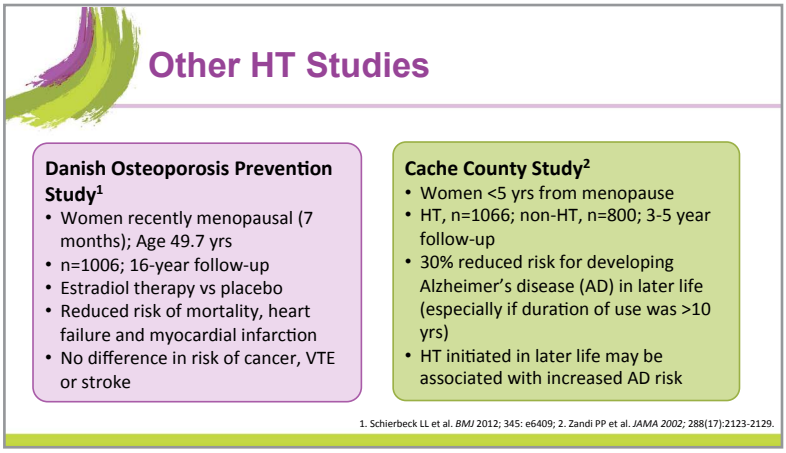
Dr. Setty:
So, what about some of these other studies? Tell us about the use of hormone therapy in women? What are these studies telling us?

Dr. Pinkerton:
So, the first trial is the KEEPS trial. This was women who initiated less than 3 years from menopause, either oral, transdermal or placebo, no cardiovascular risk, no increase in VTE risk in either group, so a nice, safe therapy. And then the ELITE trial looked at women either under 6 years from menopause or more than 10 years from menopause, and what they found was that in those women who initiated it when they were younger, they had less atherosclerotic risk, and I think those are key points. We keep coming back to that initiating early.



Dr. Lalonde:
Another important study came from Denmark, a Danish osteoporosis study. These were women that were menopausal within 6 months. There was 1,000 patients. The average age was 49 years old, and they used

estradiol as the therapy. And what they found was a reduced risk of mortality from heart disease and from myocardial infarction. They also saw no difference in breast cancer risk and VTE.



Dr. Kaunitz:

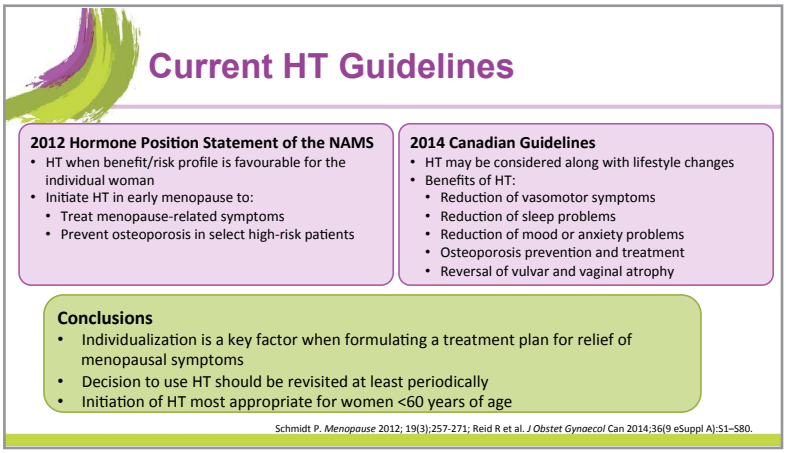
The last non-WHI study we'll discuss, in contrast to the others you just heard about, is observational, and this was the Cache County study conducted in Utah in an ethnically-homogeneous group of women, some of whom in clinical practice used hormone therapy and some who did not. The primary outcome was the diagnosis of Alzheimer's disease later in life, and the principal findings were that hormone therapy use was associated with a substantial reduction in risk of being diagnosed with Alzheimer's later in life. And the two most protective factors were starting hormone therapy soon after the onset of menopause, and this gets back to the theme you keep hearing of safety and benefits with early initiation of use, and then also long duration of hormone therapy use was protective.

Dr. Setty:

So, what do the current guidelines state about the use of hormone replacement therapy in women?

Dr. Pinkerton:

So, the North American Menopause Society currently has the 2012 guidelines, and we looked at this age, so that women under 60 and within 10 years of menopause are the key group, and we looked at prevention of hot flashes and prevention of osteoporosis as the key points that we were trying to make in that guideline.



Dr. Setty:

What about Canada?

Dr. Lalonde:

Well, in Canada, we repeat our guidelines every 4 to 5 years, and a major issue in this guideline was talking about lifestyle issues. It's very important to counsel women for issues such as smoking, exercise, nutrition, alcohol intake. And the major recommendations in the guidelines were on different estrogens. You had to think about different estrogens for different women's needs, and also, obviously, a recommendation to prevent osteoporosis, and in mood disorders and sleep disorders.

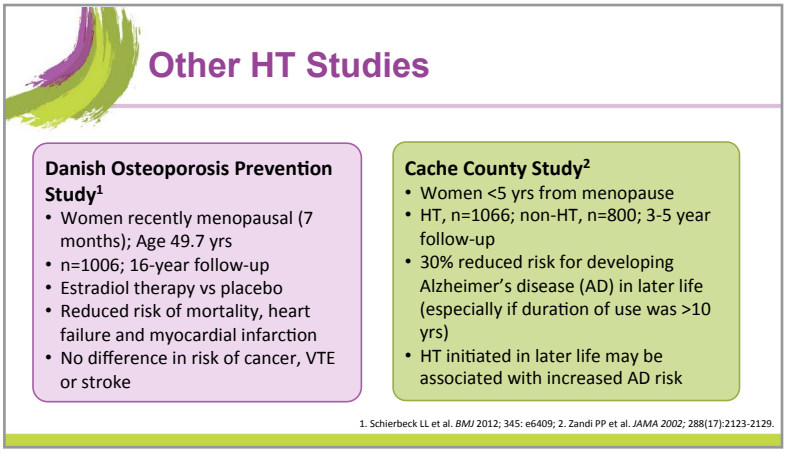
Dr. Pinkerton:

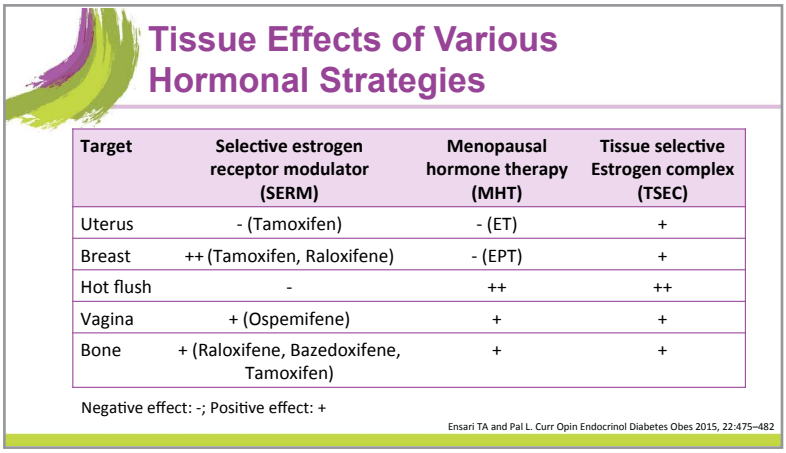
And currently, we are drafting, the North American Menopause Society is drafting, the 2016 guidelines, and we're looking at the difference between estrogen by itself, estrogen and progestin or newer therapies. We're looking at age of initiation – are you under 60, are you within 10 years of menopause – as being safer. And then we're also looking at special populations. What about women who have had oophorectomies for BRCA gene or

women who want to use extended duration past 60? What's an appropriate dose? What's an appropriate duration? How can we help clinicians make those decisions for their women?

Dr. Setty:
Yes, that will be very helpful. What about new menopausal medications, and how do these compare to the drug regimen used in the WHI in terms of safety and efficacy?

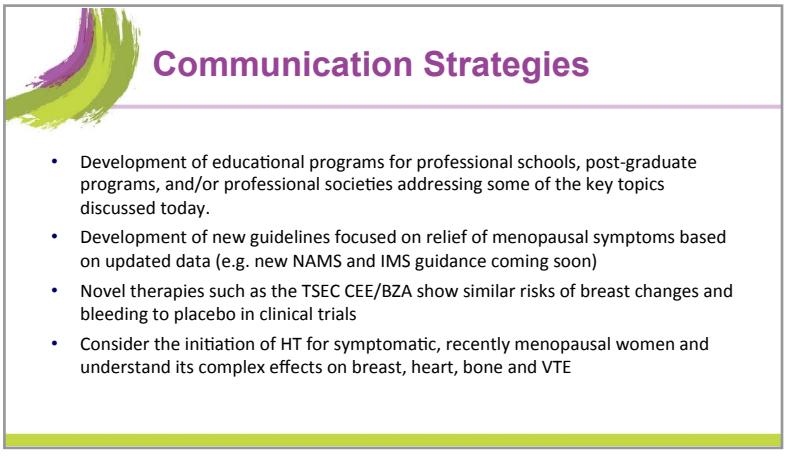
Dr. Pinkerton:
Well, it's really exciting that we have a new therapy for menopausal women, but it's also hard to get this new therapy used because people are still fearful that if you don't have a 5-year trial, long-term follow-up, how do we know the safety? But what we know about this new compound, which is an oral conjugated equine estrogen, an estrogen combined with an oral new SERM called bazedoxifene, which is a strong anti-estrogen on the uterus—you put those two together and you don't need a progestin, so we take away that increased risk of breast cancer that we saw in the WHI. And when you put those two together, we get relief of hot flashes, relief of both frequent and the severity of the hot flashes, we get prevention of bone loss, we get improvement in vaginal symptoms, and at the same time, we don't have the bleeding or the breast tenderness or the breast density changes that we saw with estrogen and progestin. So, it's so exciting that we have a new therapy, but we have to fight fear from people who are afraid to use any hormone therapy, let alone something that's new.





Dr. Setty:
The results of the 2002 WHI study led to a dramatic decrease in the use of hormone replacement therapy in postmenopausal women. However, we now know that for many women under 60, within 10 years of menopause and without any contraindications, who have bothersome hot flashes, who are at high risk for bone loss, the benefits actually exceed the risks. So, while waiting for newer guidelines to come out, how can the appropriate use of hormone therapy in postmenopausal women be communicated to clinicians?

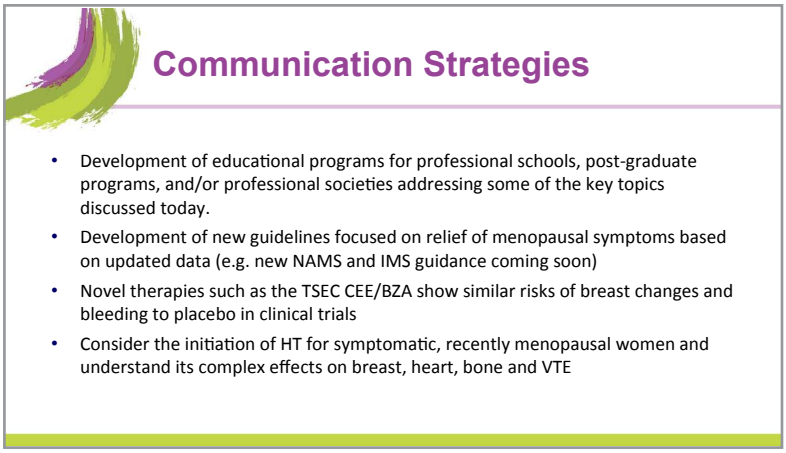
Dr. Pinkerton:
We need to take away the fear of using hormones for those women that it's indicated for and who need it, so whether it's a lecture,



a course, a discussion, we need to get the word out. Our new guidelines in 2016 will help clinicians know who it's appropriate to use. The International Menopause Society is actually looking at a global approach to who should take hormone therapy. But we have to teach and educate both our providers and our patients.

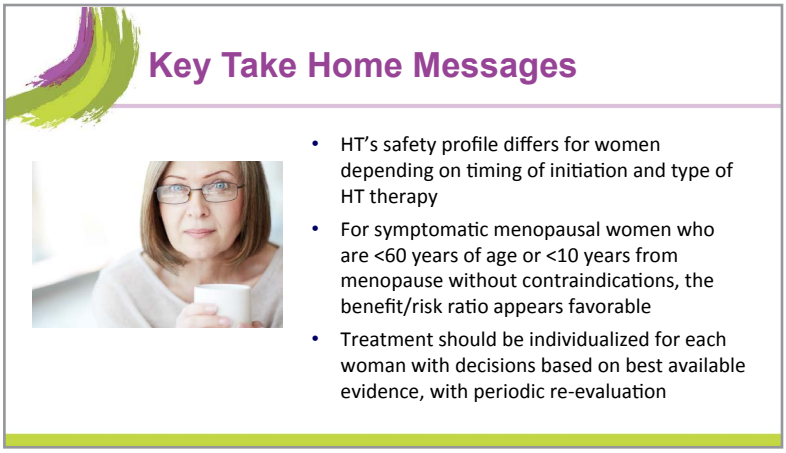
Dr. Lalonde:
We also need to demystify the relative risk and the absolute risk. People do not understand this. And we have worked very hard in Canada with the press. Some of our key menopause experts have made seminars just for the press so that the press has a tremendous influence, and they can explain that, for example, the risk of breast cancer is probably lower than the risk of taking a bicycle through the city of Washington, you know, simple examples that the public can understand and, also, primary care physicians.

Dr. Kaunitz:
So, to wrap things up and moving from communication back to clinical practice, think of Carol. As the three of us have been consistently saying, for recently menopausal or young menopausal women who have bothersome symptoms, the use of hormone therapy should be considered safe for the great majority of candidates. Having said that, if there's an intact uterus and we're talking about estrogen-progestin therapy, women do need to hear about that elevated risk of breast cancer. However, as Andre emphasized, that elevated risk is small and very much comparable to lifestyle choices; for instance, comparable to the risks associated with moderate alcohol consumption.



Dr. Setty:
So, Dr. Pinkerton, what are the key take-home messages you would like to share with our audience?

Dr. Pinkerton:
What you've heard from us today, from all of us, is that if women are symptomatic, if they're under 60 and within 10 years of menopause, that the benefits of hormone therapy exceed the risk for most women. And we need to take it back to the room where the clinician is talking to the woman, looking at her symptoms, looking at how old she is and consider what would be the best therapy for her, and if she's an older woman and wants to initiate, it's probably the wrong therapy. If she's a younger woman, hormone therapy is an appropriate choice for most women.



Dr. Setty:
So, thank you, everyone, for joining us today and being a part of this program. Thank you for sharing all of this very important information with our ReachMD audience.

Dr. Pinkerton:
It's so important. Thank you for having us.

Dr. Lalonde:
Thank you very much for having us.

Dr. Kaunitz:
It's a pleasure, thanks.

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