The Women’s Health Initiative (WHI), established in 1992, included two parallel, randomized, controlled clinical trials that sought to evaluate, respectively, the overall safety of estrogen combined with progestin in women with an intact uterus and unopposed estrogen in women without a uterus. Both studies were terminated early because of safety concerns.

The estrogen-plus-progestin arm of the WHI was stopped in 2002, after a mean follow-up of 5.2 years (more than 3 years before its scheduled completion), because women assigned to treatment had higher rates of invasive breast cancer, cardiovascular disease, and stroke. The unopposed estrogen arm was terminated in 2004, after nearly 7 years of follow-up (8 months before its scheduled completion), because women assigned to treatment gained no cardiovascular benefit; in fact, they had an increased risk of stroke, similar to that found in the estrogen-plus-progestin arm of the WHI.

Subsequently, the FDA issued a boxed warning to be included in the labeling for all estrogen products, stating in part that “Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.” This labeling continues to be a source of controversy among health care professionals.

Critics of the WHI proposed a “timing hypothesis,” suggesting that cardiovascular risks associated with estrogen therapies were confined largely to older women, 10 or more years past menopause, and called for the FDA to revise estrogen labeling. Along similar lines, in 2010, the Endocrine Society issued a scientific statement on postmenopausal hormone therapy in which they concluded that for women younger than 60 years of age, the benefits of such therapy “outweigh the risks in many instances.”

A very different type of timing hypothesis was suggested by an updated analysis of the Million Women Study in the United Kingdom. The study authors concluded that the risk of breast cancer was significantly higher in women who began using hormone therapy before or soon after the start of menopause rather than after a longer period of time.

To obtain different perspectives on best practices regarding estrogen therapies, I interviewed two experts who have published articles about hormone therapy. I asked each of them, separately, the same questions, with two slight exceptions, to see how their views on prescribing hormone therapy might differ.

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David F. Archer, MD, is a board member of the International Menopause Society; a past President and board member of the North American Menopause Society; and a Professor of Obstetrics and Gynecology and Director of the Clinical Research Center, the Obstetrics and Gynecology Residency Program, and the Reproductive Endocrinology and Infertility Fellowship Program at Eastern Virginia Medical School, Norfolk, Va. He is also a coauthor of the Endocrine Society scientific statement.

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Dr. Scialli: I think these therapies were prescribed for all of those conditions, though the manufacturer did not officially promote such indications; whether they unofficially promoted such indications is the subject of court cases. I certainly think the manufacturer promoted these medications for the prevention of heart disease, but even without the official indications, physicians were clearly prescribing hormone therapy for almost any aging-associated problem, either as prevention or as treatment. So, for example, if a woman felt that her skin was getting thin and wrinkly, a physician might prescribe hormones to help her recapture a more youthful appearance.
CONTROVERSIES IN PRACTICE: Estrogen Therapies

P&T: How would you summarize the findings leading up to current FDA recommendations and warnings regarding estrogen and estrogen-plus-progestin therapies?

Dr. Scialli: The best quality studies1-7 show that neither estrogen nor estrogen–progestin therapy is effective in decreasing heart attack or stroke risk, preventing cognitive decline, or treating urinary incontinence.

P&T: There is some disparity between the findings of the WHI and those of certain observational studies of hormone therapy. How would you explain the differences in the conclusions drawn?

Dr. Scialli: Compared with randomized clinical trials, observational studies are easier to conduct; can lead the investigators to generate hypotheses; and, in the absence of better information, can guide therapy. But it’s important to keep in mind that the observational studies aren’t the best-designed form of research.

In an observational study, you find associations. Most, though not all, observational studies have shown that women who took hormones had a lower risk of cardiovascular disease. That means that taking hormones is associated with a reduced risk of cardiovascular disease. What these studies don’t tell you is whether the hormones are responsible for the reduced risk of cardiovascular disease or whether there’s another factor associated with hormone use that’s also associated with a decrease in cardiovascular disease, such as better nutrition and exercise. So if women who took hormone therapy also had better diets and exercised more, what you’d be seeing is a relationship that’s not causal but mediated by other factors.

The randomized clinical trial design takes women who appear to be the same at baseline and randomly assigns some to one treatment and others to a placebo or a different treatment and then compares the incidence of disease. With this design, you’re much less likely to have other factors, such as diet and exercise, interfere with the results. Women assigned to hormone therapy are just as likely as women assigned to a placebo to follow a healthy diet and to exercise.

P&T: Could you outline the risks associated with unopposed estrogen versus estrogen plus progestin for women with and without an intact uterus?

Dr. Scialli: The risks of taking any estrogen therapy, with or without a progestin, include an increase in blood clotting; an increase in gallbladder disease, which is not considered to be as serious as the risk of blood clotting; and a small risk of liver tumors.8,9 For women with an intact uterus, there is a risk of uterine cancer associated with the use of unopposed estrogen. That risk is markedly decreased, and perhaps even eliminated, when estrogen plus progestin is used. The WHI, however, showed that the increase in breast cancer associated with hormone therapy was restricted to women who received estrogen plus progestin; it was not seen in women using unopposed estrogen.1,10

Another observation that may or may not be important in distinguishing these two hormone formulations is that for women who use unopposed estrogen, certain lipid values improve, and that improvement is largely prevented by the use of a progestin. It should be noted that estrogen improves only certain lipid values; triglycerides actually worsen.2,8 That’s one reason why it’s important not to use intermediate endpoints, like lipids, to evaluate a treatment.

What you should be looking for is the punch line—the effect on risk of heart attack and stroke. Even if unopposed estrogen improves some lipid endpoints, if it doesn’t reduce the incidence of heart attack and stroke, then clearly there’s some offsetting effect, which in this case could be the triglycerides.

P&T: What are your thoughts on what has been referred to in the medical literature as the “timing hypothesis”—that within the first 10 years after menopause, the cardiovascular risk associated with hormone therapy is minimal?

Dr. Scialli: I think what’s going on with regard to age and hormone therapy is a little bit of flim-flam. The average age of women in the WHI was something like 63. One of the arguments against the WHI findings was that the women were too old, that they didn’t represent recently menopausal women. But the patients in the WHI represented the population of women for whom estrogen was being recommended at the time the study was designed, and that included women of all ages who were menopausal.

That notwithstanding, there were about 10,000 women in the WHI who were 10 years or less past menopause. Even for this very large sample of women, who met the criterion of being recently menopausal, there was no cardiovascular benefit. The risk of stroke and heart attack seen in the WHI was largely confined to older women. So although there isn’t any evidence that estrogen has a cardiovascular benefit for younger women, it might not be as harmful for them as it is for older women.

P&T: An updated analysis of the Million Women Study in the United Kingdom, published last year,12 found that breast cancer risks among users of estrogen therapies were greater in recently postmenopausal women—the same group of women who would be at less risk for cardiovascular complications. Is there any period of time in which both cancer and cardiovascular risks are minimal?

Dr. Scialli: I haven’t seen that analysis, but even if the breast cancer risk isn’t higher, there’s a breast cancer risk. So I think that in counseling women of all ages, it’s important to inform them that there’s a 24% increase in breast cancer risk associated with estrogen plus progestin,11 and that means there is a lower absolute risk in younger women. In other words, a 50-year-old woman who is not using an estrogen therapy has a 1% chance of being diagnosed with breast cancer. If she’s using estrogen plus progestin, that risk rises to 1.24%. For a woman in her 80s, the risk of having a breast cancer diagnosis is about 12%. Increasing that by 24% raises her risk from 12% to 15%, so for a woman of that age, estrogen plus progestin has
a greater absolute impact.

**P&T:** From your observations, would you say that since the FDA ordered labeling changes on estrogen products, most practitioners now prescribe hormone therapy primarily or exclusively for vasomotor symptoms associated with menopause, or are there other conditions, related or unrelated to menopause, for which it’s still widely prescribed?

**Dr. Scialli:** Now you’re asking me a question to which I don’t know the answer, which is, “What are people doing?” My bet is that most practitioners in the U.S. prescribe systemic estrogen for vasomotor symptoms only, and there are probably many who are prescribing local estrogen for vaginal dryness.

**P&T:** Are local estrogen preparations associated with the same adverse effects as systemic estrogen preparations?

**Dr. Scialli:** Maybe, and that’s a guarded maybe, because it almost certainly depends on the dose—and it may depend on the kind of estrogen. Giving small amounts of estrogen vaginally might not be associated with a rise in the risks of blood clots or endometrial cancer, but I don’t think we have enough data to say.

**P&T:** For which conditions, if any, would you consider prescribing an estrogen therapy?

**Dr. Scialli:** I would offer it as an option for treating vasomotor symptoms.

**P&T:** If a physician is considering prescribing an estrogen therapy, which factors should he or she take into account? Which elements should figure into the physician’s risk assessment?

**Dr. Scialli:** I think that the risk assessment is actually made by the patient. I would offer estrogen therapy to any woman with vasomotor symptoms, along with the other treatments that can be used to relieve vasomotor symptoms, and I would let the woman decide. I don’t think it’s my decision. Of course, if she had a personal history of breast or uterine cancer, blood clots, or one of a number of genetic conditions, often called thrombophilias, that make a person more prone to clotting, I wouldn’t recommend against using estrogen.

**P&T:** In July 2010, the Endocrine Society released a scientific statement in which it was concluded that for menopausal women 50 to 59 years of age or for those younger than age 60, the benefits of menopausal hormone therapy outweighed the risks in many instances, particularly for relief of symptoms caused by estrogen deficiency. Do you feel that is an accurate assessment of the current data?

**Dr. Scialli:** No, I don’t find that to be an acceptable statement at all. It’s the woman who weighs the benefits and risks of hormone therapy—not me, not the Endocrine Society. It’s ludicrous to say that benefit outweighs risk unless you specify that this is the determination of a particular patient. By way of analogy, if a woman has an ectopic pregnancy, I can tell her roughly what her chances are of dying if she has surgery and if she doesn’t have surgery, and she can take those numbers and make a decision. I’ve told her what I’m comparing.

But therapeutic decisions regarding hormone therapy deal with less easily quantifiable matters, such as the woman’s comfort in putting the pill in her mouth every day and her concern about breast cancer and blood clots. A woman whose mother or sister died of a blood clot complication may have a different perspective on that risk than a woman who’s never known someone who has had blood clots. And neither position is right or wrong.

I also dislike the characterization of menopause as “estrogen deficiency.” It treats menopause as a disease, and it’s not a disease; it’s a part of life. Normally, a woman who is having regular menstrual periods has a 17-beta estradiol level of 200 to 400 pg/mL. After menopause, eventually, that level goes down to around 5 to 10 pg/mL.

So when residents or students use the term estrogen deficiency, I pose the following scenario: “One of your patients is an 80-year-old woman with a 17-beta estradiol level of 200 to 400 pg/mL. What do you do?” And they say, “I’d evaluate her for an estrogen-secreting tumor,” which is the correct answer. In other words, if her estrogen level is 5 to 10 pg/mL, she’s not estrogen-deficient; she’s normal. If you saw a menopausal woman with a reproductive-age estrogen level, you’d be very concerned because that would be distinctly abnormal. Similarly, if your patient is a 5-year-old girl, her estrogen level is also somewhere around 5 pg/mL, but I don’t think anyone would suggest that she’s estrogen-deficient.

**P&T:** A manuscript published last March in the *American Journal of Medicine* concluded the following:

Emerging data suggest that the decision to prescribe menopausal hormone treatment and how long to continue should be flexible, based on patient characteristics (e.g., age and time since menopause) and the balance of benefits (symptom relief, coronary heart disease, and bone fractures) and risks (breast cancer, thromboembolic disease, and stroke). We believe that guidelines from the Food and Drug Administration and other official sources should be reconsidered and revised to reflect this personalized approach to the patient.

Do you believe that the FDA should consider revising its guidelines for estrogen therapies to allow for a more personalized approach to the patient?

**Dr. Scialli:** I think FDA product labeling is generally consistent with that point of view—that the decision be based on patient characteristics and the balance of benefits and risks. The problem with the “personalized approach” is that it’s often used to mean that the physician makes the decision, based on patient characteristics, rather than allowing the patient to make the decision after being informed by the physician of any risks she may face, based on specific characteristics. Even if a patient is young and has no family history of blood clotting, no personal history of cancer or blood clotting, and is experiencing severe disability from vasomotor symptoms, the decision is still hers. It shouldn’t be the physician saying, “Gosh, what an excellent candidate you are for hormone therapy!”

**P&T:** Is there any other information in this area of practice that you feel is important to disseminate to *P&T* readers?

**Dr. Scialli:** Yes. Some have theorized that greater benefit or reduced risk may be seen with different types of estrogen or different estrogen-delivery systems (for example, trans-
REFERENCES


DAVID F. ARCHER, MD

P&T: Is it fair to say that before the FDA issued a boxed warning on estrogen and estrogen-plus-progestin therapies, these products were prescribed not only to treat vasomotor symptoms and vaginal atrophy, but also to prevent other conditions associated with aging, such as heart disease, dementia, and osteoporosis?

Dr. Archer: Prior to the Women's Health Initiative (WHI), the principal, FDA-approved indications were menopausal symptoms and vaginal atrophy. Not FDA-approved, but supported by what we thought was a fairly significant amount of evidence, was the use of estrogen to maintain bone mineral density, to slow the onset of Alzheimer's disease, and to reduce the size and extent of atherosclerotic plaque, with the expectation that it would reduce the incidence of heart disease or heart attacks. At that time, it was not unusual for physicians, myself included, to prescribe estrogen therapy not only to treat vasomotor symptoms and vaginal atrophy but also to prevent bone loss and to reduce the risk of heart disease by improving patient lipid profiles and retarding the development of atherosclerosis.

With the publication of the WHI data in 2002, we were told that we could not use estrogen to prevent heart disease. That initiated a major discussion in the U.S. because the women who were enrolled in the WHI were older and further past menopause than many of the women who were receiving hormone therapy for vasomotor symptoms. There was a concern that the WHI had painted postmenopausal women with a rather broad stroke in describing the risks of estrogen, and many physicians believed that estrogen had a protective cardiovascular effect—or at least not a negative cardiovascular effect—on younger women who were closer to menopause than the WHI subjects.

Subsequent analyses from the WHI have tended to support that idea—that younger women between the ages of 50 and 60 who start taking either estrogen alone or estrogen plus progestin do not show an increase in the incidence of cardiovascular events and, with estrogen only, actually show a nonsignificant decrease, even after 10 years. As far as older women (over the age of 60 or 70) are concerned, the evidence is still more in line with the WHI presentation. Once you have established atherosclerosis, you're not going to be able to reverse it through the use of estrogen.

P&T: How would you summarize the findings leading up to current FDA recommendations and warnings regarding estrogen and estrogen-plus-progestin therapies?

Dr. Archer: With the publication of the WHI in 2002, media attention was dramatic. The argument was that we were harming women with the use of hormone therapy, and the FDA reacted very quickly. In November of that year, there was a large meeting at the National Institutes of Health to discuss WHI outcomes, and the FDA followed up by using the WHI data in hormone therapy package inserts, warning that it did not prevent...
heart disease and that women should not be using hormone therapy for that purpose. Then, in 2003, the publication of subsequent WHI analyses\(^6\) failed to show a statistically significant increase in the incidence of cardiovascular events in the hormone therapy (estrogen-plus-progestin) group, but that subsequent publication was never given the same attention as the initial publication.\(^2\)

So that has been the fodder for much ongoing debate, with some people feeling that the WHI had presented its data in a very biased manner. That doesn’t take away from the fact that, with estrogen therapy, older women were shown to have a borderline increase in the incidence of cardiovascular disease, but a large number of these women had known cardiovascular risks—hypertension, diabetes, a history of smoking, or excess weight. We don’t know how long these women had been hypertensive or the severity of their hypertension. For the practicing clinician, the WHI recommendations did not appear to allow room for clinical judgment. It’s difficult to pigeonhole an actual patient into the WHI results.

**P&T:** There is some disparity between the findings of the WHI and those of certain observational studies of hormone therapy. How would you explain the differences in the conclusions drawn?

**Dr. Archer:** The observational studies have been knocked because they commonly include “healthy” women, who are thin and exercise regularly. And the cohort studies, in which the decision to treat or not is based on a collaboration between the woman and the physician, may be subject to a degree of prescribing bias. In addition, people in the lower socioeconomic groups may be less likely to seek or spend money on hormone therapy and thus might be underrepresented in such studies. The WHI tried to bring together all of the disparate patient groups and, in doing so, might have overrepresented women from lower socioeconomic groups, who are at greater risk for heart disease.

It’s difficult to compare apples and oranges, and I certainly would not say the observational study is the be-all and end-all. At the same time, I would caution against applying the results of the WHI to every menopausal woman. Although the WHI represents an amalgamation of a large group of women, it cannot provide the appropriate management strategy for any individual woman. The physician must be allowed to make an informed clinical judgment about whether or not hormone therapy is an appropriate treatment for the patient.

**P&T:** Could you outline the risks associated with unopposed estrogen versus estrogen plus progestin for women with and without an intact uterus?

**Dr. Archer:** The purpose of using an estrogen plus progestin for women who have a uterus is to counteract the continual exposure to estrogen, which would otherwise put them at elevated risk for endometrial cancer.\(^4\) The woman who has undergone hysterectomy does not require a progestin.

To date, it’s the estrogenic component of hormone therapy that’s been implicated in causing the majority of its adverse effects, the most prominent being venous thromboembolism and stroke, either thrombotic or hemorrhagic, though thrombotic is more likely related to estrogen use. In the WHI, the risk of stroke was increased within all age brackets.

An increased risk of breast cancer had been argued to be an effect of estrogen,\(^2\) but there is evidence suggesting that progestin could be the cause. The WHI points the finger at medroxyprogesterone acetate as the progestin that increases breast cancer risk.\(^2,9\) These data are also confirmed in a French observational study called the E3N,\(^10\) which found that natural progesterone does not increase the risk of breast cancer with estrogen, although progestins do with the use of at least one type of estrogen—estradiol—rather than conjugated estrogen.

The risk of breast cancer remains a controversial issue because the estrogen-only arm of the WHI continues to show a reduced incidence of breast cancer in all age brackets,\(^4\) which would imply either that it is progestin that increases the risk or that estrogen reduces the risk of neoplasia in the breast.

**P&T:** From what you’ve said previously, it seems that you are a proponent of what has been referred to in the medical literature as the “timing hypothesis”\(^11\)—that within the first 10 years after menopause, the cardiovascular risk associated with hormone therapy is minimal. Do you believe that hypothesis has merit?

**Dr. Archer:** I do.

**P&T:** An updated analysis of the Million Women Study in the United Kingdom, published last year,\(^12\) found that breast cancer risks among users of estrogen therapies were greater in recently postmenopausal women—the same group of women who would be at less risk for cardiovascular complications. Is there any period of time in which both cancer and the cardiovascular risks associated with hormone therapy are minimal?

**Dr. Archer:** The risks are probably minimal in younger women; the incidence of both breast cancer and cardiovascular disease increases with age. I have not read the updated Beral analysis,\(^13\) but it has been argued that the Million Women Study was fraught with potential biases, reflected in both design and interpretation.\(^13\) The studies of breast cancer incidence in women using hormone therapy generally cite 1.24 as the relative risk or odds ratio.\(^5\) Most epidemiologists would argue that anything between 1 and 2 is a weak association and could be attributed to chance, even with a 95% confidence interval greater than 1.00.

In addition, there might be a degree of publication bias at work here. If you’re studying estrogen therapy, using breast cancer as an endpoint, and you don’t show an increased risk, you may not get your study published, or you might think there’s something wrong with your data and fail to report it. There are a variety of studies on breast cancer incidence, and it is my impression that incidence increases with age and that younger women who are exposed to estrogen have either no increased risk or a reduced risk compared with control groups.
The large Nurses' Health Study in the U.S. found no increase in breast cancer incidence until the women had been using estrogen therapy for 15 years.14

P&T: From your observations, would you say that since the FDA ordered labeling changes on estrogen products, most practitioners now prescribe hormone therapy primarily or exclusively for vasomotor symptoms associated with menopause, or are there other conditions, related or unrelated to menopause, for which it's still widely prescribed?

Dr. Archer: I'm not privy to prescribing data, but my impression is that the average practitioner prescribes it principally for vasomotor symptoms and vaginal atrophy. Secondarily, in younger women who have a significant family history of osteoporosis and low bone mass, they may use it to manage the low bone mass problem.

P&T: Are local estrogen preparations associated with the same adverse effects as systemic estrogen preparations?

Dr. Archer: It really depends on the local estrogens you're using. If you're using a vaginal estrogen that delivers a dosage that's high enough to reduce your hot flushes, such as the 0.5-mg or 0.1-mg/daily estradiol vaginal ring (Femring),15 you might see some of the same adverse effects as with the oral forms. If you use a vaginal product that delivers a much lower amount of estrogen, like the 7.5-mcg (0.0075-mg)/daily estradiol vaginal ring (Estring)16 or 10- to 25-mcg (0.01- to 0.025-mg)/daily estradiol vaginal tablets (Vagifem),17 which have a limited impact on circulating estradiol levels, then you might not have the same effects as with the oral formulation. The problem is that the FDA lumps them all together in class labeling.

P&T: For which conditions, if any, would you consider prescribing an estrogen therapy?

Dr. Archer: I prescribe estrogen for vasomotor symptoms, for vaginal atrophy, and for low bone density in women who have a very strong family history of osteoporosis. Those are the major reasons for which I'm prescribing hormone therapy at the present time.

P&T: If a physician is considering prescribing an estrogen therapy, which factors should he or she take into account? Which elements should figure into the physician’s risk assessment?

Dr. Archer: I think doctors should evaluate the severity and impact of the patient's vasomotor symptoms—her quality of life and how much the symptoms interfere with her normal daily activities. They should also consider other risks that patients might have, such as a family history of venous thromboembolism, breast cancer, or early-onset cardiovascular disease.

Finally, they should critically review the data they've obtained in the office setting—the patient's blood pressure, weight, and body mass index.

In the end, the physician in consultation with the consumer has to say, “These are your risks, these are the benefits. My decision, based on what I see in your history and physical findings, and what I know about estrogen, is that you are or are not a candidate for hormone therapy.”

Having said that, the pushback from the consumer is often, “I don’t want to use hormone therapy”—because of what they've seen in the lay press. Certainly, they're entitled to that decision, but after a while, I think doctors get tired of making recommendations when patients are unwilling to listen to them, and they quit.

P&T: In the 2010 Endocrine Society's scientific statement on postmenopausal hormone therapy, of which you were a coauthor, it was suggested that for menopausal women 50 to 59 years of age or for those younger than age 60, the benefits of menopausal hormone therapy outweighed the risks in many instances, particularly for relief of symptoms caused by estrogen deficiency.18 On what data is that statement based?

Dr. Archer: It’s based on a combination of findings. The number of perimenopausal women, thought to be around 25% to 30%, who have moderate-to-severe vasomotor symptoms, are best served by treatment with hormone therapy because it offers them the most improvement in quality of life. Hormone therapy is more effective in treating vasomotor symptoms than either the serotonin reuptake inhibitors or the serotonin-norepinephrine reuptake inhibitors, which act on the central nervous system,19 and such nonhormonal, over-the-counter products as black cohosh.20 Superior efficacy, combined with the fact that recent WHI analyses show no increased risk of heart disease in women who are within 10 years of menopause, is the basis of that statement.

P&T: A manuscript published last March in the American Journal of Medicine concluded the following:11

Emerging data suggest that the decision to prescribe menopausal hormone treatment and how long to continue should be flexible, based on patient characteristics (e.g., age and time since menopause) and the balance of benefits (symptom relief, coronary heart disease, and bone fractures) and risks (breast cancer, thromboembolic disease, and stroke). We believe that guidelines from the Food and Drug Administration and other official sources should be reconsidered and revised to reflect this personalized approach to the patient.

Do you believe that the FDA should consider revising its guidelines for estrogen therapies to allow for a more personalized approach to the patient?

Dr. Archer: I think it would be appropriate for the FDA to revisit the WHI data to see how findings have been reported in the package inserts. Trying to formulate guidelines, however, is very difficult because prescribing is highly individualized, with the practitioner using his or her own clinical judgment in assessing the patient’s history, physical condition, and laboratory findings. So I would be averse to any group putting together what might be called a guideline, saying these are the people who should and these are the people who should not take hormone therapy. There are well-known absolute contraindications, but when you get into relative contraindications, it becomes very difficult to apply broad recommendations.

P&T: Is there any other information in this area of practice that you feel is important to disseminate to P&T readers?

Dr. Archer: I think it’s important for P&T committees to
take into account the wide variety of estrogen products now available and to recognize that some women do better on one product than another. There may be differences between conjugated estrogen, estradiol, and ethinyl estradiol in terms of their effects on an individual patient, so to take the position that “the estrogen on our formulary is good for everybody” may deprive the consumer of some potential benefit.

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