

# Clinicians' FORUM

From time to time, the editors of *Menopause Management* field interesting clinical questions and dilemmas. In this forum, our Editorial Advisory Board members and guest commentators,\* experts in a range of fields related to midlife women's health, tell readers how they handle these situations.

The viewpoints expressed in "Clinicians' Forum" are those of the contributors, and not necessarily those of *Menopause Management* or The North American Menopause Society (NAMS).

## **Question:** Is there a place for continuous estrogen-only therapy in the symptomatic postmenopausal woman with an intact uterus?

### **Answers:**

My answer is "maybe."

There can be no doubt that what goes around, comes around—and estrogen-only therapy for a symptomatic postmenopausal woman with a uterus certainly falls into this

category. Cyclical use of estrogen without progestin was advocated up through the 1970s.

Although some physicians suggested that giving progesterone for 5 to 10 days periodically was desirable when using estrogen therapy (ET)—as a progestin promoted complete endometrial shedding and limited prolonged and irregular bleeding—this was not the standard of practice.<sup>1</sup> Early reports suggested minimal, if any, increase in endometrial hyperplasia with ET. During a 20-year period at Sloan Hospital for Women in New York, Gusberg and Hall<sup>2</sup> reported only 23 cases of uterine cancer in women who had taken ET. However, data that substantiated an increased incidence of endometrial hyperplasia and cancer with unopposed estrogen use changed this practice in the mid 1970s.<sup>3-5</sup>

Turning the clock ahead to the early 2000s, most physicians didn't consider estrogen alone as an option for their postmenopausal patients with a uterus until data began to emerge that the benefits of a progestin added to estrogen for postmenopausal therapy may not outweigh the risks. Data that Shah et al<sup>6</sup> recently reported in *Menopause* supported current thinking that progestins—although prescribed to prevent endometrial hyperplasia—may not be a



Gloria Bachmann, MD

## **Participants**

Gloria Bachmann, MD  
Professor of Ob/Gyn and Medicine  
University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School  
New Brunswick, NJ

Steven R. Goldstein, MD  
Professor of Obstetrics and Gynecology  
New York University School of Medicine  
New York, NY

Howard N. Hodis, MD  
Harry J. Bauer and Dorothy Bauer Rawlins Professor of Cardiology  
Professor of Medicine and Preventive Medicine  
Professor of Molecular Pharmacology and Toxicology  
Director, Atherosclerosis Research Unit  
Keck School of Medicine  
University of Southern California  
Los Angeles, CA

Marcie K. Richardson, MD  
Assistant Director of Ob/Gyn for Clinical Quality  
Harvard Vanguard Medical Association  
Boston, MA

Isaac Schiff, MD  
Joe Vincent Meigs Professor  
Harvard Medical School  
Chief, Vincent Memorial Obstetrics and Gynecology Service  
Massachusetts General Hospital  
Boston, MA

\*John Studd, DSc, MD, FRCOG  
Professor of Gynaecology  
Chelsea and Westminster Hospital London  
London, England

\*Ian H. Thorneycroft, PhD, MD  
Professor, Obstetrics and Gynecology  
University of South Alabama College of Medicine  
and Bay Area Physicians for Women  
Mobile, AL

neutral addition when considering other effects, especially breast effects. These investigators did a meta-analysis of 13 large observational studies, and reported that estrogen alone was less likely to be associated with breast cancer than combined estrogen and progestin hormone therapy (EPT) for postmenopausal women.<sup>6</sup>

*There can be no doubt that what goes around, comes around—and estrogen-only therapy for a symptomatic postmenopausal woman with a uterus certainly falls into this category.*

— Gloria Bachmann, MD

I propose the “maybe” answer to the question about estrogen-only use for non-hysterectomized postmenopausal women for several reasons. On the side that estrogen alone may not be such a bad idea, I refer to data showing that ultra-low-dose estrogen—such as the dose used in the transdermal estrogen patch that releases 14 mcg of estradiol daily—does not produce hyperplasia of the endometrium,<sup>7</sup> although product labeling still recommends that a progestin be given for 14 days every 6-12 months. This same rationale—that there may be minimal if any systemic absorption, and therefore a progestin may not be needed—applies to low-dose, vaginally administered estrogen. Therefore, with reduced estrogen dosage, progestin use does not appear to be necessary.

However, in support of the side advocating progestin use is the fact that low doses of estrogen are often not effective for symptom relief in postmenopausal women. Therefore, endometrial protection is still needed in women who require standard or higher doses of estrogen for control of menopausal complaints. Options that may minimize systemic progestin exposure appear to be a practical compromise. There are data suggesting that long-cycle EPT (continuous ET combined with 14 days of

progestin every 3 months<sup>8</sup> or 6 months<sup>9</sup>) may not result in endometrial hyperplasia or cancer. As well, placement of the levonorgestrel-releasing intrauterine system also would limit systemic absorption, but would produce a local progestational effect on the endometrium.<sup>10</sup>

In effect, progestin use may not be an all-(continuous progestin with estrogen) or-nothing (estrogen use without any progestin) situation. Innovative regimens that minimize progestin exposure may be the answer until a selective estrogen-receptor modulator is developed that produces both symptom relief and endometrial protection.

— Gloria Bachmann, MD

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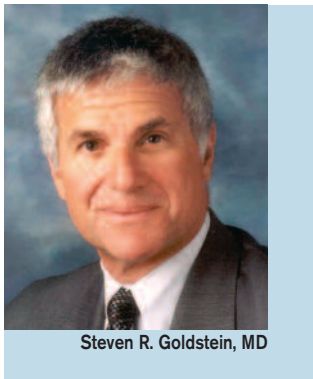
I believe the answer is a resounding “yes,” but only for the right people—for those we can be sure we are not increasing the risk for endometrial cancer. Let us examine some facts.

The desire to reduce or, in this scenario,

eliminate the progestogen component of hormone therapy (HT) is not new. In fact our esteemed editor-in-chief, Dr. Utian, talked of using “the smallest dose required to prevent endometrial cancer” in an editorial as early as 1989.<sup>1</sup> Initially, the impetus for this was to eliminate cyclical bleeding, water retention, breast discomfort, mood alterations and adverse lipid effects.<sup>2</sup> More recently, the motivation has come from the widely publicized Women’s Health Initiative (WHI) results. The use of 0.625 mg/day unopposed conjugated equine estrogens (CEE) in hysterectomized women resulted in no increase in breast cancer.<sup>3</sup> However, the addition of medroxyprogesterone acetate (MPA) 2.5 mg daily in women with a uterus resulted in a statistically significant increase in breast cancer.<sup>4</sup> Thus, it is clear why, as physicians, we would like to eliminate or even reduce progestogen exposure in women on HT.

### Protecting a Small Minority

One might ask why we give such women progestogen in the first place. Everyone reading this knows that it is because we want to prevent endometrial cancer. But how



Steven R. Goldstein, MD

many are aware that in the unopposed estrogen arm in a double-blind study of women on 0.625 mg of CEE there was an incidence of simple hyperplasia of only 7% (21/298) at 6 months.<sup>5</sup> A similar study resulted in 18% hyperplasia after 15 months of unopposed estrogen.<sup>6</sup> Thus, we are currently

treating 100% of women with a uterus to protect a small minority who may be prone to developing simple hyperplasia, and eventually complex atypical hyperplasias, and even malignancies.

Transvaginal ultrasound (TV U/S), introduced in the mid-1980s, allows a degree of image magnification as if we were doing ultrasound through a low-power microscope (sonomicroscopy).<sup>7</sup> Numerous studies in women without bleeding have consistently

shown that a distinct endometrial echo  $\leq 5$  mm has a negative predictive value of 99%.<sup>8</sup> In fact, in one study of 1,926 asymptomatic postmenopausal women, a TV U/S finding of  $\leq 5$  mm had a 99.94% negative predictive value for excluding cancer and a 99.77% negative predictive value for excluding hyperplasia!<sup>8</sup> (Unfortunately, the positive predictive value of an echo  $>5$  mm is not so helpful, but that is a story for another time.)

### Using Transvaginal Ultrasound

In a paper titled “The Case for Less-than-Monthly Progestogen in Women on HT: Is Transvaginal Ultrasound the Key?”<sup>9</sup> I suggested that some women with an initial, thin, distinct endometrial echo  $\leq 5$  mm could be monitored with TV U/S. If, after an initial progestogen withdrawal, their echo was still  $\leq 5$  mm (remembering the high negative predictive value just discussed), the intervals between progestogen withdrawals could be increased. If they continue to have withdrawal bleeding, I have empirically gone no longer than 6 months. Thus far, however, 56% of the patients in this pilot study have had no initial withdrawal bleeding, and rather than any additional progestogen, have had ongoing endometrial echo surveillance with TV U/S. As long as the endometrial thickness remains  $\leq 5$  mm they are continued on unopposed estrogen. The interval of ultrasound surveillance has been increased, such that some are now scanned only every 6 months. Some of the patients have gone as long as 30 months on unopposed estrogen with no bleeding and no increase in endometrial thickness.

There are some limitations that should be stressed. These women are on varying doses and routes of administration of estrogen consistent with personal preference and the concept of “lowest effective dose.” Second, not all patients are candidates for a meaningful TV U/S exam in which there is an adequate depiction of the endometrial echo. Previous surgeries, obesity, axial uterus and coexisting myomas can all diminish the capability of TV U/S. But, clearly, a significant number of postmenopausal women can reduce or even eliminate progestogen, and can be managed with

unopposed estrogen using TV U/S surveillance and its high negative predictive value to ensure patient safety.

– Steven R. Goldstein, MD

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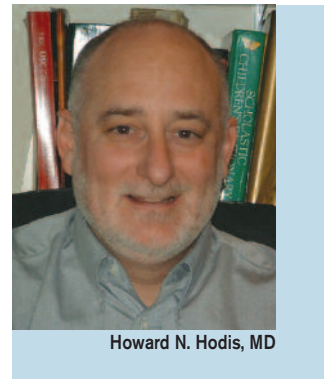
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There is a large and consistent body of literature demonstrating that HT is associated with the reduction of atherosclerotic coronary heart disease. As data from randomized controlled trials accumulate, the results look more and more like the findings from the 20-plus observational studies that indicate that young, symptomatic postmenopausal women who use HT for long periods of time have lower rates of coronary heart disease than postmenopausal women who do not use HT.<sup>1</sup>

#### Support from the Literature

Consistent with the accumulated literature, recent findings from the WHI support two

important modifying factors of HT in the reduction of coronary heart disease: timing of initiation and duration of use. In the WHI estrogen trial, hysterectomized women who were randomized to CEE therapy between the ages of 50 and 59 years had less frequent coronary heart disease events than women randomized to placebo, whereas coronary heart disease events in women who were randomized between the ages of 60 and 69 years and 70 and 79 years did not differ between treatment groups ( $P = 0.07$  for trend).<sup>2</sup> The composite end point of myocardial infarction, coronary death, coronary artery revascularization and angina was significantly reduced by 34% in the CEE group relative to placebo (RR, 0.66; 95% CI, 0.45-0.96).<sup>2</sup> This beneficial effect of CEE alone in younger postmenopausal women is similar to the significant reduction of coronary heart disease seen in women taking CEE + MPA, an effect that appears to be associated with



Howard N. Hodis, MD

time since menopause at HT initiation. In the WHI EPT trial,<sup>3</sup> women who were randomized to CEE + MPA within 10 years of menopause had an 11% reduction in coronary heart disease events, whereas women randomized between 10 and 20 years after menopause had a 22% increased risk of coronary heart disease, and women randomized more than 20 years after menopause had a 71% increased risk of coronary heart disease ( $P = 0.036$  for trend).<sup>4</sup> On a pathophysiologic level, these clinical event data are consistent with the beneficial effect of estradiol therapy in reducing the progression of subclinical atherosclerosis in relatively healthy arteries (as measured by carotid intima-media thickness),<sup>5</sup> and with HT's lack of effect on atherosclerosis progression in diseased arteries (measured as late disease by quantitative coronary angiography).<sup>6</sup> Recent data from the WHI confirm findings from previous studies, including the statistically significant trend in the reduction of coronary heart

disease events seen with CEE + MPA in the WHI EPT trial ( $P < 0.02$ )<sup>7</sup> and the Heart and Estrogen/progestin Replacement Study ( $P = 0.009$ ),<sup>8</sup> both of which show that duration of therapy is important in reducing coronary heart disease events. Consistent with the WHI estrogen and WHI EPT randomized trials, data from the WHI observational study suggest that more than 5 years of HT is necessary

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– Howard N. Hodis, MD

before reduction of coronary heart disease events becomes evident.<sup>9,10</sup> Previous studies also show a significant reduction of coronary heart disease after 5 to 10 years of HT.<sup>11-13</sup>

### A Viable Consideration

In sum, a large body of data strongly suggests that early initiation (within 6 years of menopause) and prolonged administration (for more than 5 to 10 years) of HT are important for maximizing the reduction of coronary heart disease.<sup>1</sup> A recent meta-analysis of 23 randomized controlled trials confirms the importance of initiating HT early in the postmenopausal period for the reduction of coronary heart disease.<sup>14</sup> These data are similar to the well-understood primary prevention effects of HT on osteoporotic bone fractures. Combined with data indicating that estrogen alone may not increase the incidence of breast cancer (and, in some cases—such as in estrogen-adherent individuals—may significantly reduce breast cancer [RR, 0.67; 95% CI, 0.47-

0.97], especially ductal carcinoma, the most common breast cancer [RR, 0.71; RR, 0.52-0.99]),<sup>15</sup> ET remains a viable consideration for the primary prevention of coronary heart disease in postmenopausal women.

Further investigation is warranted in determining the optimum HT regimen and appropriate population of women who will maximally benefit from the reduction of atherosclerotic coronary heart disease with HT. One such trial, the NIH-funded Early versus Late Intervention Trial with Estradiol, is specifically designed to study the hypothesis of timing of initiation of ET in the reduction of subclinical atherosclerosis progression and cognitive decline in women less than 6 versus more than 10 years postmenopause ([www.usc.edu/medicine/aru](http://www.usc.edu/medicine/aru)). Until such results become available, the large and consistent body of data demonstrating the reduction of atherosclerotic coronary heart disease with HT in primary prevention (particularly in young postmenopausal women) should be considered (and as with all medications, relative to the risks and benefits) when treating women with menopausal symptoms.

– Howard N. Hodis, MD

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A discussion of this question raises many issues, most of which menopause clinicians have been struggling with for decades. It comes down to this question: What are the risks and benefits of ET? Would that the answer to that question were clear, or even stayed in a stable state of uncertainty for a few years! That said, here are some relevant comments, I hope.

*The side effects of progestogens are one of the main reasons many clinicians wish they could be comfortable prescribing unopposed estrogen.*

– Marcie K. Richardson, MD

### **PMS in a Bottle**

One of my colleagues warns patients that MPA is like “PMS in a bottle.” The side ef-

fects of progestogens are one of the main reasons many clinicians wish they could be comfortable prescribing unopposed estrogen.

### **Endometrial Cancer**

Both observational and randomized controlled studies<sup>1,2</sup> conclusively demonstrate the risk of endometrial malignancy in a woman with an intact uterus who uses estrogen-only therapy at what used to be standard dosing. A recent observational study<sup>1</sup> suggests that this risk is for both aggressive and indolent forms of this common female cancer. Very little information exists to help quantify the endometrial cancer risk with low-dose estrogen regimens, although short-term studies are reassuring.<sup>3</sup> Nevertheless, very few clinicians have been comfortable prescribing unopposed estrogen since the 1970s.



Marcie K. Richardson, MD

### **Breast Cancer**

As was hinted at in the original WHI publication in 2004, new data from the estrogen-only arm of the WHI confirms the finding that an estrogen-only regimen may have a mild protective effect against breast cancer in women who have had hysterectomies.<sup>4</sup> This not entirely expected result, along with concerns that progestogens may increase the incidence of heart disease, suggests to me that we should be reconsidering estrogen alone—especially as we prescribe lower and lower doses. Not only should it be contemplated, but it must be investigated.

### **Local Estrogen**

The safety of long-term local estrogen to treat vulvovaginal symptoms of menopause is another topic that has not been adequately studied. A recent, very small study<sup>5</sup> suggests that more estrogen may be absorbed from vaginal tablets than was previously thought. Nevertheless, in Dennerstein and colleagues' longitudinal study of menopausal women,<sup>6</sup> 37%

*I confess that I prescribe estrogen-only therapy—not only locally but also systemically—for women who don't tolerate progestogens.*  
 – Marcie K. Richardson, MD

had genital symptoms, so this is an important area for research. In their systemic Cochrane review comparing the three available delivery systems for local estrogen, Suckling et al<sup>7</sup> point out that there is less systemic absorption and more patient satisfaction reported with use of the estradiol ring. I encourage my patients to use the estradiol ring when they opt to use local estrogen to minimize systemic exposure, and do not currently use progestogens in this setting of estrogen-only therapy.

### Estrogen-Only Therapy

I confess that I prescribe estrogen-only therapy—not only locally but also systemically—for women who don't tolerate progestogens. I warn these patients of the risks associated with the therapy, and monitor the endometrium in these patients.

I wish I could be sure I knew how to balance the risk-benefit equation of progestogen/estrogen use as I taper a woman's estrogen dose and discover that lower and lower doses of estrogen provide her with sufficient symptom relief.

– Marcie K. Richardson, MD

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I rarely use continuous estrogen-only therapy for symptomatic postmenopausal women with an intact uterus. However, there are some patients who simply cannot tolerate a progestin. In those instances, I make an exception—as long as the woman is fully informed of the risks of endometrial hyperplasia and possible endometrial cancer. The patient is told that she should call me if she has any irregular bleeding or spotting.

I perform a transvaginal ultrasound to measure the endometrial stripe, and routinely do an endometrial biopsy (once per year). A 6-month interval separates the ultrasound and biopsy. Finally, even if the patient is on extremely low-dose ET, my practice is to evaluate the endometrium; despite some recent papers suggesting that this is unnecessary, I believe this to be the most prudent course of action until we have more data. In cases of irregular bleeding, I do an ultrasound evaluation, and may follow with a biopsy within a short time interval.

– Isaac Schiff, MD

There is a small place for continuous unopposed ET in women who still have a uterus, in as much as treatment should be individualized depending upon patients' clinical needs. Although this sounds like a clinical platitude, the concept of individualization is actually not well appreciated and was certainly beyond the understanding of the investigators of the clinically unsatisfactory WHI study, who seemed to believe that one dose of Prempro suited all

women even though they were asymptomatic.

### The Key Word: "Different"

In practice, different women of different ages with different problems, symptoms and surgical statuses require different doses of different hormones—and in different combinations by different routes. Some of these women will be best served by low-dose estrogens without progestogen, but it should not become the norm because of the current anxiety about possible side effects of progestogens.

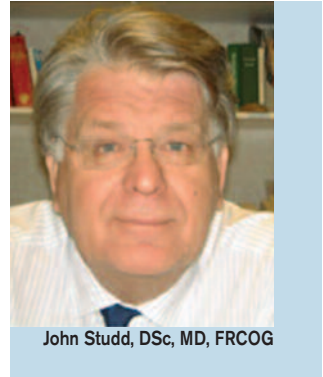
In the 1970s there was a virtual epidemic of endometrial cancer in North America because of the failure to use cyclical or continuous progestogen to protect the endometrium from overstimulation. Subsequently, 14 days of progestogen each month became the orthodox standard regimen, although the original research papers did indicate that 7-day cycles were almost as effective, producing a hyperplasia rate of 3% compared with a 10-50% incidence with unopposed therapy (depending on the dose and duration of the estrogen stimulation). This shortened course is of value for the many women who are progestogen-intolerant, as the 14-day course produces a recurrence of fatigue, loss of libido, depression, anxiety and irritability; this also occurs in patients with a history of premenstrual syndrome. The side effects are both dose- and duration-dependent. These women would also benefit from estrogen-only therapy if it is shown to be effective and safe.

### Déjà Vu

Continuous progestogen with estrogen produces amenorrhea, with a virtually zero risk of endometrial pathology, but the progestogen component of this treatment is believed to be responsible for the increase in breast cancer associated with HT. Hence, there is a move, particularly in the United States, toward low-dose estrogen-only therapy—as if we haven't been there before!

Certainly, low-dose unopposed estrogens are appropriate for a test period of about 6 months in the older woman (those past age 60) with osteoporosis or symptoms of pelvic atrophy, as this dose and this duration should not be sufficient to produce endometrial overstimulation.

Younger postmenopausal women who are progestogen-intolerant and have problems with estrogen-responsive loss of libido and energy will also benefit from this regimen, which can be continued in these exceptional cases if there are no bleeding problems and no ultrasonic evidence of hyperplasia. They might be better off with the Mirena Intrauterine System (Berlex), with tibolone (Livial), which is not yet approved for use in the United States, or even with a hysterectomy, but that is another issue.



John Studd, DSc, MD, FRCOG

### Exchanging One Extreme for Another

It would be a mistake to exchange one extreme for another. The former zeal for continuous combined estrogen and progestogen therapy should not be replaced by an enthusiasm for unopposed low-dose or ultra-low-dose estrogens (despite the current environment of "pharma-hype") as neither the medium-term efficacy nor safety are yet established. Even the logic of this suggestion is hard to comprehend.

Perhaps it is time for a safe compromise of a shorter duration of progestogen in the form of continuous estrogens by whichever route is desired. Progestogen should be taken for the first 7 days of each calendar month, which will produce a withdrawal bleed on about day 10 of each calendar month.

Despite being the principal investigator in the original endometrial studies 25 years ago—which recommended a 14-day course of progestogen—it has become my almost-routine practice to recommend a 7-day course of progestogen in order to avoid the premenstrual syndrome-type side effects of this hormone. The current anxiety about breast cancer reinforces that view. Unopposed ET, except in special situations, is not the answer.

— *John Studd, DSc, MD, FRCOG*

Please visit Dr. Studd's Web site ([www.studd.co.uk](http://www.studd.co.uk)) for pertinent references.

It is well known from observational studies that unopposed estrogen increases the risk of endometrial carcinoma. Estrogens do this in a dose- and time-dependent fashion; the higher the dose and the longer the period of treatment, the greater the probability of endometrial carcinoma.<sup>1</sup> Randomized clinical trials



Ian H. Thorneycroft, PhD, MD

have found that unopposed estrogen increases the probability of developing endometrial hyperplasia, considered a precursor to endometrial carcinoma.<sup>1</sup> Randomized, clinical studies have demonstrated that progestin use eliminates the increased endometrial hyperplasia.<sup>2,3</sup> Observational studies have demonstrated

that the addition of a progestin for at least 2 weeks out of the month, or continuously, protects the endometrium from endometrial carcinoma.<sup>4</sup> It has, therefore, become standard practice not to give unopposed estrogen to women with a uterus.

It is noteworthy that two randomized trials did not demonstrate a statistically significant increase in endometrial hyperplasia with 0.3 mg of either CEE or esterified estrogens.<sup>5</sup> Observational studies, including a meta-analysis, did demonstrate increased risks of endometrial carcinoma with 0.3 mg of CEE. It is not clear, however, in these observational studies if patients had also received higher doses of estrogen in the past. It would appear that until further evidence is available, CEE at a dose of 0.3 mg can be associated with endometrial carcinoma.

Most of the recent breast cancer literature shows no increased risk of this disease with estrogen-only therapy, and an increase with EPT. In fact, the WHI demonstrated a barely statistically significant increase in breast cancer in those patients who used EP, whereas those who used estrogen alone and were compliant had a statistically significant reduction in breast cancer.<sup>6,7</sup> The authors of the Million Women Study<sup>8</sup> propose that it may be better to treat with estrogen alone and accept the increased endometrial cancer risk in order to

reap the benefit of a lower breast cancer risk.

At this time, I believe that we still need to oppose estrogen with a progestin. It's quite possible that at some time in the future, estrogen-only therapy may be preferred to lower the risk of breast cancer. Perhaps a compromise at the present time would be to use a low-dose estrogen, and oppose it with a progestin every 3-6 months. Another possible approach would be to use estrogen alone and perform an endometrial ultrasound or biopsy every year.<sup>9,10</sup>

An important issue to keep in mind with estrogen-only therapy is that patients have breakthrough bleeding, which gets worse rather than improving over time. This troublesome side effect limits the usefulness of estrogen-only therapy.

– Ian H. Thorneycroft, PhD, MD

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