

## Hormone Therapy and Coronary Heart Disease

# Evolving evidence from clinical trials

### KEY POINTS

- Substantial evidence indicates that in premenopausal women, endogenous estrogen may slow the development of coronary heart disease. Younger menopausal age is significantly associated with higher risk of coronary heart disease.
- Exogenous estrogen administered shortly after menopause may retard the development of atherosclerosis by beneficial effects on blood lipids and endothelial function.
- Recent reanalysis of data from the Women's Health Initiative revealed that the hazard ratio for coronary heart disease with all hormone therapy was 0.76 for women who were less than 10 years from menopause at the start of the study.
- The Nurses' Health Study showed that when hormone therapy was initiated within 4 years of menopause, the risk of coronary heart disease was significantly reduced for estrogen alone or combination therapy.

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Evidence regarding the relation of estrogen and coronary heart disease (CHD) is evolving as new information becomes available. CHD is very uncommon in women of reproductive age. Before age 50 years, the incidence of myocardial infarction (MI) is much more common in men than in women.<sup>1</sup> The incidence of MI increases in individuals of both genders as they age, but after menopause the rate of increase is greater in women than men, and the incidence becomes similar in both genders after age 80 years. Data from the Nurses' Health Study found a significant association between younger menopausal age and higher risk for CHD.<sup>2</sup>

### Estrogen and the development of CHD

A substantial body of evidence indicates that endogenous estrogen may retard the development of CHD in premenopausal women. Joakimsen et al found that there was a significant inverse relation between age of menopause and extent of carotid artery atherosclerosis observed sonographically.<sup>3</sup> Premenopausal women with bilateral oophorectomy have a markedly increased risk of coronary atherosclerosis, and the risk of MI is inversely related to the age at which oophorectomy occurs.<sup>4</sup> The Framingham study showed that the incidence of cardiovascular events was lower in premenopausal than postmenopausal women of the same age.<sup>5</sup>

A large number of studies also indicate that exogenous estrogen has a similar effect in postmenopausal women. Exogenous estrogen may prevent the development of CHD in postmenopausal women by several mechanisms. After menopause in women not receiving exogenous estrogen, high-density lipoprotein cholesterol (HDL-C) levels decrease

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**Life is full of contradictions,** confusions, and conundrums. No more so than for postmenopausal woman trying to understand the pros and cons of hormone therapy (HT). What was once easy and simple has now become complex and confusing.

Daniel R. Mishell, Jr, MD, relates the odyssey of HT and coronary heart disease (CHD) from the 1980s to the present day. Observational studies, basic biology, clinical physiology, pharmacology, randomized controlled trials, and the ever-present media attention have shaped our understanding of this therapy. Reports from the Women's Health Initiative (WHI) of the risk for CHD in women who use estrogen plus progestin therapy (EPT) have evolved: First, EPT was thought to increase risk (2002), then it was posited to cause early harm in the first year of use (2003), and now it is recognized that the increased CHD risk is in women who are more than 20 years from menopause or older than 70 years (2007). Suffice it to say that the concept of CHD prevention with early exogenous hormone use in postmenopausal women is still a valid proposition today.

The optimal duration of EPT or estrogen therapy (ET) in women remains an unresolved issue after the WHI. I address this question by putting into context the age-related increase in risk of disease and the accrued and potential benefits from EPT/ET for the consumer. Although we speak in population statistics when we try to understand the effects of HT, in clinical practice it all comes down to assessing an individual's risks and benefits. Trials provide the science; the art is in the provider's ability to listen to a woman's goals, estimate her health risks, and counsel her about her concerns as best we can.

Despite the discussion, statistics, clinical studies, and opinions, the consumer is left to fend for herself. Ms Audra Mitchell provides us with a pithy essay that illustrates the concerns of the educated consumer when she reflects on the debate over menopausal therapy. If clinicians are searching for answers, what can the consumer do to make the best decision for herself?

Ms Mitchell's conclusion is that a well-informed health care provider with her best interests at heart is an invaluable resource amidst confusing information. This is one clear message that we should certainly heed.

David F. Archer, MD

and low-density lipoprotein-cholesterol (LDL-C) levels increase. A major effect of exogenous estrogen is to increase circulating levels of the cardioprotective HDL-C and lower circulating levels of the deleterious LDL-C.<sup>6</sup> Other mechanisms whereby estrogen prevents coronary artery atherosclerosis include increasing coronary artery blood flow, promoting coronary artery vasodilatation, preventing platelet aggregation, improving cardiac contractility, decreasing lipoprotein(a), and inhibiting LDL-C oxidation. The elegant studies by Clarkson et al in the nonhuman primate found that when estrogen is given immediately after bilateral oophorectomy, it markedly reduces the development of coronary artery atherosclerosis compared with animals receiving a placebo.<sup>7</sup>

### Progression of subclinical atherosclerosis

Intima-media thickness of the arterial wall is the earliest detectable anatomic change in the development and progression of atherosclerosis. It has been shown that carotid artery intima-media thickness is a marker of generalized atherosclerosis and is a predictor of clinical cardiovascular events. Hodis et al performed a prospective randomized clinical trial on a group of 222 postmenopausal women with a mean age of 62 years without pre-existing cardiovascular disease (Estrogen Replacement and Atherosclerosis Trial).<sup>8</sup> The women were randomized to receive either 1 mg estradiol orally once a day or placebo for 2 years. Carotid artery ultrasound was used to measure the intima-media thickness in the right distal common carotid artery every 6 months for 2 years. After 2 years,

the women in this study receiving estrogen had no increase in the mean carotid artery intima-media thickness (-0.0017 mm/year), while the group receiving placebo had a significant increase in the mean intima-media thickness of this artery (0.0036 mm/year). This study provided a high level of evidence that administration of exogenous estrogen to women without evidence of carotid artery atherosclerosis retards the progression of subclinical atherosclerosis.

Consistent with these findings, many observational epidemiologic studies reported that administration of estrogen to postmenopausal women reduces the incidence of coronary artery disease (CAD) and prevents MI. More than 40 observational epidemiologic studies have shown that administration of estrogen to postmenopausal women substantially reduces both cardiovascular morbidity and mortality. In these observational studies, estrogen use by postmenopausal women was associated with a reduced risk of developing CHD, with the odds ratio in the studies ranging from 0.39 to 0.81 compared with non-estrogen users.<sup>9</sup> An 8.5-year multicenter cohort study from the Lipid Research Clinics program of 2270 white women reported the multivariate adjusted relative risk (RR) of cardiovascular mortality with estrogen use was 0.37 (confidence interval [CI], 0.16-0.58).<sup>10</sup>

The largest observational cohort study that investigated the relation of estrogen to CHD in postmenopausal women is the Nurses' Health Study. This study was begun in 1976, when 121,700 female nurses aged 30 to 55 years completed a mailed questionnaire about their use of hormones postmenopausally and their medical history, including cardiovascular disease. Follow-up questionnaires were mailed every 2 years and follow-up

data were available for more than 90% of the cohort. In the 20 years of follow-up from 1976 to 1996, a total of 70,533 nurses were or became postmenopausal, and 808,825 person-years of follow-up were accumulated.<sup>11</sup> The multivariate adjusted RR of major CHD, which includes non-fatal MI, fatal CAD, coronary bypass surgery, or angioplasty was 0.61 (CI, 0.52-0.71) for current users of hormone therapy. The RR was 0.55 (CI, 0.45-0.68) for users of oral conjugated estrogen alone and 0.64 (CI, 0.49-0.85) for users of estrogen with progestin, compared with the risk of women not taking hormones.

### The Women's Health Initiative

Despite the large number of women in these observational studies, there was concern that selection bias could have influenced the results, because women taking hormones were presumed to have healthier lifestyles and be of higher socioeconomic class than non-users. To address this problem, the National Institutes of Health initiated a series of large randomized clinical trials of postmenopausal women. The primary purpose of these trials was to focus on the risks and benefits of certain strategies that could possibly reduce the risk of cardiovascular disease, cancer, and fracture in postmenopausal women. Each of these trials was designed by a group of investigators, and the entire series of studies was designated as the Women's Health Initiative (WHI).

The WHI enrolled 161,809 postmenopausal women between 1993 and 1998 for this series of trials. The WHI enrolled predominantly healthy women, in contrast to other studies that analyzed the effect of estrogen in postmenopausal women with pre-existing CHD. In the Heart and Estrogen Replacement Study

TABLE 1

### Hazard Ratios\*: CHD Events by Years Since Menopause

	Years Since Menopause at Baseline		
	<10 y	10-19 y	≥20 y
All HT	0.76 (0.50-1.16)	1.10 (0.84-1.45)	1.28 (1.03-1.58)
CEE	0.48 (0.20-1.17)	0.96 (0.64-1.44)	1.12 (0.86-1.46)
CEE + MPA	0.88 (0.54-1.43)	1.23 (0.85-1.77)	1.66 (1.14-2.41)

CEE, conjugated equine estrogen; CHD, coronary heart disease; HT, hormone therapy; MPA, medroxyprogesterone acetate.

\*Hazard ratio (95% confidence interval).

Modified from Rossouw JE, et al. *JAMA*. 2007;297:1465-1477.

TABLE 2

### Current Hormone Use and Risk of Major CHD

	RR (95% CI) Multivariate-Adjusted	
	Within 4 y	≥10 y
Never	1.0 (reference)	1.0 (reference)
ET	0.66 (0.54-0.80)	0.76 (0.57-1.00)
EPT	0.72 (0.56-0.92)	0.80 (0.53-1.23)

CHD, coronary heart disease; CI, confidence interval; ET, estrogen therapy; EPT, estrogen and progestin therapy; RR, relative risk.

Risk of major CHD related to current hormone use and time of initiation of hormone therapy with respect to menopause.

Modified from Grodstein F, et al. *J Womens Health (Larchmt)*. 2006;15:35-44.

(HERS)<sup>12</sup> and Estrogen Replacement and Atherosclerosis Trial,<sup>13</sup> estrogen did not prevent progression of atherosclerosis in women with established CHD. One of the WHI randomized trials enrolled 16,608 postmenopausal women aged 50 to 79 years with an intact uterus who were randomized to receive either 0.625 mg conjugated equine estrogen (CEE) with 2.5 mg medroxyprogesterone acetate (MPA) in a single pill, or placebo.<sup>14</sup> The primary outcome of this trial was CHD. The mean age of the women in this trial at the time of initial screening was 63 years, with one third of the women aged 50 to 59 years, about 45% aged 60 to 69 years, and 21% aged 70 to 79 years. The planned duration of the study was 8.5 years. However, the study was stopped prematurely after a mean 5.2 years of follow-up because the risk of developing

breast cancer in the hormone group exceeded the stopping boundary.

In contrast to the findings of the numerous observational studies, the results of this WHI study showed that women taking the hormones had an increased risk of CHD (acute MI), silent MI, or CHD death, with a hazard ratio (HR) of 1.29 (CI, 1.02-1.63). Subsequent analysis of this WHI study reported an adjusted HR rate of CHD of 1.24 with hormone therapy (CI, 1.00-1.54).<sup>15</sup> The increased risk of CHD was significant only in the first year of treatment (HR, 1.81; CI, 1.09-3.01). There was a lower nonsignificant increase in CHD for hormone users during years 2 to 5 of the study and a nonsignificant decrease (HR, 0.70; CI, 0.42-1.14) in women with 6 or more years' duration in the study. When the data were analyzed by subgrouping the

women into 3 groups by years since menopause, the only significant increased risk of CHD with hormone use occurred in women who were 20 or more years postmenopausal at the time of enrollment (HR, 1.71). Women 10 to 14 years postmenopausal had an insignificant increase in CHD with hormone use (HR, 1.22), while women less than 10 years postmenopausal had an insignificant decrease in CHD (HR, 0.89). Therefore, this analysis of the data from the WHI study showed that the only significantly increased risk of CHD with hormone use occurred in women more than 20 years postmenopausal at enrollment and only in the first year of the trial.

A parallel WHI randomized trial evaluated the effect of 0.625 mg CEE without a progestin compared with placebo in 10,739 healthy postmenopausal women with a prior hysterectomy.<sup>16</sup> This trial was stopped after a mean duration of 6.8 years. The HR for CHD in this study was 0.91 (nominal CI, 0.75-1.12). When the data from this study were analyzed by age group, the HR for CHD with estrogen use in women aged 50 to 59 years was 0.63 (CI, 0.36-1.08), for women aged 60 to 69 years, 0.94 (CI, 0.71-1.24), and for women aged 70 to 79 years, 1.11 (CI, 0.82-1.52).<sup>17</sup> Thus, the data from this WHI trial indicate that use of estrogen by women aged 50 to 59 years reduces their risk of CHD by about 40%, similar to the observational studies in which the vast majority of the women started estrogen at this age.

### Recent analyses: "Years since menopause" is key

The most recent publication of the WHI investigators characterized the effect of postmenopausal hormone therapy and risk of cardiovascular disease by both age and years since

menopause at the time of enrollment.<sup>18</sup> The results of this recent analysis of the data are similar to the prior analyses. The HR for CHD was 0.76 for all hormone therapy, compared with placebo for women less than 10 years since menopause at enrollment (TABLE 1). In this same short duration after menopause, CEE alone had an HR for CHD of 0.48, and for those receiving estrogen plus progestin it was 0.88. The HR for CHD in these 3 categories of analysis (no hormones, CEE alone, and CEE + MPA) for women who were 10 to 19 years postmenopausal was 1.10, 0.96, and 1.23, respectively. For women 20 or more years postmenopausal, it was 1.28, 1.12, and 1.66, respectively. In the latter group, only the HR for CEE alone and CEE + MPA were significantly increased.

Grodstein et al analyzed data from the Nurses' Health Study regarding time since menopause at initiation of therapy.<sup>19</sup> These investigators determined that for women initiating hormone therapy within 4 years of menopause, there was a significantly reduced risk of CHD

for estrogen alone (RR, 0.66) and for estrogen plus progestin (RR, 0.72) (TABLE 2). For women initiating therapy more than 10 years after menopause, the RR of CHD was 0.87 for estrogen alone and 0.90 for estrogen plus progestin. Neither of these figures was significantly different from the risk of CHD in women not taking estrogen.

In the nonhuman primate model, Mikkola and Clarkson showed that administration of estrogen immediately after oophorectomy reduced coronary atherosclerosis by 70% compared with placebo, but if estrogen treatment was delayed for 2 years—the equivalent of 6 human years—there was no reduction in atherosclerosis development (FIGURE 1).<sup>20</sup>

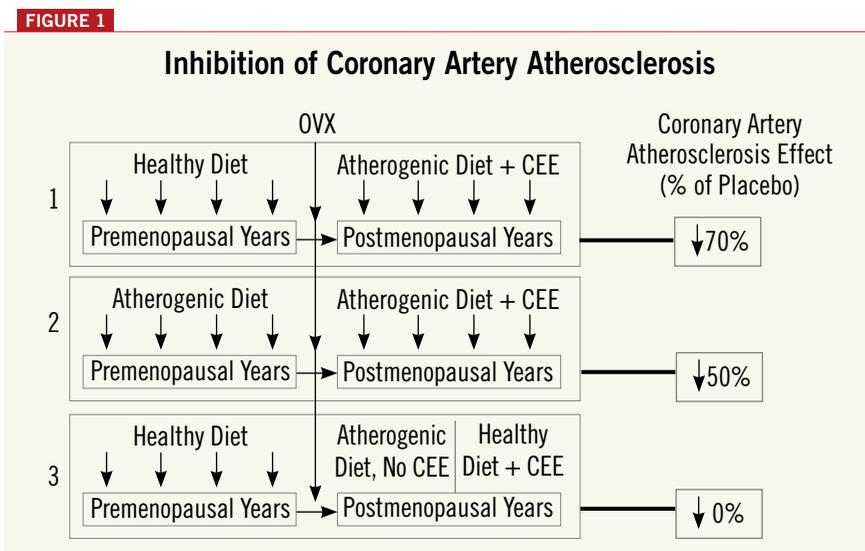
### Clinical decisions and the unified hypothesis

This large amount of data from randomized trials, observational studies, and findings in the animal model supports the belief that when estrogen is administered to women shortly after menopause, it retards the development of atherosclerosis by its beneficial effects on

blood lipids and endothelial function. However, when large doses of oral estrogen are given to women older than 70 years, coronary artery occlusion can occur rapidly in some of these women with subclinical atherosclerosis by procoagulant and inflammatory mechanisms. These actions can cause rupture of coronary artery plaques and thrombosis in these narrowed vessels.

In 2005, two WHI investigators published a paper about postmenopausal hormone therapy: "Critical Reappraisal and a Unified Hypothesis."<sup>9</sup> This thoughtful analysis of the WHI data is consistent with biological mechanisms, animal studies, human observational studies, and human clinical trials. The unified hypothesis predicts that hormone therapy begun at the time of menopause should result in a decrease of CHD over time. However, if hormone therapy is begun several years after menopause, there will be an increase in CHD events soon after starting therapy among women with subclinical coronary artery atherosclerosis, while the remaining healthy women will subsequently have a reduction in CHD events by retarding atherosclerosis development.

The authors of that paper stated that clinicians can use this unified hypothesis as a rational means to make clinical decisions. They explain that if clinicians administer estrogen to healthy postmenopausal women soon after menopause, estrogen will most likely delay the progression of atherosclerosis. Their analysis suggests that clinicians should avoid initiating high doses of oral estrogen in women older than 60 years because some of them may have subclinical coronary atherosclerosis and the prothrombotic and inflammatory effects of oral estrogen can cause coronary artery occlusion.



CEE, conjugated equine estrogen; OVX, ovariectomy.

The relation of pre- and postmenopausal conditions to the degree of, or lack of, inhibition of coronary artery atherosclerosis.

Reprinted with permission from Mikkola TS, Clarkson TB. *Cardiovascular Res.* 2002;53:605-619.

## Unanswered questions

It remains to be determined whether transdermal estrogen, which has less of a procoagulant effect, has the same adverse action on women with subclinical atherosclerosis as oral estrogen does. In contrast to oral estrogen, which causes a 3- to 4-fold increased risk of venous thromboembolism (VTE), transdermal estrogen does not appear to increase the risk of VTE.<sup>21</sup>

The effect of the addition of progestin to estrogen on CHD events also remains to be determined.

Dr Mishell disclosed that he is a consultant to Barr Pharmaceuticals and Bayer Pharmaceuticals; and he is on the speakers' bureau of Bayer Pharmaceuticals.

### References

1. Isles CG, Hole DJ, Hawthorne VM, Lever AF. Relation between coronary risk and coronary mortality in women of the Renfrew and Paisley survey: comparison with men. *Lancet*. 1992;339:702-706.
2. Hu FB, Grodstein F, Hennekens CH, et al. Age at natural menopause and risk of cardiovascular disease. *Arch Intern Med*. 1999;159:1061-1066.
3. Joakimsen O, Bonna KH, Stensland-Bugge E, Jacobsen BK. Population-based study of age at menopause and ultrasound assessed carotid atherosclerosis: the Tromso Study. *J Clin Epidemiol*. 2000;53:525-530.
4. Wuost JH, Dry TJ, Edwards JE. The degree of coronary atherosclerosis in bilaterally oophorectomized women. *Circulation*. 1953;7:801-809.
5. Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: the Framingham study. *Ann Intern Med*. 1976;85:447-452.
6. Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnikar V, Sacks FM. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. *N Engl J Med*. 1991;325:1196-1204.
7. Clarkson TB, Anthony MS, Morgan TM. Inhibition of postmenopausal atherosclerosis progression: a comparison of the effects of conjugated equine estrogens and soy phytoestrogens. *J Clin Endocrinol Metab*. 2001;86:41-47.
8. Hodis HN, Mack WJ, Lobo RA, et al. Estrogen in the prevention of atherosclerosis: a randomized, double-blind, placebo-controlled study. *Ann Intern Med*. 2001;135:939-953.
9. Phillips LS, Langer RD. Postmenopausal hormone therapy: critical reappraisal and a unified hypothesis. *Fertil Steril*. 2005;83:558-566.
10. Bush TL, Barrett-Conner E, Cowan LD, et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the lipid research clinics program follow-up study. *Circulation*. 1987;75:1102-1109.
11. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med*. 2000;133:933-941.
12. Hulley S, Grady D, Bush T, et al, for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*. 1998;280:605-613.
13. Herrington DM, Reboussin DM, Brosnihan B, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med*. 2000;343:522-529.
14. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA*. 2002;288:321-333.
15. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med*. 2003;349:523-534.
16. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. *JAMA*. 2004;291:1701-1712.
17. Hsia J, Langer RD, Manson JE, et al. Conjugated equine estrogens and coronary heart disease. *Arch Intern Med*. 2006;166:357-365.
18. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007;297:1465-1477.
19. Grodstein F, Manson JE, Stampfer MJ. Hormone therapy and coronary heart disease: the role of time since menopause and age at hormone initiation. *J Womens Health (Larchmt)*. 2006;15:35-44.
20. Mikkola TS, Clarkson TB. Estrogen replacement therapy, atherosclerosis, and vascular function. *Cardiovasc Res*. 2002;53:605-619.
21. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: The ESTHER study. *Circulation*. 2007;115:840-845.

# Determining the optimal duration of postmenopausal hormone therapy

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## KEY POINTS

- Baseline risk factors, prior hormone use, type of hormones used, and emerging medical conditions affect how the risk/benefit ratio changes for a woman as the duration of hormone therapy increases.
- The data do not support strict limitations on duration of hormone therapy.

**B**efore the termination of the Women's Health Initiative (WHI), postmenopausal estrogen therapy (ET)/estrogen-progestin therapy (EPT) was recommended for long-term use in most women. Today, guidelines recommend limiting the use of ET/EPT to the shortest duration consistent with the individual's treatment goals.<sup>1-3</sup> Although the optimal duration of

postmenopausal ET/EPT likely varies from patient to patient, ET/EPT ultimately should be discontinued before the risks of therapy outweigh its benefits. The overall risk/benefit profile for an individual woman is dynamic, changing with her age, time since menopause, risk factors, and symptomatology.

The benefits of ET/EPT have been well documented in the clinical

literature. Estrogen therapy, with or without the use of a progestin, is the most effective treatment for menopausal vasomotor symptoms, including hot flashes and night sweats.<sup>2</sup> ET/EPT is also effective for treating vaginal dryness and other symptoms of vaginal atrophy.<sup>4</sup> Postmenopausal hormone therapy effectively prevents osteoporosis and reduces fracture risk, even in women without low bone density.<sup>5,6</sup> In addition, evidence from the WHI and observational data indicate that EPT may reduce the risk of colorectal cancer.<sup>7,8</sup> Moreover, accumulating data indicate that ET/EPT, when initiated soon after menopause, may decrease the risk of coronary heart disease (CHD).<sup>9-11</sup> Another look at the use of ET and EPT in the WHI studies found no evidence for an increased risk of CHD before age 70 years.<sup>12</sup>

The risks of ET/EPT also are well established and include an increased risk of breast cancer, venous thromboembolism (VTE), stroke, and cholecystitis.<sup>10,13</sup> Recent findings also suggest an increase in the risk of dementia and impaired cognitive status in women who initiate hormone use after age 65 years.<sup>14,15</sup> Because the risks and benefits of ET/EPT are related to the duration of hormone use and the age of the patient, it is necessary to consider how the benefits and risks of therapy change throughout the course of treatment and with aging.

## Benefits and risks of ET/EPT in early postmenopause

### Established benefits of ET/EPT

Up to 80% of women in the menopausal transition experience hot flashes.<sup>1</sup> In these women, postmenopausal ET/EPT can provide valuable relief of hot flashes and their consequences, which include reduced sleep quality, irritability,

and impaired quality of life. The benefits of ET/EPT in relieving vasomotor symptoms continue as long as the symptoms persist.

The use of ET/EPT will treat the symptoms of urogenital atrophy and prevent bone loss in all women, including recently menopausal women. Since bone loss is most rapid in the first 5 to 7 years after menopause,<sup>6,16</sup> hormone use in early postmenopausal women prevents the accelerated loss in bone mineral density (BMD) that characterizes the early postmenopausal period. Recent data also suggest that initiation of EPT provides greater improvements in postural balance in early postmenopausal women than in women who have been postmenopausal for longer periods of time.<sup>17,18</sup> Improved postural balance may contribute to the protection against fracture provided by hormone use.

### Potential benefits of ET/EPT

**Coronary heart disease.** A nonsignificant trend toward an increased risk of CHD with EPT was one of the most highly publicized findings of the WHI.<sup>10</sup> A trend toward early harm with EPT with a decrease in risk with time was noted in the WHI population, which included 16,608 postmenopausal women (mean age, 63 years). Similar findings were reported in the Heart and Estrogen/progestin Replacement Study (HERS), a study of postmenopausal women with established CHD whose average age was 67 years.<sup>19</sup> It should be noted that women included in these studies were older, largely free of menopausal symptoms,<sup>10,19-21</sup> and not representative of the younger, early postmenopausal women typically treated with ET/EPT. No increase in CHD risk was observed with ET in the WHI.<sup>11</sup> A recent analysis of CHD combining

both the ET and EPT arms of the WHI did not identify any increase in the risk of CHD due to hormone therapy until the women were older than 69 years.<sup>12</sup>

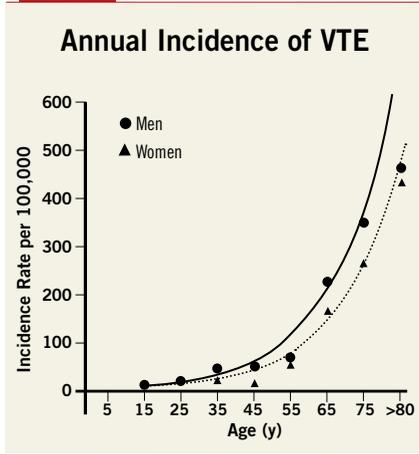
In contrast, subanalyses of data from the WHI and observational data, including a recent report from the Nurses' Health Study, demonstrate that use of ET/EPT may reduce CHD risk in women closer to the menopausal transition. For example, in the WHI, women aged 50 to 59 years at baseline assigned to ET experienced a reduced risk of coronary revascularization and several composite coronary outcomes.<sup>11</sup> These findings suggest that ET/EPT may inhibit the early stages of postmenopausal coronary artery atherosclerosis, but may have deleterious effects if initiated in older women who already have significant atherosclerosis. The duration of ET/EPT use that maximizes the potential CHD benefit in early postmenopausal women is unknown.

**Cognitive function.** The WHI Memory Study demonstrated that initiating hormone use in women older than 65 years might increase the risk of dementia and impaired cognitive status.<sup>14,15</sup> However, evidence from studies of younger women suggests that ET may provide beneficial cognitive effects (particularly improvements in verbal memory and attention) in symptomatic women and recently menopausal women.<sup>22-25</sup> It is unknown whether these findings can be generalized to older women who initiated hormones close to menopause and have used therapy for long periods of time. Additional studies exploring the impact of age at initiation of progestin use are needed.

### Effect of ET/EPT on breast cancer

The WHI demonstrated a small but statistically significant increase in

FIGURE 1

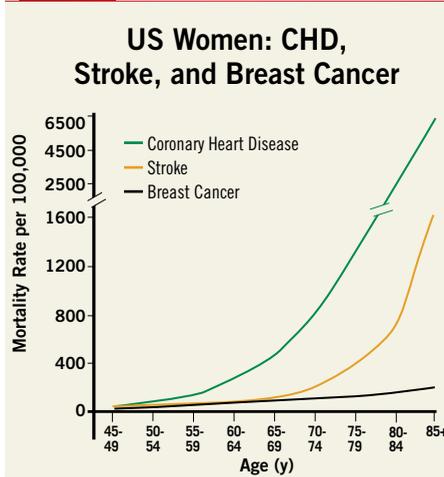


VTE, venous thromboembolism.

Annual incidence of VTE among residents of Worcester, MA, in 1986 by age.

Anderson FA Jr, et al. *Arch Intern Med.* 1991;151:933-938.

FIGURE 2



CHD, coronary heart disease.

National Center for Health Statistics. 1999;164-167.

Available at [www.cdc.gov/nchs/data/statab/hist002r\\_2.pdf](http://www.cdc.gov/nchs/data/statab/hist002r_2.pdf).

breast cancer risk with 5 years of EPT use.<sup>26</sup> However, this increase in risk was limited to women who reported previous hormone use. No increase in breast cancer risk was observed with short-term use of ET/EPT or long-term use of ET.<sup>27</sup> A current reanalysis adjusting for breast cancer risks (age, ethnicity, obesity, cigarette smoking, other breast cancer risks, etc) found a hazard ratio of 1.20, with a 95% confidence interval (CI) of 0.94-1.53.<sup>28</sup>

### Risks of ET/EPT

**Venous thromboembolism.** ET/EPT is associated with about a 2-fold increase in the risk of VTE, an increase in risk that is particularly evident in the first or second year of therapy. The increase in VTE risk with EPT in the WHI was observed in all women, including younger postmenopausal women.<sup>29</sup> Only the increase in risk of deep venous thrombosis (DVT) was statistically significant in the ET arm of the WHI.<sup>21</sup> Because the absolute risk of VTE in early postmenopausal women is very low (FIGURE 1),<sup>30</sup> the absolute increase in risk with ET/EPT in early postmenopausal women is small. The risk of VTE is 1.8 and 0.8 more cases per 1000 women in

the EPT and ET groups, respectively.<sup>10,20,21</sup> Data also indicate that VTE risk likely decreases with the duration of use.

**Stroke.** The use of ET/EPT is also associated with a significant increase in the risk of stroke. In the WHI, women using ET/EPT experienced a 30% to 40% increase in the risk of stroke compared with women using placebo. This increase in risk was apparent in all age groups and did not appear to diminish over time. Due to the low risk of stroke at baseline in early postmenopausal women (FIGURE 2),<sup>31</sup> the absolute increase in stroke risk is 0.7 and 1.2 per 1000 women using ET and EPT, respectively.

### Benefits and risks of ET/EPT with more than 5 years of use

It is clear that the improvement in vasomotor symptoms, reduction in urogenital atrophy, prevention of osteoporosis, and potential reduction in CHD risk outweigh the small increase in VTE and stroke risk observed with short-term ET/EPT use in most healthy early postmenopausal women. However, the balance between risks and benefits changes with the duration of use.

### Benefits of ET/EPT

Although ET/EPT relieves menopause-related hot flashes and night sweats at any age, the incidence of vasomotor symptoms decreases over time. Still, vasomotor symptoms may persist for more than 5 years in 25% to 75% of those affected.<sup>32</sup> Vasomotor symptoms last even longer in some women: a recent Swedish study reported that about 9% of 72-year-old women still experience hot flashes.<sup>33</sup> The need for continued treatment of vasomotor symptoms can be determined by temporarily discontinuing ET/EPT.<sup>34</sup> Hot flashes will resume in up to two thirds of women once ET/EPT is discontinued. Recent data suggest that hot flash recurrence rates are similar when ET/EPT is tapered or is discontinued immediately.<sup>35,36</sup>

Women who continue to use ET/EPT for more than 5 years continue to receive the urogenital and skeletal benefits of therapy. Women using ET/EPT for osteoporosis prevention who choose to discontinue therapy will experience bone loss when they stop therapy. Healthy postmenopausal women who continue to use ET/EPT also may experience a reduction in the risk of CHD, although more data are needed to confirm this hypothesis.

### Risks of ET/EPT

**Breast cancer.** In the EPT arm of the WHI, the risk of breast cancer began to increase after 5 years of use.<sup>26</sup> The relative risk (RR) of breast cancer was 1.09 for women with no prior use, 1.70 for women with less than 5 years of prior use, and 2.27 in women with 5 or more years of prior use, but the trend with duration of use was not statistically significant. However, even after 5 years of EPT in prior users, the absolute risk of EPT is small. The absolute increase in breast cancer cases with

EPT use went from 2.8 to 3.2 per 1000 woman-years in women aged 50 to 60 years with prior EPT use. In contrast, there was a trend toward a reduced risk of breast cancer with ET use.<sup>27</sup>

**VTE and stroke.** Although the increase in VTE risk with ET/EPT use tapers off with the duration of use, risk is increased until therapy is discontinued. The observed decline in VTE rate over time in the WHI and in observational studies may reflect a true decrease in risk resulting from tolerance to therapy or the attrition of a susceptible group.<sup>37</sup> Like the association between hormone use and VTE risk, existing data suggest that the increase in stroke risk with the use of ET/EPT continues throughout the duration of ET/EPT therapy.

In summary, women who initiated ET/EPT in their early postmenopausal years and continue therapy for more than 5 years will continue to experience the urogenital and skeletal benefits of therapy, may continue to experience improvement in menopausal symptoms (if they are still present), and may benefit from a reduced risk of CHD. The potential risks of continued therapy include a slight increase in the risks of breast cancer, VTE, and stroke. The balance between risk and benefits depends on the patient's underlying risks, goals, and preferences.

## Benefits and risks of ET/EPT in women in their 60s

### Benefits of ET/EPT

Most women who have been postmenopausal for more than 10 years will no longer experience vasomotor symptoms. However, women who continue to experience hot flashes will benefit from the effect of ET/EPT on vasomotor symptoms. In these women, ET/EPT will also

treat the symptoms of vulvovaginal atrophy and prevent osteoporosis and osteoporotic fracture. Topical vaginal estrogen cream or tablets should be considered in women who use ET/EPT for the sole purpose of vaginal symptom relief.

### Effect of ET/EPT on CHD

The cardiovascular risks and potential benefits of ET/EPT in women in their 60s likely vary, depending on their history of hormone use and risk factors at baseline. On average, by age 65 years, atherosclerotic plaques in the coronary arteries of American women begin to develop complications, including calcification, inflammation, and neovascularization.<sup>38</sup> Some plaques may become prone to rupture and increase the risk of CHD events, which become significantly more common in this age group (FIGURE 2).<sup>31</sup> Accumulating evidence suggests that administering estrogen in the presence of significant atherosclerosis may either have no protective effect (possibly due to the methylation of estrogen receptors in atherosclerotic lesions,<sup>39</sup> or due to a reduction in the vasodilatory effect of estrogen<sup>40</sup>) or may increase the risk of early CHD events by increasing plaque instability and prompting thrombosis.<sup>38</sup>

A recent report from the Rancho Bernardo Study demonstrated that women with a history of ET/EPT use had a significant reduction in coronary artery plaque burden that was independent of lifestyle and social class.<sup>41</sup> Postmenopausal women in this study who had used ET/EPT for at least 10 years had a significantly reduced plaque burden compared with shorter-term users or women who had never used ET/EPT.

These data suggest that ET/EPT may continue to provide coronary benefit in women in their 60s who

initiated therapy close to menopause. However, ET/EPT should not be initiated to prevent CHD in women in this age group who are naïve to hormone therapy.

### Risks of ET/EPT

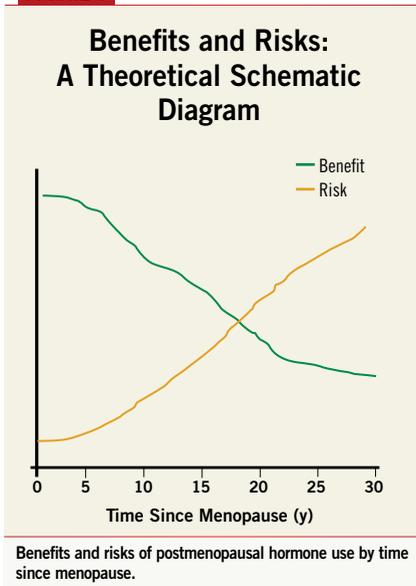
The risks of breast cancer, VTE, and stroke increase with age. Therefore, the absolute increase in risk of breast cancer, VTE, and stroke with ET/EPT use may be greater among older postmenopausal patients using EPT, even if the relative risk for the adverse event is similar among age groups. The increase in the risk for breast cancer in older patients who initiated estrogen close to menopause is likely to be particularly high. These women also are at an increased risk of stroke and DVT with ET/EPT use. As a result, initiating ET/EPT may not be appropriate in women aged 60 years or older who are at significant risk for breast cancer and stroke.

## Benefits and risks of ET/EPT in women in their 70s

The initiation of systemic ET/EPT is typically not recommended for women in their 70s. Because the vast majority of women in their 70s no longer experience vasomotor symptoms, the benefits of ET/EPT in reducing the impact of hot flashes are likely to be minimal. However, this population remains at significant risk for the symptoms of vulvovaginal atrophy, osteoporosis, and osteoporotic fracture. The effect of continued use of long-term ET/EPT on CHD in patients in this age group has not been studied, but the recent analysis of the WHI implies excess CHD events only in women older than 70 years using ET/EPT.

Women who are in their 70s also face an increased risk of breast

**FIGURE 3**



cancer, VTE, and stroke compared with younger women, even if they are not using ET/EPT. The absolute increase in risk for these adverse events in women who have used ET/EPT since menopause and continue to use it is likely to be significantly greater than the risks for younger women. This increase in risk may also differ from the risks reported for similarly aged women in the WHI without a history of ET/EPT use because of the effect of timing of hormone initiation. For example, many women in this age group in the WHI were new users of ET/EPT.<sup>20,21</sup> Because the risk of VTE is greatest in the first year of therapy, the relative risk of VTE with ET/EPT may be greater in new users than in long-term users of the same age. In contrast, the risk of breast cancer with EPT may be greater in long-term users due to its association with duration of use.

## Clinical implications and conclusions

**FIGURE 3** illustrates a theoretical graph of the risks associated with menopausal age and the potential benefits

and risks of postmenopausal ET/EPT use. As shown in **FIGURE 3**, the benefits of ET/EPT will outweigh its risks for the majority of early postmenopausal women. As the duration of therapy increases in women who initiated therapy soon after menopause, the benefits of ET/EPT in relieving menopausal symptoms, preventing osteoporosis, and reducing the risk of CHD may decrease, owing to the decreasing incidence of vasomotor symptoms with age. The cumulative risks of hormone use, which include an increased risk of breast cancer, VTE, and stroke, also begin to increase with the chronological and physiological age of the individual. As a woman ages, the risks of ET/EPT may ultimately outweigh its benefits. The point at which the risks of hormone use exceed its benefits depends on the woman's baseline risk factors, duration of prior hormone use, use of ET or EPT—and potentially, the dose of ET/EPT—and the occurrence of new medical conditions.

Nonetheless, current data suggest that strict limitations on the duration of postmenopausal ET/EPT use are not appropriate because patients vary in terms of their symptomatology, baseline risk, and preferences. The decision to continue therapy should be made annually by the clinician and the patient and should consider her individual needs, indications, and preferences, as well as the best available evidence.

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## References

1. North American Menopause Society. Recommendations for estrogen and progestogen use in peri- and postmenopausal women: October 2004 position statement of The North American Menopause Society. *Menopause*. 2004;11(6 Pt 1):589-600.

2. American College of Obstetricians and Gynecologists Women's Health Care Physicians. Vasomotor symptoms. *Obstet Gynecol*. 2004;104(4 suppl):106S-117S.
3. North American Menopause Society. Estrogen and progestogen use in peri- and postmenopausal women: March 2007 position statement of The North American Menopause Society. *Menopause*. 2007;14:168-182.
4. American College of Obstetricians and Gynecologists Women's Health Care Physicians. Genitourinary tract changes. *Obstet Gynecol*. 2004;104(4 suppl):56S-61S.
5. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA*. 2003;290:1729-1738.
6. American College of Obstetricians and Gynecologists Women's Health Care Physicians. Osteoporosis. *Obstet Gynecol*. 2004;104(4 suppl):66S-76S.
7. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med*. 2004;350:991-1004.
8. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med*. 1999;106:574-582.
9. Grodstein F, Manson JE, Stampfer MJ. Hormone therapy and coronary heart disease: the role of time since menopause and age at hormone initiation. *J Womens Health (Larchmt)*. 2006;15:35-44.
10. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med*. 2003;349:523-534.
11. Hsia J, Langer RD, Manson JE, et al. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med*. 2006;166:357-365.
12. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007;297:1465-1477.
13. American College of Obstetricians and Gynecologists Women's Health Care Physicians. Summary of balancing risks and benefits. *Obstet Gynecol*. 2004;104(4 suppl):128S-129S.
14. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004;291:2947-2958.
15. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA*. 2003;289:2651-2662.
16. Genant HK, Cann CE, Ettinger B, Gordan GS. Quantitative computed tomography of vertebral spongiosa: a sensitive method for detecting early bone loss after oophorectomy. *Ann Intern Med*. 1982;97:699-705.
17. Naessen T, Lindmark B, Lagerstrom C, Larsen HC, Persson I. Early postmenopausal hormone therapy improves postural balance. *Menopause*. 2007;14:14-19.
18. Naessen T. Fracture protection mediated through the brain? *Menopausal Medicine*. 2007;14(3):S1-S7.
19. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA*. 1998;280:605-613.
20. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321-333.
21. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291:1701-1712.

22. Maki PM. A systematic review of clinical trials of hormone therapy on cognitive function: effects of age at initiation and progestin use. *Ann NY Acad Sci.* 2005;1052:182-197.
23. Polo-Kantola P, Portin R, Polo O, et al. The effect of short-term estrogen replacement therapy on cognition: a randomized, double-blind, cross-over trial in postmenopausal women. *Obstet Gynecol.* 1998;91:459-466.
24. Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. *Psychoneuroendocrinology.* 1992;17:485-495.
25. Sherwin BB. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. *Psychoneuroendocrinology.* 1988;13:345-357.
26. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography screening in postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA.* 2003;289:3243-3253.
27. Stefanick ML, Anderson GL, Margolis KL, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA.* 2006;295:1647-1657.
28. Anderson GL, Chlebowski RT, Rossouw JE, et al. Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. *Maturitas.* 2006;55:103-115.
29. Cushman M, Kuller LH, Prentice R, et al. Estrogen plus progestin and risk of venous thrombosis. *JAMA.* 2004;292:1573-1580.
30. Anderson FA Jr, Wheeler HB, Goldberg RJ, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med.* 1991;151:933-938.
31. National Center for Health Statistics, National Vital Statistics System. Death rates for 113 selected causes by 5-year age groups, race and sex: United States, 1979-98. Available at: [http://www.cdc.gov/nchs/data/statab/hist002r\\_2.pdf](http://www.cdc.gov/nchs/data/statab/hist002r_2.pdf). Accessed June 14, 2007.
32. Belchetz PE. Hormonal treatment of postmenopausal women. *N Engl J Med.* 1994;330:1062-1071.
33. Rodstrom K, Bengtsson C, Lissner L, et al. A longitudinal study of the treatment of hot flushes: the population study of women in Gothenburg during a quarter of a century. *Menopause.* 2002;9:156-161.
34. Speroff L, Kenemans P, Burger HG. Practical guidelines for postmenopausal hormone therapy. *Maturitas.* 2005;51:4-7.
35. Aslan E, Bagis T, Kilicdag EB, et al. How best is to discontinue postmenopausal hormone therapy: Immediate or tapered? *Maturitas.* 2007;56:78-83.
36. Haimov-Kochman R, Barak-Glantz E, Arbel R, et al. Gradual discontinuation of hormone therapy does not prevent the reappearance of climacteric symptoms: a randomized prospective study. *Menopause.* 2006;13:370-376.
37. American College of Obstetricians and Gynecologists Women's Health Care Physicians. Venous thromboembolic disease. *Obstet Gynecol.* 2004;104(4 Suppl):118S-127S.
38. Karas R. Considerations in interpreting the cardiovascular effects of hormone replacement therapy observed in the WHI: timing is everything. *Menopausal Medicine.* 2003;10(4):8-12.
39. Losordo DW, Kearney M, Kim EA, Jekanowski J, Isner JM. Variable expression of the estrogen receptor in normal and atherosclerotic coronary arteries of premenopausal women. *Circulation.* 1994;89:1501-1510.
40. Herrington DM, Espeland MA, Crouse JR III, et al. Estrogen replacement and brachial artery flow-mediated vasodilation in older women. *Arterioscler Thromb Vasc Biol.* 2001;21:1955-1961.
41. Barrett-Connor E, Laughlin GA. Hormone therapy and coronary artery calcification in asymptomatic postmenopausal women: the Rancho Bernardo Study. *Menopause.* 2005;12:40-48.

# What is a perimenopausal woman to do?

From an early age, I have heard whispers about “the change” and have awaited it with both trepidation and anticipation. What would it be like? Would I enjoy it? Would I sprout hairs from my chin while needing to constantly fan myself? Of course, none of those going through “the change” would ever discuss it with someone younger—I would have to just wait and see.

Then, a few years later, along came something called Hormones. These were always spoken of with a capital “H” by those in the know, as if they were some magical substance intended only for the chosen few. Discussions among those taking Hormones were usually ac-

companied by knowing winks and nods, and often satisfied smiles. But still, no information was shared with any of us younger than they.

What was “the change”? What were these Hormones and how soon could I get some?

This was, of course, during the days of miniskirts, Janis Joplin, and the Beatles—before disco music. I was never going to be old enough to worry about the change (later openly referred to as menopause) and would therefore never need Hormones. I knew so much more than the older women in my life, and I was so sure that by the time I got to menopausal age...well, I was really never planning to be that old.

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Now, though, reality is starting to sink in. I am getting closer and closer to menopause with each passing cycle. And with that, the researchers and the media are now making it so much more difficult for me than it was for those women with their winks and nods and satisfied smiles. Now I know that they knew all this confusion was coming, and this is exactly what they were winking, nodding, and smiling about!

Ok, so let's see if I can understand the information on hormones. First of all, it's no longer Hormone

Replacement Therapy but Hormone Therapy because it's no longer trying to replace the hormones but using hormones to alleviate the consequences of our loss of hormones instead. Ok, I think I have that.

Now, I can't take Hormone Therapy because it may give me coronary heart disease. Or is it stroke? I'm so confused! About 5 years ago, I was too scared to death by all the reports in the media about the results of the Women's Health Initiative Study to ever consider taking any sort of hormones once I became menopausal. Now, here we are 5 years later, and new results are coming out from a 5-year-old study that indicate that the results may not be as grim as first thought. What gives?

And then the 2 words that frighten women most were mentioned during a report about the new findings from the WHI Study on the *Today Show*: Breast Cancer. Capital "B" and Capital "C" Breast Cancer. The 2 words that women never want to hear from their own doctor or from their friends.

These 2 words are more frightening to women than cardiovascular disease, stroke, or venous thromboembolism. I know what Breast Cancer means. I understand the consequences. I have friends and relatives who have Breast Cancer or have had Breast Cancer. One of them died. One is still undergoing chemo. It's not a pretty thing to have as a "risk," and it scares me.

What am I, as a woman nearing menopause, to do? I have tried to read everything that comes out in the newspapers and magazines about hormone therapy, and I listen intently when it is being discussed on television. I see the words "clinically insignificant" some of the time, but if it is truly insignificant...well, why mention it at all?

I am starting to have difficulty sleeping at night and am starting to be a bit more irritable. My husband, bless his heart, says that he doesn't notice my increased irritability, but I think he's just too afraid to say anything that might irritate me. I'm starting to wonder,

while I'm lying awake at night, if I am having trouble sleeping because I'm perimenopausal, or is it because I'm worried about possibly being perimenopausal? Am I irritable because I'm getting closer to menopause, or am I irritable because I'm not sleeping well because I'm worried about getting closer to menopause?

And when I finally get to that magical age of menopause, will I be able to find a physician who will have the knowledge to correctly guide me through the maze of options available to me and help me choose the one that will stop all the symptoms while not killing me?

Or should I just tell my husband that he will have to put up with the irritability that he "doesn't notice" for a few more years?

Ms Mitchell has no financial relationships to disclose.

#### Erratum

The age-standardized rate of cervical cancer was erroneously labeled on figure 4 in Koh WP, Lee HP. Postmenopausal gynecological cancers: The Singapore perspective and its general applicability. *Menopausal Medicine*. 2007;15(1):S4. The scale should have been 0 to 20 per 100,000 per year, not 0 to 60 per 100,000 per year.