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Invited Commentary

Invited Commentary: Hormone Therapy and Risk of Coronary Heart Disease—Why Renew the Focus on the Early Years of Menopause?

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After the initial report from the Women's Health Initiative estrogen-progestin trial, which found that menopausal hormone therapy was associated with an increased risk of coronary heart disease in the overall cohort (age range: 50–79 years; mean age: 63 years), researchers took a closer look at the data from this and other studies, focusing on the timing of initiation of such therapy. The results suggest that hormone therapy may have a beneficial effect on the heart if started in early menopause, when a woman's arteries are still likely to be relatively healthy, but a harmful effect if started in late menopause, when advanced atherosclerosis may be present. The implication of the timing hypothesis for clinical practice is *not* that recently menopausal women be given hormone therapy for coronary heart disease prevention but rather that clinicians can be reassured about cardiac risks when considering short-term use of hormone therapy for vasomotor symptom relief in such women. The reduction in vasomotor symptoms must be weighed against other risks and benefits of treatment, but coronary disease is typically not a major factor in the equation for women who are recently menopausal.

coronary disease; estrogens; hormone replacement therapy; menopause; observational studies; progestins; randomized controlled trials

Abbreviations: CACS, Coronary Artery Calcium Study; CHD, coronary heart disease; CI, confidence interval; HERS, Heart and Estrogen/progestin Replacement Study; WHI, Women's Health Initiative.

Accumulating data suggest that the timing of initiation of menopausal hormone therapy in relation to menopause onset may affect the association between such therapy and risk of coronary heart disease (CHD). In this invited commentary, we review the evolution of, and evidence for, this concept—now known as the ''timing hypothesis''—and discuss its implications for clinical decision making.

EVOLUTION OF, AND EVIDENCE FOR, THE TIMING HYPOTHESIS

Dozens of observational studies conducted during the past three decades indicate that women who take estrogen are 35–50 percent less likely to develop CHD than women who do not take estrogen (1). For example, the Nurses' Health Study, a 20-year follow-up of more than 70,000 initially healthy postmenopausal women, found that current use of hormone therapy, as compared with never use, was associated with a relative risk of a major coronary event of 0.61 (95 percent confidence interval (CI): 0.52, 0.71) after adjustment for potential confounders (2).

Large randomized trials testing the effect of hormone therapy on clinical coronary outcomes have not confirmed a cardioprotective effect. In the Heart and Estrogen/progestin Replacement Study (HERS), the 4-year incidence of major coronary events among 2,763 postmenopausal women with

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preexisting CHD was similar in the hormone therapy (0.625 mg of oral conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate daily) and placebo groups (3). The hormone therapy group had a 50 percent increase in risk of CHD events during the first year of the trial, although this elevation was offset by a decreased risk in later years (3, 4). The Women's Health Initiative (WHI) examined the effects of oral conjugated equine estrogens (0.625 mg/day) with or without medroxyprogesterone acetate (2.5 mg/day) in healthy postmenopausal women aged 50–79 years; 16,608 women with an intact uterus and 10,739 women with hysterectomy participated in the estrogen-progestin and estrogen-alone trials, respectively. Contrary to expectation, women assigned to a mean of 5.6 years of estrogen-progestin were more likely to experience a CHD event than those assigned to placebo (relative risk = 1.24, 95 percent CI: 1.00, 1.54), with the risk increase most apparent during the first year (5). Women assigned to a mean of 6.8 years of estrogen alone also experienced no overall reduction in CHD risk (relative risk = 0.95, 95 percent CI: 0.79, 1.16) (6). (Both WHI trials were stopped early—the estrogen-progestin trial because of an increased risk of breast cancer and an unfavorable benefit-risk balance (7) and the estrogen-alone trial because of an increased stroke risk that was not offset by a reduced CHD risk (8).)

Although the discrepant findings from observational studies and randomized trials raise concern about the validity of observational data (specifically, that the coronary benefit seen in such studies may result from selection factors and confounding by participants' baseline health and behavior), other explanations have been proposed (9, 10). One such explanation is the timing hypothesis.

To date, a key difference between participants in observational studies and those in clinical trials of hormone therapy has been the timing of initiation of treatment in relation to menopause onset, which occurs on average at age 51 years in the United States. Hormone users in observational studies usually start therapy in early menopause, whereas trial participants are often randomized to hormones long after cessation of menses. For example, women in the Nurses' Health Study were aged 30–55 years at baseline, and about 80 percent of hormone users in the cohort opted for hormone therapy within 2–3 years of menopause onset. In contrast, WHI participants, with a mean baseline age of 63 years, were generally more than a decade past menopause at the time of trial enrollment. These older women likely had more extensive subclinical atherosclerosis than their younger counterparts. In HERS, the mean baseline age was 67 years, and all participants had been previously diagnosed with CHD. It has been hypothesized that estrogen has multiple and opposing actions, slowing the earlier stages of atherosclerosis through salutary effects on the lipid profile and endothelial function but triggering acute coronary events through prothrombotic and inflammatory mechanisms when advanced lesions are present (9, 11).

This hypothesis is supported by several lines of evidence. First, trials in humans show complex, myriad effects of exogenous estrogen on cardiovascular biomarkers (12, 13). Oral estrogen lowers low-density lipoprotein cholesterol, lipoprotein(a), glucose, insulin, and homocysteine levels; inhibits oxidation of low-density lipoprotein cholesterol; raises high-density lipoprotein cholesterol; reverses postmenopausal increases in fibrinogen and plasminogen-activator inhibitor type 1; and improves endothelial function—all effects expected to *lower* coronary risk. However, oral estrogen also increases triglycerides, coagulation factors (factor VII, prothrombin fragments 1 and 2, and fibrinopeptide A), C-reactive protein, and matrix metalloproteinases—effects expected to *boost* coronary risk. Moreover, certain progestogens offset some of estrogen's benefits.

Data from controlled experiments in nonhuman primates also lend credence to the idea that the net coronary effect of hormone therapy depends on the initial health of the vasculature. Although conjugated estrogens (with or without medroxyprogesterone acetate) did not affect the extent of coronary artery plaque in cynomolgus monkeys started on this treatment at 2 years (~6 human years) after oophorectomy and well after the establishment of atherosclerosis, such therapy reduced the extent of plaque by 70 percent when initiated immediately after oophorectomy, during the early stages of atherosclerosis (14). Similarly, imaging trials in humans with significant coronary lesions at enrollment have found estrogen to be ineffective in retarding the rate of arterial narrowing (15–18). However, in an imaging trial that did not require women to have significant lesions at entry, micronized 17ß-estradiol was associated with a slower progression of carotid atherosclerosis (19).

That age or vascular health might be an important determinant of the effect of hormone therapy on coronary or other outcomes was not well recognized when the WHI trials were initiated in the early 1990s; thus, focused subgroup analyses were not emphasized at the outset, nor were the trials powered to detect potential interactions. Nonetheless, given the emerging discrepancy between earlier observational and more recent randomized findings (including data not only from the large trials with hard clinical endpoints but also from the smaller imaging and animal studies), WHI investigators took the logical next step in choosing to conduct post-hoc analyses of their data to examine—though not prove conclusively—whether the timing hypothesis might account for the seemingly contradictory evidence on coronary effects of hormone therapy.

Despite Barrett-Connor's skepticism (20), the results of subgroup analyses of WHI data are consistent with the possibility that age or time since menopause influences the hormone therapy-CHD association. Subgroup analyses have been reported by Manson et al. (5) and Rossouw et al. (21) for the estrogen-progestin data and by the WHI Steering Committee (8), Hsia et al. (6), and Rossouw et al. (21) for the estrogen-alone data. We focus primarily on the report by Rossouw et al. (21), because these analyses included the largest number of confirmed coronary endpoints; used a uniform coding scheme for age and years since menopause to examine effect modification by these factors (they were modeled as ordered categorical variables); and combined data from both trials to increase statistical power. However, the results of the above reports were largely congruent.

In the WHI, the hormone therapy-associated risk of CHD (defined in primary analyses as myocardial infarction or

coronary death) steadily increased with years since menopause (table 1). In analyses that combined data from both trials, relative risks were 0.76, 1.10, and 1.28 for women who were <10, 10–19, and ≥20 years past menopause at study entry, respectively ($p_{trend} = 0.02$) (21). Indeed, a pattern of monotonically rising relative risks was apparent in both the estrogen-alone and estrogen-progestin trials. (In the estrogen-progestin analysis of the report by Manson et al. (5) cited by Barrett-Connor (20) as evidence against the timing hypothesis, time since menopause was coded as a continuous variable, and the test for interaction was not significant. However, when time since menopause was modeled in ordered categorical fashion, clear evidence of effect modification emerged (table 1), suggesting the sensitivity of this test to choice of coding of variables.) With respect to age, hormone therapy-associated relative risks were 0.93, 0.98, and 1.26 for women aged 50–59, 60–69, and 70–79 years at study entry, respectively ($p_{trend} = 0.16$) (21). Although a trend by age group was not observed in the estrogen-progestin trial, this trend was apparent in the estrogen-alone trial, with relative risks for women in their 50s, 60s, and 70s of 0.63, 0.94, and 1.13, respectively ($p_{trend} = 0.12$) (21). Indeed, among women aged 50–59 years, assignment to estrogen alone was associated with a significant 45 percent reduction in the secondary endpoint of coronary revascularization and a significant 34 percent reduction in the composite endpoint of myocardial infarction, coronary death, or coronary revascularization (table 2) (6). (In describing the estrogen-alone findings reported by Hsia et al. (6), Barrett-Connor (20) ignores the intention-to-treat results and focuses on adherent participants. In this group, hormone therapy-associated relative risks also rose with age but, perhaps because of the smaller sample size, were accompanied by wider confidence intervals and a less suggestive trend test.) Taken together, the pattern of WHI results suggests that time since menopause influences the hormone therapy-CHD association somewhat more than chronologic age. There appears to be a beneficial or neutral effect of hormone therapy in women closer to menopause (who are likely to have less atherosclerosis) but a deleterious impact in later years.

The WHI findings have prompted closer attention to timing of hormone therapy initiation in recent analyses of observational and randomized data. In the Nurses' Health Study, women who began hormone therapy within 4 years of menopause had a lower risk of myocardial infarction than did nonusers, whereas women who initiated therapy 10 or more years after menopause appeared to derive little coronary benefit (22). In a randomized trial of 69 women assigned to 6 months of oral conjugated equine estrogens (with or without medroxyprogesterone acetate) or placebo, women in the hormone therapy group who were within 5 years of menopause experienced more favorable effects on blood pressure and vascular resistance than did women in the placebo group and those further past menopause in the hormone therapy group (23). Moreover, the increase in CHD risk noted in the early years of treatment in HERS and the WHI was not found in a combined analysis of two trials that enrolled a total of 4,065 healthy postmenopausal women with a mean age of 53 years (24).

Salpeter et al. (25) combined data from 22 smaller randomized trials with data from the WHI to provide the most comprehensive look to date at the influence of age on the relation between hormone therapy and CHD. Their analysis showed that, in trials that enrolled predominantly younger participants (women younger than 60 years or within 10 years of menopause), hormone therapy was associated with a 30–40 percent reduction in CHD risk. On the other hand, in trials with predominantly older participants, hormone therapy had little effect on such risk. The results of Salpeter et al. are more relevant for addressing the validity of the timing hypothesis than the findings of Hemminki and McPherson (26) cited by Barrett-Connor (20), since the latter report does not explicitly examine the effect of age.

In the WHI, age not only influenced the relation between hormone therapy and CHD but also appeared to modulate the effect of hormone therapy on all-cause mortality and a composite outcome (''global index'') of CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer, hip fracture, and mortality (table 1). In an analysis that combined data from the estrogen-progestin and the estrogen-alone trials, hormone therapy was associated with a significant 30 percent reduction in mortality among women in their 50s but had little effect among those in their 60s and was associated with a borderline significant increase in mortality among those in their 70s ($p_{trend} = 0.06$). This pattern was observed in both trials. For the global index, the hormone therapy-associated relative risks for women in their 50s, 60s, and 70s were 0.96, 1.08, and 1.14 ($p_{trend} = 0.09$), although the trend was apparent only in the estrogen-alone trial. A 2003 meta-analysis of 30 randomized trials, including the WHI estrogen-progestin trial, found that hormone therapy was associated with a nearly 40 percent reduction in mortality in trials in which the mean age of participants was less than 60 years but had no effect on mortality in other trials (27).

In summary, we believe that the existing evidence in support of the timing hypothesis is more compelling than Barrett-Connor believes it to be, although we certainly agree that the data are not yet conclusive and would *not* justify the use of hormone therapy for cardioprotection. However, even if the hypothesis is ultimately disproved and hormone therapy-associated relative risks for CHD are shown to be similar across groups defined by age or time since menopause, the much lower absolute baseline risks of CHD and other events in younger or recently menopausal women translate to much lower absolute excess risks associated with hormone therapy use in these women as compared with their counterparts who are older or further past menopause. Estimates of such risks based on WHI data (for CHD, total mortality, and the global index) are provided in table 3.

RATIONALE FOR THE DESIGN OF THE WHI CORONARY ARTERY CALCIUM STUDY

Upon termination of the WHI estrogen-only trial in early 2004, WHI investigators proposed the WHI-Coronary Artery Calcium Study (WHI-CACS) to elucidate the basis for the lower risk of clinical CHD observed among younger

TABLE 1. Relative risks and 95% confidence intervals for selected outcomes in the Women's Health Initiative trials of menopausal hormone therapy among US women followed from 1993 to 2002 (estrogen-progestin trial) and from 1993 to 2004 (estrogen-alone trial)*

Outcome	All women		Age (years)							Years since menopause†						
			50–59		60–69		70–79		p_{trend}	<10		10–19		≥20		p_{trend}
	Relative risk	95% confidence interval	Relative risk	95% confidence interval	Relative risk	95% confidence interval	Relative risk	95% confidence interval		Relative risk	95% confidence interval	Relative risk	95% confidence interval	Relative risk	95% confidence interval	
Coronary heart disease																
Combined trials	1.07	0.92, 1.23	0.93	0.65, 1.33	0.98	0.79, 1.21	1.26	1.00, 1.59	0.16	0.76	0.50, 1.16	1.10	0.84, 1.45	1.28	1.03, 1.58	0.02
Estrogen-progestin	1.23	0.99, 1.53	1.29	0.79, 2.12	1.03	0.74, 1.43	1.48	1.04, 2.11	0.70	0.88	0.54, 1.43	1.23	0.85, 1.77	1.66	1.14, 2.41	0.05
Estrogen alone	0.95	0.78, 1.16	0.63	0.36, 1.09	0.94	0.71, 1.24	1.13	0.82, 1.54	0.12	0.48	0.20, 1.17	0.96	0.64, 1.44	1.12	0.86, 1.46	0.15
Total mortality																
Combined trials	1.02	0.90, 1.15	0.70	0.51, 0.96	1.05	0.87, 1.26	1.14	0.94, 1.37	0.06	0.76	0.53, 1.09	0.98	0.78, 1.24	1.14	0.96, 1.36	0.51
Estrogen-progestin	1.00	0.83, 1.19	0.69	0.44, 1.07	1.09	0.83, 1.44	1.06	0.80, 1.41	0.19	0.81	0.52, 1.24	1.03	0.75, 1.41	1.11	0.83, 1.49	0.93
Estrogen alone	1.04	0.88, 1.22	0.71	0.46, 1.11	1.02	0.80, 1.30	1.20	0.93, 1.55	0.18	0.65	0.33, 1.29	0.93	0.66, 1.30	1.16	0.93, 1.45	0.42
Global index‡																
Combined trials	1.08	1.00, 1.16	0.96	0.81, 1.14	1.08	0.97, 1.20	1.14	1.02, 1.29	0.09	1.05	0.86, 1.27	1.12	0.98, 1.27	1.09	0.98, 1.22	0.82
Estrogen-progestin	1.13	1.02, 1.25	1.10	0.87, 1.38	1.15	0.99, 1.34	1.13	0.95, 1.33	0.96	1.09	0.87, 1.37	1.17	0.99, 1.38	1.13	0.95, 1.35	0.92
Estrogen alone	1.02	0.92, 1.13	0.82	0.64, 1.05	1.01	0.86, 1.17	1.16	0.98, 1.37	0.01	0.94	0.65, 1.36	1.05	0.85, 1.29	1.07	0.92, 1.23	0.63

* Data are from Rossouw et al. (21).

† Age at menopause was defined as the age at which a woman last had menstrual bleeding, had bilateral oophorectomy, or began using hormone therapy. For hysterectomy without bilateral oophorectomy, age at menopause was defined as the age at which a woman either began using hormone therapy or first had vasomotor symptoms. For hysterectomy without bilateral oophorectomy at age ≥50 years, but no use of hormone therapy or symptoms, age at menopause was defined as the age at hysterectomy.

‡ The global index is a composite outcome of coronary heart disease, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer, hip fracture, and mortality.

TABLE 2. Relative risks and 95% confidence intervals for selected outcomes in the Women's Health Initiative estrogen-alone trial among US women follwed from 1993 to 2004*

Outcome	All women		Age (years)†					
			50–59		60–69		70–79	
	Relative risk	95% confidence interval	Relative risk	95% confidence interval	Relative risk	95% confidence interval	Relative risk	95% confidence interval
Major CHD‡ (MI‡ or coronary death)	0.95	0.79, 1.16	0.63	0.36, 1.08	0.94	0.71, 1.24	1.11	0.82, 1.52
Coronary revascularization (CABG‡ or PCI‡)	0.93	0.78, 1.10	0.55	0.35, 0.86	0.99	0.78, 1.27	1.04	0.78, 1.39
Composite CHD (MI, coronary death, CABG, or PCI)	0.98	0.85, 1.13	0.66	0.44, 0.97	1.02	0.83, 1.25	1.08	0.85, 1.38

* Data are from Hsia et al. (6).
† $p_{interaction}$ by age < 0.10 (0.07 for CHD, 0.09 for coronary revascularization, and 0.09 for composite CHD).
‡ CHD, coronary heart disease; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

hormone users in the estrogen-alone trial. Specifically, the aim of this ''explanatory'' ancillary study was to determine whether assignment to estrogen was predictive of a lower coronary artery calcium level among women in their 50s. High coronary artery calcium indicates a greater atherosclerotic plaque burden and has been shown to predict risk of future coronary events (28). Barrett-Connor (20) believes that a valuable opportunity to test the timing hypothesis was lost by excluding older participants from WHI-CACS. Although we agree that comparing coronary artery calcium results across age groups would have been of interest, the requisite design was not implemented for three reasons. First, it was logistically impossible. In addition to budgetary constraints, there was an exceedingly narrow time window of opportunity to carry out this study. Coronary artery calcium scanning needed to be completed before WHI clinic staffing was markedly reduced and, more importantly, as close to the time of treatment discontinuation as possible to minimize dilution of any effect of estrogen therapy. Limiting the study to women in their 50s helped to ensure optimally timed scans in this group and to avoid potential dilution bias that would complicate interpretation of results. Second, from a scientific standpoint, such a design would not yield results that would affect clinical decision making regarding hormone therapy initiation among women in their 60s or 70s; few clinicians would consider starting their older patients on hormone therapy, irrespective of coronary artery calcium findings in these age groups. Finally, findings in older women would shed little mechanistic light on the findings for younger women. Although Barrett-Connor states, ''If the timing hypothesis is correct, this test ... would be expected to show less calcium in the estrogen than in the placebo group in the younger women and little or no difference in the older women'' (20, p. 508), this is not necessarily so. As described earlier, estrogen appears to have complex effects on the cardiovascular system. Therefore, whether or not estrogen leads to coronary artery calcium reduction in older women, a greater risk of hormone therapy-associated clinical events in these women would still be expected if estrogen promotes clotting or rupture of vulnerable plaque in the presence of late-stage atherosclerosis (because this condition is more prevalent in older populations). Thus, WHI-CACS was limited to women younger than 60 years.

TABLE 3. Estimated absolute excess risks per 10,000 person-years* for selected outcomes in the combined trials of menopausal hormone therapy of the Women's Health Initiative among US women followed from 1993 to 2002 (estrogen-progestin trial) and from 1993 to 2004 (estrogen-alone trial)†

Outcome	Age (years)			Years since menopause		
	50–59	60–69	70–79	<10	10–19	≥20
Coronary heart disease	−2	−1	19‡	−6	4	17‡
Total mortality	−10	−4	16‡	−7	−1	14
Global index§	−4	15	43	5	20	23

* Estimated absolute excess risk per 10,000 person-years = ((annualized percentage in placebo group) × (hazard ratio in placebo group − 1)) × 1,000.
† Data are from Rossouw et al. (21).
‡ $p = 0.03$ compared with age 50–59 years or <10 years since menopause.
§ The global index is a composite outcome of coronary heart disease, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer, hip fracture, and mortality.

The results of WHI-CACS have recently been published (29). Coronary artery calcium measurements following trial completion were lower among women randomized to estrogen than those randomized to placebo. Comparing the former with the latter group, odds ratios for increasingly high coronary artery calcium prevalence cutpoints (coronary artery calcium >0, ≥10, and ≥100) were 0.78 (95 percent CI: 0.58, 1.04), 0.74 (95 percent CI: 0.55, 0.99), and 0.69 (95 percent CI: 0.48, 0.98), respectively, after coronary risk factor adjustment. Corresponding odds ratios among women with 80 percent or higher adherence to study pills were 0.64, 0.55, and 0.46 ($p = 0.01$–<0.001). These findings support the hypothesis that estrogen therapy reduces progression of atherosclerosis and subclinical coronary artery disease in younger women who are closer to the onset of menopause.

That said, new trials are under way to address questions raised by Barrett-Connor (20) and other investigators concerning possible differential effects of hormone therapy on the development and progression of atherosclerosis according to age at initiation (30) and type (31) of therapy.

IMPLICATIONS OF THE TIMING HYPOTHESIS FOR CLINICAL DECISION MAKING

Perhaps the most serious flaw in Barrett-Connor's commentary is her misconception regarding implications of the timing hypothesis for clinical decision making. Barrett-Connor appears to believe that clinicians who give credence to this hypothesis would automatically recommend that women start hormone therapy in early menopause and use it long term for the prevention of heart disease. This assumption is false, and we would certainly not endorse this strategy. Although we cannot speak for every last clinician, there is a clear consensus among mainstream health organizations and many health-care providers that unbridled enthusiasm for hormone therapy as a cardioprotective agent for younger women is unwarranted. The US Preventive Services Task Force (32), American College of Obstetricians and Gynecologists (33), American Heart Association (34), Canadian Task Force on Preventive Health Care (35), and the North American Menopause Society (36) recommend against the use of hormone therapy at any age to prevent CHD and other chronic diseases.

Clinical decision making involves balancing potential benefits against potential risks for individual patients. Benefits of hormone therapy include relief from hot flashes, night sweats, and vaginal dryness, and, possibly, improvements in sleep, mood, and concentration. In addition, hormone therapy preserves bone density and protects against osteoporotic fractures. Risks include higher rates of breast cancer, stroke, and venous thromboembolism. For CHD, if the timing hypothesis is correct, excess risk is limited largely to older women many years past the menopausal transition. (If the timing hypothesis is incorrect and hormone therapy-associated relative risks do *not* vary according to age or time since menopause, older women would still experience much higher absolute excess risks of coronary and other vascular events from hormone therapy use than their younger counterparts because advancing age confers higher absolute baseline risks of these conditions.)

Although hormone therapy should never be prescribed specifically for coronary protection, we believe that the timing hypothesis can—and should—inform clinical decision making regarding the use of systemic hormone therapy for treatment of hot flashes and night sweats that are severe or frequent enough to disrupt sleep or quality of life—the classic and currently only compelling indications for such therapy. The timing hypothesis implies that women in early menopause and at low baseline risk of CHD are unlikely to experience a hormone therapy-associated coronary event. Thus, two key factors to consider in deciding whether to initiate hormone therapy in a woman suffering from vasomotor symptoms (assuming she has a personal preference for this treatment) are where she is in the menopausal transition and whether she is in good cardiovascular health. A younger, recently menopausal woman (one whose final menstrual period was $\leq$5 years ago) at low baseline risk of CHD, stroke, or venous thromboembolism is a reasonable candidate for short-term hormone therapy. Conversely, an older woman many years past menopause, who is at higher risk of these cardiovascular conditions, is not. (For information on other contraindications and detailed guidance on hormone therapy decision making, see our recent book (37).)

Few mainstream health-care organizations or providers now suggest that women take hormone therapy indefinitely. Rather, the standard recommendation is that hormone therapy is best used for only 2–3 years and generally for no more than 5 years. Vasomotor symptoms often subside after the first few years following cessation of menses, so hormone therapy typically will be unnecessary for long-term symptom relief. Moreover, breast cancer risk increases the longer that hormones, particularly estrogen plus progestogen, are used. For women who begin hormone therapy in early menopause, it also remains unclear at what point any potential salutary (or neutral) cardiovascular effects are trumped by deleterious ones. The rising risks of breast cancer and cardiovascular disease eventually tip the risk-benefit balance into unfavorable territory for most women. However, women who have had bilateral oophorectomy before the age of 45 years, or who are at very low risk of breast cancer and also at very high risk of fracture, may be reasonable candidates to continue hormone therapy for a few years beyond the 5-year limit, provided that they experience severe vasomotor symptoms after stopping hormone therapy and have a personal preference to resume treatment.

In summary, the implication of the timing hypothesis for clinical decision making is not that recently menopausal women be prescribed hormone therapy for CHD prevention but rather that health-care providers need not be unduly concerned about coronary risks when considering short-term use of hormone therapy to relieve vasomotor symptoms in these women. This new information should aid clinical practice and improve the quality of medical care for women at midlife.

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