

# Current recommendations: what is the clinician to do?

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Menopausal hormone therapy (HT) has complex biologic effects but continues to have an important clinical role in the management of vasomotor and other menopausal symptoms. The rational use of menopausal HT requires balancing the potential benefits and risks of treatment. Findings from the Women's Health Initiative (WHI) and other randomized clinical trials have helped to clarify the benefits and risks of HT and have provided insights to improve decision making. Several clinical characteristics have utility in identifying women for whom benefits of HT are likely to outweigh the risks. Age and time since menopause are strong predictors of health outcomes and absolute risks associated with HT, and differences by age have been particularly apparent for estrogen alone. In the WHI trial of conjugated equine estrogens (CEE) alone, younger women (50–59 years) had more favorable results for all-cause mortality, myocardial infarction, and the global index, but not for stroke and venous thrombosis. Age trends were less clear for CEE + medroxyprogesterone acetate, owing to increased risks of breast cancer, stroke, and venous thrombosis in all age groups. Absolute risks of adverse events were lower in younger than in older women in both trials, however. Other predictors of lower vascular risk from HT include favorable lipid status and absence of the metabolic syndrome. Transdermal administration may be associated with lower risks of venous thrombosis and stroke, but additional research is needed. The use of risk stratification and personalized risk assessment offers promise for improved benefit-risk profile and safety of HT. One approach to decision making is presented. Key elements include: assessment of whether the patient has moderate to severe menopausal symptoms, the primary indication for initiating systemic HT (vaginal estrogen may be used to treat genitourinary symptoms in the absence of vasomotor symptoms); understanding the patient's own preference regarding therapy; evaluating the patient for the presence of any contraindications to HT, as well as the time since menopause onset and baseline risks of cardiovascular disease and breast cancer; reviewing carefully the benefits and risks of treatment with the patient, giving more emphasis to absolute than to relative measures of effect; and, if HT is initiated, regularly reviewing the patient's need for continued treatment. (Fertil Steril® 2014;101:916–21. ©2014 by American Society for Reproductive Medicine.)

**Key Words:** Hormone therapy, benefit-risk profile, clinical decision making

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One of the most complex health care decisions facing women in midlife is whether to use menopausal hormone therapy (HT). Although originally prescribed primarily to treat vasomotor symptoms, HT had been increasingly viewed as a way to forestall many chronic diseases of aging, including coronary heart disease (CHD) and cognitive impairment (1, 2). At least 40% of postmenopausal women in the United States were using HT shortly before the publication of the

initial findings from the Women's Health Initiative (WHI) (3). Although observational studies had suggested benefits of HT for cardiovascular disease (CVD) and all-cause mortality, and an overall favorable benefit-risk profile (1, 2), no large-scale randomized prevention trial had addressed the balance of risks and benefits. In observational studies, the apparent benefits may result at least in part from differences between women who opt to take postmenopausal hormones and women who do

not; those choosing HT tend to be healthier, have better access to medical care, and maintain a more health-promoting lifestyle (4). In this context, the WHI HT trials were developed and the most commonly used HT formulations in the United States at that time, conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) and CEE alone, were chosen for evaluation (5). Thus, the WHI trials were designed to determine the benefits and risks of HT taken for chronic disease prevention by predominantly healthy postmenopausal women aged 50–79 years at enrollment (5–7). WHI investigators have recently published a comprehensive integrated overview of findings from the two WHI HT trials with extended postintervention follow-up (median 13 years of cumulative follow-up) (8). That recent report includes primary,

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TABLE 1

Benefits and risks (absolute risks per 10,000 women per year, rate differences, and relative risks) of menopausal hormone therapy on chronic disease outcomes in the overall study population of women aged 50–79 years in the Women's Health Initiative (WHI) estrogen-progestin (E + P) and estrogen-alone (EA) trials.<sup>a</sup>

Outcome	Estrogen-progestin trial (n = 16,608)				Estrogen alone trial (n = 10,739)					
	No. of cases per 10,000 women per year	E + P	Placebo	Difference (b)	RR (95% CI) <sup>b</sup>	No. of cases per 10,000 women per year	EA	Placebo	Difference (b)	RR (95% CI) <sup>b</sup>
Benefits (in addition to menopausal symptom management)										
Hip fracture	11	17	-6	0.67 (0.47–0.95)	13	19	-6	0.67 (0.46–0.96)		
Type 2 diabetes	72	88	-16	0.81 (0.70–0.94)	134	155	-21	0.86 (0.76–0.98)		
Risks										
Stroke	33	24	+8	1.37 (1.07–1.76)	45	34	+11	1.35 (1.07–1.70)		
Pulmonary embolism	18	9	+9	1.98 (1.36–2.87)	14	10	+4	1.35 (0.89–2.05)		
Deep vein thrombosis	25	14	+11	1.87 (1.37–2.54)	23	15	+8	1.48 (1.06–2.07)		
Breast cancer <sup>c</sup>	43	35	+8	1.24 (1.01–1.53)	28	35	-7	0.79 (0.61–1.02)		
Gallbladder disease	131	84	+47	1.57 (1.36–1.80)	164	106	+58	1.55 (1.34–1.79)		
Neutral or uncertain risks and benefits <sup>d</sup>										
Coronary heart disease <sup>e</sup>	41	35	+6	1.18 (0.95–1.45)	55	58	-3	0.94 (0.78–1.14)		
Myocardial infarction	35	29	+6	1.24 (0.98–1.56)	44	45	-1	0.97 (0.79–1.21)		
Ovarian cancer	5	4	+1	1.41 (0.75–2.66)	-	-	-	Not available		
Colorectal cancer	10	17	-7	0.62 (0.43–0.89)	17	15	+2	1.15 (0.81–1.64)		
Dementia (age ≥ 65 y)	46	23	+23	2.01 (1.19–3.42)	44	29	+15	1.47 (0.85–2.52)		
Total mortality	52	53	-1	0.97 (0.81–1.16)	80	77	+3	1.03 (0.88–1.21)		
Global index <sup>d,f</sup>	189	168	+21	1.12 (1.02–1.24)	208	204	+4	1.03 (0.93–1.13)		

<sup>a</sup> The estrogen-progestin arm of the WHI assessed a median of 5.6 years of conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d) versus placebo. The estrogen-alone arm of the WHI assessed a median of 7.2 years of conjugated equine estrogens (0.625 mg/d) versus placebo.

<sup>b</sup> RR = relative risk; CI = confidence interval. Rate difference is rate in the hormone arm minus rate in the placebo arm.

<sup>c</sup> Divergent results for the two interventions.

<sup>d</sup> Also includes outcomes with divergent results for the two interventions.

<sup>e</sup> Coronary heart disease is defined as nonfatal myocardial infarction or coronary death.

<sup>f</sup> The global index is a composite outcome representing the first event for each participant from among the following: coronary heart disease, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer (E+P trial only), hip fracture, and death. Because participants can experience more than one type of event, the global index can not be derived by a simple summing of the component events.

Source of data: Manson JE, Chlebowski RT, Stefanick ML, et al.; JAMA 2013; 310:1353–68.

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secondary, and quality-of-life outcomes, as well as stratification of results by age, time since menopause onset, and other important variables.

## OVERVIEW OF FINDINGS

The results of the recent WHI publication are summarized in Table 1, showing intervention-phase findings (absolute risks per 10,000 women per year, rate differences, and relative risks) for a wide range of health outcomes in the two HT trials. The assessment of the overall balance of benefits and risks of HT when used for chronic disease prevention addresses a different question from whether HT is effective or appropriate for the treatment of menopausal symptoms. Compelling evidence, including data from randomized clinical trials, indicates that HT is highly effective for controlling vasomotor symptoms, as reviewed and summarized by Drs. Al-Safi and Santoro in this issue of *Fertility and Sterility*.

Results for chronic disease outcomes in the WHI HT trials are more complex. For CEE+MPA, the hazard ratio (HR) for CHD during the intervention phase was 1.18 (95% confidence interval [CI] 0.95–1.45), and increased risks of invasive breast cancer, stroke, pulmonary embolism, and the global index were observed (Table 1). Other risks included an increased rate of dementia (in women ≥ 65 years), gallbladder disease, and urinary incontinence, whereas benefits included decreased risk of hip fractures, diabetes, and vasomotor

TABLE 2

Effects of postmenopausal hormone therapy on cardiovascular outcomes in the Women's Health Initiative estrogen-progestin and estrogen-alone trials, according to age at study enrollment.

Outcome	Intervention phase <sup>a</sup>				
	Estrogen-progestin		Estrogen alone		
	RR (95% CI)	P value	RR (95% CI)	P value	
Coronary heart disease <sup>b</sup>					
50–59 y	1.34 (0.82–2.19)	.81	0.60 (0.35–1.04)	.08	
60–69 y	1.01 (0.73–1.39)		0.95 (0.72–1.24)		
70–79 y	1.31 (0.93–1.84)		1.09 (0.80–1.49)		
Myocardial infarction					
50–59 y	1.32 (0.77–2.25)	.55	0.55 (0.31–1.00)	.02	
60–69 y	1.05 (0.74–1.47)		0.95 (0.69–1.30)		
70–79 y	1.46 (1.00–2.15)		1.24 (0.88–1.75)		
Stroke					
50–59 y	1.51 (0.81–2.82)	.50	0.99 (0.53–1.85)	.77	
60–69 y	1.45 (1.00–2.11)		1.55 (1.10–2.16)		
70–79 y	1.22 (0.84–1.79)		1.29 (0.90–1.86)		
Pulmonary embolism					
50–59 y	2.05 (0.89–4.71)	.61	1.53 (0.63–3.75)	.28	
60–69 y	1.69 (1.01–2.85)		1.72 (0.94–3.14)		
70–79 y	2.54 (1.27–5.09)		0.85 (0.39–1.84)		
All-cause mortality					
50–59 y	0.67 (0.43–1.04)	.20	0.70 (0.46–1.09)	.04	
60–69 y	1.07 (0.81–1.41)		1.01 (0.79–1.29)		
70–79 y	1.03 (0.78–1.36)		1.21 (0.95–1.56)		

Note: RR = relative risk; CI = confidence interval.

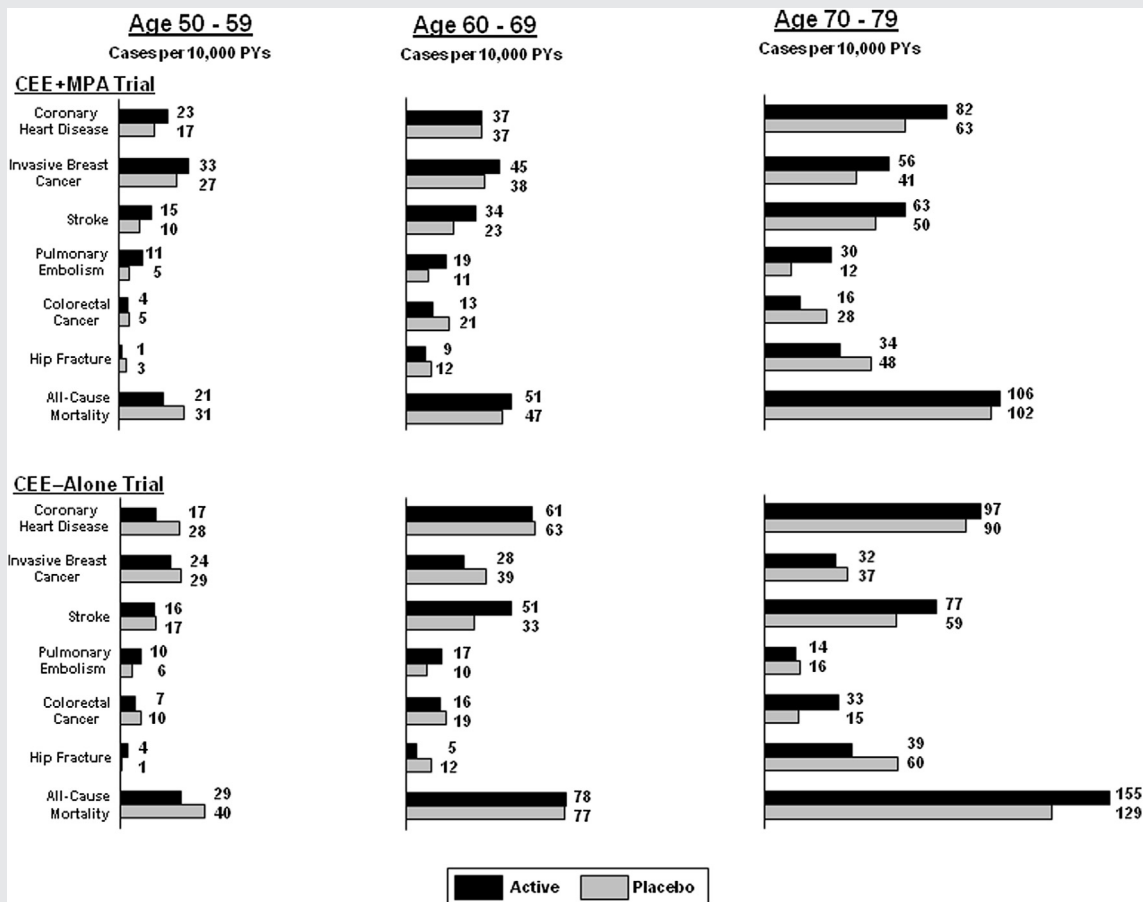
<sup>a</sup> Intervention phase was a median of 5.6 years in the estrogen-progestin trial and 7.2 years in the estrogen-alone trial.

<sup>b</sup> Coronary heart disease is defined as nonfatal myocardial infarction or coronary death.

Source of data: Manson JE, Chlebowski RT, Stefanick ML, et al.; JAMA 2013; 310:1353–68.

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**FIGURE 1**



Women's Health Initiative hormone therapy trials. Absolute risks (cases per 10,000 person-years) for outcomes in the intervention phases of the estrogen-progestin (CEE+MPA) and estrogen-alone (CEE) trials, by age group.  
 Source of data: Manson JE, Chlebowski RT, Stefanick ML, et al.; JAMA 2013; 310:1353–68.

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symptoms. Overall, the risks of CEE+MPA tended to outweigh the benefits. During the post-stopping phase, most risks and benefits dissipated, although some elevation in breast cancer risk persisted (cumulative HR 1.28, 95% CI 1.11–1.48). During intervention for CEE alone, risks and benefits were more balanced, with an HR for CHD of 0.94 (95% CI 0.78–1.14), increased risks of stroke and venous thrombosis, decreased risks of hip fractures and diabetes, and, over cumulative follow-up, decreased risk of breast cancer (HR 0.79, 95% CI 0.65–0.97). Neither regimen affected all-cause mortality rates. Thus, breast cancer findings were divergent between the two trials, and, for both cancer and CVD outcomes, results tended to be more adverse for CEE+MPA than for CEE. Despite benefits for vasomotor symptoms, the results for other quality of life outcomes in both trials were mixed (8).

Age and time since menopause, however, appeared to influence many of the findings. In the CEE-alone trial, younger women (50–59 years) had more favorable results for all-cause mortality, myocardial infarction (MI), colorectal cancer, and the global index (nominal *P* values for trend by age of <.05) (8). Both HT regimens, however, were associated with

increased risks of stroke, venous thrombosis, gallbladder disease, and urinary incontinence, and no clear differences were apparent by age for those outcomes. For CEE+MPA, breast cancer was an additional adverse effect and, although risk of MI varied by time since menopause, the overall risks of chronic disease events outweighed benefits across all age groups. Overall, differences in HRs by age were more apparent in the CEE-alone than in the CEE+MPA trial (Table 2). Importantly, however, absolute risks of adverse events were much lower in younger women than older women in both trials (Fig. 1). In fact, absolute risks measured by the global index (see definition in the footnote to Table 1) per 10,000 women per year on CEE+MPA ranged from 12 excess cases for ages 50–59 years to 38 excess cases for ages 70–79 years and, for CEE, from 19 fewer cases for ages 50–59 years to 51 excess cases for ages 70–79 years.

Regarding CHD, the potential influence of age or time since menopause on the vascular response to HT has received considerable attention (9–13). This subject is reviewed in detail by Dr. Harman in this issue. It has been postulated that estrogen may slow early stages of atherosclerosis and

TABLE 3

**Coronary heart disease risk in the Women's Health Initiative estrogen-progestin and estrogen-alone trials (pooled trial results), according to baseline levels of selected biomarkers and risk factors.**

Marker	OR (95% CI) for HT treatment effect	P value for interaction
LDL cholesterol (mg/dL)		
<130	0.66 (0.34–1.27)	.03
≥130	1.46 (1.02–2.10)	
LDL/HDL cholesterol ratio		
<2.5	0.60 (0.34–1.06)	.002
≥2.5	1.73 (1.18–2.53)	
C-Reactive protein		
<2.0	1.01 (0.63–1.62)	.16
≥2.0	1.58 (1.05–2.39)	
Metabolic syndrome <sup>a</sup>		
No	0.97 (0.58–1.36)	.03
Yes	2.26 (1.26–4.07)	
Waist circumference (cm)		
≤88	1.03 (0.62–1.70)	.12
>88	1.93 (1.08–3.44)	

Note: Coronary heart disease is defined as nonfatal myocardial infarction and coronary death. CI = confidence interval; HDL = high-density lipoprotein; HT = hormone therapy; LDL = low-density lipoprotein; OR = odds ratio.

<sup>a</sup> Metabolic syndrome was defined as having three or more of the following: waist size >88 cm (>80 cm for Asians and Native Americans); systolic blood pressure >130 mm Hg or diastolic blood pressure >85 mm Hg; fasting glucose >100 mg/dL; HDL cholesterol <50 mg/dL; triglycerides >150 mg/dL.

Sources of data: Bray et al.; Am J Cardiol 2008; 101:1599–605; and Wild et al.; Menopause 2013; 20:254–60.

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have favorable endothelial effects in recently menopausal women but have plaque-destabilizing and other adverse effects on advanced atherosclerotic lesions (9, 13). The findings that women with dyslipidemia or metabolic syndrome, but not those without these risk factors, have increased risks of coronary events on HT (14–17) is consistent with this hypothesis (Table 3). The WHI findings suggest that HT has a harmful effect on CHD risk in older women and those at higher baseline risk of CVD, whereas the results in younger and low-risk women tend to be neutral for CEE+MPA and in a favorable direction for CEE. Also, the lower absolute risks of adverse events with HT in younger women lead to lower attributable risks in these age groups in both trials.

As reviewed by Fischer et al. in this issue, a “critical window” for estrogen and cognitive function has also been proposed. In WHI, a deleterious relationship between HT and cognitive function was observed among women aged ≥65 years (18), whereas neutral relationships were seen among women aged 50–54 years at enrollment (19).

## CLINICAL RECOMMENDATIONS

So what guidance can be provided to clinicians regarding clinical decision making about HT use, given the current body of evidence? Based on the available research, HT remains appropriate for the management of moderate-to-severe menopausal symptoms in early menopause, but current evidence does not support the use of either estrogen-progestin or estrogen alone for long-term chronic disease prevention. Thus, a clear distinction between the use

of HT for symptom management in women with indications for treatment and its use for the purpose of chronic disease prevention is essential. In evaluating the patient, the following strategy represents one, but not the only, approach.

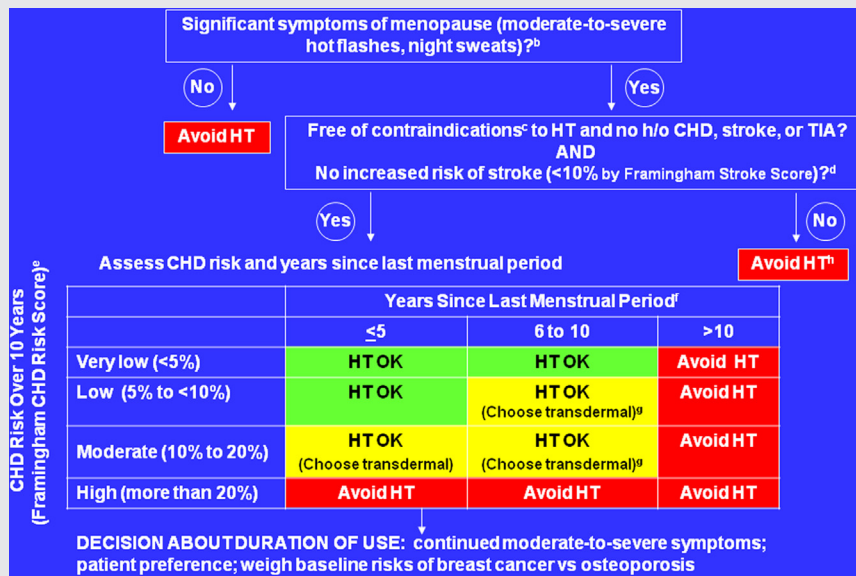
Clinical decision making about the use of menopausal HT requires balancing the potential benefits and risks (Fig. 2). In the proposed approach, the clinician should first determine whether the patient has moderate-to-severe menopausal symptoms, the primary indication for initiating systemic HT. (For women who have genitourinary symptoms in the absence of vasomotor symptoms, low-dose vaginal estrogen can be used.) Whether or not to initiate systemic HT to prevent osteoporosis is controversial, but if this is done, it is recommended that treatment be limited to women at high risk of fracture who can not tolerate alternative osteoporosis therapies. In discussing HT with the patient, the benefits and risks of treatment should be carefully reviewed, giving more emphasis to absolute than to relative measures of effect (Fig. 1; Table 1). Because chronic disease rates generally increase with age, absolute risks tend to be greater in older women (Fig. 1), even if the relative risks remain similar. It is important to point out, where relevant, the uncertainties in our clinical knowledge about HT. Potential side effects, including vaginal bleeding among women without hysterectomy and breast tenderness, should be noted. The patient's own preference regarding treatment (or avoiding treatment) should be elicited and weighed strongly in the decision. Contraindications to HT, including unexplained vaginal bleeding, active liver disease, venous thromboembolism, history of endometrial cancer or breast cancer, and history of CHD, stroke, or transient ischemic attack, should be assessed. Relative contraindications include hypertriglyceridemia (>400 mg/dL) and active gallbladder disease; in such cases, oral HT should be avoided but transdermal estrogen may be an option. An adequate trial of behavioral and lifestyle approaches to managing vasomotor symptoms is advisable before initiating pharmacotherapy.

Prevention of heart disease or cognitive decline should not be viewed as expected benefits of HT and are not considered indications for treatment. Moreover, increases in risk of stroke, venous thromboembolism (at least with oral therapy), and a small early increase in coronary artery disease risk are potential risks that warrant consideration. Nevertheless, HT will be appropriate if the expected benefits of treatment outweigh the risks. This is more likely to be the case for a recently menopausal woman with vasomotor symptoms or other quality-of-life impairments. A woman who suffers an acute coronary event, stroke, or venous thromboembolism while on HT should stop therapy immediately and avoid reinstitution of treatment.

## Duration of Treatment

Some guidelines recommend treatment for <5 years for estrogen-progestogen and <7 years for estrogen alone, based on availability of data for these durations in the WHI trials (20). These durations are only guidelines, and clinicians can use discretion in determining the treatment duration consistent with the patient's individual treatment goals, needs, and

**FIGURE 2**



Flow chart for identifying appropriate candidates for systemic menopausal hormone therapy (HT).

<sup>a</sup>Reassess each step at least once every 6–12 months (assuming patient's continued preference for HT). <sup>b</sup>Women at high risk of osteoporotic fracture but unable to tolerate alternative preventive medications also may be reasonable candidates for systemic HT even if they do not have moderate to severe vasomotor symptoms. Women who have vaginal dryness without moderate to severe vasomotor symptoms may be candidates for vaginal estrogen or other treatments. <sup>c</sup>Traditional contraindications: unexplained vaginal bleeding; active liver disease; history of venous thromboembolism due to pregnancy, oral contraceptive use, or unknown etiology; blood clotting disorder; history of breast or endometrial cancer. For other contraindications, including high triglycerides (>400 mg/dL), active gallbladder disease, and history of venous thromboembolism due to past immobility, surgery, or bone fracture, oral HT should be avoided but transdermal HT may be an option (see note f). <sup>d</sup>Ten-year risk of stroke, based on Framingham Stroke Risk Score (d'Agostino RB, Wolf PA, Belanger AJ, Kannel WB; Stroke risk profile: adjustment for antihypertensive medication; the Framingham Study; Stroke 1994; 25:40–3). <sup>e</sup>Ten-year risk of CHD, based on Framingham Coronary Heart Disease Risk Score (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; JAMA 2001; 285:2486). <sup>f</sup>Women >10 years past menopause are not good candidates for starting (first use of) HT. <sup>g</sup>Avoid oral HT. Transdermal HT may be an option, because it has a less adverse effect on clotting factors, triglyceride levels, and inflammation factors than oral HT. <sup>h</sup>Consider selective serotonin or serotonin-norepinephrine reuptake inhibitor, gabapentin, clonidine, soy, or other alternatives. Adapted from: Manson JE, Bassuk SS. The menopause transition and postmenopausal hormone therapy. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. Harrison's principles of internal medicine. McGraw Hill: New York; 2011. CHD = coronary heart disease; TIA = transient ischemic attack.

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priorities. Treatment duration should be reassessed at 6–12 month intervals, however, incorporating the patient's preference for continuing or discontinuing HT. Several years of treatment is appropriate for relief of menopausal symptoms among women without contraindications to such use. However, initiation of treatment should be avoided in women >10 years past the onset of menopause and among women with an elevated baseline risk of cardiovascular events (vascular risks can be estimated with the use of a number of risk prediction tools [21–23]). Women who have contraindications for HT or who are not appropriate candidates (including women who would prefer to avoid any hormonal treatments), may derive benefit from the use of certain antidepressant medications (including venlafaxine, fluoxetine, escitalopram, or paroxetine), gabapentin, clonidine, or other options (20). For genitourinary symptoms alone, low-dose vaginal estrogen or ospemifene would be recommended (20).

Use of systemic HT for longer durations is more problematic, because an increased risk of breast cancer must be factored into the decision, especially for estrogen-

progesterone, and because the absolute risks of other adverse events (e.g., stroke and venous thromboembolism) increase with age. Reasonable candidates for such extended use include a small percentage of postmenopausal women, including those who have persistent severe vasomotor symptoms, an increased risk of osteoporosis, and inability to tolerate other bone-protection medications (though controversial), and those who have a strong personal preference for continued therapy despite a full discussion of potential risks and benefits (when the clinician thinks that benefits are likely to outweigh risks for the individual patient). Poor candidates are women at elevated risk of CHD or stroke, those at increased risk of breast cancer (e.g., women who have a first-degree relative with breast cancer, susceptibility genes such as BRCA1 or BRCA2, or a history of cellular atypia on breast biopsy), and those at low risk of osteoporosis. Even among women considered to be reasonable candidates, strategies to minimize the dose and the duration of use should be considered. Treatment can be initiated with a low dose and increased only if needed to meet treatment goals. Because of the role of progesterone in augmenting breast cancer risk,

regimens that include cyclic rather than continuous progestogens, formulations other than MPA, or newer products such as bazedoxifene combined with CEE, could be considered. For prevention of osteoporosis, alternative therapies, such as bisphosphonates or selective estrogen receptor modulators, should be given an adequate trial. (The expanding array of pharmacologic options for bone health should reduce the reliance on HT for this purpose.) It is important to note that research on alternative progestogens and androgen-containing preparations has been limited, particularly regarding long-term safety. Additional research on cardiometabolic and breast-related outcomes with these agents will be of particular interest.

## CONCLUSIONS

Hormone therapy continues to have an important clinical role in the management of menopausal symptoms. The absolute risks of adverse events in younger women are much lower than in older women, and the quality-of-life benefits are likely to outweigh the risks for many women who seek treatment for symptoms in early menopause. Currently available evidence, however, does not support the use of HT for chronic disease prevention, owing to an increased risk of stroke, venous thromboembolism, and other adverse events with HT among women in all age groups. The use of low-dose and transdermal formulations may be associated with fewer risks, but more research is needed to confirm such differences. Risk stratification can be used to identify appropriate candidates for treatment and to facilitate a safer and more personalized approach to clinical decision making. Recent research has advanced our understanding of the benefits and risks of HT and enhanced the ability of both clinicians and patients to make informed choices about treatment.

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