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Review article

Menopausal symptom management in women with cardiovascular disease or vascular risk factors

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ABSTRACT

Women with preexisting cardiovascular disease (CVD) or vascular risk factors commonly experience bothersome symptoms of menopause, including vasomotor symptoms (VMS) and genitourinary syndrome of menopause (GSM). Due to confusion surrounding the safety of menopausal hormone therapy (HT) in symptomatic women with CVD, evidence-based guidelines should be followed regarding identifying candidates for treatment and HT decision making. This review summarizes best practices in the evaluation and treatment of VMS and GSM in women with preexisting CVD, based on international expert consensus guidelines and/or expert opinion when data are scarce.

For women with preexisting CVD or vascular risk factors who are candidates for HT, guidelines often address the appropriate formulation, dose, and route of delivery. For women who are not candidates for HT, non-hormonal options are reviewed, and their safety and efficacy in treating VMS and GSM are discussed.

Due to increased knowledge of the role that pregnancy-related complications play in maternal risk for future CVD, these conditions are considered when addressing the use of systemic HT. Women at increased risk for future CVD without the use of HT, such as women with premature or early menopause, are also discussed, as well as the safely profile of HT in these special populations.

With worldwide rates of CVD increasing among women in midlife, it is important for clinicians to have clear guidelines for identifying candidates for hormonal and nonhormonal treatments for symptom management to safeguard the health and quality of life of these patients through the menopause transition and post-menopause.

1. Introduction

As average life expectancy in women has increased to age 80 or older in many countries [1] women are spending more than 1/3rd of their lives after menopause [2]. Clinician knowledge and management of the menopause transition (MT) and of the postmenopausal period are of extreme importance for addressing the changes in health and quality of life (QOL) that women experience throughout these life stages. Most women, up to 70–80%, experience symptoms related to the loss of endogenous estrogen at menopause, with the most common symptoms being vasomotor symptoms (VMS) [3] and genitourinary syndrome of menopause (GSM) [4]. It is also common for women to experience other symptoms during the MT that may be related to the drop in endogenous estrogen levels before and after menopause. These symptoms may include changes in mood, cognition, weight gain, and declines in sexual function and bone density [5,6]. For successful partnership and shared decision making with women on menopausal symptom management, it is important to understand the patient's experience with such symptoms and consider the arsenal of treatment options available to her, including lifestyle and behavioral strategies, menopausal hormone therapy (HT), and nonhormonal medications.

Women with pre-existing cardiovascular disease (CVD) or CVD risk factors warrant special consideration when choosing therapeutic strategies for symptom management. Guidelines on the safest route and dose of systemic HT for severely symptomatic women at elevated risk of CVD are available to the clinician. If patients are not candidates for systemic HT due to contraindications, then non-hormonal options should be considered.

The timing of initiation of HT is an important consideration. Many clinicians are familiar with the initial findings from the Women's Health Initiative (WHI) released in 2002, highlighting concerns regarding cardiovascular risk with the use of HT [7]. However, subsequent analyses from the WHI have shown neutral or even favorable cardiovascular effects among women who initiate HT within ten years from their final

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menstrual period (FMP) [8]. Per the Food and Drug Administration (FDA), HT is not recommended for primary or secondary prevention of CVD. However, when weighing the benefits vs. risks in women with certain preexisting CVD risk factors, the timing of initiation of HT is a factor in the decision-making process. Randomized trials such as the Kronos Early Estrogen and Prevention Study (KEEPS) [9], and the Early Versus Late Intervention Trial (ELITE) [10] trial demonstrate neutral or favorable effects of HT on subclinical measures of atherosclerosis, including carotid intima-medial thickness, among women who initiate systemic HT closer to onset of menopause. Because women at elevated risk of CVD require an even more complex assessment of benefits vs risks of HT or other pharmacologic options, it is particularly important to understand the patient's risk factor status and encourage shared decision-making regarding menopause management.

This review provides an overview and guidance on how to manage moderate to severe VMS and GSM in women with preexisting CVD or vascular risk factors, including considerations for both hormonal and non-hormonal options.

2. Methods

This narrative review was prepared using guidelines from international professional medical societies within the fields of Menopause, Endocrinology, Cardiovascular medicine, Obstetrics and Gynecology, and Oncology/Hematology. Strong consideration was given to international menopause recommendations and consensus statements, as well as individual guidelines from North America and Europe. Guidelines were analyzed for their consistency with recommendations on menopausal treatment for women with preexisting cardiovascular diseases and then summarized for this review article.

3. Role of formulation, dose, and route of delivery of menopausal hormone therapy

For the patient who presents with moderate to severe VMS and a preexisting cardiovascular condition, the clinician must weigh the benefits of symptom relief, improved quality of life, and future benefits such as osteoporosis, against the potential adverse CVD outcomes related to systemic HT in this setting. The most notable concern is the risk of a deep vein thrombosis (DVT), pulmonary embolism (PE), or other pro-coagulable conditions such as transient ischemic attacks (TIA) or strokes, all of which have been associated with systemic HT, namely oral regimens used in the WHI [7] and several other studies, yet not seen with transdermal preparations [11].

To date, there are no large-scale randomized trials evaluating the risk of CVD events with regard to HT formulation, route, or dose. In terms of formulation, it would be advantageous to understand whether available FDA-approved estrogens (such as 17 beta-estradiol) and micronized progesterone have a cardiovascular risk profile more favorable than the conjugated equine estrogens (CEE) plus synthetic progestins such as medroxyprogesterone acetate (MPA) used in the WHI, but relevant data are limited. When a progestogen is prescribed for women with an intact uterus, preparations such as norethindrone acetate and micronized progesterone have been suggested to have less adverse CVD effects than MPA, but definitive studies are lacking [12].

Transdermal preparations of systemic HT have been shown to confer a lower risk of VTE compared to oral estrogens. The observational Estrogen and Thromboembolism Risk Study (ESTHER) evaluated the risk of venous thromboembolism utilizing transdermal 17-B estradiol and found the risk to be lower compared to oral estrogens [13]. The lower risk for VTE with transdermal estrogen has been well supported by additional studies and meta-analysis [14,15]. Oral estrogens used in HT preparations increase coagulation factors, C-reaction protein, and circulating levels of triglycerides, effects that should be avoided in women with preexisting CVD [12]. Since transdermal preparations avoid first pass hepatic metabolism, they are recommended by several medical societies as the first line of treatment in women with preexisting CVD or at elevated risk of CVD being prescribed HT for symptom management [16–20].

In generally healthy women within 10 years of menopause onset, studies have found that HT's effects on CVD morbidity and mortality risk were more favorable than in older women who were more distant from menopause onset [8–10]. Additionally, data from the Danish Osteoporosis Prevention Trial (DOPS) showed no increased risk of blood clots in women using HT who were recently postmenopausal, giving further weight to the timing of initiation of HT [15]. Moreover, in the 18-year cumulative follow up of the WHI, women close to the menopause transition (50–59y) randomized to HT showed reductions in mortality during the intervention phase (and extending past the intervention phase for the Estrogen-Alone group), demonstrating the physiologic cardiovascular benefits estrogen has on women who are recently postmenopausal [21].

Some hypothesize this is due to the vasodilatory effects of estrogen on the coronary artery, as estrogen improves arterial function by releasing nitric oxide and suppressing vasoconstrictive mechanisms [22]. Furthermore, estrogens inhibit vascular remodeling and modulate the renin-angiotensin-aldosterone (RAAS) and sympathetic system [22]. In contrast, when HT is started one or two decades after a woman's FMP, the increased risk of CVD is hypothesized to be related to the absence of a vasodilatory response and a pro-inflammatory/pro-thrombotic state in response to exogenous estrogen in the presence of advanced atherosclerosis [23]. Therefore, for the majority of women with preexisting CVD considering systemic HT, oral estrogen should be avoided. If a woman is within 10 years of menopause onset, transdermal preparations may still be an option for management of severe VMS, but decision making should be individualized, as discussed in greater detail below (incorporating guidelines from the North American Menopause Society [NAMS], the International Menopause Society [IMS], the European Menopause and Andropause Society [EMAS], the Endocrine Society, the American College of OB/GYN [ACOG], and other professional organizations) [16–20].

4. Non—hormonal management of VMS in women at elevated risk of CVD

When HT is contraindicated, as for women with prior unprovoked venous thromboembolism or women with breast cancer, the use of non-hormonal medications should be discussed (Table 1). The only non-hormonal option current approved by the US Food and Administration Federal Drug (FDA) for the treatment of VMS is low-dose paroxetine salt (7.5 mg/d), a selective serotonin reuptake inhibitor (SSRI), which is considered first line by NAMS [24]. Off label use of SSRI's and selective serotonin- norepinephrine uptake inhibitors (SNRI's) at low doses, including escitalopram, citalopram, venlafaxine and desvenlafaxine, have shown efficacy for treating VSM in randomized placebo-controlled trials, but efficacy is generally lower than for estrogen [25]. This medication class is considered generally safe to use in women with

Table 1
Non-hormonal options and their efficacy in the treatment of VMS.

Medication	Efficacy in Reducing HF Frequency vs. placebo
Paroxetine salt (7.5–25 mg)	40–50%
Escitalopram 10–20 mg	30–45%
Citalopram 10–20 mg	45–47%
Venlafaxine 75–100 mg	25–55%
Desvenlafaxine 100–150 mg	60–70%
Gabapentin 900–2400 mg	40–45%
Oxybutynin	25%
Clonidine	20–35%

Abbreviations
HF: Hot Flash
References: [17,16,28,29].

preexisting CVD. Rare events can include an elevation in BP, and caution should be used with a history of an arrhythmia [26] (consultation with a cardiologist/electrophysiologist is advisable).

Gabapentinoids can also be used off-label, with trials noting a modest 25% reduction in VMS [27]. Side effects such as drowsiness and lightheadedness should be considered with this class. The anticholinergic agent oxybutynin can also decrease VMS, Sexton et al. [28] but side effects such as dry mouth and constipation may adversely affect compliance. Lastly, clonidine, an alpha-adrenergic agent, may be considered for its modest 20 – 35% VMS reduction [29,30], but its antihypertensive effects should be considered. The most effective lifestyle modification for VMS reduction as seen in randomized controlled trials was cognitive behavior therapy (CBT), also referred to as relaxation therapies [31].

Complementary and alternative medications (CAMS) are another source of symptom relief for women who choose to avoid prescription medications. Of these, isopropanolic black cohosh (*Cimicfuga racemose)* extract, referred to as iCR, has been extensively studied for its safety and efficacy in treating menopausal symptoms, but trial results have been inconsistent. The European Medicines Agency issued in 2018 its support for the use of iCR. This may also be an option for women with hormone-sensitive diseases preventing the use of HT [32].

5. Genitourinary syndrome of menopause in the absence of VMS or other systemic symptoms

When GSM is the only menopause-related symptom, most professional societies (including NAMS, IMS, EMAS, Endocrine Society, and ACOG) recommend avoiding systemic estrogen and choosing low-dose vaginal estrogen or other local vaginal treatments [16–20]. These products demonstrate excellent safety in long term follow up studies and in meta-analysis of women with pre-existing CVD [33–36]. New options are available including vaginal dehydroepiandrosterone (DHEA; Prasterone). Although there is a black box warning on vaginal estrogens, research has concluded that local estrogen does not carry any risk of VTE or CVD [33].

However, some women are not candidates for any form of estrogen, such as women taking aromatase inhibitors (in extreme cases of severe vaginal atrophy and with shared decision making, such treatments may be an option). Also, lubricants made of hyaluronic acid and moisturizers may be sufficient for some women with GSM and should be tried first.

6. Management of VMS in women at elevated risk of CVD

6.1. Hypertension, diabetes, dyslipidemia, obesity, or metabolic syndrome

Women with cardiovascular risk factors and comorbidities are at elevated risk of CVD, including DVT and PE. These CVD risks can be augmented by systemic HT, especially when given orally. Each CVD risk factor, as well as the constellation of risk factors defining the metabolic syndrome, are discussed separately below.

6.2. Hypertension

Globally, rates of hypertension in women less then 65 years of age are less than in men, however women aged 65 years old older have a greater prevalence of hypertension compared to men in both low-and high-income countries [37].

When women with severe VMS and hypertension present for the consideration of HT, it is first important to assess for metabolic syndrome [38] by checking hemoglobin A1c (HbA1c), lipids, liver function, and a metabolic panel. If hypertension is well controlled, the atherosclerotic cardiovascular disease (ASCVD) risk score is low (calculated score of 0 to 4.9% risk) and the woman is within ten years of menopause, NAMS recommends that the patient can be considered for either oral or transdermal options [16]. When blood pressure is not controlled (consistently greater than 140/90), every effort should be made at controlling blood pressure at the time of the of HT initiation. If hypertension is a struggle to control, transdermal preparations, with a micronized progesterone for women with an intact uterus, are recommended as first line by NAMS and the Endocrine Society. Another option would be the use of commercially available oral drospirenone and estradiol combination, which has been shown to reduce blood pressure in women with hypertension, potentially due to the anti-aldosterone like activity of the drospirenone [39]. Alternatively, non-hormonal options can also be considered.

6.3. Diabetes

As with hypertension and dyslipidemia, global rates of Type II diabetes (T2DM) are steadily climbing, with an estimated prevalence of approximately 7.5–10% in women ages 50–69 [40]. For the woman with well controlled diabetes, (HbA1c $<$ 8%), transdermal estrogen preparations, bypassing first pass liver metabolism, should be selected instead of oral estrogen due to the lower risk for developing VTE or thromboembolic events. Adding micronized progesterone is a reasonable option for women with an intact uterus. Most professional guidelines encourage use of transdermal rather than oral estrogen for women with diabetes who initiate HT due to severe VMS [16,17,41].

6.4. Dyslipidemia

Dyslipidemia is another common co-morbidity seen in women at midlife. Changing guidelines on cholesterol recommendations necessitates frequent reviews by clinicians from the American Heart Association (AHA). The AHA currently states that adults ages 40–75 should undergo a ten-year ASCVD risk estimation and participate in a clinician-to-patient risk discussion [42].

Data from the WHI suggests that elevated LDL at baseline is a risk factor for adverse CVD outcomes on HT [43]. Thus, the goal for women with elevated LDL initiating HT is to determine a treatment plan to bring down LDL to below 190 (preferably below 130) mg/dL. When this is achieved, NAMS and the Endocrine Society recommend transdermal options with a micronized progesterone for women with an intact uterus, again due to the need to avoid first pass hepatic metabolism via transdermal, rather than oral preparations. [16,17] It should be noted that the use of CEE and MPA did not jeopardize lipid measurements in postmenopausal women on statins in the Heart and Estrogen/progestin Replacement Study (HERS) [44] Alternatively, if lipids cannot be controlled, non-hormonal options may also be considered.

6.5. Obesity

Obesity (Body Mass Index of greater than or equal to 30) is on the rise, with worldwide rates tripling among both men and women, and all and age groups since 1975 [45]. Obesity is associated with an increased risk of VTE, which is further amplified by the use of oral HT. When HT is considered in women who are obese, transdermal is preferable over oral due to the attenuated risk of VTE and thromboembolic events with the transdermal, compared to the oral, route.

6.6. More than one cardiometabolic risk factor

When more than one metabolic condition is present, transdermal preparations should generally be utilized and an individual benefit to risk assessment should be undertaken [16]. Table 2 provides an overview of the kinds of HT preparations recommended when risk factors for metabolic syndrome are present. When HT is contraindicated, nonhormonal options should be considered. The clinician should use caution with SSRI use in women with a history of arrythmia and should monitor all patients for elevations in blood pressure.

Table 2
Guidance for Hormone Therapy (HT) Decision Making Among Women with Cardiovascular Risk Factors and a Strong Indication for HT.

DIAGNOSIS	Hypertension	Dyslipidemia	Diabetes	Obesity	Metabolic Syndrome
CONTROLLED	Oral or transdermal	Transdermal	Transdermal	Transdermal	Transdermal
UNCONTROLLED	Transdermal Or non-hormonal options	Efforts should be made to control DLD and reduce LDL < 190 (preferably <130) mg/dL or use non-hormonal options	Efforts should first be made to reduce A1c between 7 and 8% or use non-hormonal options	Transdermal	Efforts should be made to gain control of metabolic syndrome or use non-hormonal options

Definitions:.
Controlled BP: Average blood pressure of less than 120/80 mmHg.
Uncontrolled BP: Average blood pressures of greater than 140/90 mmHg.
Abbreviations:
HT: Hormone Therapy
A1c: Glycated Hemoglobin
References: [16–18].

6.7. The metabolic syndrome

The prevalence of metabolic syndrome has increased dramatically over the last several decades, and while global rates are difficult to measure, it is estimated that about one in eight female adults (or about half a billion women) have metabolic syndrome [46]. Due to the association of metabolic syndrome with obesity and increased risk of VTE and thromboembolism, use of oral HT should be avoided in this setting. When the benefits of systemic HT are determined to outweigh the risks for a patient with metabolic syndrome, transdermal (rather than oral) preparations of estrogen and micronized natural progesterone have advantages [16].

7. Women with a prior clinical cardiovascular event

Adverse cardiovascular events remain the leading cause of death in women in developed countries, a finding consistent across all racial and ethnic groups [47]. Severe adverse cardiovascular events include both ST elevation myocardial infarctions (STEMI) and non-ST elevation myocardial infarctions (NSTEMI), strokes, and the development of heart failure (HF).

7.1. Myocardial infarction

In the clinical scenario of a woman presenting with severe VMS and a history of a serious cardiovascular event, it is important to classify her diagnosis as a STEMI vs. NSTEMI. In either case, HT should be avoided due to the increased risk of adverse cardiovascular events, as seen in the WHI [48]. Non-hormonal options should be considered for systemic symptoms. However, vaginal estrogen products can safely be utilized in women with a history of a MI for GSM [35].

7.2. Stroke and TIA

Stokes and TIA's present as other serious adverse cardiovascular events and represent a clear contraindication to HT use due to the risk of another pro-thrombotic event. It is also important to rule out the diagnosis of atypical migraine, which can present in a similar manner to TIA's and may obscure the true diagnosis. Non-hormonal options are available to women with a history of stroke or TIA. For women with GSM, local vaginal estrogen therapies are considered safe to use [35].

7.3. Heart failure

Heart failure (HF) is less common in recently menopausal women than in women in later menopause. Due to its low incidence in midlife women, there are limited data on HT use in women with HF. Therefore, if recently diagnosed without clear etiology, all efforts should be made to improve heart function before or while initiating pharmacologic therapy for menopausal symptoms. When improvements are made, or ejection fraction (EF) returns to steady state, and the patient has control over modifiable risk factors, transdermal preparations are preferred at low doses for women who do not respond to non-hormonal treatment.

8. Clotting disorders

A prior personal history of a VTE or other clotting disorder may be encountered in women entering menopause and seeking care for severe vasomotor symptoms. Women in midlife may have prior risk for clotting disorders throughout their lifetime, and eliciting a history of thrombotic complications from the use of combined oral contraceptive (COC) use, pregnancy, or a surgical history can help frame a women's potential risk for a clot with the use of systemic HT.

A history of a PE represents a clear contraindication to the use of HT. However, if the patient reports a history of a DVT alone, it is imperative to understand the context. A history of an unprovoked blood clot is a clear contraindication to the use of systemic HT, as it has been established that the patient has a strong predisposition and should avoid exogenous estrogen. If a DVT is diagnosed in the setting of oral contraception use or pregnancy, HT should be avoided due to the history of clot in the setting of exogenous estrogen. A provoked blood clot sustained after prolonged immobilization or after trauma, such as a motor vehicle accident, fall, or immediately post-operatively, are indications that the pro-inflammatory state inciting the clot may have been unrelated to the effects of estrogen. In the event of a unprovoked blood clot not due to oral contraception use or pregnancy (and in the context of a strong indication for treatment), it is recommended to use transdermal routes of HT (NAMS) [16].

For women with a family history of clotting disorders, attempts should be made to obtain a detailed family history to understand the context of the thrombotic event. With a concerning family history of VTE, genetic and lab testing can be done to better assess the patient's risk [49].

Migraines also represent a clinically challenging scenario for the clinician. Combined oral contraceptives are contraindicated in women with a history of migraines with aura due to the increased clot risk; the excess risk for women using COC's that contain >20 mg of ethinyl estradiol is estimated to be 1 to 3 cases per 10 000 women-years [50]. However, postmenopausal doses of estrogen are significantly lower than COC's and provide a steady state of a low daily dose. Available data suggest there is no increased risk of stroke in women with a history of migraine who use transdermal systemic HT [51], and hence these women may be candidates for transdermal HT administration with oral micronized natural progesterone (as per guidance from NAMS) [16,52]. However, it is advisable to avoid oral estrogen in these patients. Table 3 summarizes the recommendations for women with clotting disorders.

Table 3
Recommendations for women with elevated risk of clotting disorder.

DIAGNOSIS	RECOMMENDATION
Pulmonary Embolism	Strong Contraindication to HT
Unprovoked blood clot	Strong Contraindication to HT
Provoked blood clot:	Trauma: transdermal preparations can be used
Traumatic setting:	Setting of COC use/pregnancy: Contraindication to HT
In setting of COC use/ pregnancy	
Family history of clotting disorder	Check family history and lab work
History of migraines	transdermal preparations can be used.

Abbreviations:
COC: Combined oral contraceptive
HT: Menopausal hormone therapy
References: [16,18,50,51].

9. Pregnancy-related complications

A detailed medical history should include any pregnancy complications when evaluating a woman in the menopause transition or postmenopause. Hypertensive disorder of pregnancy (HDP), defined as having elevated blood pressure during pregnancy (from gestational hypertension, preeclampsia or eclampsia) is known to be associated with increased future risk of chronic hypertension in later adulthood (2–8 fold increase) [52]. The diagnosis of gestational diabetes mellitus (GDM) has been shown to be linked to a 17- 63% increase in the risk of T2DM within 5–16 years from the diagnosis [53]. Research from the Nurses' Health Study II has also shown that preterm birth is a marker for increased risk of maternal hypertension, T2DM, and hypercholesterolemia following pregnancy [54].

When treating menopausal women, knowledge of pregnancy-related complications should be noted, as the woman's prior gestational diagnosis is a marker for increased risk for future cardiovascular events and risk factors. When a woman with a history of HDP or GDM presents with severe menopausal symptoms, transdermal options could be considered first line. However oral HT could be considered when there is good control of blood pressure, glucose, and lipids. The exception would be a woman with a pre-existing history of preeclampsia or eclampsia, as the best route for HT administration would be transdermal due to the prior response of the cardiovascular system to this stressor [55].

10. Special populations

Premature menopause is defined as menopause before age 40, while early menopause is defined as menopause prior to the age of 45. Due to the pathophysiology of premature and early menopause, this population should be considered another high-risk group compared to women who experience natural menopause after age 45. Similarly, women who experience surgical menopause (bilateral oophorectomy) at an age of less than 45 years of age should also be differentiated from natural menopause at a young age, due to the early and abrupt loss of endogenous estrogen. Importantly, both early and premature menopause are associated with 1.5–2-fold increases in future CVD risk [56].

Most randomized trials of HT don't apply to women with menopause before age 45. Research has clearly shown that menopause before age 45, and especially prior to age 40, poses excess cardiovascular risks for women not treated with exogenous estrogen therapy. Due to the elevation in future cardiovascular related co-morbidities, these women should be treated with HT at least until the age of natural menopause to prevent cardiovascular disease, bone loss, and other conditions that result from the loss of estrogen prior to the age of 45 (as recommended by NAMS, IMS and EMAS) [16,19,20].

Conclusions

Knowledge on how to treat women with bothersome menopausal symptoms who present with preexisting CVD or vascular co-morbidities is of critical importance for the clinician and the provision of optimal medical care. Rates of cardiovascular conditions have been rising in this patient population. Women who are within ten years of menopause may be candidates for systemic HT, preferably transdermal, and utilizing a risk-stratified and algorithmic approach to their treatment plan is critical to ensure optimal care and satisfactory symptom management. For women with cardiovascular co-morbidities that are well controlled, transdermal and low dose HT preparations may be an option, even for those at higher-than-average risk of CVD. Data from the WHI shows that women with pre-existing CVD who are more than 10 years past menopause onset are generally not appropriate candidates for initiating systemic HT; however, an individual assessment may be necessary for patients with severe or distressing symptoms. When HT is contraindicated, there are several non-hormonal options for consideration. It is vital that clinicians have working knowledge of the risks that CVD poses over time, yet balance this with the risks of leaving severe VMS and GSM untreated, which may ultimately worsen a woman's overall health. Patient choice must also be an important factor in the clinician's decision, which can be achieved using shared decision-making skills. Evidence-based management of menopause is an evolving field; it will be important for clinicians to revisit these guidelines and future updates on the management of women with cardiovascular co-morbidities and disruptive menopausal symptoms.

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