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Rethinking Menopausal Hormone Therapy: For Whom, What, When and How long?

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Abstract

Menopausal hormone therapy (HT) was widely used in the past, but with the publication of seminal primary and secondary prevention trials which reported an excess cardiovascular (CV) risk with combined estrogen-progestin, HT use declined significantly. However, over the past 20 years, much has been learned about the relationship between timing of HT use with respect to age and time since menopause, HT route of administration, and cardiovascular disease risk. Four leading medical societies recommend HT for treatment of menopausal women with bothersome menopausal symptoms. In this context, this review, led by the ACC CVD in Women Committee along with leading gynecologists, women's health internists and endocrinologists, aims to provide guidance on HT use, including selection of patients and HT formulation with a focus on caring for symptomatic women with CVD risk.

Keywords

Menopause; Hormone therapy; Cardiovascular disease; Atherosclerotic heart disease; Venous thromboembolism; Hyperlipidemia; Hypertension

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Introduction

Menopause, the permanent cessation of menstruation caused by loss of ovarian function, occurs at a mean age of 52 years (1). Based on the latest United States (U.S.) Census Bureau data, as of 2020, more than 63 million women in the US are age 50 years or older and approximately 6000 women enter menopause each day (2). Vasomotor symptoms (VMS), which include hot flashes and night sweats, represent the most lifestyle limiting symptoms of menopause and are the most common reason women present for care at the time of the menopause transition (3). VMS often include a sudden sensation of heat in the face and chest, persist for up to several minutes and are associated with anxiety, sleep disruption, and reduced quality of life (4). VMS occur in about 75% of women during the menopause transition, and are more prevalent among Black/African- American women, women who smoke, those with mood disorders and those with low income and/or low educational attainment (4).

Menopausal HT was at one time almost universally recommended but with the publication of Heart and Estrogen/Progestin Replacement Study (HERS)(5) and Women's Health Initiative (WHI) randomized trials, (6, 7) which reported excess cardiovascular risk, HT use has declined substantially (8). Appropriately, no medical societies currently recommend HT for the primary or secondary prevention of CVD (9–14) (Table 1).

However, over the past 20 years, the relationship of CVD risk with timing of menopause, initiation of HT, and route of HT delivery has been better understood (15–18). As such, four major North American medical societies, the American College of Obstetricians and Gynecologists (ACOG), American Association of Clinical Endocrinology (AACE), The Endocrine Society (ENDO), and The North American Menopause Society (NAMS), now recommend HT in appropriate patients for the management of menopausal symptoms (10–13) (Table 1). Likewise, in Europe, societies and organizations have recommended HT in low risk patients for the management of menopausal symptoms (19–22). Despite these evidence-based recommendations, physicians, including cardiologists, are reluctant to use HT due to confusion and lack of education regarding who is an appropriate patient for HT use (23, 24).

In this context, the aim of this review, led by the ACC CVD in Women committee along with leading gynecologists, women's health internists, and endocrinologists who specialize in menopause management, is to provide guidance regarding current understanding of risk and benefits of HT, which women are appropriate candidates for HT and which routes and doses of HT minimize CVD risks in women.

History of Hormone Therapy & Cardiovascular Disease

The intersection between cardiology and reproductive endocrinology dates back to 1905 when Ernest Starling, a physician whose foundational work in cardiovascular physiology is well known, first introduced the concept of the hormone (25). The history of modern-day HT in the U.S. began during the Great Depression when the first commercially available menopausal estrogen product was produced from the urine of pregnant women. For cost-savings, this was later replaced in the early 1940's with conjugated equine estrogen (CEE),

derived from the urine of pregnant mares, and aggressively marketed for the treatment of vasomotor symptoms in postmenopausal women.

Fueled by a popular book called “Feminine Forever” published in 1966 which proposed that menopause was a hormone deficiency state that led not only to painful intercourse but also to the loss of sex appeal and youth, coupled with the changing status of women and the feminist movement, HT was increasingly prescribed with annual prescriptions exceeding 50 million in the U.S. alone by the 1970’s (26, 27). However, in 1975, several studies demonstrated increased risk of endometrial cancer with unopposed estrogen therapy (ET), prompting a significant reduction in HT use (28, 29). By the early 1980s, recognition that the addition of a progestogen to ET mitigated endometrial (uterine lining) cancer risk and subsequent development of combination estrogen-progestogen therapy (EPT) formulations, prompted a revival and firmly established HT as part of women’s health therapies. The next two decades saw a dramatic increase in HT use, propelled in large part by observational data supporting benefits of estrogen with respect to CVD (25). The most notable of these was the Nurses’ Health Study, a prospective cohort study that demonstrated marked reduction in incident coronary disease and CV death in estrogen users (30). By the late 1990s, HT use reached an all-time peak, 90 million HT prescriptions per year, representing approximately 15 million women (27, 31) (Figure 1).

Ironically, the first secondary prevention clinical trial assessing CVD effects of estrogen was conducted exclusively in men (32). The Coronary Drug Project randomized over 8000 men after myocardial infarction (MI) to estrogen, niacin, thyroid, clofibrate or placebo. The Estrogen (both 5mg and later 2.5 mg a day arm of the trial) was terminated early due to increased thrombosis and myocardial infarction (32). Two decades later in 1998, the HERS trial, the first randomized trial of EPT vs placebo for the secondary prevention of coronary heart disease (CHD) events among postmenopausal women with established CHD, found no overall CV benefit and a pattern of an early increase in CHD events with HT use, arguing against the initiation of HT for secondary prevention of CHD (5). The HERS data led to a slight reduction in HT prescribing rates following its publication, but the early termination of the landmark Women’s Health Initiative (WHI) EPT trial in 2002, a primary prevention trial (6, 7), led to a dramatic decline in the use of HT worldwide (Figure 1).

The WHI randomized trial enrolled women without CVD between the ages of 50–79 years and represents the largest randomized placebo-controlled trial of systemic HT designed to evaluate the risks and benefit for the primary prevention of chronic diseases, including cardiovascular disease (6, 7). Women with a uterus were randomized to continuous combined oral conjugated equine estrogen (CEE) with medroxyprogesterone acetate (MPA) (CEE+MPA) or placebo and women without a uterus were randomized to CEE-alone or placebo. The initial publications which detailed WHI findings in 2002 (CEE+MPA) and 2004 (CEE-alone), with median age of 63.2 and 63.6 years of age at the time of enrollment, respectively, aggregated participants of all ages, and reported that compared to placebo, risks of coronary heart disease (CHD), stroke and venous thromboembolism (VTE) including pulmonary embolism were increased with HT (6, 7).

However, subsequent to the initial publication of the primary WHI results, age-stratified analyses with longer cumulative follow up (median duration 13 years) supported a more nuanced approach to HT (15, 16). These analyses demonstrated that the absolute risks of adverse events following HT initiations were much lower for younger women (aged 50–59 years) than for older women and for those who initiated HT within a decade of menopause (Figure 2).

These findings support the “timing hypothesis”, which postulates that CV risk associated with HT appears to depend on the timing of initiation in relation to menopause onset (33). This hypothesis arose from a primate model, in which CEE prevented atherosclerosis only in animals treated early after surgically induced menopause and before the onset of atherosclerosis (34). In support of this hypothesis, a reanalysis of the Nurses’s Health Study observed a benefit to starting HT less than four years compared to more than 10 years after menopause (35). In women who started HT earlier, there was a reduced risk of CHD (RR = 0.66, 95% CI 0.54–0.80 for estrogen alone; RR = 0.72, 95% CI 0.56–0.92 for estrogen with progestin). Furthermore, in 2012, the Danish Osteoporosis Prevention study, designed to assess the long term impact of HT (open-label with no placebo) on bone mineral density in 1006 recently menopausal and perimenopausal women, reported on over 10 years of randomized follow up and another 5.7 of post intervention follow up (36). Women receiving HT had a reduced risk of composite cardiovascular safety outcomes, death or hospitalization for myocardial infarction or heart failure (HR 0.48, 95% CI 0.26 to 0.87; P=0.015)(36).

A more recent meta-analysis of 19 randomized controlled trials with a total of 40, 410 postmenopausal women on HT (the majority of which was oral) found no significant increase in all-cause mortality, death from CVD, or MI with HT in both primary and secondary prevention populations. A subgroup analysis based on HT timing found that those who initiated HT within 10 years after menopause had lower mortality (RR 0.70, 95% CI 0.52 to 0.95) and fewer cardiac events (composite of CV death and non-fatal myocardial infarction) (RR 0.52, 95% CI 0.29 to 0.96)(18). In contrast, women who started HT more than 10 years from the onset of menopause were found to have an increased risk of stroke without any effect on mortality or other CVD outcomes (18). Of note, in both groups regardless of the HT timing, investigators observed an increase in venous thromboembolism events (18).

Along with these studies, the ELITE study (Early vs Late Intervention trial with Estradiol) published in 2016, randomized 643 healthy menopausal women to oral estradiol and vaginal progesterone (if a uterus was present) or placebo. HT attenuated progression of subclinical atherosclerosis as measured by carotid intima media thickness for women who were less than 6 years from last menses while those women greater than 10 years from last menses derived no benefit (37). The KEEPS (Kronos Early Estrogen Prevention Study) randomized 727 women within 36 months of their last menses to lower dose oral CEE or transdermal estradiol (E2) plus progesterone in women with a uterus did not identify any difference in the progression of subclinical atherosclerosis between HT vs. placebo. The lack of benefit in the latter study was thought to be due to the lower dose of HT used as well as to the younger age of the women enrolled in the trial and shorter duration of follow up (38). Reassuringly, these studies did not show harm with early initiation of HT.

The studies summarized above have given credibility to the hypothesis that CV risk associated with HT appears to depend on the timing of initiation in relation to menopause onset. Estrogen may have plaque-destabilizing and other adverse effects in the setting of advanced atherosclerosis, but provides an appropriate and safe option for treatment of menopausal symptoms when initiated in healthy women under age 60 or within 10 years of menopause onset.

Types of HT

It is important for cardiologists to understand the various types of HT. We will discuss differences with regard to systemic vs. local, oral vs. transdermal as well as US Food and Drug Administration (FDA) approved HT vs. compounded bioidentical HT.

Systemic Hormone Therapy

Systemic estrogen therapy represents an effective treatment for VMS and other menopause symptoms, including genitourinary syndrome of menopause (GSM). Oral and transdermal estrogen formulations have similar efficacy, with the lowest effective dose generally recommended (4). Most systemic estrogen formulations are also approved for the prevention of osteoporosis. Because the use of estrogen therapy (ET) alone in women with a uterus increases the risk of endometrial hyperplasia and cancer, a progestogen should also be prescribed. The most commonly prescribed systemic oral estrogens and progestogens are detailed in Table 2. A variety of combination oral estrogen and progestogens therapy (EPT) formulations, all of which have demonstrated endometrial safety, are also detailed in Table 2. Of note, oral CEE combined with the selective estrogen receptor modulator, bazedoxifene, is also approved to treat VMS and prevent osteoporosis in women with a uterus. This formulation may be useful for women who prefer not to use a progestogen, including those intolerant of progestogen-related side effects, including adverse effects on mood, weight, headaches and fluid retention (13).

Transdermal Estrogens and Progestogens

Transdermal HT formulations, including estrogen alone and estrogen plus progestogen are detailed in Table 3. No randomized controlled trials have compared VTE risk with oral vs. transdermal vs. placebo therapy. However, observational studies have consistently observed lower rates of venous thromboembolism with transdermal compared to oral HT (39–41) (Table 3). Moreover, in 11 randomized controlled studies of lipid metabolism, transdermal HT has shown neutral effects on triglycerides, in contrast with oral HT, which increases triglyceride levels (41). In a randomized trial of 196 women, oral HT significantly increased CRP level compared to placebo (42). However, at 6 months, transdermal estrogen had no significant effect on CRP levels compared to placebo (42). This is likely related to first-pass hepatic metabolism of oral estrogens, which increases triglycerides, coagulation factors, C-reactive protein, and sex hormone-binding globulins (43, 44).

Compounded Hormone Therapy

Among U.S. women using HT, approximately one-third use compounded HT, often marketed as ‘bioidentical’ or ‘natural.’ (45). Most users are unaware that these formulations

are not monitored for safety or approved by the FDA. Concerns with compounded HT include risk of contamination, variability in dosing and absorption, limited data on safety and efficacy, lack of a package insert describing risks and significant out-of-pocket cost. FDA-approved 'bioidentical' HT, which includes oral, transdermal and vaginal estradiol formulations as well as oral and vaginal progesterone, is biochemically identical to the sex steroids produced by the ovary. Current guidelines and position statements indicate that the FDA approved HT is preferable to compounded HT(46). No studies have compared FDA approved bioidentical HT to standard synthetic HT with regard to cardiovascular outcomes.

Vaginal Estrogen Therapy

In contrast with VMS, which diminish over time, GSM, which includes symptomatic vulvovaginal atrophy, painful intercourse, and recurrent urinary tract infections, increases in prevalence as women age. Low dose vaginal ET is currently the most effective treatment for GSM when symptoms persist after use of nonhormonal, over-the-counter options (47). Low dose vaginal ET formulations are available by prescription, including tablets, inserts, and creams used several times weekly, and a vaginal ring changed every 3 months (Table 4). Low dose vaginal ET is minimally absorbed at current recommended dosing, with circulating estrogen levels typically maintained within the normal postmenopausal range (48). Of note, Estring (estradiol) vaginal ring should not be confused with Femring (estradiol acetate) since Femring delivers systemic doses of estrogen. Use of a progestogen is not recommended with low dose vaginal ET, although any vaginal bleeding in a postmenopausal woman should be thoroughly evaluated irrespective of HT use. Given minimal systemic absorption, low dose vaginal ET is an option for women in whom systemic HT may be contraindicated, including those with a history of estrogen-responsive cancers, CVD, stroke, or VTE (47).

Due to 'class labeling', the package insert for low dose vaginal ET includes the same boxed warning regarding risks of CVD, endometrial and breast cancer, and probable dementia that accompanies all menopausal HT products. Due to minimal systemic estrogen absorption, this warning is not evidence-based and adversely affects women's quality of life by discouraging use of these highly effective therapies (49). Several large observational studies confirmed no increased risk of adverse health outcomes, including CVD, VTE or cancer in vaginal ET users (50,51). Women prescribed low dose vaginal ET should be prepared for the black box warning and informed that it is based on the use of higher doses of estrogen to treat VMS while very low doses of estrogen placed directly in the vagina do not appear to be associated with these risks.

Recommendations for HT

Low risk with HT—Women less than 60 years, or within 10 years of menopause onset, with 10-year estimated ASCVD risk <5% and do not have an increased risk of breast cancer or history of VTE are considered low risk for major adverse cardiovascular events with initiation of HT for the treatment of menopausal symptoms (Figure 3).

Moderate Risk with HT—Decision making is more difficult when a woman has one or more chronic medical conditions potentially impacting the risk-to-benefit balance of HT

use. However, this is the most common scenario faced by clinicians as 80% of women over age 55 have at least one chronic medical condition (52). The presence of CVD risk factors alone does not preclude the use of HT, but a patient's worsening CV risk profile around the menopause transition emphasizes the need to optimize primary prevention efforts, including lifestyle and pharmacologic management (24).

We review existing evidence for HT use in symptomatic women with prevalent medical conditions including obesity, dyslipidemia, hypertension and diabetes, and provide guidance as to when transdermal ET preparations may be preferred over oral ET (Figure 3).

Obesity—Almost half of women aged 40–59 years in the U.S. are affected by obesity, and the prevalence of obesity in women continues to rise (53). While HT use has shown favorable effects on body composition with preservation of lean body mass and reduction in visceral adiposity, it has not demonstrated a consistent impact on weight (54,55). Moreover, obesity is a risk factor for VTE, and oral HT appears to have a significant additive effect on the increased risk of VTE in overweight women (56). In the WHI, randomized trial of oral systemic HT, there was a threefold increased risk of VTE in overweight women (BMI 25–30) randomized to EPT vs lean (BMI <25) postmenopausal women on placebo (HR 3.80, 95% CI 2.08–6.94). In obese women (BMI >30), there was almost a six-fold increased risk in the EPT group compared to the placebo lean group (HR 5.61, 95% CI 3.12–10.11) (56). In the WHI Observational study (WHI-OS) of over 45,000 women, oral EPT in obese women (BMI>30) was associated with higher cardiovascular event rates (HR 1.21, 95% CI 1.03–1.42) whereas transdermal HT was not associated with greater risk (HR 1.61, 95% CI 0.83–3.12) (57).

In the absence of RCT data, and given that observational studies have consistently found a lower risk of VTE with transdermal vs. oral HT, transdermal ET is preferred.

Dyslipidemia—Despite the favorable impact of oral ET on low-density lipoprotein cholesterol (LDL-C), lipoprotein(a) levels and high density lipoprotein cholesterol (HDL-C), these subclinical benefits have not translated into reduction in CVD events or death (24). In a pooled analysis, the WHI clinical trials found an excess CHD risk among women with a baseline LDL-C ≥130 mg/dL or an LDL-C/HDL-C ratio of >2.5. (HR 1.46, 95% CI 1.02–2.10 and HR 1.73, 95% CI 1.18–2.53, respectively) taking CEE with or without MPA (58). In the HERS trial, during the first year, women not using statins at baseline and assigned to HT appeared to have higher cardiac event rates than women assigned to HT who were taking statins at baseline. However, at 4.1 years of follow up, the event rates were similar between the two groups (59). Moreover, in the WHI trials, statin use did not lower the event rate in women on EPT (6, 7).

Notably, as a deleterious effect on lipids, oral HT use increases triglycerides. Eleven randomized trials have compared lipid effects of oral vs transdermal HT (41). Consistently, these trials have found that, in contrast with oral HT, which increases triglycerides by 5–15%, transdermal HT decreases triglyceride levels by 5–30% (41, 60, 61)(Table 5). In this context, we recommend the transdermal route of ET for symptomatic menopausal women with dyslipidemia, particularly those with a tendency toward hypertriglyceridemia.

Hypertension—While some studies examining the impact of HT on blood pressure in women with pre-existing hypertension show no clinically meaningful change in blood pressure in oral ET users, WHI showed that CEE either alone or in combination with MPA increased blood pressure by 1–1.5mmHg (62–64). Given that meta-analysis of clinical trials showed that 1 mmHg reduction in systolic blood pressure translated into 2% relative risk reduction in major CVD and 3% reduction in heart failure events, we recommend caution starting HT in women with HTN (65). Of note, uncontrolled blood pressure ≥180/110 is a relative contraindication to starting HT due to the possibly increased risk for stroke. HT can be reconsidered once hypertension is controlled. In the WHI-OS, transdermal ET was associated with lower risk of development of HTN and with neutral effect on blood pressure compared to oral HT (66, 67).

Diabetes—Diabetes increases the risk of CVD by about 4-fold in women but only about two 2-fold in men, and diabetic women have worse outcomes after MI and more CHF compared with diabetic men (68). Women are also at higher risk of other diabetes-related end organ damage. In the WHI trials, regardless of HT treatment, women with diabetes had a 2–3 fold higher risk of all-cause, CVD, and cancer mortality than women without diabetes (69,70). While there is robust evidence supporting favorable impact of HT on glycemic control and insulin resistance in postmenopausal women with and without T2DM, this has not translated into fewer cardiovascular events nor into clinical recommendations for use of HT to prevent diabetes (71–73). In WHI, neither EPT nor ET use in diabetic women increased mortality or cardiovascular events. However, given that diabetic women are at increased risk of cardiac events with concomitant comorbidities such as obesity, hypertension, and hyperlipidemia (specifically hypertriglyceridemia), the transdermal route of ET is preferred for diabetic women with menopause symptoms.

Metabolic Syndrome—The WHI clinical trials found that women with metabolic syndrome randomized to CEE+MPT and CEE alone compared with placebo, had a 2 fold increased CVD risk (74, 75). Metabolic syndrome is often characterized by hypertriglyceridemia and obesity, which portends greater risk of VTE. Therefore, although there are no studies comparing systemic vs. transdermal HT and CV outcomes in women with metabolic syndrome, we recommend transdermal route of ET for menopause symptom relief in this setting.

Monitoring, Discontinuation and Consideration of Extended Use—In the clinical scenarios above, shared-decision making is important, and the need for ongoing HT should be reassessed annually or when new clinical concerns arise, taking into consideration any changes in the patient's medical history, family history, symptom burden, personal preferences, and treatment goals. HT use should be individualized with dose adjustments based on symptom response. Expert opinion suggests it is reasonable to lower the dose of HT or discontinue HT after several years of use, particularly given that VMS tend to improve for most women over time (76) (Table 1). However, age alone should not dictate when HT is discontinued (10, 77). Among women who initiated systemic HT within 10 years of the onset of menopause, extended use of systemic HT may be appropriate for the treatment of persistent VMS and prevention of osteoporosis in select patients (Table 6).

Extended use of systemic HT should not be confused with the initiation of systemic HT by women older than age 60 or more than 10 years following menopause onset—a practice that is known to be associated with an elevated risk of CVD. Women considering extended use of systemic HT should be aware that risk of breast cancer increases with longer duration of combined EPT. Since older age is an independent risk factor for VTE, the use of transdermal ET should be considered, and lower than standard doses can often be used in this setting. When women discontinue systemic HT, the likelihood of recurrent VMS appears to be similar whether HT is abruptly stopped or gradually tapered. Stopping systemic HT often results in an accelerated loss of bone mass and progression of GSM. If GSM represents the only indication for continuing (or starting) HT, low dose vaginal ET should be used (78).

Who Should Generally Avoid Hormone Therapy—While many women with menopause-related symptoms can safely use HT, certain cardiovascular and non-cardiovascular conditions constitute relative or absolute contraindications for use. For patients with these conditions, shared decision making is advised employing an individualized approach incorporating an assessment of symptom severity, evidence for safety vs. harm relative to the woman's underlying condition(s)/medical history, and collaboration with other members of her healthcare team (Figure 3).

Coronary Heart Disease and Cardiovascular Risk Factors—HT is generally contraindicated in women with known CHD, including history of myocardial infarction or peripheral artery disease (13). Although discontinuation of HT after acute myocardial infarction is advised, a meta-analysis of 10 trials of HT in 5,766 secondary prevention patients suggest that in this setting the absolute risk of death, MI, angina or revascularization is low (79)(Table 7).

Non-atherosclerotic/non-thrombotic CHD is especially prevalent in women, but current guidelines do not stratify risk of HT use by subtype of disease. For women aged 50–59 years with a history of myocardial infarction with no obstructive coronary artery disease, spontaneous coronary artery dissection, coronary microvascular dysfunction, or coronary vasospasm, an individualized approach to HT is required. Due to the presumed pathophysiological association with female sex hormones in spontaneous coronary artery dissection, we recommend that in general, oral ET be avoided in this group. This recommendation stems from the fact that over 90% of patients with spontaneous coronary artery dissection are female and the observed increase in coronary artery dissection incidence around pregnancy and during the postpartum period, both times characterized by high systemic estrogen levels.

HT is generally contraindicated in women at high risk for CHD with comorbid conditions that remain uncontrolled, including blood pressure ≥ 180/110 mmHg, total cholesterol > 310 mg/dL, and triglycerides > 400 mg/dL (12, 80). Once these risk factors are better controlled, initiation of systemic HT can be considered. Women with high 10-year ASCVD risk (>10%) are generally advised to avoid systemic HT, regardless of years since menopause onset; however, if severe symptoms persist despite use of alternative therapies, individualized risk assessment and shared-decision-making is warranted. The use of a menopause decision-support algorithm, which incorporates the American College of Cardiology (ACC)/

American Heart Association (AHA) 10-year risk of cardiovascular disease and years since menopause may aid in risk stratification and determine the appropriateness and continuation of HT (12). Transdermal HT is typically preferred in the setting of significant cardiovascular risk factors, particularly diabetes, hypertension and hypertriglyceridemia.

Venous Thromboembolism and Pulmonary Embolism—Given that oral HT increases the risk of VTE, we recommend that, in general, a history of VTE including deep venous thrombosis and pulmonary embolism should be considered a contraindication to use of systemic oral HT. A large meta-analysis of RCT HT trials showed an increased risk of VTE with both primary (RR 1,92 95% CI 1.24 to 2.99 in 33, 477 participants in 6 studies compared to placebo) and secondary prevention (RR 2.02, 95% CI 1.13 to 3.62; 4399 in 6 studies compared to placebo) trials (18)(Table 7–9). Pulmonary embolism risk was also increased with HT in primary prevention trials (RR 1.89, 95% CI 1.17 to 3.04; 31,732 participants in 3 trials) and in secondary prevention, there was a trend toward increase (RR 2.48, 95% CI 0.92 to 6.70; 3920 participants in 3 studies) (18).

An underlying thrombophilia without a history of VTE represents a relative contraindication to use of HT (12, 81). Women considering HT who have a personal or family history of VTE or pulmonary embolism, particularly if idiopathic/unprovoked, should undergo an evaluation for potential underlying and/or modifiable thrombophilia. Low dose transdermal HT is not associated with thrombotic risk in observational studies and off-label use may be considered in women with significant VMS and a history of VTE if appropriately anticoagulated (11,40, 42, 82–84). In women with systemic lupus erythematosus (SLE) and high disease activity, positive anticardiolipin antibody, and/or positive lupus anticoagulant, oral HT should generally be avoided. Conversely, HT may be prescribed to women with SLE who have mild to moderate disease activity who do not have additional risk factors for VTE (85).

Stroke—HT is generally contraindicated in patients with history of ischemic stroke. In the WHI trials, an increased risk of ischemic stroke was noted in both the EPT and ET groups regardless of the baseline risk of the patient (86,87). In a meta-analysis of primary prevention trials (719 participants, 4 studies), stroke risk was increased (RR 1.32, 95% CI 1.12 to 1.56) compared to placebo (18)(Table 7–9). In a meta-analysis of secondary prevention trials (5172 participants, 5 studies), there was a trend toward increase in risk (RR 1.09, 95% CI 0.89 to 1.33)(18).

Congenital Heart Disease—Many women with congenital heart disease are now surviving long enough to experience menopause, but there are no data on the safety of HT in this population (88). The treatment strategy should be individualized, with a focus on the underlying cardiopulmonary and postoperative physiology and associated risks. For instance, women with Fontan circulation are predisposed to VTE and therefore should avoid oral HT (89).

Cardiac Transplant—There are little data regarding HT for women after cardiac transplant (90). Given the absence of data, caution and shared decision making should be exercised.

Non-cardiovascular contraindications to HT—Non-cardiovascular contraindications to HT include unexplained vaginal bleeding, history of breast cancer, estrogen-sensitive and/or intermediate-to high-risk stage endometrial cancer, porphyria cutanea tarda, dementia, and active liver or gallbladder disease (13). A detailed analysis of these conditions is beyond the scope of this review.

Premature and Early Menopause—Premature menopause is defined as menopause occurring before age 40 years, and early menopause is defined as menopause occurring before age 45 years. Premature or early menopause may be spontaneous or induced by surgery (bilateral oophorectomy with or without hysterectomy), chemotherapy or radiation therapy. Compared with women who experience menopause at the average age, VMS in women with premature or early menopause are often more severe (4). Furthermore, observational data have indicated that untreated premature menopause regardless of the cause is associated with an elevated risk of CHD, Parkinsonism, cognitive decline, dementia, osteoporosis, and mortality (91). In this population, systemic ET should be initiated unless clear contraindications are present and continued *at least* until the average age of menopause at age 52(13, 92).

Although clinical trial data are not available, clinical experience suggests that doses higher than the standard doses detailed in Tables 1 and 2 are often needed to adequately treat VMS in patients with premature or early menopause.

Multidisciplinary Co-management of Patient and Shared Decision making—The value of a multidisciplinary approach to care for complex patients has been increasingly recognized throughout the cardiovascular community (93, 94). Successful models for multidisciplinary menopausal medicine clinics have been reported (95, 96). Given the high prevalence of medical comorbidities among perimenopausal women, this approach can be particularly beneficial for safe and effective management of menopausal symptoms (95, 96). A recent study reported significant menopausal symptom improvement in women with a history of malignancy receiving care through a multidisciplinary menopause clinic (95). Comprehensive multidisciplinary care may allow for more streamlined risk assessment, initiation of appropriate therapies for menopause symptoms and longitudinal CV risk reduction through a patient-centered, holistic approach.

Conclusion

Since the publication of landmark HERS and WHI trials, we have learned much regarding benefits and risks of systemic HT that is highly relevant to cardiologists who care for women at risk for or with established CVD. These last two decades have brought nuanced insights into HT use regarding timing and route of administration and have resulted in our recommendation that initiating systemic HT is appropriate for younger, healthy menopausal women with lifestyle limiting bothersome VMS. This paper provides guidance for management of symptomatic women, including those with risk factors for CVD as well as those with stable CVD. Going forward, we need additional data to better understand the risk to benefit balance of initiating HT early and continuing long term and to more fully

delineate the differences between various formulations and routes of HT with respect to CVD risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosure

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Non-standarrd abbreviations and acronyms

CEE	conjugated equine estrogen
CVD	cardiovascular disease
CHD	coronary heart disease
DVT	deep vein thrombosis
EPT	estrogen progesten therapy
ET	estrogen therapy
GSM	genitourinary syndrome of menopause
HT	hormone therapy
MI	myocardial infarction
MPA	medroxyprogesterone acetate
VSM	vasomotor symptoms
VTE	venous thromboembolic event
WHI	Women’s Health Initiative
WHI-OS	Women’s Health Initiative Observational Study

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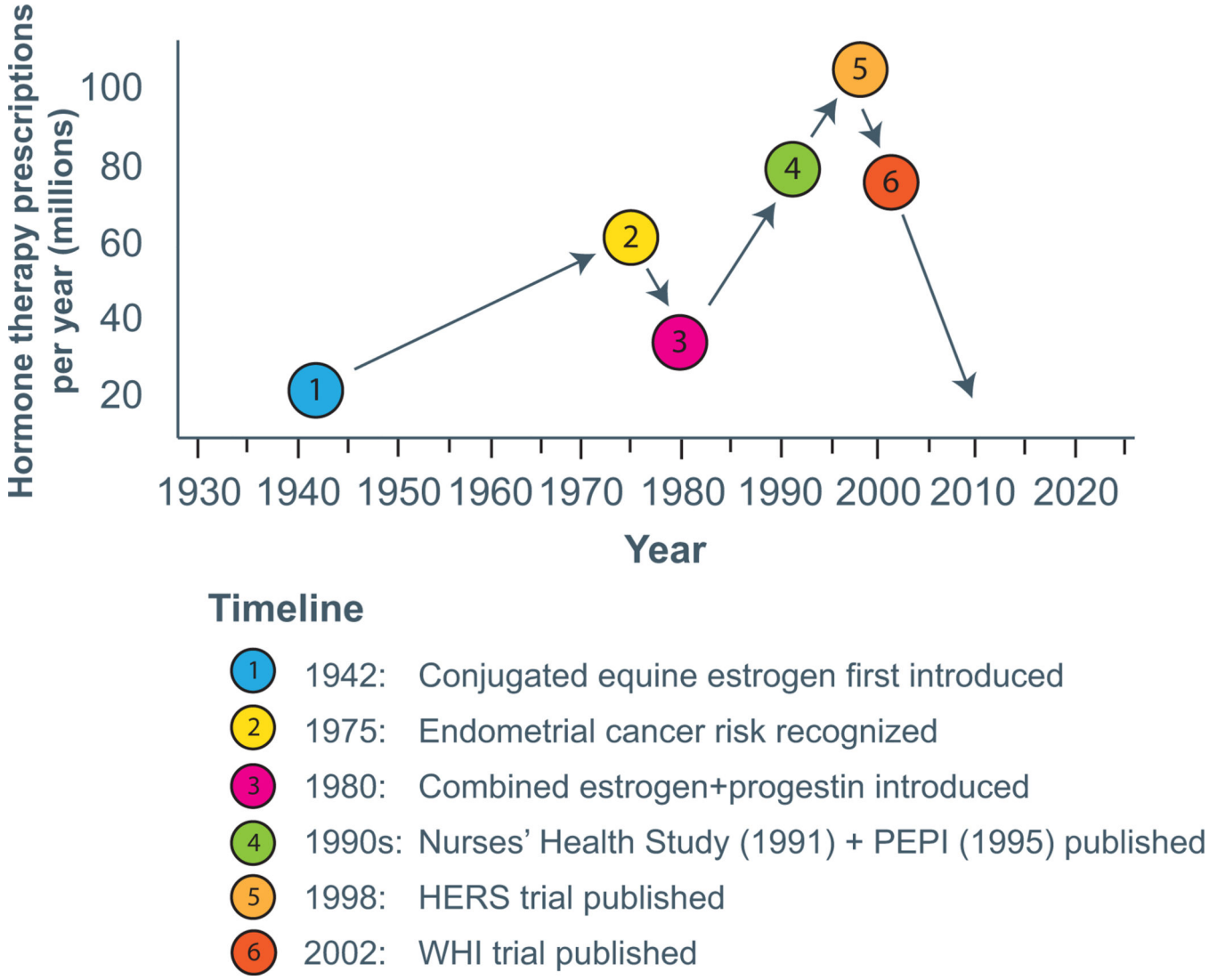

Figure 1:

Timeline of HT use in US

HT hormone therapy; HERS Heart and Estrogen/progestin Replacement Study; PEPI Postmenopausal Estrogen/Progestins Interventions; WHI Women's Health Initiative;

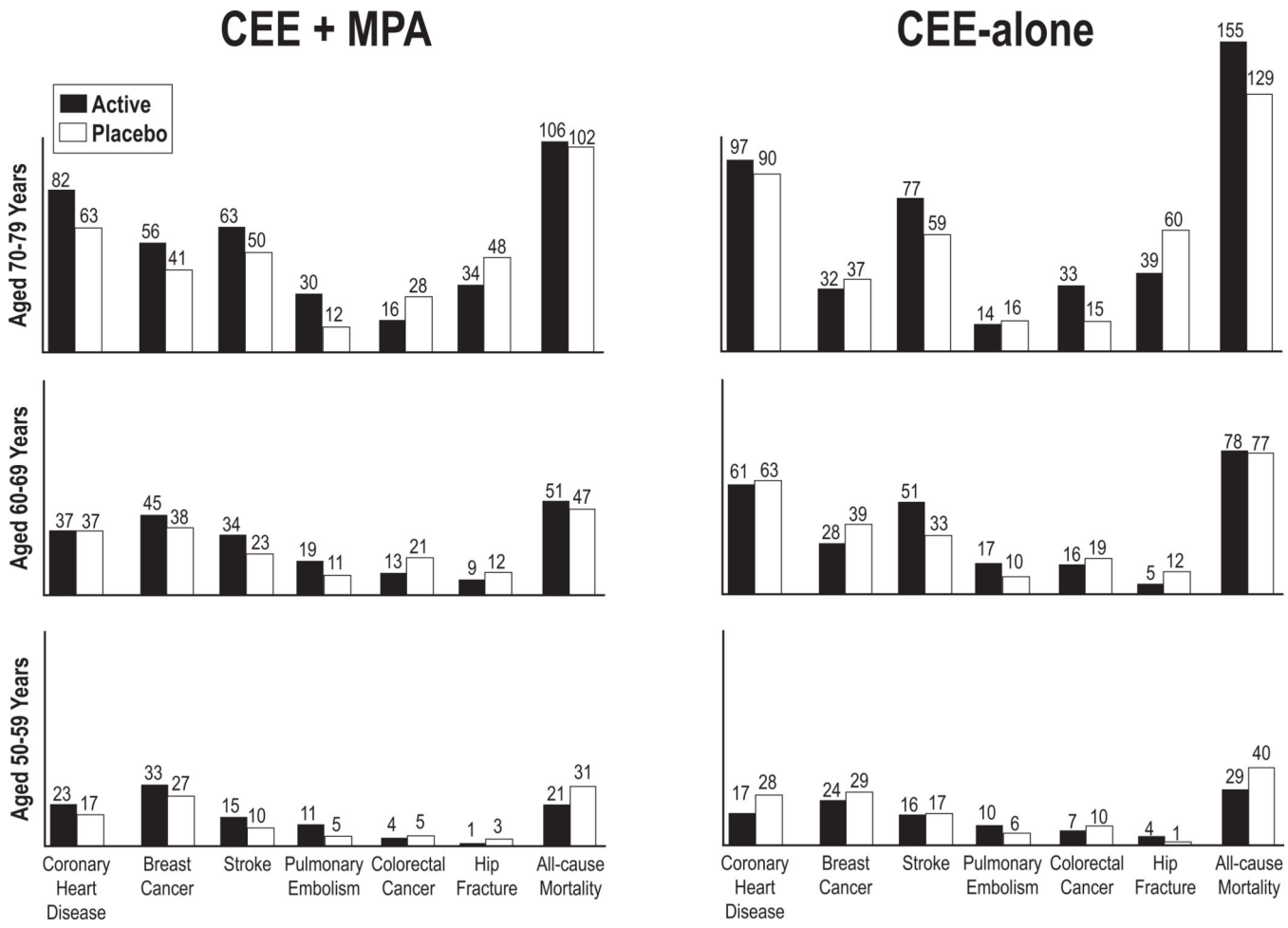

Figure 2:

CEE+MPA and CEE-alone by age

From the Women's Health Initiative hormone therapy trials: absolute risks (cases per 10,000 person-years) for outcomes in the CEE+MPA and CEE-alone by age group. CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate. Modified from Manson JE JAMA 2013; 310:1535–68 (15)

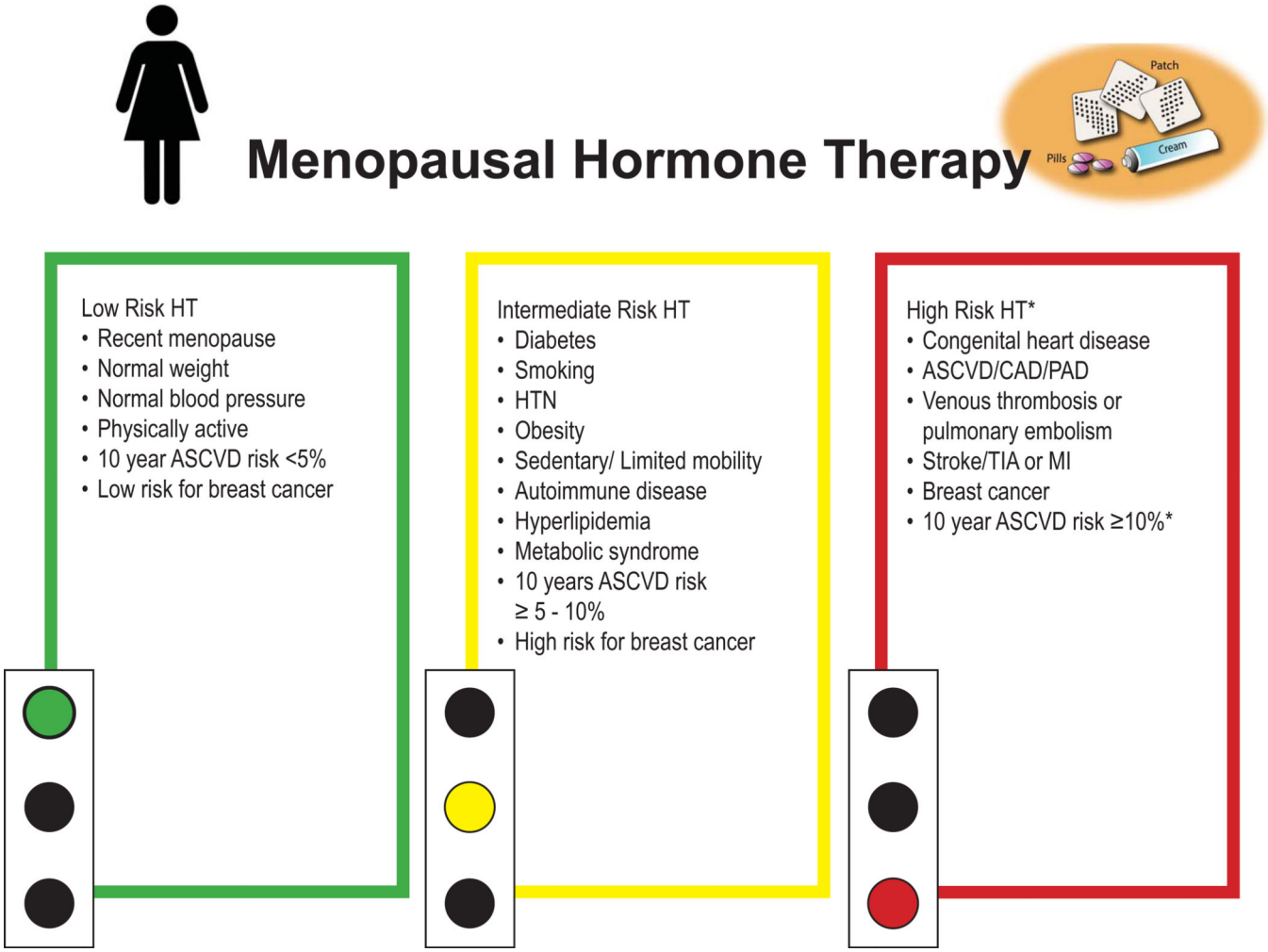

Figure 3:

Menopausal hormone therapy recommendation by patient risk

*Generally advised to avoid systemic HT. Consider alternative therapy and if severe VSM persists, individualized, shared decision making recommended. All women are candidates for low dose vaginal estrogen therapy for GSM.

ASCVD atherosclerotic cardiovascular disease, CAD coronary artery disease, PAD peripheral arterial disease, TIA transient ischemic attack, MI myocardial infarction, HTN hypertension

GSM genitourinary symptoms of menopause

Table 1:

Recommendations for HT from 4 different medical societies

Aspect of treatment	**ACOG (10)**	**NAMS (13)**	**AACE & ACE (11)**	**Endocrine Society(12)**
Principal Indication	Menopause symptoms	Menopause symptoms	Menopause symptoms	Menopause symptoms
Prevention of CHD	Not recommended	Not recommended	Not recommended	Not recommended
Special Considerations	None	Consideration of age and time from menopause onset	Consideration of age, time from menopause onset and risk of CVD, with lipid profile, smoking history	Consideration of age, time from menopause, and baseline risks of CVD and breast cancer
Dose & Route of Administration	Lowest effective dose	Appropriate dose to manage symptoms with consideration of route	Lowest effective dose	Shared decision making to determine formulation, dose, and route
Duration of use	Shortest period based on risk-benefit analysis, with recommendation against routine discontinuation in patient ≥ 65 yr of age	May be extended for persistent vasomotor symptoms, prevention of bone loss, or quality of life after attempt at stopping; Reassess benefits and risks regularly	Recommended for ≤ 5 yrs with reduction of dose if continuing	Shortest total duration consistent with the treatment goals and evolving risk assessment of the individual woman

Table 2:

Oral Hormone Therapy

Oral Estrogen Formulations for Menopausal Hormone Therapy commonly prescribed in the U.S.	
Estradiol	0.5, 1.0, 2.0 mg Standard: 1.0 mg Low: 0.5 mg
Conjugated equine estrogen	0.3, 0.45, 0.625, 0.9, 1.25 mg Standard: 0.625 mg Low: 0.3 mg, 0.45 mg
Combination oral estrogen- progestogen formulations available	
Estradiol (0.5 mg, 1.0 mg)	Drospirenone (0.25 mg, 0.5 mg)
Estradiol (0.5 mg, 1.0 mg)	Norethindrone acetate (0.1 mg, 0.5 mg)
Estradiol (1.0 mg)	Norgestimate (0.09 mg)
Estradiol (1.0 mg)*	Progesterone (100 mg)*
Ethinyl Estradiol (2.5 μg, 5 μg)	Norethindrone acetate (0.5 mg, 1.0 mg)
Conjugated equine estrogen (0.3 mg, 0.45 mg, 0.625 mg)	Medroxyprogesterone acetate (1.5 mg, 2.5 mg, 5 mg)
Oral Progestogen Formulations for Menopausal Hormone Therapy commonly prescribed in the U.S.	
Medications	**Available doses**
Medroxyprogesterone acetate	2.5 mg, 5 mg, 10 mg
Progesterone*	100 mg, 200 mg

*formulation contains peanut oil; hypnotic effect, so should be taken at bedtime

Table 3:

Transdermal Hormone Therapy

Transdermal Estrogen Formulations for Menopausal Hormone Therapy commonly prescribed in the U.S.	
Medications	**Available doses***
Weekly Estradiol patch	0.014, 0.025, 0.0375, 0.05, 0.06, 0.075, 0.1 mg Standard: 0.0375–0.05 mg Low: 0.025 mg Ultra-Low: 0.014 mg
Twice weekly estradiol patch	0.025, 0.0375, 0.05, 0.075, 0.1 mg Standard: 0.0375–0.05 mg
Combination transdermal estrogen- progestin formulations available*	
Estrogen	**Progestin**
Estradiol 0.05 mg	Norethindrone 0.14 mg, 0.25 mg
Estradiol 0.045 mg	Levonorgestrel 0.015 mg

* Daily release note

Table 4:

Low Dose Vaginal Estrogen Therapy

Vaginal Tablets/Inserts	**Formulation**
Estradiol Tablet	E2 10 mcg
Estradiol Insert	E2 10 mcg, E2 4 mcg
Vaginal Creams	
Estradiol Cream	E2 (variable) *
Conjugated Estrogen Cream	CE (variable) *
Vaginal Ring	
Estradiol Ring	E2 7.5 mcg (vaginal therapy)

Abbreviations: E2 estradiol, CE conjugated estrogens, mcg microgram, g gram

* US Food and Drug Administration approved doses of estrogen creams are higher than those proven effective and recommended for clinical practice

Table 5:

Studies comparing Systemic vs. Transdermal HT

	Study Type	Study Quality	Findings
Lipid	11 Randomized studies 1 Cohort study	Reasonable	Overall, greater LDL lowering with oral systemic HT. Consistently higher TG levels with oral systemic HT. Lower TG levels with transdermal HT.
VTE	7 case controlled studies 3 Cohort studies	Low	Oral Systemic HT increases VTE risk. Transdermal has neutral effect
MI	4 case controlled studies 2 cohort studies	Poor	None designed to compared the difference between systemic vs. transdermal

Table 6:

ASCVD risk score and years since menopause onset for initiating HT

CVD Risk over 10 years ACC/AHA ASCVD Risk Score	Years since menopause onset			
		≤ 5	6–10	≥ 10
	Low Risk (<5%)	HT Acceptable	HT Acceptable	Consider alternatives; HT acceptable with individualized, shared-decision making
	Intermediate Risk (≥ 5.0% - < 10%)	HT Acceptable Consider transdermal HT depending on risk factors	HT Acceptable Consider transdermal HT depending on risk factors	Generally advised to avoid systemic HT. Consider alternative therapy and if severe VMS persist, individualized, shared decision making
	High Risk (≥ 10%)	Generally advised to avoid systemic HT. Consider alternative therapy and if severe VMS persist, individualized, shared decision making	Generally advised to avoid systemic HT. Consider alternative therapy and if severe VMS persist, individualized, shared decision making	Avoid HT Consider alternative therapy and if severe VMS persist, individualized, shared decision making

Table 7:

Risk with HT in primary and secondary prevention from meta-analysis of 19 RCT trials (18)

	Primary prevention	**Secondary prevention**
Death All Cause	RR 1.00 (95% CI 0.89–1.12)	RR 1.04 (95% CI 0.87–1.24)
Death from CVD	RR 0.81 (95% CI 0.47–1.40)	RR 1.00 (95% CI 0.78–1.29)
MI	RR 1.02 (95% CI 0.80–1.31)	RR 0.98 (95% CI 0.81–1.18)
Angina	RR 0.90 (95% CI 0.74–1.08)	RR 0.91 (95% CI 0.74–1.12)
Revascularization	RR 0.96 (95% CI 0.85–1.09)	RR 0.98 (95% CI 0.63–1.53)
VTE	**RR 1.92** (95% CI 1.24–2.99) **Absolute risk increase 0.008 with NNTH 118**	**RR2.02** (95% CI 1.13–3.62) **Absolute risk increase 0.014 with NNTH 71**
Stroke	**RR 1.32** (95% CI 1.12–1.56) **Absolute risk increase 0.006 with NNTH of 165**	RR 1.09 (95% CI 0.89–1.33)
PE	**RR 1.89** (95% CI 1.17–3.04) **Absolute risk increase 0.004 with NNTH 242**	RR 2.48 (95% CI 0.92–6.70)

CVD Cardiovascular disease; MI myocardial infarction; VTE venous thromboembolism; PE pulmonary embolism; RCT randomized control trials; NNTH number needed to harm (18)

Table 8:

HT initiated <10 years after menopause from Cochrane Review (18)

	Relative Effect (95% CI)	**# of participants (# of studies)**	**Quality of the evidence**
Death All Cause	RR 0.70 (95% CI 0.52–0.95)	9088 (5)	Moderate
Death from CHD	RR 0.52 (95% CI 0.29–0.96)	8311 (4)	Moderate
VTE	**RR 1.74** (95% CI 1.11–2.73) **Absolute risk increase 0.008 with NNTH 214**	9838 (3)	High
Stroke	RR 1.37 (95% CI 0.80–2.34)	8143 (3)	High

CHD Coronary Heart; NNTH number needed to harm (18)

Table 9:

HT initiated >10 years after menopause from Cochrane Review (18)

	Relative Effect (95% CI)	**# of participants (# of studies)**	**Quality of the evidence**
Death All Cause	RR 1.06 (95% CI 0.95–1.18)	27,750 (12)	High
Death from CHD	RR 1.07 (95% CI 0.96 – 1.20)	23,491 (12)	High
VTE	**RR 1.96** (95% CI 1.37–2.80) **Absolute risk increase 0.01 with NNTH 101**	27,475 (9)	High
Stroke	**RR 1.21** (95% CI 1.06–1.38) **Absolute risk increase 0.01 with NNTH 102**	22,722 (8)	High

CHD Coronary Heart; NNTH number needed to harm (18)