Cardiovascular risk in hormone replacement therapy

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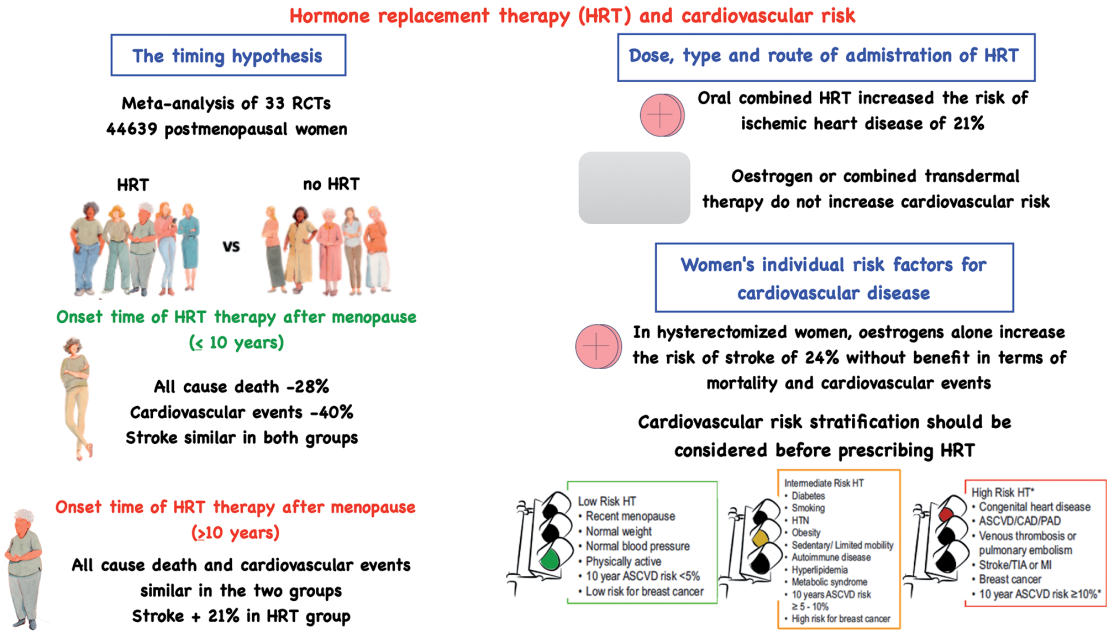
GRAPHICAL ABSTRACT



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ABSTRACT

Hormone replacement therapy (HRT) effectively alleviates vasomotor symptoms related to menopause, but it can also raise the risk of cardiovascular disease. Several factors influence the likelihood of developing coronary artery disease or ischemic stroke, including a woman's age, the time since menopause, the type, dose, and route of hormone therapy administration, as well as woman's personal risk factors and existing or past health conditions. Starting HRT at an older age or more than 10 years after menopause increases the risk of ischemic stroke by 21% (RR=1.21, 95% CI 1.07-1.38), without any benefit in reducing mortality (RR=1.06, 95% CI 0.95-1.18) or cardiovascular events (RR=1.03, 95% CI 0.92-1.15). In contrast, beginning HRT at a younger age and within 10 years of menopause lowers all-cause mortality by 28% (RR=0.72, 95% CI 0.54-0.97), reduces cardiovascular events by 40% (RR=0.60, 95% CI 0.41-0.86), and does not significantly increase the risk of ischemic stroke (RR=1.37, 95% CI 0.91-2.05). Oral estrogen-progestin combinations are linked to a higher risk of ischemic heart disease (HR=1.21, 95% CI 1.00-1.46), and this effect depends on the dose. Therefore, it is advised to use the lowest effective estrogen dose. Progesterone, dydrogesterone, and levonorgestrel should be selected because they do not elevate cardiovascular risk. Transdermal estrogens or estrogen-progestins do not increase the risk of cardiovascular events and are recommended for women at moderate to high risk of stroke and coronary heart disease. A multidisciplinary approach may be beneficial for the safe and effective management of both menopausal symptoms and related conditions.

Key words: Hormone replacement therapy; cardiovascular risk; women's health.

Introduction

Menopause is defined as the absence of menstrual periods for 12 consecutive months, not attributable to other underlying causes. This natural physiological process typically begins at a mean age of about 52 years. It is characterized by a decrease in estrogen levels due to the loss of ovarian function.[1]

According to the Study of Women's Health Across the Nation (SWAN) study,[2] a multisite, multiethnic, longitudinal cohort study that began in 1996, menopause is associated with several typical symptoms that can significantly impact a woman's quality of life (Figure 1).

These symptoms include sleep disturbances, sudden mood swings, osteoarthritis pain, bone loss, and genitourinary syndrome of menopause. However, the most common reason women seek consultation with a gynecologist during this time is the onset of hot flashes and night sweats, also known as vasomotor symptoms (Figure 2). These symptoms can further limit a woman's quality of life. Although they often improve over time, they may persist with moderate to severe intensity for up to 10 years. Hormone replacement therapy (HRT), involving estrogen alone or combined with progestins, effectively relieves vasomotor symptoms. Additionally, it can reduce the long-term risk of vertebral and hip fractures. However, some studies have indicated a potential link

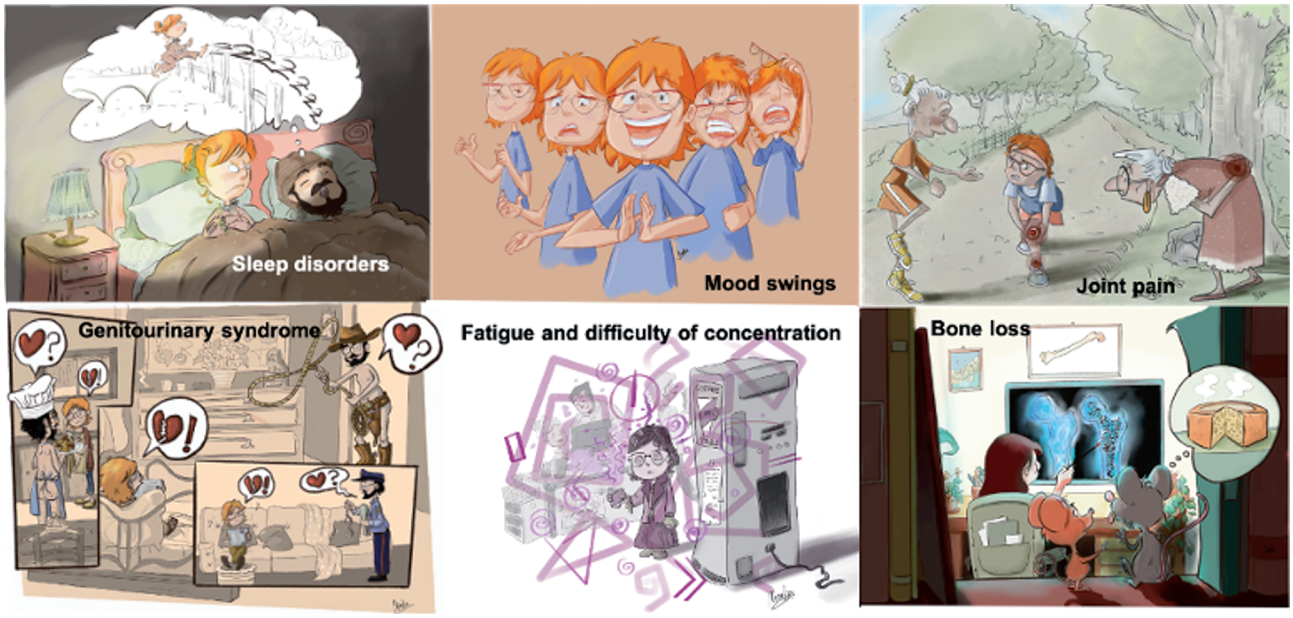

Figure 1. Menopause's typical symptoms.

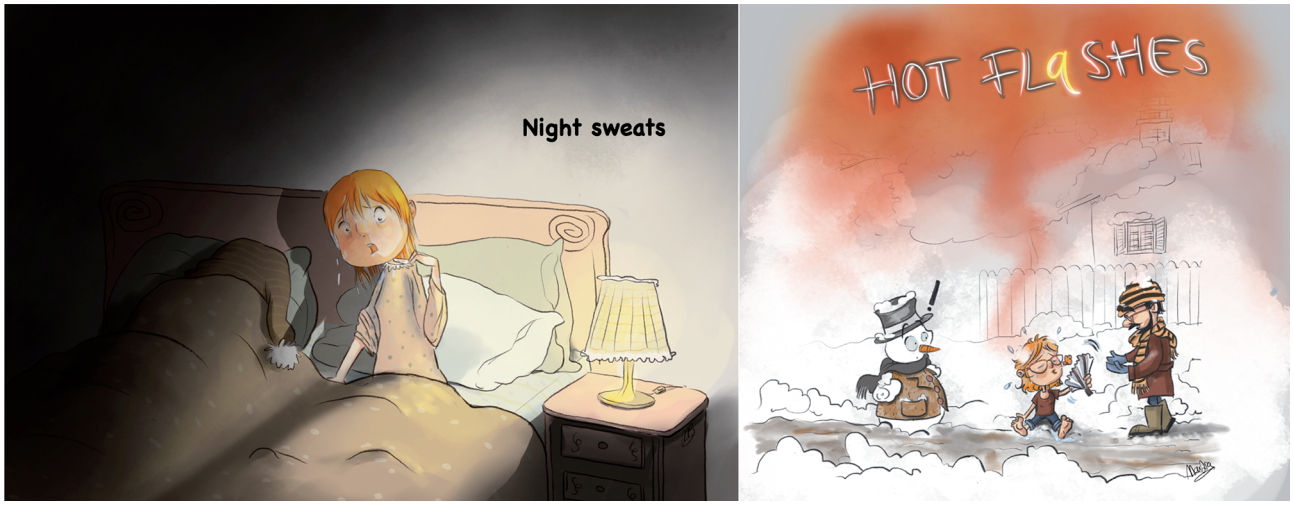

Figure 2. Vasomotor symptoms.

between the use of HRT and an increased risk of cardiovascular disease. This narrative review summarized the main cardiovascular risks associated with HRT, particularly myocardial infarction, coronary heart disease, and ischemic stroke, and discusses guideline-based recommendations to inform clinical practice.

Literature search methods

A comprehensive search of the MEDLINE database was conducted up to September 2025, using the following keywords: «menopause, HRT, HRT AND cardiovascular risk factors, HRT AND myocardial infarction, HRT AND stroke». Only peer-reviewed articles published in English were included, favoring meta-analyses, randomized clinical trials and observational studies. Screening was performed by examining titles and abstracts, followed by critical appraisal of articles based on clinical relevance, study methodology, and reported results.

A brief history

Between 1929 and 1934, German biochemist Adolf Friedrich J. Butenandt isolated the hormones estrone and progesterone from the urine of pregnant women, laying the groundwork for the development of the first hormone therapy.[3] In the early 1940s, in an effort to reduce production costs, human estrogens were replaced with conjugated equine estrogens, which are derived from the urine of pregnant mares. The Food and Drug Administration approved the first drug, Premarin®, for the treatment of hot flashes. From then until the 1970s, HRT prescriptions exceeded 50 million annually in the United States.[4]

This rapid growth was fueled by aggressive marketing and the 1966 publication of a bestseller titled «Feminine Forever,» which described HRT as an elixir of vitality and youth.[5] However, the first major decline in HRT use happened in 1975, when several studies showed an increased risk of endometrial cancer caused by hyperplasia from using estrogen alone.[6] In the early 1980s, the development of combined estrogen-progestin therapy, which lowered the risk of endometrial cancer due to progesterone's protective effect, sparked a revival of HRT. The subsequent two decades witnessed a sharp increase in HRT use, primarily driven by observational studies that emphasized a protective effect of hormone therapy on cardiovascular health. By the late 1990s, HRT use peaked at 90 million prescriptions annually. However, starting in 1998, the publication of randomized clinical trials challenged the findings of observational studies, leading to a critical reassessment of HRT use and prompting the FDA to issue a warning about the risk of cardiovascular disease associated with all hormone preparations. This resulted in a significant worldwide decline in HRT use.

Observational studies and randomized clinical trials

Among the observational studies, the most notable was the Nurses' Health Study.[7] It was a prospective cohort study that, during a follow-up of up to 10 years, evaluated 48,470 postmenopausal women aged 30 to 63 who had no cancer or cardiovascular disease. The results showed that, compared to women who did not use hormone therapy, women who used it had a 44% reduction in the incidence of coronary heart disease [relative risk (RR)=0.56, 95% CI 0.40-0.80], a 38% reduction in cardiovascular disease mortality (RR=0.72, 95% CI 0.55-0.95), and a similar risk of stroke (RR=0.97, 95% CI 0.65-1.45). The study suggested that estrogen therapy was associated with a protective effect in the primary prevention of cardiovascular events in postmenopausal women.

The first randomized clinical trial, the HERS study, was published in 1998.[8] Its purpose was to determine whether conjugated equine estrogens combined with medroxyprogesterone acetate increased the risk of new cardiovascular events during a 4-year follow-up in 2,763 postmenopausal women with established coronary artery disease, compared with women taking a placebo. The study showed no significant differences between the two groups of women regarding the primary endpoints: nonfatal myocardial infarction [Hazard Ratio (HR)=0.91, 95% CI 0.71-1.17] and cardiovascular mortality (HR=1.24, 95% CI 0.87-1.75), as well as secondary endpoints such as ischemic stroke, transient ischemic attack, need for coronary revascularization, or onset of unstable angina or heart failure.

In 2002, the HERS II study was published, involving 2321 of the 2763 women randomized in the original HERS study to receive estrogen-progestin or placebo.[9] The follow-up period was extended by approximately three years. The primary and secondary endpoints remained the same as in the original HERS study. The results showed that rates of primary or secondary cardiovascular events were similar among women assigned to the hormone group compared to the placebo group when considering the HERS and HERS II studies, either separately or combined. The combined results of HERS and HERS II indicated that HRT was not effective for the secondary prevention of cardiovascular events in postmenopausal women.

The WHI study was also published in 2002.[10] It was a large, randomized, controlled trial involving 16,608 postmenopausal women aged 50 to 79 who did not have coronary artery disease. The women were randomly assigned to receive conjugated equine estrogens combined with medroxyprogesterone acetate or a placebo. Although the study was planned to last 8.5 years, it ended just over 5 years early. It was stopped not because of an excess of adverse cardiovascular events but due to a higher incidence of breast cancer in women taking hormone therapy. Despite early discontinuation, the study demonstrated a link between HRT use and a higher risk of both coronary heart disease (HR=1.29; 95% CI 1.02-1.63) and ischemic stroke (HR=1.41; 95% CI 1.07-1.85). The absolute risk per 10,000 women-years attributable to HRT was 7 additional coronary heart events and 8 additional ischemic strokes, indicating that HRT was not effective for the primary prevention of cardiovascular events in postmenopausal women.

The discrepancy between observational studies and randomized clinical trials was initially attributed to differences in population characteristics and methodological biases. Actually, the main factors influencing the results were the women's average age and the duration since menopause. Compared to observational studies, women in randomized clinical trials were generally older and had been menopausal for a longer period.

After the initial publication of the WHI study, the results were reevaluated with a longer follow-up period (median of 13 years) and analyses separated by age and time since menopause

in women treated with HRT or placebo.[11] Regarding the risk of coronary heart disease, the HRs were similar by age (1.34, 1.01, and 1.31 for women aged 50 to 59, 60 to 69, and 70 to 79, respectively). However, the absolute risk per 10,000 woman-years attributable to HRT was 19 additional coronary events among women 20 years after the onset of menopause, compared with 5 additional events among women within 10 years of menopause. The highest rate of ischemic stroke was observed in women aged 60 to 69 (HR=1.45, 95% CI 1.00-2.11), and the absolute risk per 10,000 woman-years attributable to HRT increased from 5 additional strokes in women aged 50 to 59 to 11 and 13 additional strokes in women aged 60 to 69 and 70 to 79. Overall, the WHI findings suggest that HRT has a harmful effect on the risk of coronary heart disease and ischemic stroke in older women more than 10 years post menopause, as a higher absolute risk of adverse events with HRT was observed in these age groups.

The timing hypothesis

Following the release of the WHI study results, stratified by age and time since menopause, the ELITE study was published in 2016.[12] This prospective, randomized, placebo-controlled, double-blind study assessed the effects of HRT on atherosclerosis progression through semiannual measurements of carotid intima-media thickness and CT scans of coronary atherosclerosis. The goal of the ELITE study was specifically to compare these measurements in early postmenopausal women (<6 years after menopause) and late postmenopausal women (10 years after menopause). To achieve this, 643 healthy women were randomly assigned to receive 17β-estradiol with progesterone in vaginal gel form or a placebo, and they were followed for 6-7 years.

The rate of atherosclerosis progression, measured by carotid intima-media thickness, varied with the time since menopause began. In women who had been postmenopausal for 10 or more years, carotid intima-media thickness was similar in those treated with estrogen-progestin and those given a placebo. However, among women who had been postmenopausal for less than 6 years, progression of atherosclerosis was slower and less pronounced in women on HRT compared to those on placebo. Computed tomography scans revealed no differences in coronary atherosclerosis (defined as the presence of calcifications, plaques, or total vessel stenosis) between treated and untreated women, based on time since menopause. This may be due to the study's 6-7-year follow-up period, which might have been too short to detect the development of atherosclerotic lesions. Subsequent studies confirmed the impact of age and time since menopause on the link between higher cardiovascular risk and HRT.

The latest meta-analysis, published in 2024, included 33 randomized clinical trials involving 44,639 postmenopausal women with a mean age of 60.3 (48-72) years.[13] The results showed that starting HRT at a young age, within the first 10 years of menopause, reduced all-cause mortality by 28% (RR=0.72, 95% CI 0.54-0.97), cardiovascular events by 40% (RR=0.60, 95% CI 0.41-0.86), and did not increase the risk of ischemic stroke (RR=1.37, 95% CI 0.91-2.05). Conversely, starting HRT later in life and after the first 10 years of menopause not only failed to provide any benefit in reducing mortality (RR=1.06, 95% CI 0.95-1.18) and cardiovascular events (RR=1.03, 95% CI 0.92-1.15), but also increased the risk of ischemic stroke by 21% (RR=1.21, 95% CI 1.07-1.38).

These findings support the so-called "timing hypothesis", which suggests that the cardiovascular risk linked to HRT depends on the time since menopause. Studies in primates and other animal models support the evidence that the beneficial effects of HRT in preventing atherosclerosis occur only if started before the development of advanced vascular lesions.

In endothelial cells, estrogens cause rapid activation of nitric oxide synthase, allowing for an increase in nitric oxide concentration, and stimulate cyclooxygenase-2 (COX-2) to produce prostacyclin (PGI2), thus preventing platelet aggregation and promoting vasodilation.[14] Furthermore, animal studies have shown that estrogens increase endothelial cell regrowth, reduce the size of vascular lesions, and inhibit the proliferation of vascular smooth muscle cells, promoting rapid re-endothelization after vascular injury.[15] Some studies, including a large randomized, controlled trial,[16] have shown that estrogen therapy in postmenopausal women improves the lipid profile by reducing total cholesterol, low-density lipoprotein (LDL), and Lp(a) while increasing high-density lipoprotein (HDL) concentrations. This results in increased vasodilation, reduced inflammation, and lipid concentrations, thus slowing the progression of atherosclerotic lesions. Conversely, if HRT is initiated when atherosclerosis is already advanced, the opposing effects of reduced vasodilation, increased inflammation, and the onset of dyslipidemia, due to reduced estrogen receptor expression and function, could cause instability in atherosclerotic plaques, potentially leading to cardiovascular events.[17]

Dose, type, and route of HRT administration

The cardiovascular impact of HRT appears to depend on the dose, formulation, and route of administration. This area remains uncertain because most randomized clinical trials and observational studies have used conjugated equine estrogens combined with medroxyprogesterone acetate as HRT, but pharmaceutical formulations have changed over time. Although direct comparative randomized clinical trials are lacking, observational studies indicate that lower doses of estrogen or transdermal therapy are less or not linked to an increased risk of cardiovascular disease.

In a large French case-control study, 3,144 women aged 51 to 62 years with no prior cardiovascular disease who were hospitalized for a first ischemic stroke, were evaluated in comparison with 12,158 healthy women.[18]

HRT users were classified based on the route of estrogen administration (oral or transdermal), the dose (low, intermediate, or high), and the type of accompanying progestin (progesterone and pregnane derivatives, norpregnane derivatives, or nortestosterone derivatives). The results indicated that oral estradiol is linked to a higher risk of stroke. Because this risk is dose-dependent, the lowest effective dose should be prescribed. Transdermal estradiol, however, does not seem to increase the risk of stroke beyond the risk factors each woman already has (Table 1).

Regarding the concurrent use of progestins, no link was found between ischemic stroke and the use of progesterone (OR=0.78; 0.49-1.26), pregnane derivatives such as medrox-

yprogesterone acetate, dydrogesterone, and cyproterone acetate (OR=1.00; 0.60-1.67), and nortestosterone derivatives like norethisterone and levonorgestrel (OR=1.26; 0.62-2.58). However, norpregnane derivatives such as nomegestrol were linked to a higher risk of ischemic stroke (OR=2.25; 1.05-4.81).

More recently, a large Swedish study utilizing data from national registries examined the impact of menopausal hormone therapy on cardiovascular disease risk based on administration route and hormone combination.[19] A total of 919,614 women aged 50 to 58 years who met the inclusion criteria, had not used hormone therapy in the previous two years, and had no history of cardiovascular disease, cancer, or previous hysterosalpingo-oophorectomy, were identified from the Swedish population. They were enrolled in the study and assigned to one of eight treatment groups: oral estrogen only, continuous or sequential combined oral therapy, oral estrogen and local progestin, tibolone, combined transdermal therapy, transdermal therapy with estrogen only, or no hormone therapy. HRT was started by 77,512 women, while 842,102 women did not initiate treatment. In intention-to-treat analyses, tibolone was associated with an increased risk of cardiovascular disease (HR=1.52, 95% CI 1.11-2.08) compared to women who had not started hormone therapy. Taking tibolone or oral estrogen-progestins was associated with an increased risk of ischemic heart disease (HR=1.46, 95% CI 1.00-2.14; and HR=1.21, 95% CI 1.00-1.46, respectively). In per-protocol analyses, tibolone use was linked to a higher risk of cerebral infarction (HR=1.97, 95% CI 1.02-3.78) and myocardial infarction (HR=1.94, 95% CI 1.01-3.73). No increased cardiovascular risk was observed for transdermal estrogen-only or combined formulations.

Women's comorbidities and individual risk factors

Other essential factors to consider are comorbidities and personal risk factors, as these can raise the likelihood of cardiovascular disease during HRT.

In women who have had a hysterectomy, hormone therapy involves only estrogens. In the WHI study, women taking conjugated equine estrogens did not have an increased risk of coronary heart disease (HR=0.94, 95% CI 0.78-1.14) compared to placebo, but the HR for stroke was 15% higher in the hormone therapy group, although the result did not reach statistical significance (HR=1.15, 95% CI 0.97-1.37).[11]

However, a meta-analysis including 33 randomized clinical trials involving a total of 44,639 postmenopausal women showed that HRT is not linked to a benefit in reducing cardiovascular events (RR=0.94, 95% CI 0.80-1.10) or mortality (RR=0.97, 95% CI 0.84-1.11), but it raises the risk of stroke by 24% (RR=1.24, 95% CI 1.03-1.50).[13]

Furthermore, traditional cardiovascular risk factors, including obesity, dyslipidemia, hypertension, diabetes, metabolic syndrome, smoking, and lifestyle must be evaluated. The American College of Cardiology Committee on Cardiovascular Disease in Women, together with gynecologists, internists specializing in women's health, and endocrinologists, recommends categorizing women into low, intermediate, and high risk based on the time since menopause and the woman's current or past health conditions (Table 2).[4]

Additionally, the guidelines published by the Society of En-

Table 1. Dose and route of administration of estrogens and cardiovascular risk.

Dose	Oral estrogens	Transdermal estrogens
	OR (95% C.I.)	OR (95% C.I.)
Non use	1 (reference)	1 (reference)
Low	1.39, 1.00-1.99	0.69, 0.37-1.28
Intermediate	1.84, 1.02-3.30	0.79, 0.40-1.58
High	2.41, 1.43-4.07	0.88, 0.57-1.37

Table 2. Risk stratification in women who needs hormone replacement therapy.

Low risk	Intermediate risk	High risk
Recent menopause	Diabetes	Congenital heart disease
Normal weight	Smoking	ASCVD/CAD/PAD
Normal blood pressure	Hypertension	VTE
Physically active	Obesity	Stroke/TIA or MI
10-year ASCVD risk <5%	Sedentary/limited mobility	Breast cancer
Low risk of breast cancer	Autoimmune disease	10-year ASCVD risk ≥10%
	Hyperlipemia	
	Metabolic syndrome	
	10-year ASCVD risk ≥5%-10%	
	High risk of breast cancer	

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; PAD, peripheral artery disease; VTE, venous thromboembolism; TIA, transient ischemic attack; MI, myocardial infarction.

docrinology recommend evaluating cardiovascular risk before prescribing hormone therapy, even for women under 60 or less than 10 years after menopause, because cardiovascular risk can differ among women of the same age.[17]

From a practical perspective, young women within 10 years of menopause and have low cardiovascular risk can use hormone therapy. If their cardiovascular risk is intermediate, hormone therapy remains acceptable, with transdermal therapy being the preferred option. For women with high cardiovascular risk, hormone therapy should be avoided in favor of alternative treatments. When more than 10 years have passed since menopause, alternative therapies should be considered unless the woman has a low cardiovascular risk, a decision that should involve discussion with her.

Recently published guidelines by the American Heart Association and American Stroke Association for primary stroke prevention agree with these recommendations. In the absence of contraindications, they suggest using either an oral or transdermal formulation. Alternative therapies are advised if contraindications are present.[18]

Some authors have proposed using cardiovascular age instead of chronological age to assess a woman's cardiovascular risk.[19] The primary factor determining cardiovascular age is the development of coronary plaques and the potential occurrence of acute coronary syndrome. Because diagnostic techniques that examine the coronary arteries are costly and invasive, a surrogate measure -namely, a woman's 10-year risk of developing heart disease- has been suggested.

Using a sample of women from the WHI study, followed until 2005, and a subgroup whose follow-up was extended until 2017, a study evaluated cardiovascular events during HRT using two risk scores.[20] The Framingham Cardiovascular Disease (CVD) Risk Score is sex-specific, validated, and estimates the 10-year risk of cardiovascular events by including variables such as age, systolic blood pressure, use of antihypertensive medications, cigarette smoking, diabetes, and HDL cholesterol concentration or BMI.[21]

The American College of Cardiology/American Heart Association Atherosclerotic Cardiovascular Disease (ASCVD) Risk Score is also sex-specific, validated for women aged 40 to 75, and estimates the 10-year risk of cardiovascular disease.[22] This score evaluates the same variables as the Framingham CVD risk score but also includes ethnicity. The study compared hazard ratios obtained using the Framingham CVD and ASCVD risk scores with those derived from considering age and time since menopause. The results indicated better cardiovascular risk assessment with the scores, as hazard ratios were higher on average. Calculating the C-index also demonstrated improved predictability of cardiovascular events (Framingham CVD risk score C-index=0.71) compared to using age (C-index=0.65) or time since menopause alone (C-index=0.62). Since menopause onset is linked to the development of several comorbidities, such as hypertension, dyslipidemia, and metabolic syndrome, a multidisciplinary approach may be beneficial for the safe and effective management of both menopausal symptoms and related conditions.

Conclusions

Hormone therapy should not be automatically withheld in postmenopausal women. Individualized assessment of risks and benefits is essential to optimize symptom relief and quality of life minimizing cardiovascular complications. Thorough counseling enables shared decision-making, ensuring that treatment aligns with each woman's clinical profile and preferences.

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