Does Hormone Replacement Therapy (HRT) Have A Beneficial Or Detrimental Effect On Cardiovascular Outcomes In Postmenopausal Women? A Systematic Review On The Evaluation Of Risk And Effectiveness

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ABSTRACT

Background: Hormone Replacement Therapy (HRT) involves the supplementation or substitution of hormones, such as estrogen and progesterone, to alleviate menopausal symptoms. However, its impact on cardiovascular diseases (CVDs) has been widely debated. CVDs remain the leading cause of mortality worldwide, necessitating early detection, prevention strategies, and effective management. Initially, HRT was believed to provide cardiovascular benefits by improving cholesterol levels and arterial function. However, subsequent research has produced conflicting findings. Some studies suggest HRT increases the risk of cardiovascular events, such as blood clots and strokes, while others indicate potential benefits. Consequently, the decision to use HRT for CVD prevention requires careful risk assessment and individualized consultation with healthcare providers.

Objective: To systematically evaluate the impact of Hormone Replacement Therapy (HRT) on cardiovascular outcomes in postmenopausal women, assessing both its benefits and risks.

Methods: A systematic review of literature was conducted, analyzing 53 articles from reputable journals published between January 1, 2018, and August 13, 2023. Eight studies were selected for in-depth analysis. The review focused on distinct cardiovascular conditions in menopausal women, considering both those with and without prior CVDs or associated risk factors, as well as the effects before and after HRT administration.

Results: Vaginal HRT reduces the risk of heart attack and stroke, whereas oral HRT has no significant effect on heart disease. Higher dosages of oral or transdermal HRT may increase the risk of stroke and venous thromboembolism (VTE). Transdermal estradiol (t-E2), either alone or combined with micronized progesterone, lowers the risk of thromboembolism. Unlike t-E2, oral conjugated equine estrogen (o-CEE) helps mitigate the negative effects of increased pericardial adipose tissue on atherosclerosis progression. According to the Timing Hypothesis, the cardiovascular effects of HRT vary based on the age of initiation, with younger women potentially experiencing greater benefits.

Conclusion: Low-dose HRT and oral administration appear safer for individuals at higher risk of stroke and blood clots. The use of transdermal estradiol and progesterone may lower the risk of thromboembolism, while o-CEE slows atherosclerosis progression. Additionally, earlier initiation of HRT is associated with a reduced risk of CVD. However, individualized decision-making remains essential, and further research is necessary to fully understand HRT's cardiovascular implications in postmenopausal women.

INTRODUCTION

Postmenopausal women are at a significantly higher risk of cardiovascular disease (CVD) than premenopausal women, who generally have a lower risk (1). Menopause, defined as the cessation of menstruation for a full year, marks the end of a woman's reproductive phase. This transition often includes irregular menstrual cycles and the onset of menopausal symptoms, which can begin years before (2). Studies suggest that these symptoms may persist from six months to several years (2).

The increased risk of CVD following menopause is primarily linked to a sharp decline in estrogen levels, suggesting that endogenous estrogen may have previously played a protective role in women's cardiovascular health (2). Middle-aged women experience increased atherosclerosis progression and unfavorable changes in body fat distribution during this period (3). These hormonal changes pose risks not only to cardiovascular health but also to bone health and overall well-being (4).

Lipid metabolism plays a crucial role in CVD risk. Elevated low-density lipoprotein cholesterol (LDL-C) and reduced high-density lipoprotein cholesterol (HDL-C) levels contribute to cardiovascular risk. Other factors, including Apolipoprotein B (Apo-B), lipoprotein (a) [Lp(a)], and triglycerides (TG), further influence CVD progression. Conversely, Apolipoprotein A1 (Apo-A1), found in HDL-C, may offer cardioprotective benefits (5). Emerging research indicates that small, dense LDL particles and elevated Lp(a) levels contribute to vascular dysfunction, especially during menopause (5).

There has been long-standing debate about the protective role of hormones in cardiovascular health. Some studies suggest that postmenopausal women who opt for HRT experience a reduced risk of cardiac events, depending on the formulation and timing of administration (5). The distribution of epicardial adipose tissue (EAT) and pericardial adipose tissue (PAT) also appears to influence coronary artery disease (CAD)

progression in women at different menopausal stages (6). Notably, EAT is strongly associated with early-stage artery disease in menopausal women, whereas PAT exhibits a stronger link in postmenopausal women with lower estrogen levels (6).

HRT is available in various formulations, including estrogen-only (for women with prior hysterectomy) and combined estrogen-progesterone therapy (for women with an intact uterus). Administration routes include oral, transdermal (patches, gels), and vaginal applications (2). The type, dosage, and duration of HRT use significantly influence cardiovascular outcomes (2).

The Timing Hypothesis suggests that the cardiovascular impact of HRT is influenced by the age of initiation and time since menopause. A randomized trial investigating this hypothesis assigned 643 healthy postmenopausal women to either HRT or placebo. Women were categorized based on menopause duration (≤6 years vs. ≥10 years). After five years, younger women receiving HRT exhibited a significant reduction in carotid artery wall thickness progression, whereas this effect was not observed in older participants (7).

Following the 2002 Women's Health Initiative (WHI) trial, which reported increased risks of myocardial infarction, thrombotic events, and breast cancer, HRT use declined dramatically. HRT usage dropped from 12% in 2004 to 5% by 2010 (8,9). Despite this, recent studies suggest that early initiation of HRT may provide cardiovascular benefits without increasing long-term CVD risk (2).

Given the persistent controversies surrounding the risks and benefits of HRT, this systematic review evaluates its impact on cardiovascular health, considering factors such as estrogen levels, route of administration, timing, duration, baseline health conditions, and CVD risk factors in postmenopausal women.

Objective

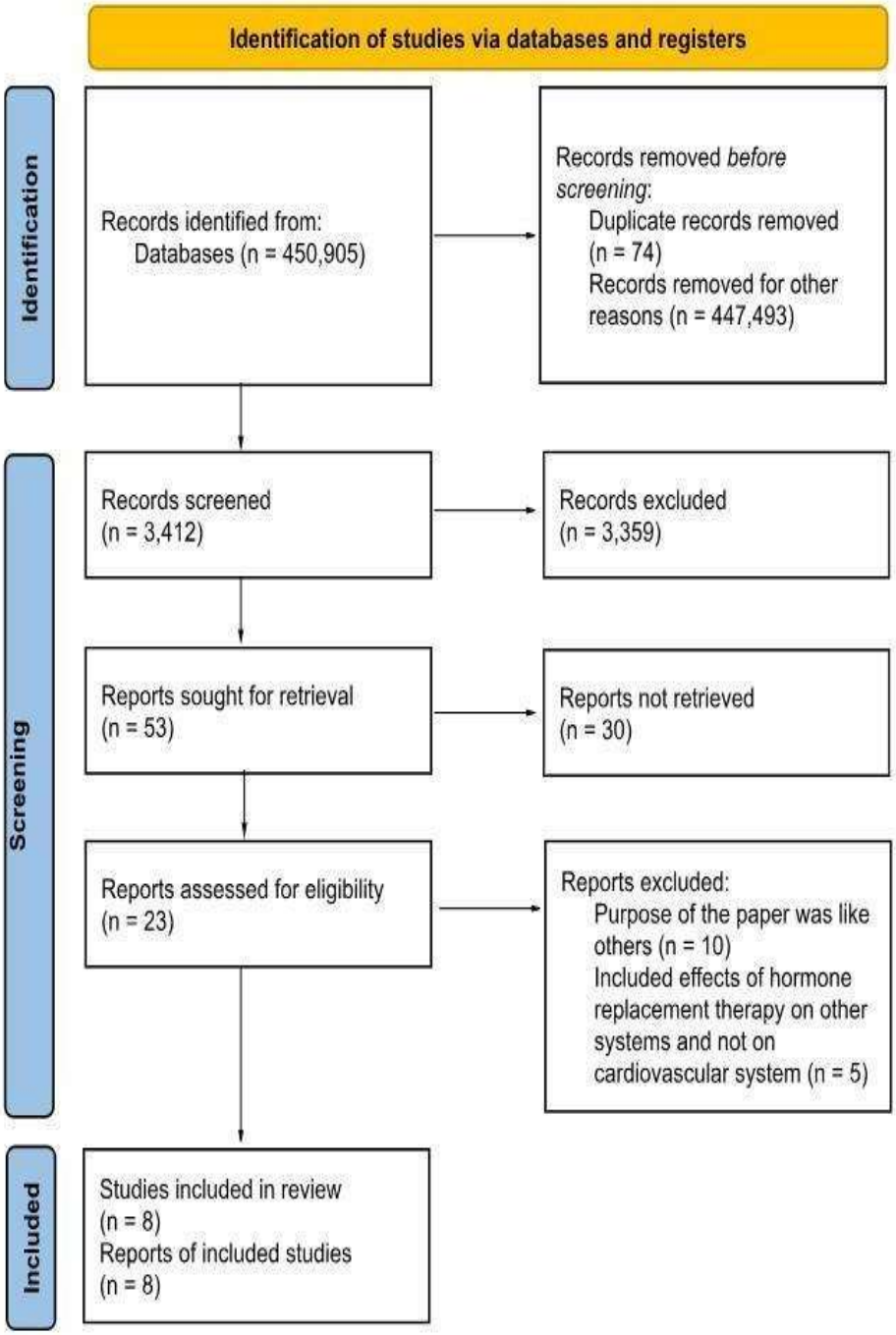
This systematic review aims to clarify conflicting findings and provide a comprehensive overview of HRT's cardiovascular effects in postmenopausal women. By synthesizing data from multiple studies, this review seeks to determine whether HRT predominantly exerts beneficial or detrimental effects on cardiovascular outcomes and to identify key factors influencing these results.

Research Question

Does Hormone Replacement Therapy (HRT) Exert a Positive or Negative Impact on Cardiovascular Outcomes in Postmenopausal Women?

MATERIALS AND METHODS

This review focuses on clinical studies investigating the cardiovascular effects of HRT. Studies on non-cardiovascular outcomes and animal research were excluded. The review adheres to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (30), as illustrated in Figure 1. Since only published data were used, ethical approval was not required.



Systematic Literature Search and Study Selection

A comprehensive literature search was conducted using PubMed, Medline, and Google Scholar to identify relevant studies. PubMed was also used to track references cited in reviews, editorials, and commentaries. We systematically identified and selected studies based on predefined inclusion and exclusion criteria (Table 1).

Study Screening and Selection Process

A total of 490,905 articles were initially identified. After applying inclusion and exclusion criteria, 447,419 articles were excluded. Of the remaining 3,486 articles, 3,433 were excluded due to duplication or irrelevant titles/abstracts. A full-text review of 53 papers was conducted, resulting in the exclusion of 45 studies that did not meet the eligibility criteria. Ultimately, eight studies were included in this systematic review (Figure 1).

Inclusion and Exclusion Criteria

To ensure the relevance and quality of included studies, predefined eligibility criteria were established. These criteria focused on human studies examining HRT and cardiovascular outcomes in postmenopausal women while excluding studies on unrelated conditions or populations.

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Human studies	Animal studies
Studies published from 2018 to 2023	Studies focusing solely on non-cardiovascular outcomes
Articles written in English	Non-English texts
Gender: Female	Gender: Male
Age: ≥ 45 years (Postmenopausal women)	Age: < 45 years or Premenopausal women
Free-access papers	Paid papers requiring purchase
Studies focusing on cardiovascular diseases and HRT	Studies investigating other health conditions unrelated to CVD

Search Strategy

A structured search was conducted using the PICO (Population, Intervention, Comparison, and Outcome) framework. The MeSH (Medical Subject Headings) technique was applied to refine searches in PubMed, Medline, and Google Scholar.

Table 2: Search Strategy and Results from Different Databases

Database	Search Strategy	Results
PubMed	"Hormone Replacement Therapy AND Cardiovascular Disease"	13
	"Postmenopausal Hormone Therapy AND Heart Disease OR Coronary Artery Disease"	395
	"Hormone Replacement Therapy OR HRT OR Postmenopausal Hormone Therapy AND Cardiovascular Outcomes OR Cardiovascular Diseases"	433,705
Google Scholar	"Hormone Replacement Therapy AND Cardiovascular Diseases OR Postmenopausal Hormone Therapy OR Cardiac Disease"	17,200

Quality Appraisal

To ensure the reliability and validity of selected studies, various quality assessment tools were employed:

Table 3: Quality Appraisal Tools Used for Study Assessment

Quality Appraisal Tool	Study Type
Cochrane Bias Tool Assessment	Randomized Control Trials (RCTs)
PRISMA Checklist	Systematic Reviews/Meta-Analyses
SANRA Checklist	Narrative Reviews without a clear methodology

*Cochrane Bias Tool Assessment for Randomized Control Trials (RCTs); PRISMA Checklist for Systematic Reviews and Meta-Analyses; Critical Appraisal Skills Program (CASP) Checklist for qualitative studies; Scale for the Assessment of Narrative Review Articles (SANRA) for non-systematic reviews; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SANRA: Scale for the Assessment of Narrative Review Articles

RESULTS

Following the literature screening process, eight studies were selected for inclusion. Table 4 summarizes their key findings, including study design, country of origin, and conclusions regarding HRT and cardiovascular outcomes.

Table 4: Summary of Selected Studies on HRT and Cardiovascular Outcomes

Author/Year	Country	Study Design	Database Used	Key Findings
Clare Oliver-Williams et al. (2019) (2)	UK	Systematic Review	Google Scholar	HRT effects depend on baseline CVD risk, age, and time since menopause. Transdermal estrogen may be safer for women with CVD.
Ida Gregersen et al. (2019) (5)	Norway	Systematic Review	Google Scholar	HRT positively impacts lipid profiles and reduces plasma Lp(a) levels.
Ji-Eun Kim et al. (2020) (1)	-	Systematic Review & Meta-Analysis	Google Scholar	HRT benefits CVD and VTE risk but requires careful assessment, especially for high-risk patients. Non-oral forms are preferable.
Marina Sprem Goldstajn et al. (2023) (8)	-	Systematic Review	Google Scholar	Oral HRT increases VTE risk compared to transdermal HRT, but no significant differences were

				noted for glucose metabolism, lipid profile, or cardiovascular risk.
Matthew Nudy et al. (2019) (7)	USA	Systematic Review & Meta-Regression Analysis	Google Scholar	HRT reduces all-cause and cardiac mortality in younger women but increases stroke and embolism risk with age.
Samar R. El Khoudary et al. (2019) (6)	USA	Meta-Analysis	PubMed, Medline	o-CEE slows pericardial adipose tissue accumulation, while t-E2 may exacerbate atherosclerosis progression.
Samar R. El Khoudary et al. (2020) (3)	-	KEEPS Trial Analysis	PubMed	Compared to t-E2, o-CEE may mitigate adverse effects of heart fat accumulation on atherosclerosis progression in recently menopausal women.
Shirvan Salaminia et al. (2019) (4)	Iran	Meta-Analysis	Google Scholar	HRT improves quality of life and prevents osteoporosis but may increase stroke risk. Not recommended for primary CVD prevention.

KEEPS: Kronos Early Estrogen Prevention Study

DISCUSSION

Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide, making them a major global health concern. Therefore, it is essential to explore preventive measures, early detection strategies, and comprehensive management approaches. Within this context, hormone replacement therapy (HRT) has been widely researched and debated. HRT involves the supplementation or replacement of hormones such as estrogen and progesterone, primarily to mitigate the effects of menopause. This systematic review

evaluates the impact of HRT on cardiovascular outcomes, weighing both its potential benefits and associated risks.

Premenopausal women have a lower risk of developing CVD than men, but this protection diminishes after menopause. (1) Menopause is characterized by hormonal changes, irregular menstrual cycles, and the onset of symptoms such as vasomotor disturbances (hot flashes, night sweats) and vaginal dryness, which affect 50.3% to 82.1% of menopausal women. (2) Interestingly, postmenopausal women exhibit a significant increase in carotid intima-media thickness (CIMT), a marker of atherosclerosis, regardless of chronological age. (3) Additionally, they tend to accumulate more pericardial and visceral adipose tissue, both of which are linked to cardiovascular risk. (3)

Given these physiological changes, HRT—administered as estrogen alone or in combination with progesterone—has been proposed as a potential intervention to mitigate postmenopausal health risks. However, despite extensive research, the cardioprotective role of HRT remains controversial. (5) Observational studies have consistently shown a lower incidence of coronary heart disease (CHD) among postmenopausal women using HRT, and a meta-analysis of over 100 randomized trials involving 39,049 postmenopausal women found that HRT reduced CHD events in younger postmenopausal cohorts. (5)

The effects of HRT on cardiovascular diseases—including atherosclerosis, thromboembolism, coronary artery disease, and stroke—vary depending on factors such as dosage, mode of administration, duration of use, and timing of initiation. The influence of HRT on heart fat storage and atherosclerosis is particularly relevant, given the role of endogenous estrogen in cardiovascular health. (6) While younger menopausal women on HRT appear to have an increased risk of stroke rather than CHD events, (7) the route of administration also plays a critical role—oral HRT is linked to a higher risk of venous thromboembolism (VTE) compared to transdermal HRT. (8)

The cardiovascular benefits of HRT may also be influenced by the timing of initiation. Research suggests that estrogen therapy is more likely to be cardioprotective when initiated around menopause, whereas delayed initiation (more than 10 years post-menopause) may be harmful. (2) Contradictions in findings further complicate the discussion, with studies reporting both positive and negative cardiovascular outcomes associated with HRT.

Estrogen levels decline significantly after menopause, and both excessively low and high estrogen levels have been linked to adverse cardiovascular outcomes. HRT, which modulates estrogen levels, can thus influence cardiometabolic risk depending on individual patient characteristics. (2) While HRT is primarily used for alleviating menopausal symptoms rather than as a direct preventive measure for CVD, some studies suggest that vaginal HRT may lower the risk of myocardial infarction (MI) and stroke. Additionally, lower doses of oral and transdermal HRT may offer cardioprotective benefits. (2)

HRT is known to improve serum lipid profiles in postmenopausal women. Studies have reported reductions in LDL-C, ApoB, non-HDL cholesterol, and total cholesterol/HDL-C ratios, alongside decreases in HDL-C and ApoA1 levels. (5) However, when HRT is initiated in women with pre-existing atherosclerosis, the overall cardiovascular benefits appear limited, and there may be an initial increase in CVD risk. (14) The timing of HRT use is crucial—long-term estrogen therapy may improve lipid profiles and slow atherosclerosis progression, but its effects vary based on the stage of atherosclerosis and patient-specific factors. (5)

Postmenopausal women exhibit increased pericardial adipose tissue (PAT) accumulation compared to premenopausal women, which is associated with coronary artery disease (CAD). (11) This adipose tissue influences local inflammation through cytokine release. (12) The KEEPS trial found that postmenopausal women taking oral conjugated equine estrogen (o-CEE) did not experience an increase in epicardial adipose

tissue (EAT) over 48 months, whereas those on a placebo did. (6) A rise in EAT volume has been associated with deteriorating myocardial function, as indicated by a decline in left ventricular global longitudinal strain. (13)

HRT also influences coronary artery calcification (CAC), with studies indicating that endogenous and exogenous estrogen levels modify the relationship between PAT and CAC progression. (3) Research suggests that transdermal estradiol (t-E2) may be more beneficial than o-CEE in mitigating the adverse effects of increased PAT on atherosclerosis progression. (3)

The risk of venous thromboembolism (VTE) is significantly influenced by the mode of HRT administration. Transdermal HRT has a safer profile compared to oral HRT, as it bypasses hepatic metabolism, reducing the impact on procoagulant factors. (8) However, larger doses of both oral and transdermal HRT increase the risk of VTE and stroke in a dose-dependent manner. (2) Women at high thromboembolic risk are generally advised to use transdermal estradiol, alone or in combination with micronized progesterone. (2)

The risk of stroke is notably higher with combined estrogen-progestogen therapy. (4) The increased risk may be due to estrogen's effects on coagulation, inflammatory markers, and neuronal function. (4) Non-oral HRT is preferable for women at elevated stroke risk. (1)

The scientific discourse surrounding HRT's cardiovascular effects remains dynamic, with conflicting findings fueling ongoing debates. Early studies suggested that HRT could offer cardioprotective effects by improving cholesterol levels and vascular function. However, results from the Women's Health Initiative (WHI) contradicted these expectations, revealing an increased risk of heart attacks among women using estrogen-progestin therapy. (18,19)

Conflicting evidence is not limited to adverse events; some studies have revealed intricate associations based on the administration route. Transdermal HRT, particularly with estradiol, appears to be linked to a lower risk, whereas oral HRT has been associated with an increased risk of venous thromboembolism, emphasizing the complex relationship between the mode of administration and its potential impact on cardiovascular outcomes (20). Another area of debate is the timing of HRT initiation. The timing hypothesis suggests that the cardiovascular effects of HRT may vary depending on the age at which treatment begins (21). Some studies indicate that initiating HRT in younger postmenopausal women may be beneficial; however, this notion has not been consistently supported across research findings (22). This discrepancy underscores the importance of further investigating how age influences the cardiovascular effects of HRT (23). A comprehensive evaluation of the available data is essential to provide informed recommendations that consider both the potential advantages and risks of HRT in postmenopausal women (24).

The long-term effectiveness of HRT in preventing cardiovascular disease among postmenopausal women remains a subject of ongoing debate. Some medical experts argue that prescribing HRT to mitigate cardiovascular risk is unwarranted (4). Findings from the Women's Health Initiative (WHI) revealed that the use of combined estrogen and progesterone therapy was associated with a 31% increased risk of stroke compared to non-intervention groups (25). The notion that the risks and benefits of HRT depend on the individual characteristics of the women receiving treatment is supported by studies incorporating data from multiple sources. However, when carefully considering a woman's health status and the timing of HRT initiation, its use may offer cardiovascular benefits and improved survival in postmenopausal women experiencing severe menopausal symptoms. Nevertheless, HRT is not currently recommended for the prevention of chronic diseases. Additionally, women at high risk of venous thromboembolism and stroke may be advised to opt for non-oral HRT formulations instead of oral preparations for managing menopausal symptoms (1).

Limitations

This review has several limitations. We focused on peer-reviewed, English-language articles and restricted our analysis to studies involving participants aged 45 and older. Additionally, we only included open-access studies, which may introduce selection bias. Given the heterogeneity of the included studies, further research is necessary to draw definitive conclusions.

CONCLUSION

HRT exerts diverse cardiovascular effects in postmenopausal women, demonstrating both beneficial and adverse outcomes. While oral HRT does not significantly elevate cardiovascular risk, vaginal hormone therapy may reduce the risk of myocardial infarction and stroke. However, higher doses increase the risk of VTE and cerebrovascular accidents. Transdermal HRT at lower doses appears to have a safer profile, particularly for women at high thromboembolic risk.

This review also examined HRT's influence on cardiac fat accumulation and CAC progression, highlighting variations based on estrogen formulation. The timing hypothesis suggests that HRT's effects differ depending on when it is initiated, with younger women potentially experiencing greater benefits. However, personalized decision-making remains critical, and further research is required to fully understand HRT's role in cardiovascular health.

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