Iran Red Crescent Med J. 2019 February; 21(2):e82298. doi: 10.5812/ircmj.82298.

Published online 2019 February 27. **Systematic Review**

Hormone Replacement Therapy and Postmenopausal Cardiovascular Events: A Meta-Analysis

Shirvan Salaminia [1], Yousof Mohsenzadeh [2], Morteza Motedayen [3,*], Fatemeh Sayehmiri [4] and Majid Dousti [5]

[1]Department of Cardiac Surgery, Yasuj University of Medical Sciences, Yasuj, Iran
[2]Department of Cardiology, School of Medicine, Ilam University of Medical Sciences, Ilam, Iran
[3]Department of Cardiology, Faculty of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
[4]Proteomics Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5]Department of Parasitology, Faculty of Medicine, Shiraz University of Medical Sciences, Fars, Iran

[*]*Corresponding author*: Assistant Professor, Department of Cardiology, Faculty of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran. Email: mor.mot2@gmail.com

Received 2018 July 17; **Revised** 2018 September 28; **Accepted** 2019 January 29.

Abstract

Context: Hormone replacement therapy (HRT) is widely used to control postmenopausal symptoms. This therapy is also used to prevent diseases such as osteoporosis and dementia. However, clinical trials suggest some negative effects regarding postmenopausal HRT. This study evaluates the effects of HRT on postmenopausal cardiovascular events.

Evidence Acquisition: We collected data from 32 articles by using valid keywords and searching databases of PubMed, Medlib, ScienceDirect, EmBase, Scopus, Index Copernicus, SID, and Iranmedex. Analysis was performed by comparing three groups of postmenopausal women: combined hormone therapy (estrogen + progesterone), estrogen alone treated group, and placebo-receiving group (control group). Data were analyzed using the random effect model meta-analysis by using R software and Stata software Version 11.2.

Results: Of the collected 32 studies between 1998 and 2016, there were 1277686 subjects with an average age of 60.6 years. The prevalence of myocardial infarction were (2.64%), coronary heart disease (1.7%), stroke (254%), cardiovascular death (1.54%), revascularization (3.26 %), and cerebrovascular disease (CVD) (2.78%) in the combined hormone therapy group. Also, in the estrogen-treated group were 2.95%, 3.41%, 2.49%, 2.8%, - , 3.14%, respectively. In the placebo-receiving group these events were 2.09%, 2.73%, 2.9%, 2.25%, 4.96%, and 11.92, respectively. The results showed that estrogen therapy could increase the incidence of stroke. Moreover, HRT could have positive effects on the serum lipid profile in postmenopausal women.

Conclusion: Postmenopausal HRT appears to be non-effective on coronary artery disease, revascularization, myocardial infarction, and cardiac-related deaths; however, it could play a role in increasing the stroke rate.

Keywords: Cardiovascular, Hormone Therapy, Meta-Analysis, Postmenopausal

1. Introduction

Menopause is considered to be a stage in the life of a woman, which is associated with permanent menstrual cessation and lack of ovarian hormonal activity. Today with increased life expectancy, almost a third of a woman life is during the postmenopausal period. After cardiac disease, menopause is the leading cause of elapsed years of life with disabilities in the age group of 45 - 70 years old (1, 2). Following the menopause and the decrease of ovarian activity accompanied by estrogen reduction, there are several symptoms such as menstrual disorder, vasomotor instability, genital atrophy, painful intercourse, itching, urethral inflammation, cystitis, and urinary incontinence. In long-term, major problems resulting from estrogen deprivation such as cardiovascular disease and osteoporosis threaten the health of postmenopausal women (3). There are significant changes in the level of lipoproteins and lipids (increased total cholesterol and LDL (low-density lipoprotein) and reduced HDL (High-Density Lipoprotein). These changes increase the risk of cardiovascular diseases (4). Cardiovascular diseases seem to be related to the menopause and this condition is one of the major causes of death in women with low-risk coronary artery disease (5). One measure available to support postmenopausal women's health is the use of hormone replacement therapy (HRT) in which steroid hormones are prescribed in the form of estrogen with or without progesterone (6). Although the protective effect of HRT against Alzheimer's, os-

teoporosis and urogenital atrophic changes (7) is currently known, some studies revealed that this treatment might increase the incidence of diseases such as breast cancer (8).

The long-term use of HRT in postmenopausal women to lessen cardiovascular diseases is debatable. Some doctors believe that HRT should not be prescribed to reduce the risk of cardiovascular diseases (9). Pharmacological evaluations have shown that estrogen and progesterone have cytoprotective properties, and thus they can affect the severity and frequency of cardiovascular events (10, 11). Several studies have displayed that HRT is associated with a drop in the risk of coronary artery disease (4, 12, 13); however, in several other randomized controlled trials, HRT has increased the risk of cardiovascular events such as coronary artery disease, stroke, and thromboembolic events (14-16). According to Women's Health Initiative (WHI), combined estrogen-progesterone therapy increased 31% the risk of stroke compared with placebo. In estrogen therapy alone, the risk of stroke was significantly increased compared with placebo (17).

Neglecting the characteristics and clinical differences of the case and control groups, small sample sizes of the studied groups, short duration of follow-up, and the methodological limitations of observational studies could be among the reasons for these discrepancies in the results.

With this regards, it is not easy to decide whether to or not to use HRT, which also may be affected by the individual characteristics and beliefs of women and their doctors. An earlier meta-analysis (18) failed to demonstrate the beneficial use of HRT on cardiovascular events and declared that HRT does not affect coronary events and myocardial infarction; however, it can raise the risk of stroke in postmenopausal women.

Over the past two decades, various controlled randomized studies evaluated the effects of HRT on cardiovascular events in postmenopausal women on a large scale. However, due to the lack of inconsistency between the findings from these studies and also a better understanding of the effect of HRT on cardiovascular events, it seems necessary to conduct a meta-analysis study to assess the effect of HRT on cardiovascular events among postmenopausal women. Over time, improvements in medical facilities, the increase in community awareness, and attitudes of physicians and patients could be changed; therefore, updating the results of studies is essential to understand the effects of HRT in postmenopausal women.

2. Objectives

This work clarified data from randomized controlled trials about the effect of HRT on cardiovascular events in postmenopausal women by a meta-analysis.

3. Materials and Methods

3.1. Data Sources and Search Strategies

The present study is a meta-analysis of all data resources considering the effect of hormone replacement therapy on cardiovascular events in postmenopausal women. Using the acronym PICO (participants or population [P], intervention or exposure [I], comparison or comparator [C], and outcome [O]), the main concepts of the study search question identified. Hence, "P" stands for postmenopausal women, "I" for hormone therapy, "C" for comparing to the placebo group, and "O" for coronary heart disease, stroke, myocardial infarction, death from these diseases, and the need for revascularization. The study was conducted by the review and meta-analysis of existing electronic resources between 1998 and 2016. All scientific journals, as well as all articles presented at seminars and conferences and also all databases, including PubMed, Medlib, ScienceDirect, EmBase, Scopus, Index Copernicus, SID, and Iranmedex, were reviewed. The search for articles was mainly done in a systematic approach and by using valid keywords such as postmenopausal women, stroke, cardiovascular disease, randomized controlled trial, and their possible English combinations. Our keywords standardized in Mesh and ultimately the search string of ((((hormone replacement therapy) OR estrogen replacement therapy) OR estradiol) OR progesterone) OR HRT))) AND (((cardiovascular) OR lipid profile) OR low-density lipoprotein) OR high-density lipoprotein) OR Cholesterol) OR LDL) OR HDL) OR Triglyceride) OR TG))) AND (((woman) OR female) AND Humans [Mesh])))) was used. Furthermore, the reference lists and citations of the selected articles were screened for relevant studies.

3.2. Study Selection

At first, a list of titles and abstracts of all collected articles were prepared by two researchers to select the related topics independently. Inclusion criteria consisted of (1) randomized controlled trial studies, (2) reported cardiovascular events in postmenopausal women, (3) done in the past twenty years [to reduce the effect of time passage]. Exclusion criteria consisted of (1) qualitative studies, (2) studies with no control group [The lack of a placebo control group may increase the effect of other factors and deteriorate the results], and (3) studies published in non-English language publications. The related articles independently entered the research process. If the two researchers did not agree on the choice of a particular article, the judgment left to the third researcher.

3.3. Data Extraction

In the next step, after determining the relevant study titles, the abstracts of various selected articles were evaluated by the researcher using the Ottawa quality assessment scale and studies with a score of below 3 were deleted. In the first stage, 19570 articles were found that according to the criteria mentioned for entry and exit, in total 32 articles were selected to enter the meta-analysis stage (Figure 1). The selected articles were completely evaluated and all of their data were extracted in a previously designed format, then the data entered Excel software. The Excel data sheet transferred to the R and the Stata software. The collected data were the author's name, year of publication, the sample size in each study, mean age of participants, follow-up duration, underlying illness, regimen, and the frequency of risk factors for cardiovascular events. The evaluated cardiovascular events included the frequencies of coronary artery disease (CHD), myocardial infarction (MI), stroke, revascularization, cardiovascular mortality, and cardiovascular disease (CVD). Serum lipid profiles, including Low-Density Lipoprotein, High-Density Lipoprotein, total cholesterol and triglyceride (TG) levels were also recorded.

3.4. Data Synthesis and Analysis

Data pooled and analyzed based on sample size, mean, and standard deviation. Weight in each study is proportional to its reverse of variance. For evaluation of heterogeneity, Q-test and I2 index were tested at α error level less than 10%. In cases of heterogeneity, we used a random effect model for analysis. A subgroup analysis performed based on the mean age (mean age < 65 years or > 65 years) and the number of patients (< 10,000 persons or > 10,000 persons) in each treatment group. The data were analyzed using both R Statistical software and Stata Version 11.2 software.

4. Results

After removal of duplicates and unrelated studies, 32 papers from different countries were selected and appraised for analysis (Table 1). Figure 1 shows the study selection flow-chart. All studies were cross-sectional analytical studies. In all of these studies, a census sampling method had been used to collect information from the hospital profile and questionnaires, which were completed by interview and observation. In this meta-analysis, the Q-Cochran test showed incongruity of the findings in the selected studies (I_2 = 98.3%), hence the Random Effects model was used in all subsequent stages. The total sample size was 1277686 persons with an average age of 60.6 years and a follow-up period of 2 to 16 years (average; 5.2 years).

Of this 32 article, 24 (410253 postmenopausal women) reported the effect of combined estrogen hormone therapy (CEE) and medroxyprogesterone acetate (MPA) versus placebo or estrogen. In 16 studies (108499 postmenopausal women) the therapeutic effects of estrogen alone was reported compared with placebo. Considering medical history, 23 studies were conducted on healthy postmenopausal women, 7 on postmenopausal women with the previous cardiovascular disease, and 2 on high-risk postmenopausal women (history of any of the factors of high blood pressure, hyperlipidemia, diabetes, and smoking). In all studies, risk factors for cardiovascular events (such as the history of hypertension, diabetes, smoking, etc.) were the same between groups.

The prevalence of coronary artery disease was 1.70% in the combined hormone therapy group after sensitivity analysis and removal of outlier studies in the remaining studies.

The results of these studies showed that combined hormone therapy could increase coronary events; however, this increase was not statistically significant (Figure 2).

The single effect of estrogen therapy on CHD was 3.41 (Figure 3). The prevalence of myocardial infarction was 2.73% after sensitivity analysis. Overall, combined hormone therapy did not significantly alter the risk of myocardial infarction compared with placebo (Table 2). In addition, the single effect of estrogen therapy on myocardial infarction was studied in 14 studies (after sensitivity analysis) and the prevalence of heart attacks was 2.64% in this group. In general, there was no evidence of the effect of estrogen therapy on the increased risk of myocardial infarction.

The prevalence of stroke after sensitivity analysis was 2.54% in the remaining 15 studies. Overall, combined hormone therapy did not significantly change the risk of stroke compared with placebo (Figure 4).

Also, the effect of estrogen therapy alone on stroke was studied in 17 studies (after sensitivity analysis), and the prevalence of stroke was 2.49% in this group. Generally, estrogen therapy was associated with an increased risk of stroke (Figure 5).

The impact of hormone therapy (combination therapy or estrogen therapy alone) on the frequency of cardiovascular mortality, revascularization, and cerebrovascular diseases (CVDs) were presented in Table 2.

Interestingly, this study showed some important findings in the lipid profile of postmenopausal women. In comparison to the placebo group, combined hormone therapy reduced serum Low-Density Lipoprotein and total cholesterol levels meanwhile increased serum High-Density Lipoprotein and triglyceride concentrations. The

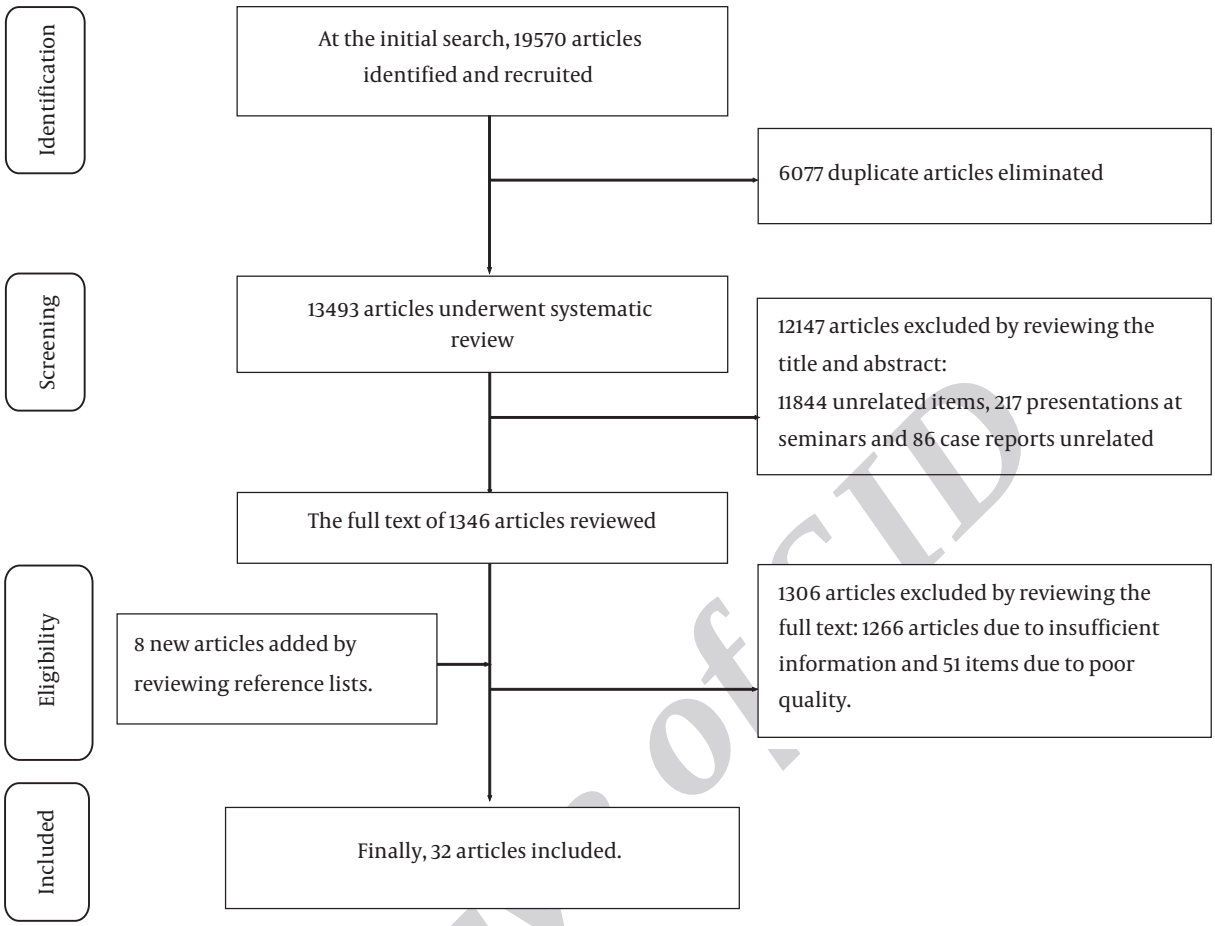

Figure 1. Meta-analysis flowchart

study also showed that estrogen therapy increased serum triglycerides, High-Density Lipoprotein meanwhile decreased serum Low-Density Lipoprotein and total cholesterol levels compared with placebo. However, none of the changes were statistically significant (Table 3).

To determine the effect of age on the onset of hormone therapy on cardiovascular events, studies were categorized into two groups based on population age (< 65-year old or > 65-year old). Twenty-two studies were in the group under 65 years and ten studies in the group over 65 years (Table 1). In the group more than the 65-year-old, the incidence of cardiovascular events was higher than those under 65-year old (Table 4). In a subgroup analysis of the study population (15 studies < 10,000 persons and 17 studies > 10,000 persons), the incidence of cardiovascular events was higher in subgroups below 10,000 persons (Table 4). According to the publication bias analysis, the effect of bias in these studies was not significant (P = 0.317).

5. Discussion

The present meta-analysis was designed to evaluate all studies about the effect of postmenopausal hormone replacement therapy on cardiovascular diseases. This study revealed that combined hormone therapy is associated with an increased risk of stroke meanwhile did not affect the rate of coronary artery disease, cerebrovascular disease, revascularization, heart attacks, and cardiovascular mortality. We also found that estrogen therapy is associated with an increased stroke rate and a decreased revascularization rate, meanwhile did not affect the rate of coronary artery disease, myocardial infarction, and the death rate of cardiovascular or cerebrovascular disease events. Moreover, the evaluation of lipid profiles showed that hormone therapy could have a favorable effect on serum lipid profiles of postmenopausal women.

Interestingly, the findings of this study suggest that

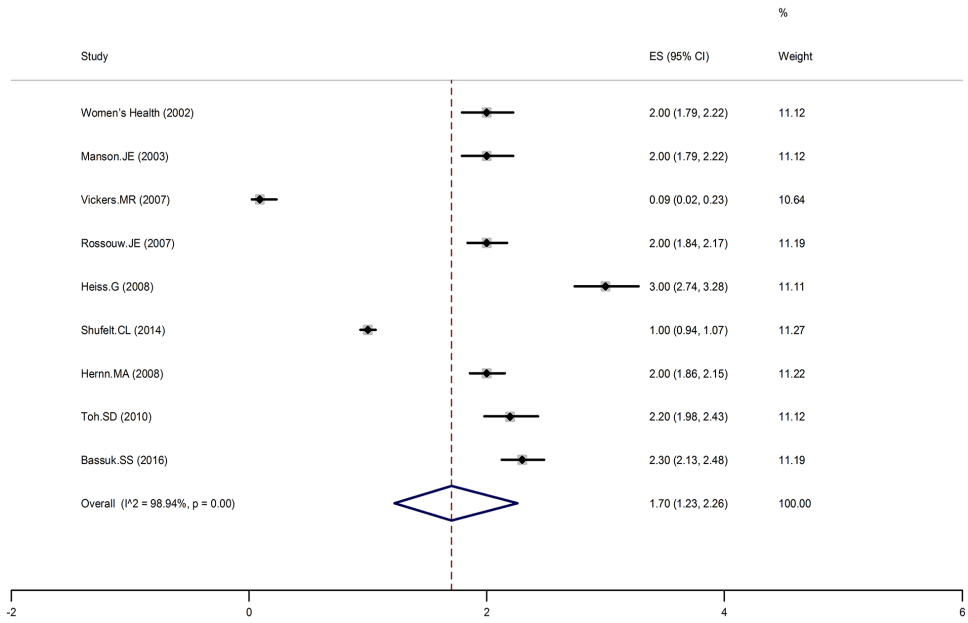

Figure 2. The rate of coronary heart diseases with combination therapy (95% CI, random effect model)

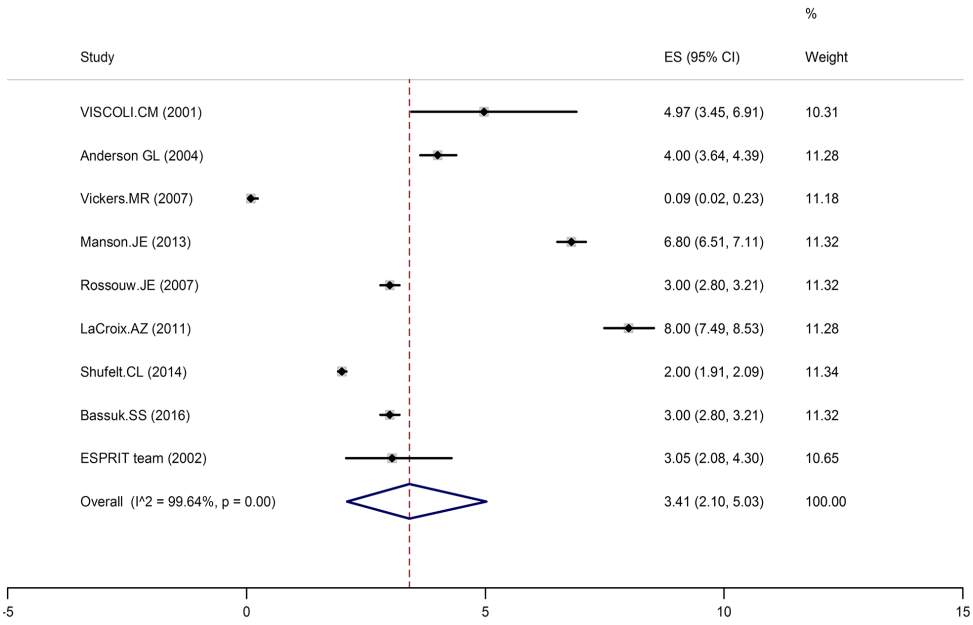

Figure 3. The rate of coronary heart diseases with estrogen treatment (95% CI, random effect model)

hormone therapy does not affect coronary heart disease (CHD), myocardial infarction (MI), cardiac death, revascularization, and cerebrovascular disease. Two other previous meta-analytic studies (18, 48) showed similar results. On the other hand, this study contrasted with that of many prior observational studies in evaluating cardiovascular

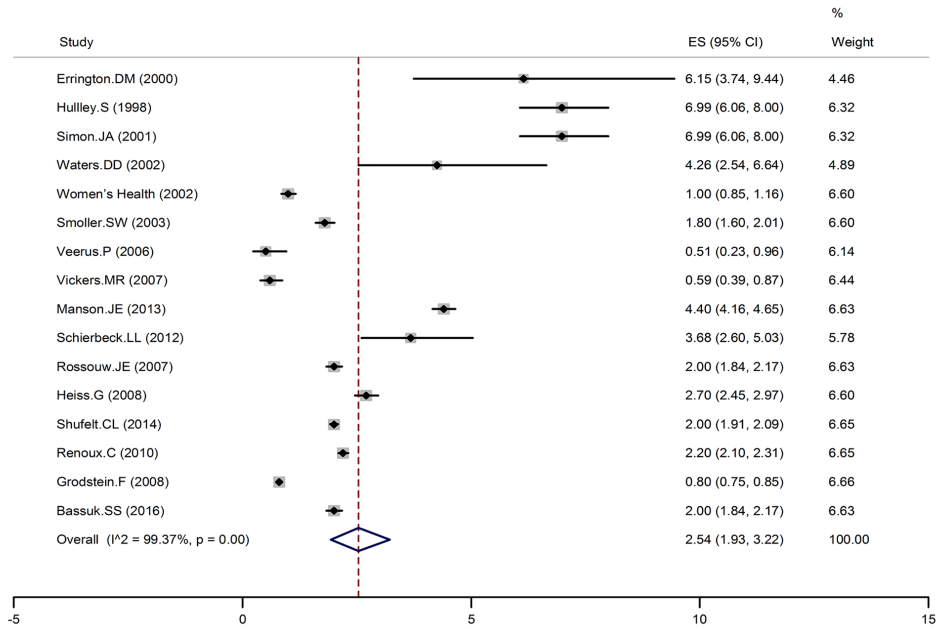

Figure 4. Stroke rate with combination therapy (95% CI, random effect model)

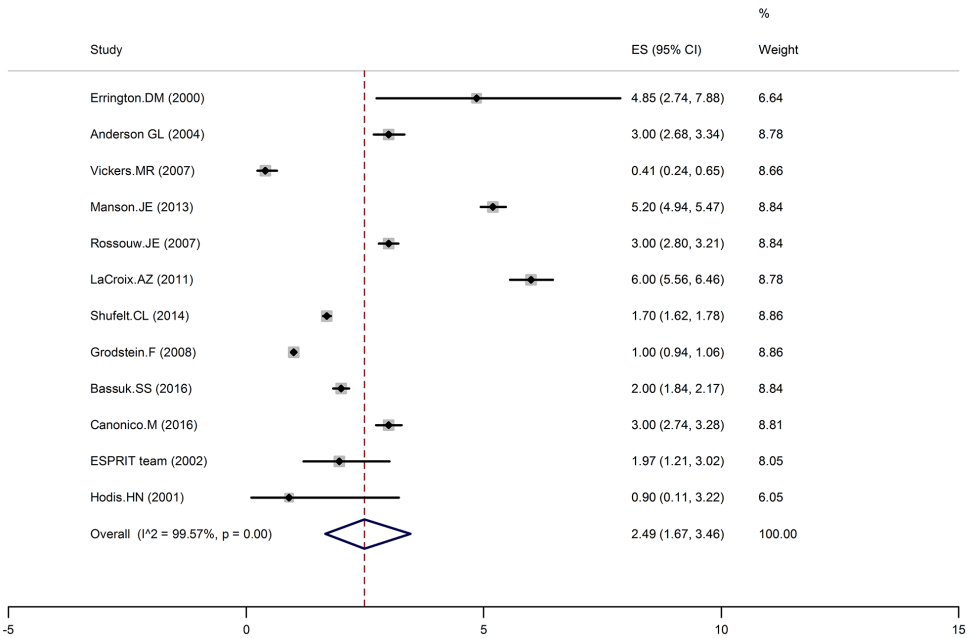

Figure 5. Stroke rate with estrogen treatment (95% CI, random effect model)

events, suggesting that hormone therapy can reduce cardiovascular events (49-52).

Lack of significant difference in the incidence of coronary artery disease in women receiving HTR or placebo could be due to the protective effects of estrogen and progesterone on the lipid profile of postmenopausal women.

Table 2. The Frequency of Reported Events

Event/Intervention	Prevalence
CHD	
Combined	1.7
Estrogen	3.41
Placebo	2.73
MI	
Combined	2.64
Estrogen	2.95
Placebo	2.09
Stroke	
Combined	2.54
Estrogen	2.49
Placebo	2.90
Death	
Combined	1.54
Estrogen	2.80
Placebo	2.25
Revascularization	
Combined	3.26
Estrogen	-
Placebo	4.96
CVD	
Combined	2.78
Estrogen	3.14
Placebo	11.92

Abbreviations: CHD, coronary artery disease; CVD, cerebrovascular disease; MI, myocardial infarction.

Cardiovascular diseases are multifactorial but many studies have shown the association of serum lipid level with these diseases (53). Serum triglyceride level has a strong relationship with atherogenic properties of Low-Density Lipoprotein particles. This relationship may increase Low-Density Lipoprotein atherogenic properties and the risk of coronary artery disease up to three times (54). In an epidemiological study, there was an inverse association between the level of High-Density Lipoprotein and the incidence of atherosclerosis (55). The clearance of chylomicrons and also chylomicron residues is increased with hormone therapy, which can be a protective effect of estrogen against cardiovascular diseases (56). Nevertheless, estrogen has adverse physiological effects such as increased serum triglyceride and Low-Density Lipoprotein level, and also increased inflammatory factors such as C-reactive protein. These adverse effects could reduce estrogen's cardiovascular protective effects (57, 58).

Moreover, this study revealed that the prevalence of coronary artery disease was higher in postmenopausal women who received combined hormone therapy in comparison to those of estrogen therapy alone (Table 2). The reason could be that the estrogen significantly reduces serum Low-Density Lipoprotein and total cholesterol levels while progesterone (MPA) positively moderated blood lipid levels (13, 59).

Remarkably, this review suggested that HRT in comparison to placebo leads to an increase in the incidence of stroke (Table 2). This rise presumably is due to the impact of hormones on coagulation pathways and inflammatory factors. The estrogen has an impact on the synthesis of some coagulation factors such as plasminogen, fibrinogen, and C-reactive protein (60-62). Estrogen increases the sensitivity of brain neurons to ischemic conditions (63), which could increase the stroke rate. There was no significant difference between the relative risk of myocardial infarction, cerebrovascular disease, and cardiovascular mortality of HRT and placebo groups (Table 2). The reason for this may be the fact that despite the positive effects of HRT on the cardiovascular system, coincidently HRT has a negative effect on the cardiovascular system through its effect on coagulation and inflammatory factors. Studies have shown that increasing the amount of coagulation and inflammatory factors (especially C-reactive protein) is responsible for the development of cardiovascular disease (64).

Data analysis based on the mean age as a mediating factor suggested an increase in the incidence of cardiovascular events with increased age. However, this was not an unexpected event considering the impact of higher age on cardiovascular events (65).

Overall, this study showed that HRT could have positive effects on serum lipoprotein levels in postmenopausal women, which is consistent with the results of previous studies (66-68) and this can justify part of the effects of HRT on cardiovascular events. As seen in the 5th paragraph of the discussion, this effect could be small in the case of combined hormone therapy.

5.1. Weaknesses and Strengths

The most important limitations to this study are as follow (1) Different period of tracking the effects of HRT in collected studies that may affect HRT regarding cardiovascular events. (2) Differences between reviewed articles such as dosage, HRT technique, and duration of HRT in postmenopausal women. (3) Based on the intrinsic character of our meta-analysis, our data were derived from the published articles or information provided by the authors, which resulted in our lack of access to the original data and

Table 3. Serum Lipoprotein Profile

Intervention	LDL, mg/dL	HDL, mg/dL	Total Cholesterol, mg/dL	TG, mg/dL
Combined hormone	133.2	53	217.3	160.1
Estrogen	130.8	54.3	217.1	147.2
Placebo	136.6	53.8	217.6	146.9

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.

Table 4. Hormone Replacement Therapy and Cardiovascular Events in Subgroup Analysis

Event/Intervention	Subgroups			
	Mean Age > 65 y	Mean Age < 65 y	Study Population < 10000	Study Population > 10000
CHD				
Combined	19.6	4.9	20.2	2.4
Estrogen	10	8.79	13.1	4.6
Placebo	12.2	8.07	16.9	3.2
MI				
Combined	7.2	2.8	4.4	3.3
Estrogen	4.6	3.71	3.5	4.4
Placebo	7.16	2.19	4.5	2.4
Stroke				
Combined	9.02	4.2	6.4	5.1
Estrogen	10.6	3.5	8.5	4.3
Placebo	7.6	2.1	5.6	2.7
Death				
Combined	5.1	1.6	6.2	2.07
Estrogen	7.7	2.8	6.5	3.6
Placebo	7.5	2.2	7.4	2.2
Revascularization				
Combined	8.45	9.9	10.5	3.3
Estrogen	5	7.5	-	7.5
Placebo	14.4	3	16.3	6
CVD				
Combined	10	8.5	-	-
Estrogen	8	13.5	-	-
Placebo	15	14	-	-

Abbreviations: CHD, coronary artery disease; CVD, cerebrovascular disease; MI, myocardial infarction.

consequently lack of comprehensive analysis of the source data. 4) The articles in this study did not address the socioeconomic status of women. The socioeconomic status of postmenopausal women could affect HRT regarding cardiovascular events (69).

This meta-analysis carried out on high-quality studies. Statistical findings did not show significant heterogeneity between the appraised studies and the similarities were more than the differences. However, small differences existed such as the hormone dosage, the method hormone received, and the racial differences of the subjects, which could affect the results. The important strength point of this article is the use of high-quality studies and comparable features. All studies were homogeneous, with a placebo-control group, and acceptable randomizations.

Despite these limitations, this study suggests that HRT

is not recommended for the prevention of cardiovascular events in postmenopausal women. Menopausal women who have intolerable symptoms may benefit from HRT in relieving menopausal symptoms. HRT could also be useful in preventing osteoporosis and improving their quality of life; however, it increases the risk for certain diseases such as stroke. Hence, the balance between the advantages and disadvantages of HRT should be assessed individually by the physician for each patient.

Footnotes

Conflict of Interests: None declared.

Funding/Support: No funding.

References

1. Rajaeefard A, Mohamadbeygi A, Mohammadsalehi N. [The estimated mean age at menopause in Iranian women: A study Mtanalyz]. *Komesh*. 2011;**13**(1). Persian.
2. Nanbakhsh F, Mohadesi H, Mirabi A, Hagishafieiha M, Bromand F, Bahadori F. [Elderly health effects of education on knowledge, attitude and practice of older women]. *J Fac Tehran Univ Med Sci (Payavard Salamat)*. 2011;**5**(1):47–57. Persian.
3. Rogerio A. *Treatment of the postmenopausal woman*. 2nd ed. 1999. p. 157–8. 581.
4. Bush TL, Barrett-Connor E, Cowan LD, Criqui MH, Wallace RB, Suchindran CM, et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: Results from the Lipid Research Clinics Program Follow-up Study. *Circulation*. 1987;**75**(6):1102–9. doi: 10.1161/01.CIR.75.6.1102. [PubMed: 3568321].
5. Whayne TF Jr, Mukherjee D. Women, the menopause, hormone replacement therapy and coronary heart disease. *Curr Opin Cardiol*. 2015;**30**(4):432–8. doi: 10.1097/HCO.0000000000000157. [PubMed: 25695898].
6. Hickey M, Davis SR, Sturdee DW. Treatment of menopausal symptoms: What shall we do now? *Lancet*. 2005;**366**(9483):409–21. doi: 10.1016/S0140-6736(05)66519-1. [PubMed: 16054942].
7. Bagger YZ, Tanko LB, Alexandersen P, Hansen HB, Mollgaard A, Ravn P, et al. Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: The PERF study. *Bone*. 2004;**34**(4):728–35. doi: 10.1016/j.bone.2003.12.021. [PubMed: 15050905].
8. [No authors listed]. Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet*. 1997;**350**(9084):1047–59. doi: 10.1016/S0140-6736(97)08233-0. [PubMed: 10213546].
9. Gibson CL, Gray LJ, Murphy SP, Bath PM. Estrogens and experimental ischemic stroke: A systematic review. *J Cereb Blood Flow Metab*. 2006;**26**(9):1103–13. doi: 10.1038/sj.jcbfm.9600270. [PubMed: 16437060].
10. Gibson CL, Gray LJ, Bath PM, Murphy SP. Progesterone for the treatment of experimental brain injury; a systematic review. *Brain*. 2008;**131**(Pt 2):318–28. doi: 10.1093/brain/awm183. [PubMed: 17715141].
11. Suzuki S, Brown CM, Wise PM. Mechanisms of neuroprotection by estrogen. *Endocrine*. 2006;**29**(2):209–15. doi: 10.1385/ENDO:29:2:209. [PubMed: 16785597].
12. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: A quantitative assessment of the epidemiologic evidence. *Prev Med*. 1991;**20**(1):47–63. doi: 10.1016/0091-7435(91)90006-P. [PubMed: 1826173].
13. Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med*. 1992;**117**(12):1016–37. doi: 10.7326/0003-4819-117-12-1016. [PubMed: 1443971].
14. Kaplan NM, Burton DR. *Effect of oral contraceptives and postmenopausal hormone therapy on blood pressure*. 2016. Available from: http://www.uptodate.com.
15. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA*. 1998;**280**(7):605–13. doi: 10.1001/jama.280.7.605. [PubMed: 9718051].
16. Herrington DM, Reboussin DM, Brosnihan KB, Sharp PC, Shumaker SA, Snyder TE, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med*. 2000;**343**(8):522–9. doi: 10.1056/NEJM200008243430801. [PubMed: 10954759].
17. Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, Kooperberg C, Baird A, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: The Women's Health Initiative: A randomized trial. *JAMA*. 2003;**289**(20):2673–84. doi: 10.1001/jama.289.20.2673. [PubMed: 12771114].
18. Yang D, Li J, Yuan Z, Liu X. Effect of hormone replacement therapy on cardiovascular outcomes: A meta-analysis of randomized controlled trials. *PLoS One*. 2013;**8**(5). e62329. doi: 10.1371/journal.pone.0062329. [PubMed: 23667467]. [PubMed Central: PMC3648543].
19. Simon JA, Hsia J, Cauley JA, Richards C, Harris F, Fong J, et al. Postmenopausal hormone therapy and risk of stroke: The Heart and Estrogen-progestin Replacement Study (HERS). *Circulation*. 2001;**103**(5):638–42. doi: 10.1161/01.CIR.103.5.638. [PubMed: 11156873].
20. Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA*. 2002;**288**(1):49–57. doi: 10.1001/jama.288.1.49. [PubMed: 12090862].
21. Waters DD, Alderman EL, Hsia J, Howard BV, Cobb FR, Rogers WJ, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: A randomized controlled trial. *JAMA*. 2002;**288**(19):2432–40. doi: 10.1001/jama.288.19.2432. [PubMed: 12435256].
22. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;**288**(3):321–33. doi: 10.1001/jama.288.3.321. [PubMed: 12117397].
23. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med*. 2003;**349**(6):523–34. doi: 10.1056/NEJMoa030808. [PubMed: 12904517].
24. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med*. 2001;**345**(17):1243–9. doi: 10.1056/NEJMoa010534. [PubMed: 11680444].
25. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. *JAMA*. 2004;**291**(14):1701–12. doi: 10.1001/jama.291.14.1701. [PubMed: 15082697].
26. Veerus P, Hovi SL, Fischer K, Rahu M, Hakama M, Hemminki E. Results from the Estonian postmenopausal hormone therapy trial [ISRCTN35338757]. *Maturitas*. 2006;**55**(2):162–73. doi: 10.1016/j.maturitas.2006.01.012. [PubMed: 16504428].

27. Vickers MR, MacLennan AH, Lawton B, Ford D, Martin J, Meredith SK, et al. Main morbidities recorded in the women's international study of long duration oestrogen after menopause (WISDOM): A randomised controlled trial of hormone replacement therapy in postmenopausal women. *BMJ*. 2007;**335**(7613):239. doi: 10.1136/bmj.39266.425069.AD. [PubMed: 17626056]. [PubMed Central: PMC1939792].
28. Harman SM, Black DM, Naftolin F, Brinton EA, Budoff MJ, Cedars MI, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: A randomized trial. *Ann Intern Med*. 2014;**161**(4):249–60. doi: 10.7326/M14-0353. [PubMed: 25069991].
29. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. 2013;**310**(13):1353–68. doi: 10.1001/jama.2013.278040. [PubMed: 24084921]. [PubMed Central: PMC3963523].
30. Hodis HN, Mack WJ, Henderson VW, Shoupe D, Budoff MJ, Hwang-Levine J, et al. Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med*. 2016;**374**(13):1221–31. doi: 10.1056/NEJMoa1505241. [PubMed: 27028912]. [PubMed Central: PMC4921205].
31. Schierbeck LL, Rejnmark L, Tofteng CL, Stilgren L, Eiken P, Mosekilde L, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: Randomised trial. *BMJ*. 2012;**345**. e6409. doi: 10.1136/bmj.e6409. [PubMed: 23048011].
32. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007;**297**(13):1465–77. doi: 10.1001/jama.297.13.1465. [PubMed: 17405972].
33. Manson JE, Allison MA, Rossouw JE, Carr JJ, Langer RD, Hsia J, et al. Estrogen therapy and coronary-artery calcification. *N Engl J Med*. 2007;**356**(25):2591–602. doi: 10.1056/NEJMoa071513. [PubMed: 17582069].
34. Heiss G, Wallace R, Anderson GL, Aragaki A, Beresford SA, Brzyski R, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA*. 2008;**299**(9):1036–45. doi: 10.1001/jama.299.9.1036. [PubMed: 18319414].
35. LaCroix AZ, Chlebowski RT, Manson JE, Aragaki AK, Johnson KC, Martin L, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: A randomized controlled trial. *JAMA*. 2011;**305**(13):1305–14. doi: 10.1001/jama.2011.382. [PubMed: 21467283]. [PubMed Central: PMC3656722].
36. Shufelt CL, Merz CN, Prentice RL, Pettinger MB, Rossouw JE, Aroda VR, et al. Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: Findings from the Women's Health Initiative Observational Study. *Menopause*. 2014;**21**(3):260–6. doi: 10.1097/GME.0b013e31829a64f9. [PubMed: 24045672]. [PubMed Central: PMC3872264].
37. Renoux C, Dell'aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke: A nested case-control study. *BMJ*. 2010;**340**:c2519. doi: 10.1136/bmj.c2519. [PubMed: 20525678].
38. Hernan MA, Alonso A, Logan R, Grodstein F, Michels KB, Willett WC, et al. Observational studies analyzed like randomized experiments: An application to postmenopausal hormone therapy and coronary heart disease. *Epidemiology*. 2008;**19**(6):766–79. doi: 10.1097/EDE.0b013e3181875e61. [PubMed: 18854702]. [PubMed Central: PMC3731075].
39. Toh S, Hernandez-Diaz S, Logan R, Rossouw JE, Hernan MA. Coronary heart disease in postmenopausal recipients of estrogen plus progestin therapy: Does the increased risk ever disappear? A randomized trial. *Ann Intern Med*. 2010;**152**(4):211–7. doi: 10.7326/0003-4819-152-4-201002160-00005. [PubMed: 20157135]. [PubMed Central: PMC2936769].
40. Huang AJ, Sawaya GF, Vittinghoff E, Lin F, Grady D. Hot flushes, coronary heart disease, and hormone therapy in postmenopausal women. *Menopause*. 2009;**16**(4):639–43. doi: 10.1097/gme.0b013e31819c11e4. [PubMed: 19325499]. [PubMed Central: PMC2856618].
41. Grodstein F, Manson JE, Stampfer MJ, Rexrode K. Postmenopausal hormone therapy and stroke: Role of time since menopause and age at initiation of hormone therapy. *Arch Intern Med*. 2008;**168**(8):861–6. doi: 10.1001/archinte.168.8.861. [PubMed: 18443262]. [PubMed Central: PMC4001717].
42. Tannen RL, Weiner MG, Xie D, Barnhart K. Estrogen affects post-menopausal women differently than estrogen plus progestin replacement therapy. *Hum Reprod*. 2007;**22**(6):1769–77. doi: 10.1093/humrep/dem031. [PubMed: 17347166].
43. Bassuk SS, Manson JE. The timing hypothesis: Do coronary risks of menopausal hormone therapy vary by age or time since menopause onset? *Metabolism*. 2016;**65**(5):794–803. doi: 10.1016/j.metabol.2016.01.004. [PubMed: 27085786]. [PubMed Central: PMC4834454].
44. Lokkegaard E, Andreasen AH, Jacobsen RK, Nielsen LH, Agger C, Lidegaard O. Hormone therapy and risk of myocardial infarction: A national register study. *Eur Heart J*. 2008;**29**(21):2660–8. doi: 10.1093/eurheartj/ehn408. [PubMed: 18826989].
45. Canonico M, Carcaillon L, Plu-Bureau G, Oger E, Singh-Manoux A, Tubert-Bitter P, et al. Postmenopausal hormone therapy and risk of stroke: Impact of the route of estrogen administration and type of progestogen. *Stroke*. 2016;**47**(7):1734–41. doi: 10.1161/STROKEAHA.116.013052. [PubMed: 27256671]. [PubMed Central: PMC4927222].
46. Cherry N, Gilmour K, Hannaford P, Heagerty A, Khan MA, Kitchener H, et al. Oestrogen therapy for prevention of reinfarction in postmenopausal women: A randomised placebo controlled trial. *Lancet*. 2002;**360**(9350):2001–8. doi: 10.1016/S0140-6736(02)12001-0. [PubMed: 12504395].
47. Hodis HN, Mack WJ, Lobo RA, Shoupe D, Sevanian A, Mahrer PR, et al. Estrogen in the prevention of atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2001;**135**(11):939–53. doi: 10.7326/0003-4819-135-11-200112040-00005. [PubMed: 11730394].
48. Magliano DJ, Rogers SL, Abramson MJ, Tonkin AM. Hormone therapy and cardiovascular disease: A systematic review and meta-analysis. *BJOG*. 2006;**113**(1):5–14. doi: 10.1111/j.1471-0528.2005.00797.x. [PubMed: 16398764].
49. Arnson Y, Rozanski A, Gransar H, Otaki Y, Doris M, Wang F, et al. Hormone replacement therapy is associated with less coronary atherosclerosis and lower mortality. *J Am Coll Cardiol*. 2017;**69**(11):1408. doi: 10.1016/s0735-1097(17)34797-6.
50. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med*. 2000;**133**(12):933–41. doi: 10.7326/0003-4819-133-12-200012190-00008. [PubMed: 11119394].
51. Finucane FF, Madans JH, Bush TL, Wolf PH, Kleinman JC. Decreased risk of stroke among postmenopausal hormone users. Results from a national cohort. *Arch Intern Med*. 1993;**153**(1):73–9. doi: 10.1001/archinte.1993.00410010097008. [PubMed: 8422201].
52. Sourander L, Rajala T, Raiha I, Makinen J, Erkkola R, Helenius H. Cardiovascular and cancer morbidity and mortality and sudden cardiac death in postmenopausal women on oestrogen replacement therapy (ERT). *Lancet*. 1998;**352**(9145):1965–9. doi: 10.1016/S0140-6736(98)05066-1. [PubMed: 9872245].
53. Schaefer EJ, Genest JJ Jr, Ordovas JM, Salem DN, Wilson PW. Familial lipoprotein disorders and premature coronary artery disease. *Atherosclerosis*. 1994;**108 Suppl**:S41–54. doi: 10.1016/0021-9150(94)90152-X. [PubMed: 7802728].
54. Gofman JW, Delalla O, Glazier F, Freeman NK, Lindgren FT, Nichols AV, et al. The serum lipoprotein transport system in health, metabolic

disorders, atherosclerosis and coronary heart disease. *J Clin Lipidol*. 2007;**1**(2):104–41. doi: 10.1016/j.jacl.2007.03.001. [PubMed: 21291675].
55. Jonas HA, Kronmal RA, Psaty BM, Manolio TA, Meilahn EN, Tell GS, et al. Current estrogen-progestin and estrogen replacement therapy in elderly women: Association with carotid atherosclerosis. CHS Collaborative Research Group. Cardiovascular Health Study. *Ann Epidemiol*. 1996;**6**(4):314–23. doi: 10.1016/S1047-2797(96)00048-8. [PubMed: 8876842].
56. Suk Danik J, Rifai N, Buring JE, Ridker PM. Lipoprotein(a), hormone replacement therapy, and risk of future cardiovascular events. *J Am Coll Cardiol*. 2008;**52**(2):124–31. doi: 10.1016/j.jacc.2008.04.009. [PubMed: 18598891]. [PubMed Central: PMC2958092].
57. Shlipak MG, Simon JA, Vittinghoff E, Lin F, Barrett-Connor E, Knopp RH, et al. Estrogen and progestin, lipoprotein(a), and the risk of recurrent coronary heart disease events after menopause. *JAMA*. 2000;**283**(14):1845–52. doi: 10.1001/jama.283.14.1845. [PubMed: 10770146].
58. Cushman M, Legault C, Barrett-Connor E, Stefanick ML, Kessler C, Judd HL, et al. Effect of postmenopausal hormones on inflammation-sensitive proteins: The Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. *Circulation*. 1999;**100**(7):717–22. doi: 10.1161/01.CIR.100.7.717. [PubMed: 10449693].
59. Akbari-Asbagh F, Mahmudan A. [Comparison of the effect of different HRT (estrogen alone and 2.5 and 5 mg medroxyprogesterone acetate) on blood lipids, fasting blood glucose, and glucose tolerance testing and postmenopausal women at Mirza Kuchak Khan Hospital, 82-81]. *Tehran Uni Med J*. 2005;**63**(9):742–50. Persian.
60. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med*. 1999;**340**(23):1801–11. doi: 10.1056/NEJM199906103402306. [PubMed: 10362825].
61. Nabulsi AA, Folsom AR, White A, Patsch W, Heiss G, Wu KK, et al. Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. The atherosclerosis risk in communities study investigators. *N Engl J Med*. 1993;**328**(15):1069–75. doi: 10.1056/NEJM199304153281501. [PubMed: 8384316].
62. Aune B, Oian P, Omsjo I, Osterud B. Hormone replacement therapy reduces the reactivity of monocytes and platelets in whole blood–a beneficial effect on atherogenesis and thrombus formation? *Am J Obstet Gynecol*. 1995;**173**(6):1816–20. doi: 10.1016/0002-9378(95)90433-6. [PubMed: 8610768].
63. Murphy DD, Cole NB, Greenberger V, Segal M. Estradiol increases dendritic spine density by reducing GABA neurotransmission in hippocampal neurons. *J Neurosci*. 1998;**18**(7):2550–9. doi: 10.1523/JNEUROSCI.18-07-02550.1998. [PubMed: 9502814].
64. Emerging Risk Factors C, Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: An individual participant meta-analysis. *Lancet*. 2010;**375**(9709):132–40. doi: 10.1016/S0140-6736(09)61717-7. [PubMed: 20031199]. [PubMed Central: PMC3162187].
65. Gordon T, Kannel WB, Hjortland MC, McNamara PM. Menopause and coronary heart disease. The Framingham Study. *Ann Intern Med*. 1978;**89**(2):157–61. doi: 10.7326/0003-4819-89-2-157. [PubMed: 677576].
66. Kardos A, Casadei B. Hormone replacement therapy and ischaemic heart disease among postmenopausal women. *J Cardiovasc Risk*. 1999;**6**(2):105–12. doi: 10.1177/204748739900600207. [PubMed: 10353070].
67. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, et al. Helsinki heart study: Primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*. 1987;**317**(20):1237–45. doi: 10.1056/NEJM198711123172001. [PubMed: 3313041].
68. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and recurrent events trial investigators. *N Engl J Med*. 1996;**335**(14):1001–9. doi: 10.1056/NEJM199610033351401. [PubMed: 8801446].
69. Humphrey LL, Chan BK, Sox HC. Postmenopausal hormone replacement therapy and the primary prevention of cardiovascular disease. *Ann Intern Med*. 2002;**137**(4):273–84. doi: 10.7326/0003-4819-137-4-200208200-00012. [PubMed: 12186518].

Table 1. General Characters of Entered Studies

First Author	Sample Size	Year	Mean Age, y	Follow-Up, y	Condition	Interventions	Events
Herrington (16)	309	2000	65.8	3.2	Coronary artery disease	0.625 mg of CEE; 0.625 mg of CEE plus 2.5 mg of MPA	CHD, MI, Stroke, death, Lipid Profile Revascularization
Hulley (15)	2763	1998	66.7	4.1	Coronary artery disease	0.625 mg of conjugated estrogen and 2.5 mg of MPA	CHD, MI, Stroke, death, Lipid Profile Revascularization
Simon (19)	2763	2001	66.7	4.1	Coronary artery disease	0.625 mg of conjugated estrogen and 2.5 mg of MPA	Stroke, Lipid Profile
Grady (20)	2763	2002	66.7	6.8	Coronary artery disease	0.625 mg of conjugated estrogen and 2.5 mg of MPA	CHD, MI, Stroke, death, Lipid Profile Revascularization
Waters (21)	423	2002	65.5	2.8	15% - 75% coronary stenosis	0.625 mg of CEE plus 2.5 mg of MPA	CHD, MI, Stroke, death, Lipid Profile
Rossouw (22)	16608	2002	63.2	5.2	Healthy women	0.625 mg of CEE plus 2.5 mg of MPA	CHD, MI, Stroke, death
Wassertheil-Smoller (17)	16608	2003	63.2	5.6	Healthy women	0.625 mg of CEE plus 2.5 mg of MPA	Stroke, death
Manson (23)	16608	2002	63.2	5.2	Healthy women	0.625 mg of CEE plus 2.5 mg of MPA	CHD,MI, Revascularization
Viscoli (24)	664	2001	71.5	2.8	Recently had an ischemic stroke or transient ischemic attack	1 mg of estradiol-17β	CHD, MI, Stroke, death
Anderson (25)	10739	2004	63.6	6.8	Previous hysterectomy	0.625 mg of CEE	CHD, MI, Stroke, death, CVD
Veerus (26)	1778	2006	58.7	3.4	Healthy women	0.625 mg of CEE plus 2.5 mg of MPA	CHD, MI, Stroke
Vickers (27)	4385	2007	62.8	3.8	Healthy women	0.625 mg of CEE; 0.625 mg of CEE plus 2.5 mg of MPA	CHD, MI, Stroke, death
Harman (28)	727	2014	52.7	4	Healthy women	50 mcg/d of transdermal 17β-estradiol plus 0.45 mg/d of Oral CEE	CHD, MI, Stroke, Lipid Profile
Manson (29)	27374	2013	63.3	5.6	Healthy women	0.625 mg of CEE; 0.625 mg of CEE plus 2.5 mg of MPA	CHD, MI, Stroke, death, CVD
Hodis (30)	643	2016	55.4	5	Healthy women	1 mg of estradiol-17β	CHD,MI, Lipid Profile
Schierbeck (31)	1006	2012	50	16	Healthy women	2 mg 17-β-estradiol plus 1 mg orethisterone acetate	MI, Stroke, Lipid Profile
Rossouw (32)	27347	2007	65	5	Healthy women	0.625 mg of CEE; 0.625 mg of CEE plus 2.5 mg of MPA	CHD, Stroke, death
Manson (33)	1064	2007	55.2	8.7	Healthy women	0.625 mg of CEE	CHD
Heiss (34)	15730	2008	63.3	7.8	Healthy women	0.625 mg of CEE plus 2.5 mg of MPA	CHD, MI, Stroke, death, CVD, Revascularization
Lacroix (35)	10739	2011	64.5	10.7	Previous hysterectomy	0.625 mg of CEE	CHD, MI, Stroke, death, CVD, Revascularization
Shufelt (36)	93676	2014	62.3	10.4	Healthy women	0.625 mg of CEE; 0.625 mg of CEE plus 2.5 mg of MPA	CHD, Stroke, death, CVD
Renoux (37)	75668	2010	70.3	6.68	Healthy women	0.625 mg of CEE plus 2.5 mg of MPA	Stroke
Hernan (38)	34575	2008	60	5.9	Healthy women	0.625 mg of CEE plus 2.5 mg of MPA	CHD
Toh (39)	16608	2010	64.6	5.6	Healthy women	0.625 mg of CEE plus 2.5 mg of MPA	CHD
Huang (40)	2763	2009	66.7	5	Coronary artery disease	0.625 mg of CEE plus 2.5 mg of MPA	CHD

Grodstein (41)	121700	2008	64	4	Healthy women	0.625 mg of CEE; 0.625 mg of CEE plus 2.5 mg of MPA	Stroke
Tannen (42)	29201	2007	63.6	6.8	Previous hysterectomy	0.625 mg of CEE; 0.625 mg of CEE plus 2.5 mg of MPA	MI, Stroke, death
Bassuk (43)	27347	2016	65	7.2	Healthy women	0.625 mg of CEE; 0.625 mg of CEE plus 2.5 mg of MPA	CHD, MI, Stroke, death, CVD, Revascularization
Løkkegaard (44)	698098	2008	60	6	Healthy women	0.625 mg of CEE plus 2.5 mg of MPA	MI
Canonico (45)	15797	2016	56.7	3	20% Stroke	50 μg/d of estrogens	Stroke, Lipid Profile
Cherry (46)	1017	2002	62.6	2	Previous myocardial infarction	2 mg of oestradiol valerate	CHD, MI, Stroke, death
Hodis (47)	222	2001	61.2	2	low-density lipoprotein cholesterol, levels of 3.37 mmol/L or greater	1 mg of estradiol-17β	CHD, MI, Stroke, Lipid Profile

Abbreviations: CEE, combined estrogen hormone therapy; CHD, coronary artery disease; CVD, cerebrovascular disease; MI, myocardial infarction; MPA, medroxyprogesterone acetate.