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Original Research

Estrogen replacement therapy is not a recommended therapy for postmenopausal women with coronary heart disease: a meta-analysis

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Summary

Aim: This study was to investigate the effect of estrogen replacement therapy (ERT) on clinical outcomes for postmenopausal women with established coronary heart disease (CHD). *Materials and Methods:* The authors conducted a meta-analysis using 12 eligible studies. The overall odds ratios (OR) or standardized mean difference (SMD) and their corresponding 95% confidence interval (CI) were calculated. *Results:* For the incidence of adverse events, significant difference was observed in the occurrence rates of CHD death (OR = 1.166, 95% CI: 1.000-1.360, $p = 0.050$) and death of any cause (OR = 1.221, 95% CI: 1.057-1.410, $p = 0.007$) in postmenopausal women with CHD between ERT and placebo groups, whereas there was no significant difference ($p > 0.05$) in the occurrence rates of CHD events, myocardial infarction (MI), revascularization, unstable angina (UA), venous thromboembolic event, stroke/transient ischemic attack, and congestive heart failure between two groups. With respect to the alterations of other clinical outcomes, the SMD for the alteration of TC level was -0.192 (95% CI: -0.346—0.047, $p = 0.015$), and a significant difference was detected between the two groups, whereas there was no significant difference ($p > 0.05$) in the alterations of MLD and TG in patients between the two groups. Additionally, patients treated with ERT had lower LDL and higher HDL levels. *Conclusion:* This meta-analysis suggests that postmenopausal women with CHD receiving ERT are more likely to suffer from CHD death, death of any cause, lower LDL, and higher HDL and TC levels. Therefore, ERT should not be recommended to postmenopausal women with CHD for the secondary prevention of cardiovascular disease (CVD) clinically.

Key words: Estrogen replacement therapy, postmenopausal women with CHD, clinic outcomes, meta-analysis.

Introduction

Cardiovascular disease (CVD) represents a leading cause of morbidity and mortality worldwide, especially among postmenopausal women in western countries [1, 2]. In Europe, there is 22% death of women caused by coronary heart disease (CHD)[2]. For women over 50-years-old, the risk of CVD increases remarkably [3]. A 39% lifetime risk of dying of CVD has been estimated for a 50-year-old woman, and CHD is one of the predominant CVD [4]. Currently there is no definitive therapy to preserve effectively the vascular health of women in modern preventive medicine [2].

Estrogen replacement therapy (ERT), also called postmenopausal hormone therapy and hormone replacement therapy, has been used to relieve menopausal symptoms for a long time [5]. Ovarian hormone deficiency is regarded as related to the development of CVD for women [6]. A randomized controlled trial whose purpose was to explore the long term effect of ERT in recently postmenopausal women on cardiovascular outcomes, demonstrated that the risk of mortality, heart failure, and myocardial infarction (MI) significantly decreased after ten years of ERT, and it was beneficial for recently postmenopausal women [7]. It is believed that ERT is the only primary prevention therapy for women to extend life and to reduce mortality [8].

For postmenopausal women with established CHD, a prospective case-control study found that ERT (therapy of transdermal estrogen or combined topical estrogen/progesterone) might increase the occurrence rate of acute coronary disease by 30–50%, and ERT was not recommended for the purpose of secondary prevention in postmenopausal women with ischemic heart disease [9]. However, several relevant studies showed that hormone therapy had a null effect on reducing risk of CVD in postmenopausal women with established CHD [10-14]. In order to comprehensively evaluate the effect of ERT on clinical outcomes for postmenopausal women with established CHD, the authors performed the current meta-analysis with the incidence of CHD events, CHD death, MI, revascularization, UA, venous thromboembolic event, stroke/transient ischemic attack, congestive heart failure, death of any cause, and the alterations of MLD, TC, TG, HDL, and LDL as indices.

Materials and Methods

The authors conducted a literature retrieval by a computer-aided method involved in databases including PubMed, EMBASE, Web of Science, Springerlink, and ProQuest. The search items were a combination of Medical Subject Headings (MeSH) and terms

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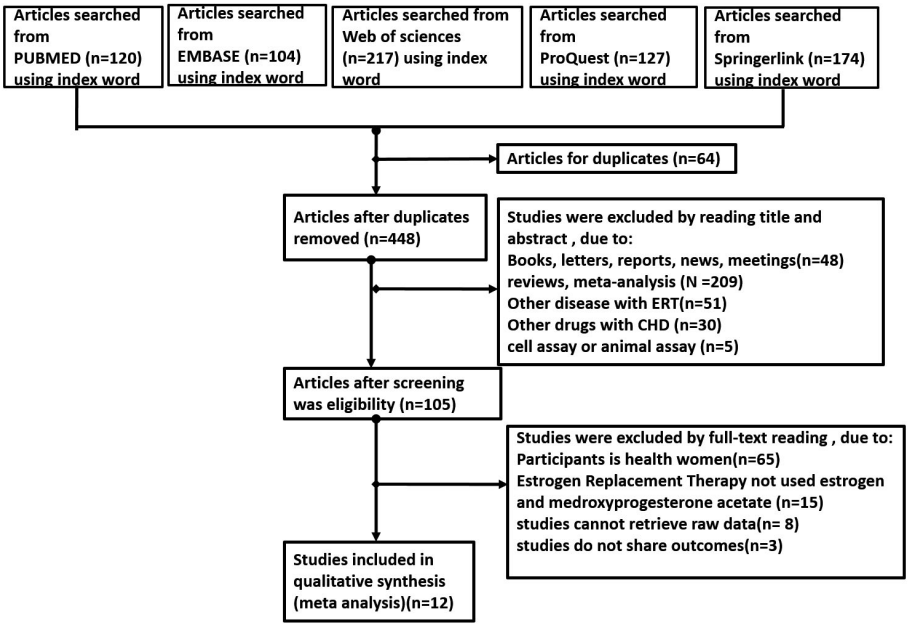

Figure 1. — Flow chart of study selection and specific reasons for exclusion from the meta-analysis.

Table 1. — *Summary of characteristics of studies in the meta-analysis.*

Study	Population	Disease	The usage of ERT before study	Drug(case/control)	Age	Number of patients	Follow-up (year)	Diagnostic method for CHD
David M. Herrington *et al.* [15]	England	Angiographically verified coronary disease	No	CEE plus MPA and placebo	65.8	309	3.2±0.6	Quantitative coronary angiography
David D. Waters *et al.* [16]	USA	At least one 15% to 75% coronary stenosis	≤ 3 months	CEE with or without MPA and placebo	65	423	2.8±0.6	Quantitative coronary angiography
Deborah Grady *et al.* [10]	USA	Experienced CHD	NR	CEE with or without MPA and placebo	67	42068	6.8	Angiography
Howard N. Hodis *et al.* [17]	USA	At least one - coronary-artery lesion	-	CEE with or without MPA and placebo	63.5 ±6.5	1369	3.3	Underwent coronary-artery bypass
Judith Hsia *et al.* [18]	USA	Experienced CHD	-	CEE plus MPA and placebo	67	311	4.1	Angiography
Mark A. Hlatky *et al.* [19]	USA	Documented CHD	-	CEE plus MPA and placebo		2763	-	Documented
Michael G. Shlipak *et al.* [20]	USA	Documented CHD	-	CEE plus MPA and placebo	67	2763	4.1	-
S. C. Clarke *et al.* [9]	England	Have significant ischaemic heart disease	Yes	CEE with or without MPA and no use		255	2.6	Quantitative coronary angiography
Stefania Lamon-Fava *et al.* [21]	USA	Established coronary atherosclerosis	-	CEE with or without MPA and placebo	66	309	3.2	Quantitative coronary angiography
Stefania Lamon-Fava *et al.* [22]	USA	Established coronary atherosclerosis	-	CEE with or without MPA and placebo	65	309	3.2	Quantitative coronary angiography
Stephen Hulley *et al.* [23]	USA	Coronary artery disease	Not used in last 3 months	CEE plus MPA and placebo	67	2763	6.8	-
Stephen Hulley et *al.* [23]	USA	Coronary artery disease	Not used in last 3 months	CEE plus MPA and placebo	67	2321	2.7	-

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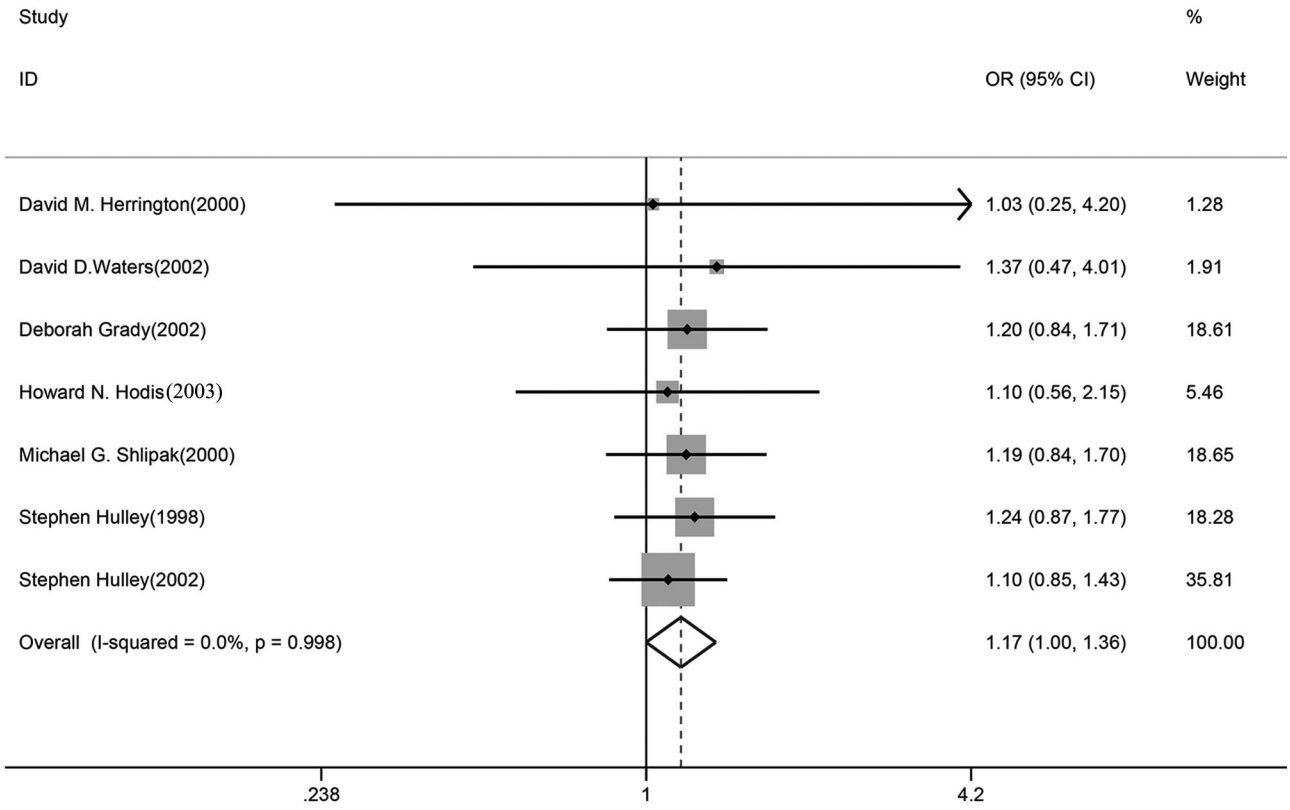

Figure 2. — Forest plot of study evaluating the effect of ERT for postmenopausal women with CHD on the occurrence rate of CHD death.

such as "coronary disease ", " postmenopausal women "," estrogen Replacement therapy", and " hormone therapy". The literature retrieval was completed on October 25, 2015. The authors also manually examined the reference list of retrieved reviews and potential included articles for prevention of any omission of eligible studies.

Literatures satisfy the following inclusion criteria were included in the present meta-analysis: (1) all the participants were postmenopausal women with CHD, (2) patients in case group were treated with conjugated equine estrogen (CEE) with or without medroxyprogesterone acetate (MAP), (3) studies in which the raw data could be retrieved, and (4) full-text studies published in English. The exclusion criteria were as follows: (1) duplicated studies, (2) studies performed on cell assay and animal assay rather than on human, and (3) literature types such as news, books, letters, comments, and meetings.

The eligibility of literature was assessed by two independent reviewers and controversy was solved by consensus. The following information was extracted from incorporated studies: the first author, year of publication, experimental population, details of CHD for participants, the usage of ERT before study, treatment for patients in case and control groups, the age and number of patients, the follow-up period, and diagnostic method for CHD. The authors also collected the information of CHD events, CHD death, MI, revascularization, UA, venous thromboembolic event, stroke/transient ischemic attack, congestive heart failure, death of any cause, and MLD, TC, TG, HDL, and LDL from the included studies.

In the present study, the indices such as the incidence of CHD events, CHD death, MI, Revascularization, UA, venous thromboembolic event, stroke/transient ischemic attack, congestive heart failure, and death of any cause were dichotomous variables, and the alterations of MLD, TC, TG, HDL and LDL were continuous variables. The authors firstly used the Mantel-Haenszel (M-H) fixed-effects model to calculate the I^2 index that was considered as estimation of heterogeneity inter-incorporated studies. Then different models were selected for the calculation of the OR or SMD and 95% CI based on the heterogeneity. When there was no significant heterogeneity ($I^2 < 50\%$), the Mantel-Haenszel (M-H) fixed-effects model was adopted to calculate the OR and its corresponding 95% CI, while the Inverse-Variance (I-V) fixed-effects model was used for the calculation of the SMD with 95% CI. Otherwise, the DerSimonian and Laird (D-L) random-effects model was chosen for both dichotomous and continuous variables. The authors constructed the forest plots using the STATA 12 software to illustrate the relatively quantitative effects of each pooled study addressing the same question. A p value less than 0.05 was considered to be statistically significant difference.

For CHD events, CHD death, MI, revascularization, UA, venous thromboembolic event, stroke/transient ischemic attack, congestive heart failure, death of any cause as dichotomous variables, and an OR > 1 indicated that the occurrence rates of these clinical outcomes in case group (receiving ERT) were higher than those in control group (treated with placebo). With respect to the alterations of MLD, TC, TG, HDL, and LDL, as continuous variables, a SMD > 0 indicated that the alterations of these indices in control group were more obvious than that in the case group.

Table 2. — *Meta-analysis of the effect of ERT on the incidence of adverse events for postmenopausal women with established CHD.*

study	n	OR	Lower limit	Upper limit	*p* (OR)	I^2	*p* (heterogeneity)
CHD events	10919	0.975	0.871	1.093	0.666	0.00%	0.966
CHD death	11568	1.166	1.000	1.360	0.050	0.00%	0.998
MI	14360	0.924	0.816	1.045	0.207	0.00%	0.941
Revascularization	16440	0.898	0.798	1.011	0.076	0.00%	0.952
UA	11174	0.913	0.805	1.037	0.161	0.00%	0.534
Venous thromboembolic event	13354	1.384	0.970	1.976	0.073	74.10%	0.002
Stroke/transient ischemic attack	11005	1.149	0.974	1.356	0.100	0.00%	0.712
Congestive heart failure	7847	1.089	0.919	1.289	0.325	0.00%	0.828
Death of any cause	9159	1.221	1.057	1.410	0.007	14.40%	0.317

n: number of participants.

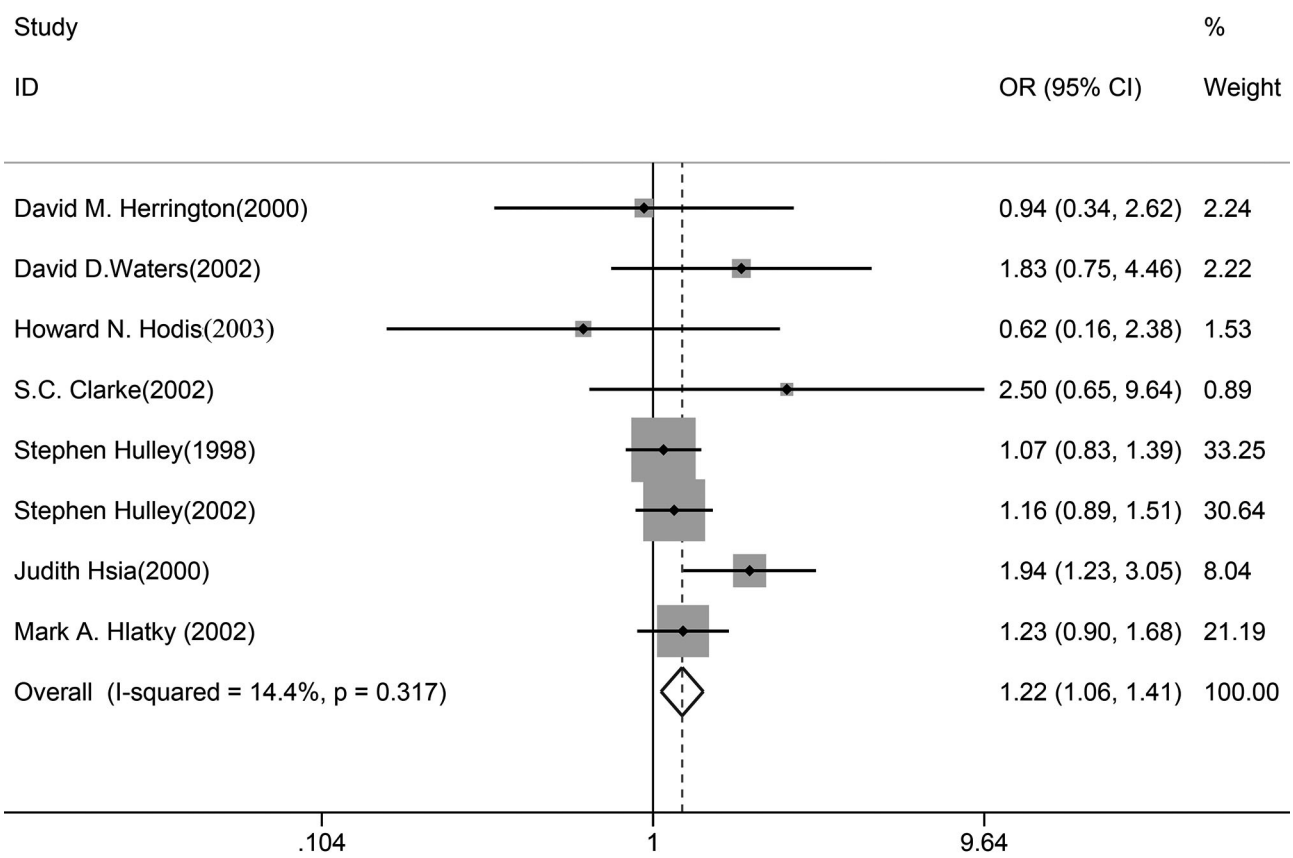

Figure 3. — Forest plot of study assessing the effect of ERT for postmenopausal women with CHD on the occurrence rate of death of any cause.

Results

After the first round search, the authors retrieved 120 articles from PubMed, 104 from EMBASE, 217 from Web of Science, 127 from ProQuest, and 174 from Springerlink. Duplicate literature was removed, leaving 448 articles for further assessment. The authors then scanned the titles and abstracts and eliminated 343 articles. The remaining 105 articles were carefully evaluated based on the above inclusion and exclusion criteria, and finally 12 eligible studies were included for this meta-analysis. The study selection process and reasons for exclusion are displayed in Figure 1. The characteristics of the included studies are exhibited in Table 1 [9, 10, 15-23].

The authors regarded CHD events, CHD death, MI, revascularization, UA, venous thromboembolic event, stroke/transient ischemic attack, congestive heart failure, and death of any cause as adverse events in this meta-analysis. The results are shown in Table 2. The OR for CHD events (OR = 0.975, 95% CI: 0.871-1.093), MI (OR = 0.924, 95% CI: 0.816-1.045), revascularization (OR =

Table 3. — *Meta-analysis of the effect of ERT on the alterations of other clinical outcomes for postmenopausal women with established CHD.*

Study	n	OR	Lower limit	Upper limit	*p* (SMD)	I^2	*p* (heterogeneity)
MLD	888	-0.163	-0.444	0.119	0.257	75.80%	0.006
TC	697	-0.192	-0.346	-0.047	0.015	0.00%	0.657
TG	732	-0.126	-0.404	0.152	0.374	69.50%	0.038

n: number of participants.

Table 4. — *LDL and HDL levels between participants in the case and control groups.*

Factor	Study	Case group			Control group			t	*p*
		n	Mean	SD	n	Mean	SD		
Change of HDL level	Howard N. Hodis *et al.* [17]	150	10.72	11.52	76	5.7	8.5	3.36	0.0009
	Stefania Lamon-Fava *et al.* [21]	168	7.61	1.91	88	2.2	0.7	25.66	<0.0001
	Stefania Lamon-fava *et al.* [22]	164	6.93	8.61	86	1.36	5.84	5.38	<0.0001
	S.C. Clarke *et al.* [9]	134	0.74	0.36	121	0.92	0.38	3.88	0.0001
	Stephen Hulley *et al.* [23]	1380	8.39	0.74	1383	-1.97	0.47	439.35	<0.0001
Change of LDL level	Howard N. Hodis *et al.* [17]	150	-21.31	14.03	76	-14.9	19.8	2.81	0.005
	Stefania Lamon-Fava *et al.* [22]	164	-17.5	39.81	86	2.06	28.44	4.04	<0.0001
	S.C. Clarke *et al.* [9]	134	-1.18	1.19	121	-1.44	1.46	1.56	0.11899

SD: standard deviation; n: number of participants.

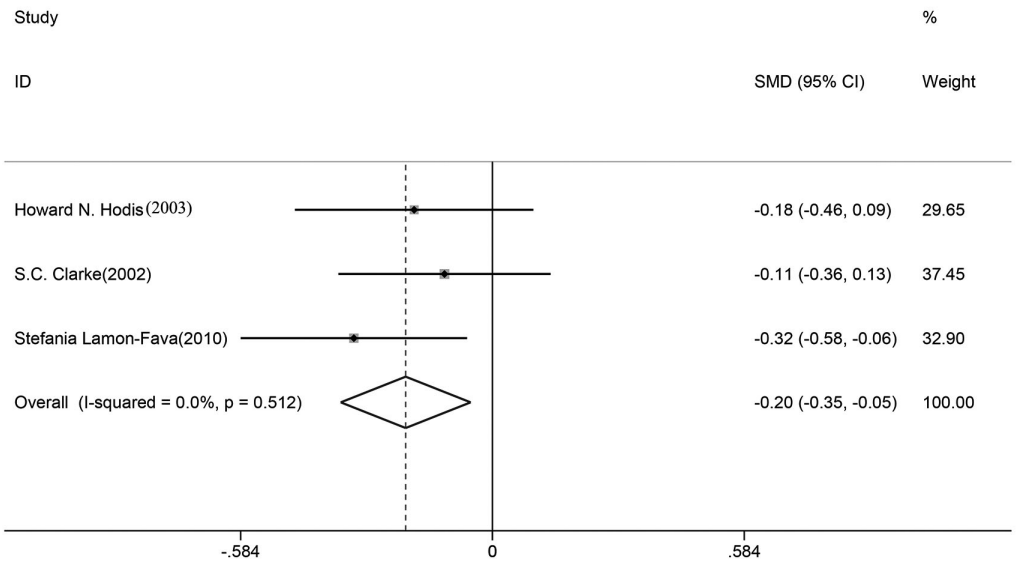

Figure 4. — Forest plot of study estimating the effect of ERT for postmenopausal women with CHD on the alteration of TC level.

0.898, 95% CI: 0.798-1.011), and UA (OR = 0.913, 95% CI: 0.805-1.037) was lower than 1, and the *P* values were higher than 0.05, which suggested that no significant difference in the occurrence rates of CHD events, MI, revascularization, and UA were observed for postmenopausal women with established CHD between ERT and placebo treatment. Although the OR for venous thromboembolic event (OR = 1.384, 95% CI: 0.970-1.976), stroke/transient ischemic attack (OR = 1.149, 95% CI: 0.974-1.356), and congestive heart failure (OR = 1.089, 95% CI: 0.919-1.289) was higher than 1, the corresponding *p* values of were higher than 0.05, implying that there was no significant difference in the occurrence rates of these adverse events between patients treated with ERT and placebo.

As for the index of CHD death, there were seven eligible studies pooled for the analysis, and the results are displayed in Table 2.The fixed-effects model was applied for the calculation of OR and 95% CI due to the small heterogeneity (I^2 = 0.00%). The *p* value = 0.050 and the OR was higher than 1 (OR = 1.166,95% CI: 1.000-1.360, Figure 2), which suggested that the occurrence rate of CHD death in patients treated with ERT was higher than that in patients treated with placebo. With regards to the death of any cause, eight included studies were incorporated to conduct the analysis, the results are shown in Table 2. Since there was no significant heterogeneity (I^2 = 14.40%), the fixed-effects model was adopted to calculate the OR and 95% CI. The OR was higher than 1 (OR = 1.221, 95% CI: 1.057-1.410, Figure

3), and the p was lower than 0.05 ($p = 0.007$), indicating that significant difference in the occurrence rate of death of any cause was detected between patients treated with ERT and placebo.

For the alterations of MLD and TG, considering the large heterogeneity ($I^2 > 50\%$), the random-effects model was chosen to calculate the SMD and 95% CI. The SMDs for both indices were less than 0 (MLD: SMD = -0.163, 95% CI: -0.444-0.119; TG: SMD = -0.126, 95% CI: -0.404-0.152), and the p values were higher than 0.05, implying that there was no significant difference in the alterations of MLD and TG for postmenopausal women with established CHD between the two treatments. In terms of the alteration of TC, the fixed-effects model was used to calculate the SMD and 95% CI for no heterogeneity existed ($I^2 = 0.00\%$). The SMD was -0.192 with 95% CI ranged from -0.346 to -0.047 ($p = 0.015$, Figure 4), which demonstrated that the alteration of TC level in patients treated with ERT was smaller than that in patients treated with placebo, and there was more reduction of TC level in patients of placebo group.

With respect to the alterations of HDL and LDL levels, the relevant studies were not suitable for incorporation and corresponding meta-analysis could not be performed due to the extremely large heterogeneity ($I^2 > 99\%$). So the authors collected and extracted the useful information of the alterations of HDL and LDL levels from the eligible studies as described in Table 4 [9, 17, 21-23], and the alteration of level was calculated by the value of endpoint minus the baseline level. The authors generalized from the five eligible studies which were related to the alteration of HDL level that the elevation of HDL level after treatment in the case group (ERT) was significantly larger than that in the placebo group. For the alteration of LDL level, although one of the three eligible studies exhibited no significant difference, the authors still deduced from the specific alteration of the three relevant studies that the reduction of LDL level after treatment in case group was significantly larger than that in control group.

Discussion

In this study, the authors performed the current meta-analysis to comprehensively evaluate the effect of ERT for postmenopausal women with established CHD on clinical outcomes including the occurrence of CHD events, CHD death, MI, revascularization, UA, venous thromboembolic event, stroke/transient ischemic attack, congestive heart failure and death of any cause, and the alterations of MLD, TC, TG, HDL, and LDL. The results show that compared to patients treated with placebo, the occurrence rates of CHD death and death of any cause in patients treated with ERT are elevated after treatment, and more CHD deaths and death of any cause occur for patients treated with ERT, while the ERT has a null effect on the occurrence of CHD events, MI, revascularization, UA, venous thromboembolic event, stroke/transient ischemic attack, and congestive heart failure. As for the alterations of other clinical outcomes, postmenopausal women with established CHD who receive ERT have lower LDL levels and higher HDL levels after treatment than those treated with placebo, and the reduction of TC level in ERT group is smaller than that in placebo group, while the ERT cannot significantly affect the alterations of MLD and TG. Hence the authors believe that the ERT is contraindicated for the secondary prevention of cardiovascular disease for postmenopausal women with established CHD.

Nowadays, regardless of race and ethnicity, the heart disease becomes the first threat of life for women [25]. For adults, the alterations of metabolism, hormone and hemostatic pathway may lead to the development of coronary heart disease [26]. Women usually take in excessive fat and carbohydrates, lack of regular exercise, and have insufficient rest time, which may cause overweight, diabetes, and dyslipidemia [25]. Moreover, more and more women tend to smoke, which together with diabetes is predictive of coronary disease for both men and women, yet, the risk of coronary disease for women is two to four-fold greater than that in men [25]. Across-sectional study reported that compared with premenopausal women, there was an increase in intima-media thickness for postmenopausal women, which led to higher plasminogen activator inhibitor-1 (PAI-1) levels that caused a decrease in fibrinolytic activity for postmenopausal women, thus, a higher risk of coronary disease for postmenopausal women [3].

Estrogen receptors distribute widely among different organs and systems, so estrogens can play important roles in multiple biological processes and pathways, which makes it difficult to estimate the overall benefits or risks of ERT on the cardiovascular system [27]. A randomized controlled trial covered 16,608 postmenopausal women from Women's Health Initiative (WHI) observed that the incidence of vascular and thromboembolic events increased after ERT treatment, especially within the first two years of ERT, and concluded that ERT should not be prescribed for the initiated or continued for primary prevention of CHD [28]. However, the study only enrolled healthy postmenopausal women, which results in its conclusion not being popularized. So the authors selected postmenopausal women with established CHD as their subjects and found that patients receiving ERT are more likely to experience CHD death, death of any cause, lower LDL levels, and higher HDL and TC levels.

The chronically elevated cholesterol levels are directly related with the incidence of CHD, and the reduced TC is thought to be the gold standard for preventative cardiovascular medicine [29]. It has been reported that the CHD risk of individuals with elevated TC levels is twice as high than that of those with optimal levels [30].HDL, which is an important element to reverse the cholesterol transport from

peripheral tissues back to the liver for recycling and disposal, has anti-atherogenic property, and low HDL-cholesterol (HDL-C) level is associated with the development of CHD [31]. The high LDL-cholesterol (LDL-C) level, representing surplus lipids in blood and indicates a high risk of cardiovascular complications [29]. A meta-analysis of 170,000 subjects from 26 randomized trials observed that participants with reduced LDL-C levels had lower incidence of heart attacks and ischemic strokes [32]. Although the present study show that for postmenopausal women with established CHD, when treated with ERT, the patients have lower LDL and higher HDL levels, which are favorable markers in clinic, the TC levels and the occurrence rates of CHD death and death of any cause increase significantly. Therefore ERT should not be recommended to postmenopausal women with established CHD for the secondary prevention of CVD.

The current study is the first meta-analysis to evaluate the effect of ERT on clinical outcomes for postmenopausal women with established CHD. However, there is some limitations in this study. Firstly, all the eligible studies were conducted on participants from England and USA, so the results should be interpreted with caution. Secondly, though the therapy for patients in case group was ERT, some patients were treated with CEE and ERT, and others were treated with CEE alone. With more relevant studies available, subgroup analysis stratified by whether ERT was added would be performed. Additionally, the unpublished articles were not considered in this study.

Conclusion

The current meta-analysis suggests that for postmenopausal women with established CHD who received ERT, have higher occurrence rates of CHD death and death of any cause, lower LDL levels, and higher HDL and TC levels than those who received placebo, and it is inappropriate to recommend ERT to postmenopausal women with established CHD for the secondary prevention of CVD clinically.

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