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Association between hormone replacement therapy and subsequent arterial and venous vascular events: a meta-analysis

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Aims Randomized controlled trials (RCTs) have shown that the risk of stroke and venous thromboembolism (VTE) is increased with hormone replacement therapy (HRT); the effect on coronary heart disease (CHD) remains unclear.

Methods and results RCTs of HRT were identified. Event rates for cerebrovascular disease [stroke, TIA (transient ischaemic attack)], CHD (myocardial infarction, unstable angina, sudden cardiac death), and VTE (pulmonary embolism, deep vein thrombosis) were analysed. Sensitivity analyses were performed by type of HRT (mono vs. dual) and subject age. 31 trials (44 113 subjects) were identified. HRT was associated with increases in stroke (odds ratio, OR, 1.32, 95% confidence intervals, CI, 1.14–1.53) and VTE (OR 2.05, 95% CI 1.44–2.92). In contrast, CHD events were not increased (OR 1.02, 95% CI 0.90–1.11). Ordinal analyses confirmed that stroke severity was increased with HRT (OR 1.31, 95% CI 1.12–1.54). Although most trials included older subjects, age did not significantly affect risk. The addition of progesterone to oestrogen doubled the risk of VTE.

Conclusion HRT is associated with an increased risk of stroke, stroke severity, and VTE, but not of CHD events. Although most trials studied older patients, increased risk was not related to age. Combined HRT increases the risk of VTE compared with oestrogen monotherapy.

Keywords Hormone replacement therapy • Myocardial infarction • Randomized controlled trial • Stroke • Venous thromboembolism

Introduction

Hormone replacement therapy (HRT), which involves giving sex steroid hormones in the form of an oestrogen, with or without progesterone, is regularly used in the treatment of menopausal symptoms.[1] It is also used in women with premature ovarian failure, and has also been advocated for the prevention of osteoporosis since it reduces fracture risk.[2] In observational studies, HRT was reported to reduce the risk of arterial vascular events[3,4] and this led to trials investigating whether HRT could prevent stroke and coronary heart disease (CHD) events.

Unfortunately, adverse effects of HRT have been proposed, including a possible increased risk of breast cancer,[5] whilst there is debate over whether the benefits of protecting bone density may be lost once treatment is discontinued.[6] Furthermore, HRT has been shown, in meta-analyses, to increase the risk of stroke[7] and venous thromboembolic disease [including both pulmonary embolism (PE) and deep vein thrombosis (DVT)].[8,9] However, the effects of HRT on CHD remains unclear[10] although the possibility of benefit in younger women (age <60 years) has been suggested.[11,12]

Both oestrogen and progesterone have shown cytoprotective properties in laboratory studies[13–15] suggesting that they might alter the severity as well as frequency of vascular events. Conversion of binary vascular events (e.g. stroke/no stroke) into an ordinal scale (e.g. fatal stroke/non-fatal stroke/no stroke) allows the effect

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of interventions on severity to be assessed.[16] This is of practical clinical value as severity is clearly relevant; it is preferable to have a non-fatal event than a fatal one, and severity impacts on quality of life, especially with respect to stroke.[17]

In parallel, there are no randomized data comparing the relative effects of the addition of progesterone with oestrogen (dual-HRT) vs. oestrogen monotherapy. This reflects that trials have chosen to use dual or monotherapy depending on the presence or absence of the uterus. However, it is possible to assess the additive effects of progesterone on thrombotic event rates using indirect comparison of existing trial data.[18]

We have reviewed systematically all trials of HRT assessing effects on arterial and venous vascular events including cerebrovascular events, CHD events, and venous thromboembolism (VTE); analyses assessed both the frequency and severity of events, and examined the effect of progesterone on the risk of thrombotic events.

Methods

Selection

Completed and published non-confounded randomized controlled trials (RCTs) of HRT vs. no HRT (open or placebo-controlled) in women were included. Trials had to report event rates for one or more of cerebrovascular disease (CVD), CHD or VTE. Trials were included if these events were primary outcomes or if it was possible to accurately ascertain event rates from reported adverse events.

Searching

Potential trials were identified from searches of The Cochrane Library, Pubmed, Embase, Medline (to Jan 2008), and previous reviews[7,11,19–22] using combinations of the search terms 'HRT', 'hormone replacement therapy', 'clinical trial', 'vascular', 'cerebrovascular disease', 'CVD', 'stroke', 'coronary heart disease', 'CHD', 'ischaemic heart disease', 'IHD', 'venous thromboemb*', 'deep vein thrombosis', 'DVT', 'pulmonary embolism', 'PE'. Abstracts were reviewed to determine if the study was an eligible controlled trial. The papers were obtained for suitable studies and assessed to determine whether vascular events were adequately reported. Further studies were identified from reference lists from identified articles. No unpublished trials were included. Non-English language publications were excluded.

Quality assessment

Studies were assessed for quality in five areas: method of randomization (such as computer randomization, randomization lists, etc.), blinding, reporting of withdrawals, generation of random numbers, and concealment of allocation. Trials scored one point for each area addressed, therefore receiving a score between 0 and 5, with 5 reflecting the highest level of quality.[23]

Data abstraction

All data were extracted in duplicate, independently by two researchers (L.J.G. and G.M.S.). Disparities were resolved by P.M.W.B.

Study characteristics

Information on trial size, treatment regimen (oestrogen with or without progesterone, and type), length of follow-up, and outcome/adverse events were recorded. Vascular outcome events were counted (identified as adverse events in some trials), ideally by intention-to-treat, including CVD [stroke, TIA (transient ischaemic attack)], CHD [myocardial infarction (MI), sudden cardiac death, unstable angina] and venous thromboembolic disease (DVT, PE, cerebral venous thrombosis). Coronary interventions such as angioplasty were not counted in CHD events as these are open to bias.[24] Information on trials of raloxifene, a selective oestrogen receptor modulator, was collected, but this was only included in the raloxifene specific sensitivity analysis (described later) and not in either the dichotomous or ordinal analyses.

Each outcome event (e.g. stroke, TIA, MI, etc.) was counted separately and as total outcomes under the pooled headings CVD, CHD and VTE as mentioned earlier. Trials which explicitly stated that no events occurred were included in the total number of patients; this will have reduced the proportion of subjects have an event, but will not have altered the odds ratios (OR) and 95% confidence intervals (CI). Where sufficient information was given, events were further categorized by severity (described later). If data were taken from lists of adverse events rather than tabulations of outcomes, the trial was only included if it could be determined that adverse events had been reported for each treatment group. Where it was possible to ascertain that more than one event of the same category had occurred in a single subject, only one event was counted (the most severe event, i.e. fatal rather than non-fatal stroke). Since it was not usually possible to tell which event occurred first, the most severe was chosen. DVT and PE were counted as separate events but the VTE total represents the most severe event in a single patient.

Quantitative data synthesis

The effect of HRT on dichotomous outcomes was assessed using the OR calculated using a random effects model since the trials were expected to be heterogeneous in their design, patient populations, and interventions.

Pre-specified sensitivity analyses were defined to examine any heterogeneity in trial design, including age group (<60, ≥ 60 years), type of HRT (mono/unopposed oestrogen, dual/opposed), type of oestrogen (oestradiol, conjugated equine oestrogen, CEE, all trials), type of oestrogen in monotherapy trials alone, phase of prevention (primary, secondary), method of administration (oral vs. transdermal), length of follow-up (≤ 3 years, >3 years), quality ($<5/5$, 5/5 only), and smaller vs. larger trials (>3000, <3000 subjects). Trials of raloxifene were only included in the sensitivity analysis assessing the effect of raloxifene. These analyses were carried out by performing separate meta-analyses for each of the specified subgroups to determine an OR for CVD, CHD, and VTE. Subgroups differed if the 95% CI around the ORs did not overlap.

In order to analyse the effect of HRT on outcome severity, outcomes were recoded in an ordered categorical manner where appropriate data were published:[25] In order to be suitable for this analysis, trials needed to provide data on the outcome of events, e.g. fatal vs. non-fatal events or TIA vs. stroke: three-level stroke (fatal stroke/non-fatal stroke/no stroke); four-level CVD (fatal stroke/non-fatal stroke/TIA/no stroke); three-level CHD (fatal MI/non-fatal MI/no MI); four-level CHD (fatal MI/non-fatal MI/unstable angina/no MI) and three-level PE (fatal PE/non-fatal PE/no PE). Insufficient data were available to do this for DVT and VTE. These ordinal outcomes were assessed using ordinal logistic regression with trial as a covariate.

As there are not randomized data directly comparing dual- and mono-HRT, an indirect comparison was performed, using the method described by Song *et al.*[18] The relative effects for dual- and mono-HRT for each outcome (CVD, CHD, and VTE), were measured by calculating ORs and 95% CI. The indirect comparison (the effect of progesterone in addition to oestrogen) was calculated by adjusting these by the common contribution of oestrogen.[18]

Statistical heterogeneity was examined using Higgin's and Thompson's[26] I^2-test. Publication bias was examined using Egger's test.[27] Data were analysed using Stata (version 8) with weighting for size of trial.

Results

Thirty one trials (44 113 patients) using progesterone and/or oestrogen, and four trials of raloxifene (17 699 patients) were identified (see Supplementary material online, *Table S1*, *Figure 1*), these ranging in size from 50 to 16 608 patients (median 222). The trials comprised 22 in which vascular prevention was primary, 10 in patients with prior CHD, two in patients with previous stroke or TIA, and one in patients with VTE. The average age of the patients varied between 47 and 75 (median 62.7). Mono-HRT (oestrogen alone) was studied in seven trials, with various combinations of oestrogen and progesterone studied in the others. The dose of oestrogen varied (see Supplementary material online, *Table S1*), e.g. CEE, 0.3–2.5 mg with the most commonly used dose 0.625 mg, oestradiol, transdermal 0.05 mg, oral 1–2.5 mg. Some trials used more than one dose. Follow-up varied between 16 weeks and 6.8 years (median 2 years). CVD was reported in 29 studies, CHD in 27 and VTE events in 25. One hundred and forty one studies were excluded (*Figure 1*), as they were either not randomized; because they contained inadequate data on thrombotic events; were trials of men or included both men and women and did not present data separately; or because they were confounded (i.e. the control group received an active treatment not received by the HRT group).[28]

Data quality

The RCTs varied in their quality score[23] from 2/5 to 5/5 (median 4/5). It was possible to ascertain numbers of subjects with events rather than absolute event rate (which may include multiple events in one subject) in 27 trials (3049 confirmed subjects with events out of 4883 total events analysed). There was no evidence for publication bias for CVD as an outcome (Egger's test,[27] $P = 0.27$), or CHD (Egger's test, $P = 0.50$) but there was evidence of publication bias for VTE (Egger's test, $P = 0.01$). Funnel and Forrest plots are shown in *Figures 2* and *3*.

Quantitative data synthesis

Table 1 shows the results for all outcomes. The control event rate is given to provide information on the background risk of each event; the changes in risk associated with treatment are therefore quantifiable. HRT increased the odds of having any CVD event by 24% (*Table 1*, *Figure 3A*), and stroke by a third. Non-fatal stroke was increased by 28%; both TIA and fatal stroke showed trends to increased odds of having an event with HRT although the power of the TIA was limited owing to the limited number of events (*Table 1*). No relationship was seen between HRT and CHD events, including MI (*Figure 3B*). Those taking HRT had a two-fold increase in VTE (*Figure 3C*), this including increases in DVT (97%) and PE (74%). Taking all outcomes together in a single analysis, HRT significantly increases a person's odds of having any thrombotic event by 23%. No statistical heterogeneity was found for any outcome (*Table 1*).

Sensitivity analyses

Sensitivity analyses were performed for pre-specified subgroups for CVD, CHD, and VTE (*Figure 4*). The OR for VTE differed between monotherapy (OR 1.21, 95% CI 0.92–1.59) vs. dual therapy (OR 2.45, 95% CI 1.91–3.16) such that the 95% CI did not overlap. There were no other differences for subgroups

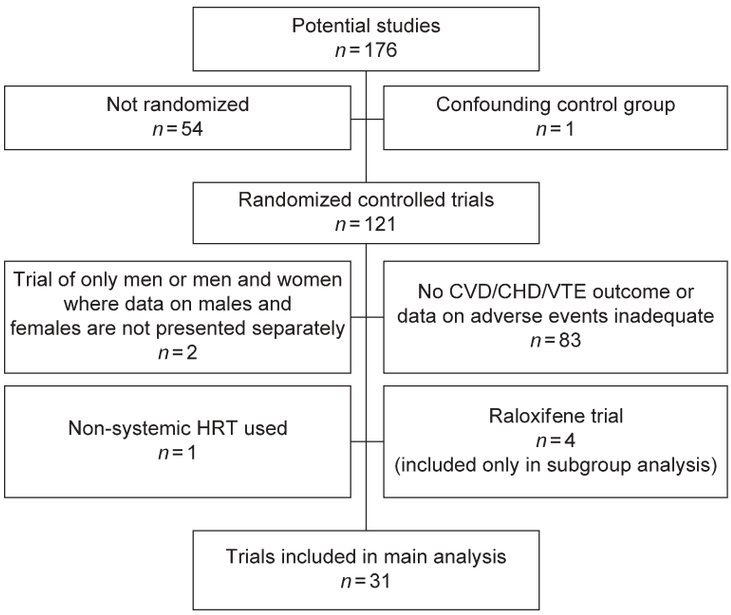


Figure 1 Flowchart for inclusion and exclusion of trials of hormone replacement therapy.

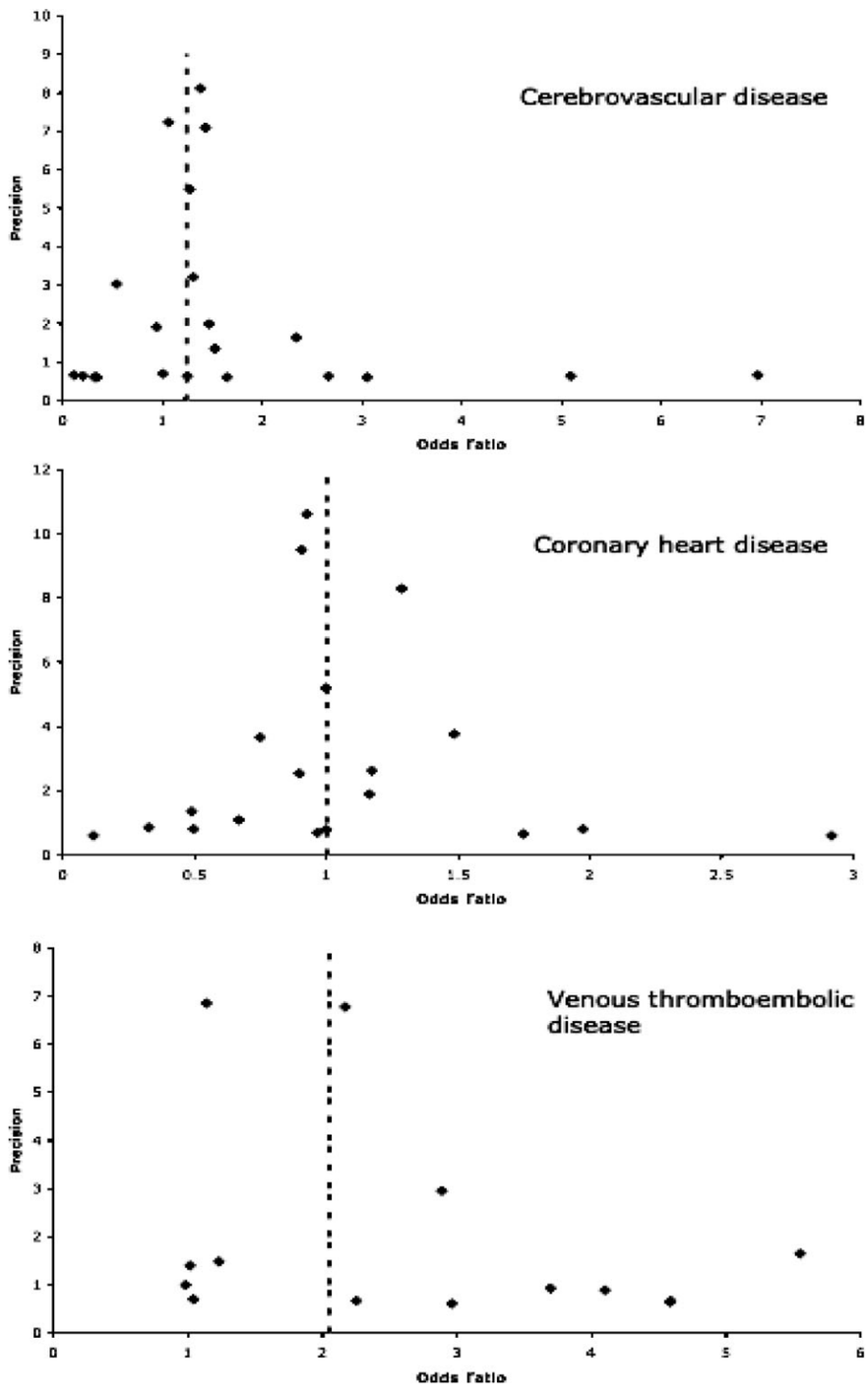


Figure 2 Funnel plots assessing publication bias showing the distribution of odds ratios for trials of cerebrovascular disease, coronary heart disease and venous thromboembolic disease.

including average age <60 years (nine trials) vs. age ≥60 years (16 trials), examining primary vs. secondary prevention, mono vs. dual-HRT (CVD and CHD only), CEE vs. oestradiol (examined in all trials and in oestrogen monotherapy trials), shorter vs. longer follow-up, and high vs. lower quality and larger vs. smaller trials for CVD, CHD, and VTE.

Severity of events

When assessing ordered categorical data, a statistically significant result was seen for stroke severity assessed as fatal stroke, non-fatal stroke, and no stroke (*Table 2*). The OR of 1.31 signifies that HRT treatment is associated with a shift to increased stroke severity. Ordinal regression requires the assumption of 'proportionality of odds' to be adhered to and this was present in all of the trials with more than two levels of data (likelihood ratio test). Non-significant trends to increased severity were seen for stroke-TIA assessed at four levels, and three-level PE; both of these assessments suffered from limited published data on event severity thereby restricting the power of these analyses. No significant difference was seen for three-level or four-level CHD, and no data were available for DVT, and VTE.

Indirect comparison of dual- and mono-hormone replacement therapy

Seventeen trials that examined combined oestrogen and progesterone therapy and seven trials that examined oestrogen monotherapy (see Supplementary material online, *Table S1*) were included in this indirect analysis. The remaining trials each used both combined therapy, usually in non-hysterectomized women, and oestrogen monotherapy in hysterectomized women. Only two of these trials report separate findings for the two groups and are therefore included in this indirect comparison in addition to the other trials.[29,30] The results from the indirect comparison of oestrogen vs. oestrogen plus progesterone are given in *Table 3*. The addition of progesterone to oestrogen doubles the odds of VTE but has no effect on CVD or CHD. These findings are supported by the subgroup sensitivity analysis of oestrogen monotherapy vs. combined HRT (*Figure 3*).

Discussion

This systematic review extends the findings of previous trials and meta-analyses of HRT with the additional of ordinal regression analysis to assess effect of HRT on severity and an indirect analysis to examine the contribution of progesterone on top of oestrogen to vascular risk. It also includes the most recent study, the 'Women's International Study of Long Duration Oestrogen after the Menopause' (WISDOM) trial.[29] In essence, HRT is associated

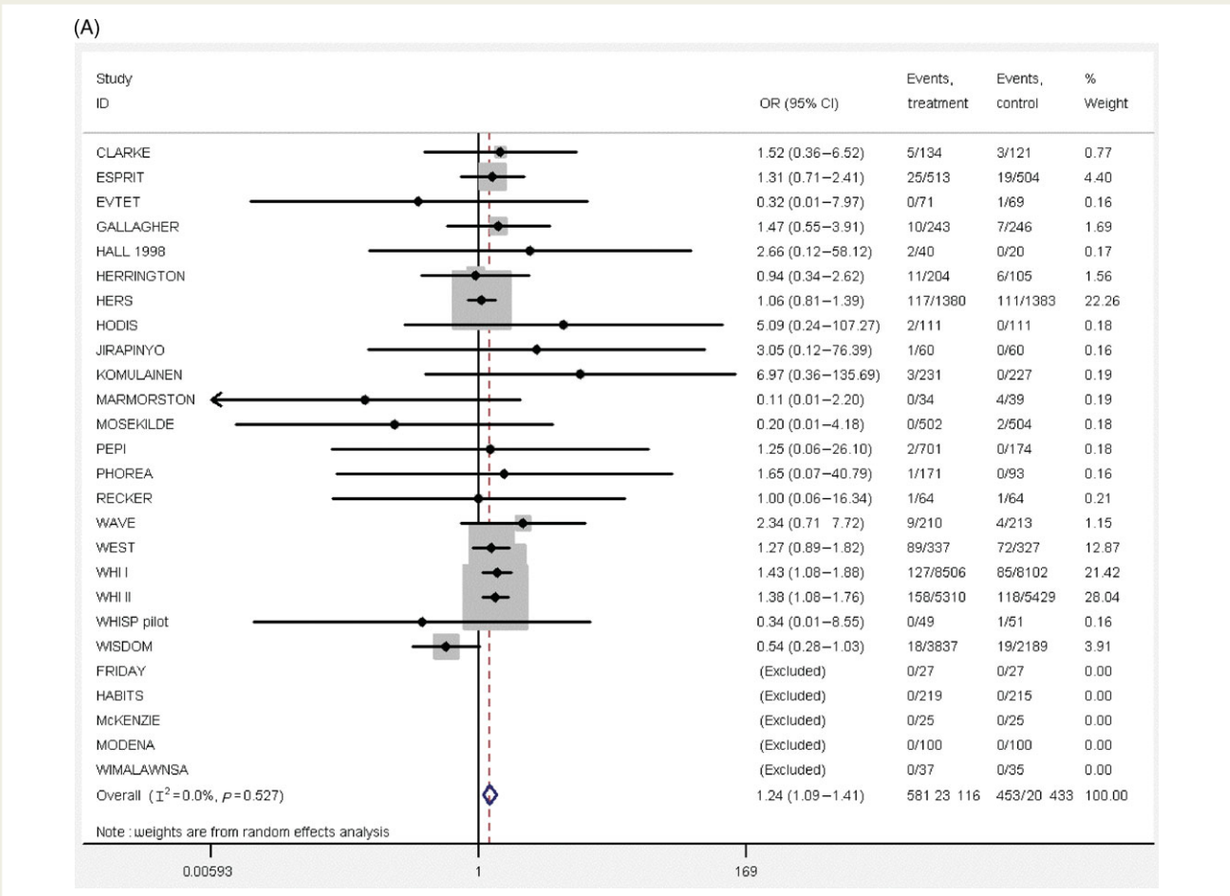
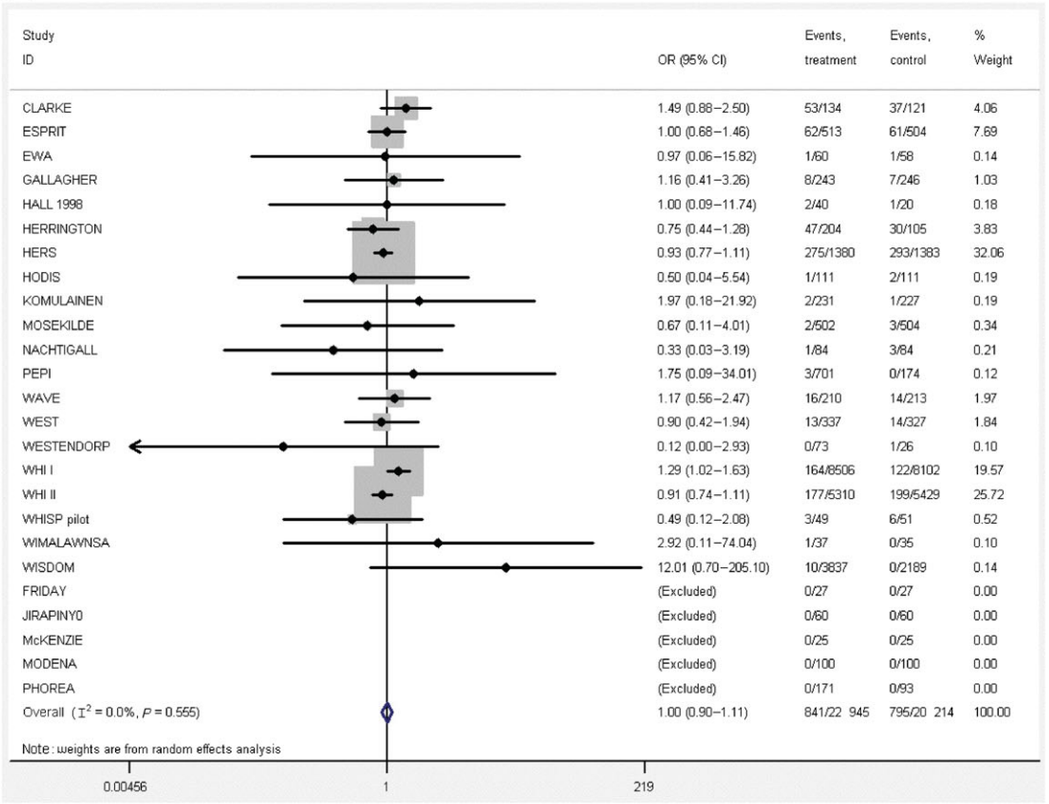


Figure 3 Forrest plots of the effect of hormone replacement therapy. Shaded squares represent the weighting of each trial in the analysis: (*A*) Cerebrovascular events (including stroke and TIA); (*B*) coronary heart disease events (including myocardial infarction); (*C*) venous thromboembolism (including pulmonary embolism, deep vein thrombosis and cerebral sinus thrombosis).

(B)



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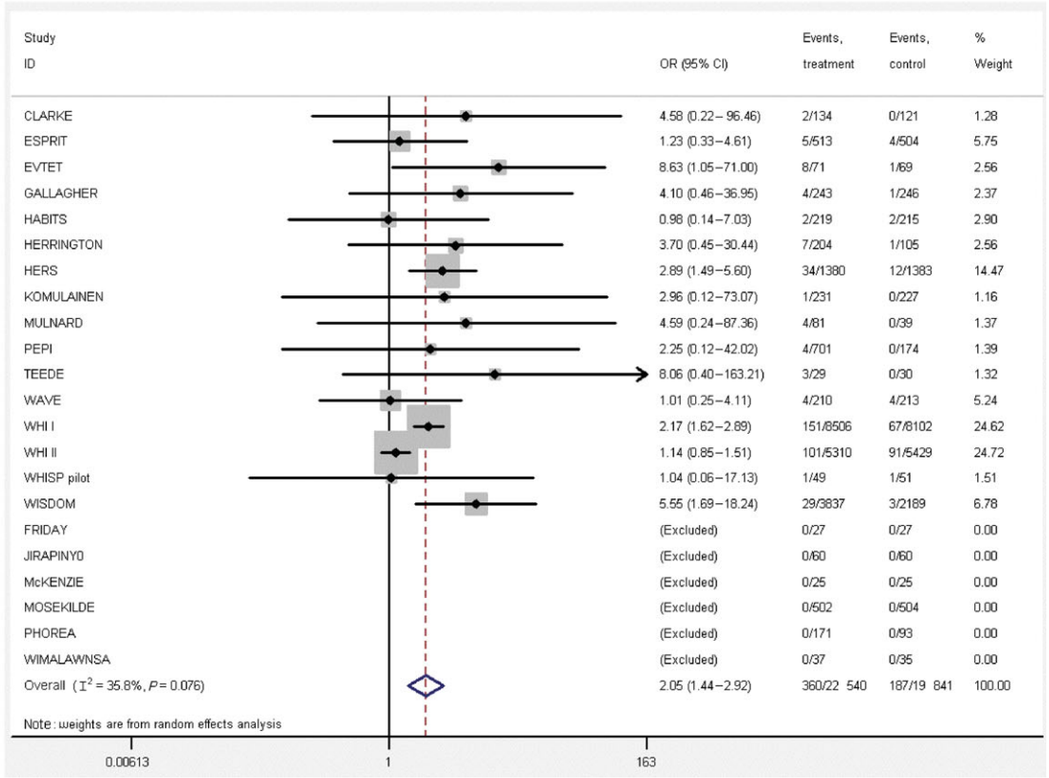

Figure 3 *Continued.*

Table 1 Effect of hormone replacement therapy on arterial and venous events (cerebrovascular disease, coronary heart disease and venous thromboembolism and their constituent parts); with odds ratio (95% confidence intervals) using random effects model

	Trials	Subjects	Events	Control event rate (events per person/year)	Odds ratio (95% confidence interval)	*P*-value	Heterogeneity *P*
Cerebrovascular disease	26	43 549	1034	0.02	1.24 (1.09–1.41)	0.001	0.53
Stroke	18	36 523	741	0.02	1.32 (1.14–1.53)	<0.0001	0.87
Transient ischaemic attack	7	6035	153	0.03	1.05 (0.76–1.45)	0.78	0.53
Fatal stroke	11	32 935	105	0.003	1.35 (0.89–2.03)	0.16	0.39
Non-fatal stroke	10	32 680	581	0.02	1.28 (1.08–1.52)	0.004	0.58
Coronary heart disease	25	43 159	1636	0.04	1.00 (0.90–1.11)	0.97	0.56
Myocardial infarction (MI)	21	41 849	1238	0.03	1.02 (0.91–1.15)	0.70	0.78
Fatal MI	15	40 319	396	0.01	1.03 (0.84–1.26)	0.77	0.49
Non-fatal MI	15	40 319	846	0.02	1.02 (0.88–1.18)	0.77	0.41
Unstable angina	5	9413	360	0.04	0.97 (0.71–1.40)	0.98	0.23
Venous thromboembolism	22	42 381	547	0.02	2.05 (1.44–2.92)	<0.0001	0.07
Deep vein thrombosis	16	40 417	376	0.01	1.97 (1.58–2.46)	<0.0001	0.58
Pulmonary embolism	12	39 612	230	0.004	1.74 (1.32–2.30)	<0.0001	0.66
All thrombotic events	31	44 113	3217	0.08	1.23 (1.07–1.41)	0.004	0.06

with increased CVD, stroke, and stroke severity, VTE, and its components DVT and PE. In contrast, CHD rates are not increased. The addition of progesterone in dual therapy doubles the risk of VTE over oestrogen alone.

HRT was found to increase the rate of total CVD by a quarter. Ordering the severity of stroke by vital status (fatal stroke/non-fatal stroke/no stroke) allowed ordinal meta-analysis to be performed; HRT increased stroke severity by a third. Since the assumption of proportionality of odds was adhered to in all of the trials reporting more than two levels (and trials which do not adhere to this would tend to attenuate any treatment effect), this finding of increased severity is likely to be real. This finding of increased severity is supported by a trend to more fatal strokes in patients receiving HRT using standard dichotomous analysis (although this analysis is underpowered because of the limited number of events). Sensitivity analyses did not reveal any modulating effects on the relationship between HRT and CVD; importantly, the findings do not appear to be driven by lower quality trials.

The finding that HRT increases VTE extends previous reviews based on fewer trials.[8,22] HRT appears to double the risk of VTE and one of its components, DVT, and increase PE by three-quarters. Ordinal analysis revealed that HRT might more than double the severity of PE although this finding was not significant due to the paucity of trials reporting PE by vital status. Subgroup analysis of type of HRT (mono vs. dual) was significantly different with VTE; dual-HRT significantly increases the risk of VTE compared with oestrogen monotherapy. This finding is supported by the indirect analysis, which demonstrated a doubling of the risk of VTE events with the addition of progesterone to oestrogen. Egger's test for VTE was significant suggesting publication bias. However, this finding is likely to be explained by the difference in effect with monotherapy vs. dual-HRT.

In contrast to its effects on stroke and VTE, HRT did not alter either beneficially or adversely the rate of CHD events, including MI. Data on >1600 events occurring in >43000 subjects were present so the neutral finding is unlikely to reflect inadequate statistical power. Similarly, ordinal analysis did not suggest that the severity of CHD events was altered. Sensitivity analysis did not reveal any significant difference in the magnitude of hazard with any subgroup.

The neutral effect of HRT on CHD events has been noted in the large WHI trials[31,32] and in previous meta-analyses[12] and our extended analysis (including the increased power of ordinal analysis[16]) replicates this finding. This is in contrast to previous observational studies,[3] which have demonstrated protective effects of HRT on CHD events. Various hypotheses have been suggested to explain this conflicting finding, including: differing effects of HRT on the vascular endothelium with advancing age (conferring benefits of HRT near the menopause);[33,34] the effect of higher doses of HRT (increased coagulation activity and vascular remodelling);[35] detrimental effects of CEE on insulin resistance

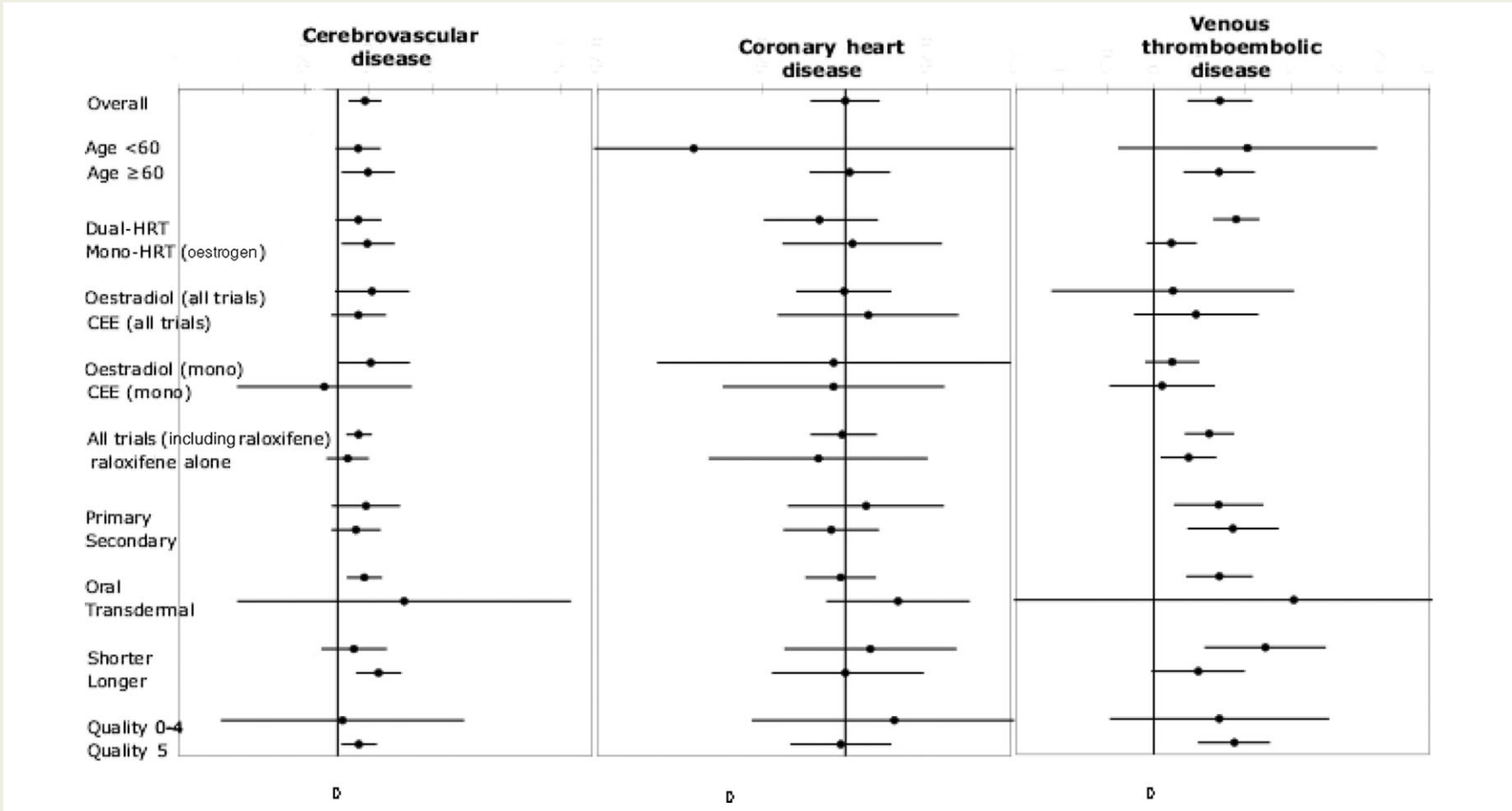

Figure 4 Tabulated results of pre-specified sensitivity analysis for cerebrovascular disease, coronary heart disease, and venous thromboembolism. Odds ratios and 95% confidence intervals are plotted on a log scale with no effect at 0.

Table 2 Effect of hormone replacement therapy on the severity of arterial and venous events; by ordinal logistic regression

Outcome	Trials	Subjects	Ordinal outcome	Odds ratio	95% Confidence interval	*P*-value
Three-level cerebrovascular disease (fatal stroke/non-fatal/no stroke)	10	32 679	104/581/31 997	1.31	1.12–1.54	0.001
Four-level cerebrovascular disease (fatal stroke/non-fatalstroke/TIA/no stroke)	4	12 440	57/291/159/11 933	1.10	0.91–1.33	0.34
Three-level coronary heart disease (fatal MI/non-fatal MI/no MI)	15	40 252	396/846/39 010	1.04	0.93–1.17	0.49
Four-level coronary heart disease (fatal MI/non-fatal MI/unstable angina/no MI)	5	7765	140/248/360/7017	1.00	0.85–1.17	0.96
Three-level pulmonary embolism (fatal PE/non-fatal PE/no PE)	3	7527	4/13/7510	2.57	0.73–9.01	0.14

Table 3 Indirect comparison of dual (combined oestrogen and progesterone) vs. mono (oestrogen only) hormone therapy on arterial and venous events (odds ratios shown represent the contribution of progesterone to the risk of cerebrovascular disease, coronary heart disease and venous thromboembolism in addition to oestrogen therapy)

Outcome	Trials oestrogen/oestrogen + progesterone	Odds ratio	95% Confidence interval
Cerebrovascular disease	8/14	0.93	0.70–1.22
Coronary heart disease	7/16	1.16	0.85–1.53
Venous thromboembolism	6/12	2.02	1.39–2.92

(not seen with oestradiol);[36] oral vs. transdermal administration;[36] and detrimental effects of some forms of progesterone.[37,38] In the present analysis of these hypotheses have, where possible, been addressed using subgroup analysis.

Of note, CHD events were not significantly reduced in younger women (OR 0.63, 95% CI 0.23–1.77, $P = 0.38$) in contrast to a previous analysis (reported OR 0.68, 95% CI 0.48–0.94 in women <60 years).[12] Although the point estimates are similar, the CI and *P*-values differ considerably. We explored three points that may explain this difference in findings. First, the authors used a fixed effects model for meta-analysis which assumes that any underlying treatment effect will be the same across trials; however, this assumption is unlikely to be correct since HRT trials are heterogeneous in nature (different types of HRT, mono/dual therapy, different baseline characteristics and follow-up times) and it is more appropriate to use the more conservative random effects model (as used here) which allows for such variation in trial design. However, this alone does not explain the significant CI seen; performing the present analysis with a fixed effects model in women <60 reveals OR 0.62 95% CI 0.23–1.64, the OR being very close to the analysis using the random effects model. Secondly, the previous meta-analysis used data from the large WHI trials divided by age >60 and <60 years. However, this divided data are a secondary post-hoc analysis of the WHI, and the primary analysis, which uses all the data as a whole, is used in the present analysis. A recent analysis of the WHI data examines the effect of age and time from menopause on vascular events.[39] This shows a non-significant trend towards reduced CHD in both younger women, and with reduced time from menopause. Taking this data into account in our analysis (and noting differing definitions of CHD) the risk of CHD in patients (60 years remains non-significant, with a point estimate nearer neutral, OR 0.90 (CI 0.64–1.27). Thirdly, they defined CHD events as MI and cardiac causes of death which may have included heart failure, an outcome that is unlikely to be influenced by HRT and less likely to occur in younger women, and one not counted in the present analysis.

The finding that younger women do not benefit from HRT was also shown in a recent observational study.[40] One problem in assessing response by age is that few papers provide information on time between menopause and recruitment; previous studies used a cut in age at 60,[12,32] although this is arbitrary. Using another cut at 55 years does not greatly alter the findings (OR 0.69, 95% CI 0.19–2.57) and the recent WHI analysis showed age and time from menopause to be well correlated.[39]

Subgroup analyses showed no difference in CHD events by type of oestrogen (CEE vs. oestradiol) with and without progesterone, or oral vs. transdermal administration (although the number of trials using transdermal administration was small). The diverse dosing regiments precluded meaningful analysis of the effect of dose of HRT.

In comparison with other meta-analyses[22] we have counted the number of patients with at least one event rather than the total number of events. This is important as many patients suffer more than one event during the course of a trial (i.e. a patient with a non-fatal stroke may go on to have a fatal stroke) and the

present approach may provide a more accurate estimate of the risk associated with HRT to an individual.

Several caveats should be made about the present study. First, data from heterogeneous trials have been aggregated, for example, duration and type of HRT. This is unlikely to have altered the results materially since most data came from modern large trials (e.g. WHI, WISDOM) involving tens of thousands of patients and the impact of data from older smaller trials will have been small. Secondly, sensitivity analyses did not reveal any differences in hazard between different types of intervention, participant, or trial design. Lastly, several of the analyses had limited power since trial authors did not report uniformly the effect of HRT on stroke, MI, and VTE, or on the outcome after these events. It is vital that future trial reports give such data.

This analysis provides robust information on the relative risks of arterial and venous vascular events and can be used to help inform the physician and patient. Any increased risk should be taken within the context of the underlying absolute risk for each individual patient, including consideration of other risk factors for vascular disease, and the possible benefits of treatment.

In summary, HRT is associated with increased rates and severity of CVD, and increased VTE. The addition of progesterone to oestrogen doubles the risk of VTE. In contrast, HRT does not appear to alter CHD events, including MI. Taking account of the other negative effects of HRT, HRT cannot be recommended for long-term vascular prophylaxis in most subjects. This does not affect current advice on using HRT during the peri-menopausal period or in women with premature ovarian failure.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: none declared.

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The above article uses a new reference style being piloted by the EHJ that shall soon be used for all articles.