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Hormone therapy for preventing cardiovascular disease in post-menopausal women (Review)

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[Intervention Review]

Hormone therapy for preventing cardiovascular disease in post-menopausal women

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ABSTRACT

Background

Evidence from systematic reviews of observational studies suggest that hormone replacement therapy (HT) may have beneficial effects in reducing the incidence of cardiovascular disease (CVD) events in post-menopausal women. This is an updated version of a Cochrane review first published in 2005 (Gabriel-Sanchez 2005).

Objectives

To assess the effects of HT for the prevention of CVD in post-menopausal women, and whether there are differential effects between use of single therapy alone compared to combination HT and use in primary or secondary prevention.

Search methods

We searched the following databases to April 2010: Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library, MEDLINE, EMBASE and LILACS.

Selection criteria

Randomised controlled trials (RCTs) of women comparing orally administered HT with placebo with a minimum of six-months follow-up.

Data collection and analysis

Two authors independently assessed study quality and extracted data. Risk Ratios (RR) with 95% confidence intervals were calculated for each outcome. Results were combined using fixed-effect meta-analyses, and where possible, further stratified analyses conducted to assess the effect of time on treatment. Additionally, univariate meta-regression analyses were undertaken to assess whether length of trial follow-up, single or combination treatment, or whether treatment for primary or secondary prevention were potential predictors for a number of CVD outcomes in the trials.

Main results

Four new trials were identified through the update; one trial included in the previous review was excluded. Therefore the review included 13 trials with a total of 38,171 post-menopausal women. Overall, single and combination HT in both primary and secondary prevention conferred no protective effects for all cause mortality, CVD death, non-fatal MI, or angina. There were no significant differences in the number of coronary artery by-pass procedures or angioplasties performed between the trial arms. However there was an increased risk of stroke for both primary and secondary prevention when combination and single HT was combined, RR 1.26 (95% CI 1.11 to 1.43), in venous thromboembolic events, RR 1.89 (95% CI 1.58 to 2.26) and in pulmonary embolism RR 1.84 (95% CI 1.42 to 2.37) relative to placebo. The associated numbers needed-to-harm (NNH) were 164, 109 and 243 for stroke, venous thromboembolism and pulmonary embolism respectively.

Authors' conclusions

Treatment with HT in post-menopausal women for either primary or secondary prevention of CVD events is not effective, and causes an increase in the risk of stroke, and venous thromboembolic events. HT should therefore only be considered for women seeking relief from menopausal symptoms. Short-term HT treatment should be at the lowest effective dose, and used with caution in women with predisposing risk factors for CVD events.

PLAIN LANGUAGE SUMMARY

Hormone therapy for preventing cardiovascular disease in both healthy post-menopausal women and those with pre-existing cardiovascular disease

Hormone therapy (HT) is used for controlling menopausal symptoms. It has also been used for the management and prevention of cardiovascular disease (CVD) in older post-menopausal women. The present review assessed the clinical effects of using HT for six-months or more. Thirteen randomised controlled trials (involving 38171 women aged 42 - 91) compared oral HT (oestrogen, with or without progestogen) with placebo. Most participants were post-menopausal American women, and the mean age in most studies was over 60 years. The length of time women were on treatment varied across the trials from 11.9 months to 7.1 years.

Overall, results showed no evidence that HT provides any protective effects against the development of CVD, either in healthy women or women with pre-existing heart disease. Rather, in relatively healthy post-menopausal women both single (oestrogen alone) and combination HT (oestrogen plus progestogen) significantly increased the risk of stroke and obstruction of a vein by a blood clot (venous thrombo-embolism). Combination HT, additionally, significantly increased the risk of suffering from a non-fatal heart attack or blood clots on the lungs (pulmonary embolism). Among women with existing CVD, combination HT significantly increased the risk of both venous thrombo-embolism and pulmonary embolism, but not stroke.

Summary of findings for the main comparison. HT compared to placebo for prevention of cardiovascular events in postmenopausal women

HT compared to placebo for prevention of cardiovascular events in post-menopausal women

Patient or population: patients with prevention of cardiovascular events in post-menopausal women
Settings:
Intervention: HT
Comparison: placebo in primary and secondary prevention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo in primary and secondary prevention	HT				
Death (all causes) Follow-up: mean 3.2 years	**Study population**		**RR 1.03** (0.94 to 1.14)	37905 (10 studies)	⊕⊕⊕⊖ **moderate**[1]	
	39 per 1000	**40 per 1000** (37 to 44)				
	Moderate					
	45 per 1000	**46 per 1000** (42 to 51)				
Death (CV causes) Follow-up: mean 3.3 years	**Study population**		**RR 1.03** (0.86 to 1.23)	37254 (11 studies)	⊕⊕⊕⊖ **moderate**[2]	
	12 per 1000	**12 per 1000** (10 to 15)				
	Moderate					
	28 per 1000	**29 per 1000** (24 to 34)				
Non-fatal MI Follow-up: mean 3.1 years	**Study population**		**RR 1.04** (0.92 to 1.18)	38125 (12 studies)	⊕⊕⊕⊖ **moderate**[3]	
	24 per 1000	**25 per 1000** (22 to 28)				

	Moderate				
	25 per 1000	**26 per 1000** (23 to 29)			
Stroke Follow-up: mean 3.8 years	**Study population**		**RR 1.26** (1.11 to 1.43)	33197 (8 studies)	⊕⊕⊕⊕ **high**
	25 per 1000	**31 per 1000** (27 to 35)			
	Moderate				
	21 per 1000	**26 per 1000** (23 to 30)			
Angina Follow-up: mean 3.7 years	**Study population**		**RR 0.91** (0.8 to 1.03)	34928 (7 studies)	⊕⊕⊕⊖ **moderate**[4]
	26 per 1000	**23 per 1000** (21 to 27)			
	Moderate				
	32 per 1000	**29 per 1000** (26 to 33)			
Venous thromboembolism Follow-up: mean 4.1 years	**Study population**		**RR 1.89** (1.58 to 2.26)	35609 (7 studies)	⊕⊕⊕⊖ **moderate**[5]
	10 per 1000	**20 per 1000** (16 to 23)			
	Moderate				
	9 per 1000	**17 per 1000** (14 to 20)			
Pulmonary embolism Follow-up: mean 3.4 years	**Study population**		**RR 1.84** (1.42 to 2.37)	36316 (7 studies)	⊕⊕⊕⊖ **moderate**[6]
	5 per 1000	**9 per 1000** (7 to 12)			
	Moderate				
	6 per 1000	**11 per 1000**			

		(9 to 14)		

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Low event rate in EPAT 2002; EPHT 2006 and WISDOM 2007 and therefore 95% CI wide
[2] Low event rate in EAGAR 2006; EPAT 2001; HALL 1998 and WISDOM 2007 and therefore 95% CI wide
[3] Low event rate in EAGAR 2006; EPAT 2001; EPHT 2006; EVTET 2000 and WISDOM 2007 and therefore 95% CI wide
[4] Low event rate in HALL 1998 and WISDOM 2007 and therefore 95% CI wide
[5] High level of heterogeneity between the trials. This appears to be due to the high event rate in HT arms in both EVTET 2000 and WISDOM 2007 which both had 1-year follow-up.
[6] Low event rate in ESPRIT 2002; EVTET 2002; WEST 2001 and WISDOM 2007 and therefore 95% CI wide

BACKGROUND

Despite a recent drop in both the incidence and prevalence of cardiovascular disease (CVD) it still remains the leading cause of death in the developed world (Deedwania 1990). The main forms of CVD are coronary heart disease (CHD) and stroke. In 2007, CVD caused 34% of deaths in the UK, and killed just over 193,000 people, with approximately 25% of these deaths from CHD and 9% from stroke (British Heart Foundation Statistics database). CVD is therefore the most common cause of death in the UK, accounting for one in five deaths in men and one in seven in women.

In terms of premature mortality (death before the age of 75) in 2008, approximately 30% of premature deaths in men and 22% in women were attributable to CVD (Townsend 2012). The burden of CHD is costly both in terms of reduced patient health-related quality of life (HRQoL) and high health care costs in the management of the conditions. Morbidity statistics indicate that CVD is the leading single cause of disability in Europe, with a prevalence of 6.0% to 6.5% in men and 4.0% to 4.5% in women within the UK. CVD is therefore costly in terms of both direct and indirect health care costs, accounting for 9.8% of total disability-adjusted years (Townsend 2012). In 2006 it was estimated that CVD cost the UK health care system approximately £14.4 billion, equating to approximately just under £250 per capita. The costs for the treatment of stroke are similar to those for other forms of CHD (Hsia 2006).

Description of the condition

The risk of CVD is higher in men than in women in younger age groups, with women's CVD incidence rates found to lag approximately ten years behind those of men. Between 45 and 64 years of age, the prevalence of CVD in men is several times that of age-matched women (Isles 1992; Tracy 1996). Most women experience the menopause (the last menstrual period) in their early fifties, after a phase of changing ovarian function (the peri-menopause) that may last several years and which is characterised by irregular menstrual cycles (Greendale 1999). Following menopause and loss of endogenous estradiol (major ovarian oestrogen), these gender-based differences narrow (Barrett-Connor 1997; Maxwell 1998). Most women who enter menopause are asymptomatic for CVD, and 95% of women who develop CVD do so after menopause. Evidence suggests that younger age at natural menopause is associated with CVD (Hu 1999) and CVD mortality (Jacobsen 1997; van der Schouw 1996) when comparing age-matched post-menopausal women. Menopause has an adverse effect on lipid profile. Low-density lipoprotein (LDL) rises for approximately 10 to 15 years after the menopause, and high-density lipoprotein (HDL) drops (Matthews 1989). Weight gain and a change in body fat distribution, increases in blood pressure and a host of other metabolic factors are amongst the other changes that may affect the risk for the development of CVD.

Description of the intervention

The term "hormone replacement therapy" has been replaced by "hormone therapy" as the older term infers that hormone therapy is replacing the function of a defective organ. Hormone therapy (HT) is now the preferred term for this intervention. Hormone therapy includes either oestrogen alone (estrogen-only HT) or oestrogen in combined with a progestogen (combined HT). It is used in a variety of formulations and doses which can be taken orally, vaginally, intra-nasally or as an implant, skin patch, cream or gel. The clinical effects vary according to the type of HT and the duration of its use. Formulations of oral oestrogen generally comprise 1 - 2 milligrams of estradiol daily and may include oestradiol (an oestrogen derived from wild Mexican wild yam), oestradiol valerate (a pro-drug for oestradiol), or conjugated equine oestrogen (CEE) a blend of equine estrogens extracted from horse urine. The progestogens used for HT include synthetic derivatives of progesterone, synthetic derivatives of testosterone, and natural progesterones derived from plants. These differ in their metabolic action and potential for adverse effects, and the risk-benefit profile of each type of progestogen for use in HT is currently unclear. In combined HT, progestogen can be taken either every day (continuous combined therapy), cyclically with estrogens taken daily and progestogens taken for part of the month (sequentially combined HT), or less frequently.

The addition of a progestogen to oestrogen reduces the risk of endometrial hyperplasia associated with the use of oestrogen alone in women with a uterus (Furness 2009). However, the addition of progestogens can be problematic as they have adverse effects on blood lipid profiles and may cause symptoms such as headaches, bloating and breast tenderness (McKinney 1998).

How the intervention might work

The finding that CVD rates in women rise sharply after the menopause has led to the suggestion that endogenous estradiol may attenuate age-related vascular remodelling in pre-menopausal women. Age-associated vascular remodelling involves endothelial dysfunction, enhanced growth of intimal smooth muscle cells (SMCs), and increased prevalence of vascular plaques. The same cellular processes participate in atherosclerosis (Lakatta 2003). Additionally, changes in the androgen-to-estradiol ratio may contribute to the negative effects observed on the cardio-vascular system post menopause. The decline in estradiol levels during menopause leads to a higher androgen-to-estradiol ratio. Androgens induce vasoconstriction and SMC growth and exacerbate diet-induced atherosclerosis, plaque formation, and pro-atherosclerotic arterial remodelling. This suggests that the increase in the androgen-to-estradiol ratio in post-menopausal women may be another mechanism which contributes to the acceleration of atherosclerosis observed.

The exact mechanism by which CVD risk may be reduced by oestrogen is not completely understood, but it is widely known that estradiol inhibits many processes involved in age-associated vascular remodelling, including SMC proliferation and endothelial dysfunction, and lowers cholesterol and improves vascular tone (Dubey 2001; Mendelsohn 1999). Other factors that may play a role are changes in coagulation factors, blood pressure, insulin, and body fat distribution (Lieberman 1994; PEPI Trial Writing Group 1995). Exogenous ovarian steroid hormones have multiple target tissues in addition to the vascular system, including the bones, endometrium, and breast, and HT has the potential to effect the risk of several additional conditions including osteoporosis and dementia (Grady 1992).

Why it is important to do this review

Hormone therapy to treat menopausal oestrogen deficiency has been in widespread use for more than 60 years (Wallach 1959).

Long-term treatment was assumed to prevent atherosclerosis, and the increased CVD and mortality risk observed following

the menopausal transition (Robinson 1959; Wallach 1959; Wilson 1963). Since the early 1980's several observational studies consistently showed that HT users, many of whom started treatment shortly after menopause, had a significant reduction in total mortality and risk of CVD events of approximately 30% to 50% relative to women who chose not to use HT (Grady 1992; Grodstein 1999; Grodstein 2000; Mann 1994; Psaty 1994; Rosenberg 1993; Stampfer 1991). This reduction in risk was apparent whether the HT regimen used was oestrogen alone or oestrogen in combination with progestogen. However, most observational data sets suggest that the risk reduction in mortality and CHD events, is coupled with a higher impact of the risk of venous thromboembolic events and an apparent increased incidence of stroke but lower stroke mortality (Paganini-Hill 2001). Overall, the accumulated available epidemiological evidence supported the use of HT to increase longevity in post-menopausal women (Mishell 1989).

It was recognised that there was a need for randomised controlled trials (RCTs) in the area (Barrett-Connor 2001; Hemminki 2000a), and that the wide prescribing of HT in the 1990's, despite the lack of RCT evidence of its effects, might reflect a conflict between commercial and professional interest groups and good public policy (Hemminki 2000b).

The publication of the results from the Heart and Estrogen/progestin Replacement Study (HERS I 1998) and the Women's Health Initiative (WHI I 2002) trials appeared to strongly contradict conventional clinical practice based on the evidence from observational studies. HERS I 1998 was a secondary prevention trial studying the effects of combination therapy (oestrogen and progestogen) on the risk of CHD events (non-fatal myocardial infarction plus CHD-related death) in 2763 post-menopausal women with established CHD. Whilst, there was an excess risk of CHD events in the HT group in the first year on treatment; for the overall 4.2 years of follow-up, there were no differences in CHD events between the HT and placebo groups, coupled with an increased risk of both venous thromboembolism and pulmonary embolism. A further 2.7 year of follow-up still showed no CHD benefit (Grady 2002). The WHI I 2002 was a primary prevention trial conducted in 16,609 post-menopausal women without hysterectomy. Participants were randomly assigned to combination therapy (the same regimen as used in HERS I 1998) or placebo. There was an excess risk of CHD in the first year and a nearly 30% increased risk of coronary events after 5.6 years. A sub-group analysis of the 400 women included in the trial who had a history of myocardial infarction or coronary revascularization showed a similar risk.

In light of these trials not confirming a cardioprotective effect of estrogens, the age of the women enrolled in both HERS I 1998 and WHI I 2002 (mean age: 65 years), and subsequent WHI I 2002 analyses, in which non-significant data trends suggested HT did not lead to excess coronary risk when started close to the menopause, interest alighted upon the timing of initiation of HT in relation to the time of menopause. This 'timing hypothesis' suggests that there is a window of opportunity where HT may be beneficial for prevention of CVD in women 10-years post menopause, but that in older women, it does not appear to have the same benefits and may be associated with excess CVD risk. Biological plausibility exists to support the timing hypothesis, in which it is posited that oestrogen therapy has a negative impact on atherosclerotic arteries (i.e. causes events when vulnerable plaques are present) but prevents atherosclerosis if begun early enough. This hypothesis fits with results in the Clarkson non-human primate model, where conjugated equine oestrogen (CEE) prevented atherosclerosis only in animals treated early after castration (within the calculated equivalent of six human post-menopausal years) before the onset of diet-induced atherosclerosis (Mikkola 2002). It is plausible therefore that oestrogen effects differ with the stage in the natural history of the disease and the severity of subclinical disease.

In support of the 'timing hypothesis' a stratified meta-analyses by Salpeter 2004 indicated differential treatment effects with HT relative to placebo according to the participants' baseline age. The Salpeter 2004 analyses assessed 30 RCTs which compared HT with placebo that included 26,798 participants and reported at least one death, to assess the effect of HT on total mortality, mortality due to CV disease, cancer, or other causes. Results indicated a significantly reduced risk of death in women with a mean age of under 60 years taking HT compared to a placebo group, though no difference was found when older women were compared. However, this meta-analysis pooled trials which differed widely with respect to the type of HT used, the clinical status of the participants, and in many of the trials death was not a pre-specified outcome. Furthermore, 60% of the events in the meta-analysis of trials in younger women were observed in women with poor prognosis ovarian cancer. It is therefore unclear, as to how applicable the results of this meta-analysis are to either healthy post-menopausal women or those with an existing CVD taking either oestrogen alone or oestrogen in combination with progestogen.

The original Cochrane Review on HT for the prevention of CVD in post-menopausal women (Gabriel-Sanchez 2005) identified a total of ten RCTs which included 24,283 post-menopausal women (12,353 randomised to HT and 11,930 to placebo). The review reported no protective cardiovascular effects for HT observed in either healthy women or women with one or more pre-existing CVD risk factors, but a higher risk of stroke, venous thromboembolic events and pulmonary embolism was observed.

Since the publication of the original Cochrane review a number of further trials, for example, the Estonian Postmenopausal Hormone Trial (EPHT 2006), and the Women's Health Initiative trial on the effects of oestrogen alone in women with hysterectomy (WHI II 2004) have been published. These, along with other trials that have been published in the interim time, will up-date the evidence base regarding the risks and benefits observed with HT use compared with placebo, and provide up to date evidence on these to help aid both clinicians and patients in their decision making regarding the potential use of HT. Additionally, the previous review (Gabriel-Sanchez 2005) did not include Health Related Quality of Life (HRQoL) as an outcome measure, which may be of importance to patients.

Moreover, the original review, statistically pooled trial data for each outcome measure of interest from trials with different lengths of follow-up. Whilst it is acknowledged that this is standard practice, the addition of further trial evidence may allow stratified analyses to be conducted to assess the impact of age (as a proxy for time since menopause) on CVD outcomes, and the effect of time on treatment, or provide the additional power (from more trials assessing the same outcome) for this to be explored using either univariate or multivariate meta-regression models (Higgins 2010).

OBJECTIVES

To assess the effects of HT for the prevention of CVD in post-menopausal women, and whether there are differential effects between use of single therapy alone compared to combination HT and use in primary or secondary prevention.

Secondary aims were (i) to undertake exploratory analyses to assess the impact of mean age of trial participants at baseline as a proxy for time since menopause (> 60 versus < 60 years of age) and (ii) effects of length of time on treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing oral HT with either placebo or a no treatment control for a follow-up duration of six months or longer were included. RCTs which compared two or more different types of oral HT were included provided that they were additionally compared with a placebo or a no treatment control arm.

Types of participants

Post-menopausal women (with either spontaneous or induced cessation of menstrual bleeding for a continuous period of six months or more), either with or without evidence of existing CVD.

Types of interventions

Oral Hormone Therapy (HT), consisting of either oestrogen alone or in combination with a progestogen compared with either a placebo or a no treatment control. Combined HT (oestrogen plus progestogen) could be delivered continuously daily (continuous combined HT) or sequentially (oestrogen taken daily with progestogens taken for part of the month).

RCTs in which HT was delivered to the body via either patches, tablets, creams, troches, an intrauterine device (IUD), vaginal ring, gels or injections compared with placebo or no treatment were excluded in accordance with the inclusion criteria from the previous review (Gabriel-Sanchez 2005). Likewise RCTs assessing the effects of selective oestrogen receptor modulators (SERMs) (e.g. raloxifene) compared to placebo or a no treatment control were not included.

Types of outcome measures

Primary outcomes

- Death from any cause.
- Cardiovascular death.
- Non-fatal acute myocardial infarction.
- Stroke.
- Angina.

Secondary outcomes

- Pulmonary emboli.
- Venous thromboemboli (pulmonary emboli plus deep vein thromboses).
- Coronary artery by-pass graft (CABG).
- Angioplasty (with or without a stent).

Any included trials were then searched for additional assessment and reporting of health-related quality of life (HRQoL) obtained using a validated outcome measure.

Trials reporting only intermediate CVD outcomes, such as blood pressure, cholesterol levels, or coagulation factors were not included.

Search methods for identification of studies

Electronic searches

Randomised controlled trials (RCTs) that assessed the effects of HT compared to placebo with a minimum of 6-months duration were identified through searching electronic databases. Electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library (April 2010), MEDLINE (OVID;1950 to April 2010), EMBASE (OVID; 1966 to Week 15 2010) and LILACS (OVID; 1982 to April 2010) were conducted. Additionally the National Research Register (NRR) and www.clinicaltrials.gov were searched for any ongoing trials on CV diseases (2002 to September 2010).

No language restrictions were applied and appropriate consideration was given to variations in terms and the spelling of terms in different countries so that potentially relevant studies would not be missed by the search strategy due to these variations. A full list of the search strategies applied are detailed in Appendix 1.

Searching other resources

Reference lists of all eligible RCTs and systematic reviews were searched for additional relevant trials. All references were managed using Reference Manager.

Data collection and analysis

Selection of studies

Relevant studies were identified in two stages. Two authors independently screened the titles and abstracts returned by the database searches for relevance. The full texts of any references that were considered as potentially relevant by either author were obtained. The relevance of each paper was then assessed according to the criteria set out above for the review question by two authors independently. This assessment was performed unblinded. Any discrepancies between the authors were resolved by recourse to the papers, and if necessary a third author was consulted.

Data extraction and management

Data were extracted from the included studies using a standardised data extraction form in Microsoft Access by two authors independently. This was checked for agreement and any discrepancies were resolved through recourse to the papers. The following study details were assessed:

Trial characteristics

1. Method of randomisation.
2. Method of allocation concealment.
3. Use of stratification.
4. Adequacy of double blinding.

5. Means of recruitment.
6. Number of participants screened for eligibility, randomised, analysed, excluded, lost to follow-up or dropped-out (i.e. withdrew from the trial but were followed-up).
7. Baseline equality of treatment groups.
8. Level of adherence to therapy.
9. Whether analyses were conducted on an intention-to-treat (ITT) basis.
10. Study design (parallel versus multi-arm, single centre or multi-centre).
11. Funding source.

Characteristics of the trial participants

1. Inclusion and exclusion criteria.
2. Age and other recorded prognostic baseline variables.
3. Menopausal status (definition of menopause and how this was defined, surgical or natural menopause) of participants.

Interventions

1. Type of HT (estrogen-only or combination oestrogen and progestogen).
2. Dosage.
3. Duration of therapy (minimum six-months).

Outcomes

1. Which relevant primary and secondary outcomes were measured.
2. How relevant outcomes were defined and measured.

See Description of studies; Risk of bias in included studies

Assessment of risk of bias in included studies

Risk of bias was assessed according to the risk of bias assessment criteria detailed in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2010). These criteria focus upon the quality of random sequence generation and allocation concealment, blinding (participants, trial personnel and outcome assessors), incomplete outcome data, selective outcome reporting and other sources of bias. Assessment of risk of bias was undertaken by two review authors independently, with any disagreements resolved by discussion.

Data synthesis

Statistical analyses were undertaken following the guidelines of the Handbook of the Cochrane Collaboration (Higgins 2010).

For dichotomous data, two by two tables were generated for each study and expressed as a risk ratio (RR) with 95% confidence intervals (CI). The data were grouped firstly according to intervention (single versus combination therapy) and secondly whether the intervention was primary or secondary prevention. Further analyses were undertaken to assess the effect of both single and combination therapy in the overall patient population (both primary and secondary prevention). Data were combined for meta-analysis in RevMan software using the Peto-modified Mantel-Haenszel method using a fixed effect model to provide an overall estimate of treatment effect. For comparisons showing statistically significant differences between treatment groups, the number needed to treat harm (NNH) was calculated.

Heterogeneity between studies was explored qualitatively (by comparing the characteristics of included studies) and quantitatively using the chi-squared test of heterogeneity and the I^2 statistic. Trials with a chi-squared test resulting in a p-value < 0.10 were considered indicative of significant statistical heterogeneity. In order to assess and quantify the possible magnitude of heterogeneity between trials, and the potential impact for undertaking meta-analyses, an I^2 statistic of 0% to 40% was interpreted as potentially not being important; 30% to 60% as representing moderate heterogeneity; 50% to 90% as representing substantial heterogeneity, and 75% to 100% as being considerably heterogeneous and potentially unsuitable for meta-analyses (Deeks 2009). Published graphs display the results of analysis using the fixed-effect model. Reporting bias was assessed though the examination of funnel plots.

To assess the potential impact of time since menopause trials were stratified according to the mean age of participants at baseline (> 60 versus < 60 years of age). Where data were reported for more than two different time points for each outcome (either between different trials or longitudinally within the same trial) meta-analysis were conducted stratified by length of time on treatment. These analyses were a priori classified as exploratory given the heterogeneity between the different HT regimens assessed and the patient populations in the different trials. To conduct the analyses time points for the reporting of outcomes in the trials had to be rounded up or down.

Data were rounded as follows:

WISDOM 2007 reported results after a median follow-up of 11.9 months (range 7.1 – 19.6). Results are therefore reported as though there was one year of follow-up. EVTET 2000 was conducted for a 1.3 year period; results from this trial are therefore also reported for one year follow-up. EPAT 2001, ESPRIT 2002 and HALL 1998 are all reported for two-years of follow-up. EPHT 2006 [median length of follow-up: 3.4 years (range: 2 – 4.9)], EAGAR 2006 [mean follow-up: 3.5 years (range: 25 – 41)], ERA 2000 [mean follow-up: 3.2 years (range: 2.8 – 3.8)], WAVE 2002 [mean follow-up: 2.8 years (range: 2.1 – 3.9)] and WEST 2001 [mean follow-up: 2.8 years (range: 1.6 – 4.1)] were all classified as having a three-year follow-up period.

HERS I 1998 was classified as having a four-year follow-up period. Results within the blinded part of the trial were reported at a mean of 4.1 years, with selected clinical outcomes reported for each year of follow-up. Outcome data for the 4 – 6.8 (unblinded open label) follow-up period were not included in the standard pair-wise meta-analyses but were included in the relevant stratified analyses. WHI I 2002 reported results after a mean follow-up of 5.2 or 5.6 years (range: 3.5 – 8.5). Selected clinical outcomes were also reported for each year of follow-up. Since all women had been enrolled on active treatment for at least 3.5 years at study termination, data for each of the first three year time points, and final follow-up were included in the analyses. WHI II 2004 reported results for a mean follow-up duration of 6.8 and 7.1 years (range: 5.7 - 10.7) depending on the outcome. Data were therefore classified as having 6.8 or 7.1 years of follow-up as appropriate.

Given the lack of standardisation in the HRQoL measures used in the trials, and the variation in methods and reporting, we were unable to undertake meta-analyses for these measures. Instead differences between outcomes in the HT versus placebo group for outcomes within each domain were compared and the p-value presented.

Univariate meta-regression analyses were undertaken to assess whether any particular features of the trials were potential predictors of the CVD outcomes for all cause mortality, CVD mortality, non-fatal MI, stroke, angina, venous thromboembolism and pulmonary embolism. Due to the small number of trials included in the review, we limited our exploration of outcome predictors to three variables: length of trial follow-up; whether treatment was single or combination HT; and whether treatment was for primary or secondary prevention. All analyses were conducted using Stata version 11.

RESULTS

Description of studies

See: Included studies; Excluded studies.

Results of the search

The literature searches retrieved 4508 references before de-duplication, and 3728 unique references after de-duplication. Fifty-seven were ordered as full paper copies and considered for inclusion. Thirteen trials (reported in 38 papers) were included and 19 were excluded. The process of study selection for the review is displayed in Figure 1.

Figure 1. Figure 1: Process of study selection for the review

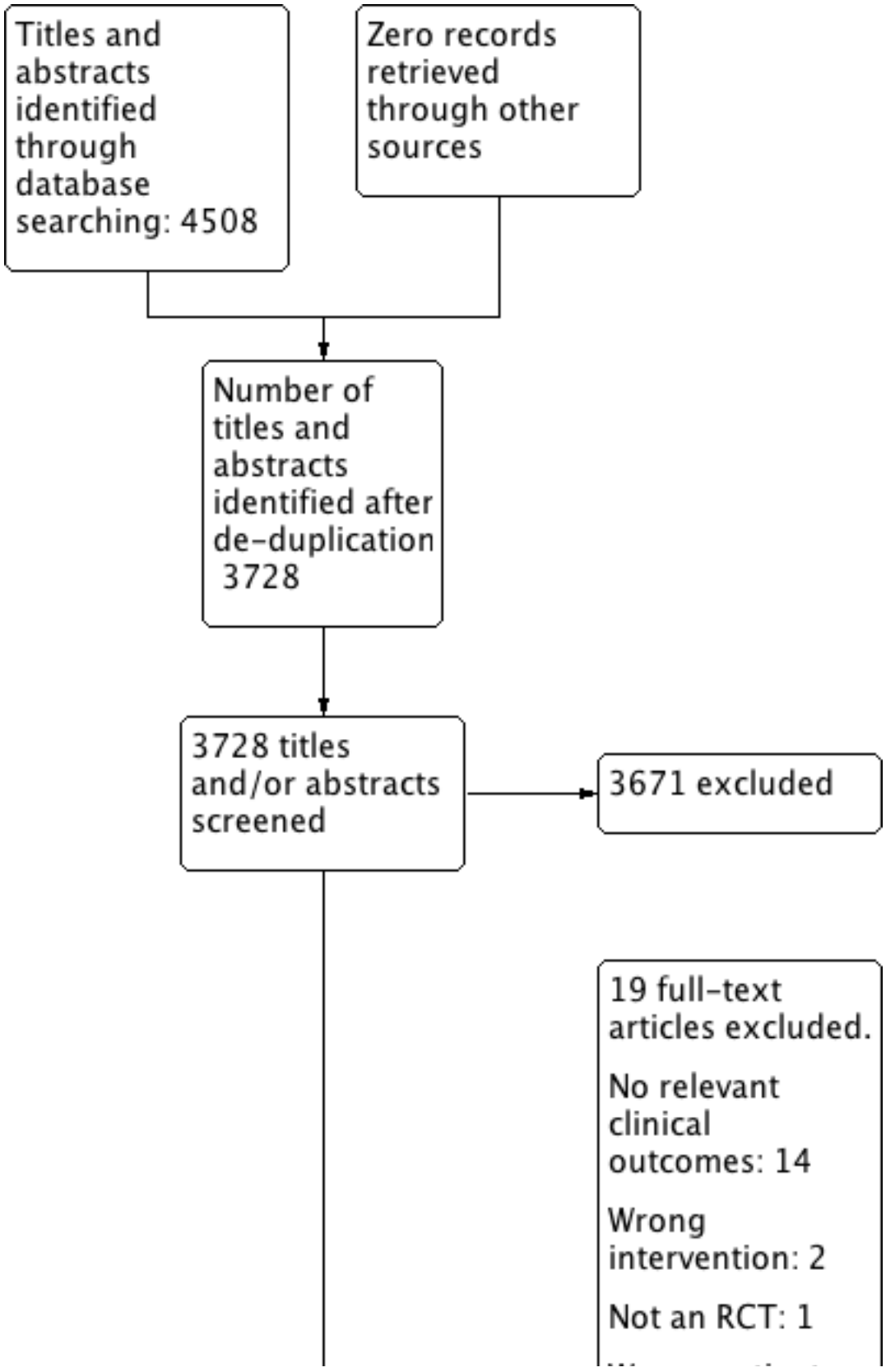
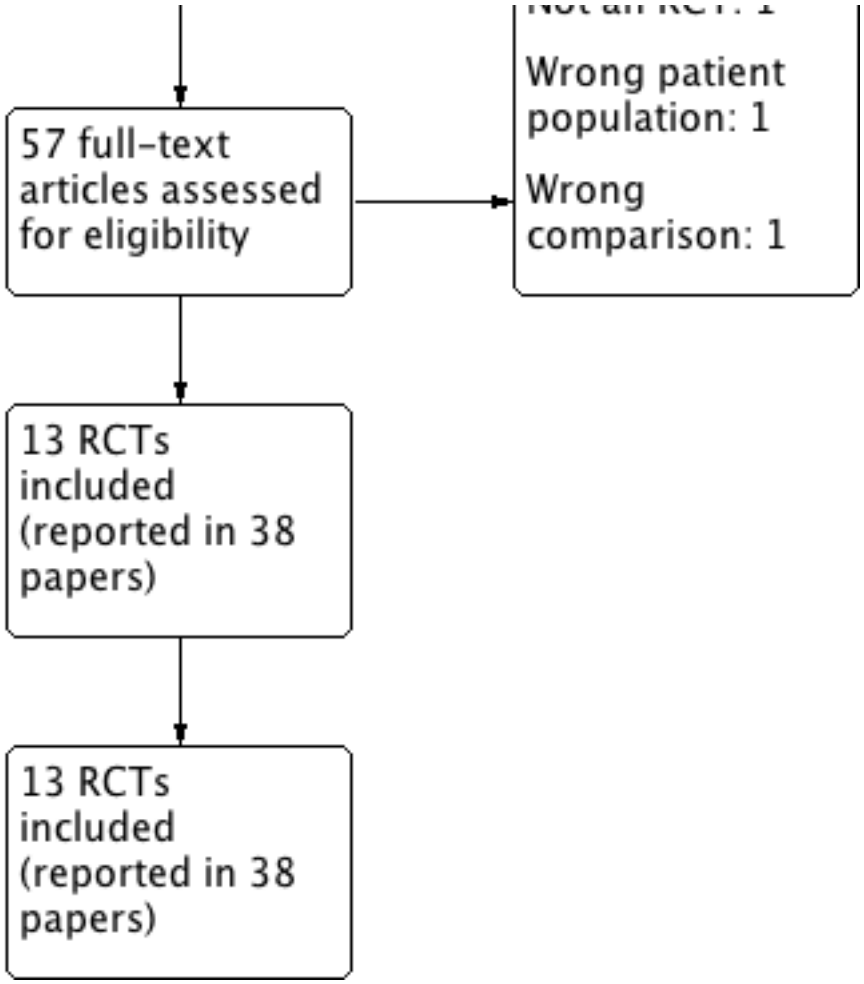


Figure 1. (Continued)



Included studies

In total we identified 13 randomised controlled trials with at least six-months follow-up that compared HT to placebo or a no treatment control published between 1998 and 2007 (EAGAR 2006; EPAT 2001; EPHT 2006; ERA 2000; ESPRIT 2002; EVTET 2000; HALL 1998; HERS I 1998; WAVE 2002; WEST 2001; WHI I 2002; WHI II 2004 and WISDOM 2007). Nine of the identified trials had been included in the previous review, and one trial also originally included in the previous review (HERS II) was excluded from this up-date. This trial was the long-term open label follow-up phase of HERS I 1998, and therefore not included as a separate trial, as done in the original review. Additonally, data from the single therapy oestrogen alone trial arm from the three-armed trial ERA 2000 was also included in the analyses. This had been excluded from the previous review, with only data from the combination arm being included in the analyses. Four new trials were therefore identified for the up-date review (EAGAR 2006; EPHT 2006; WHI II 2004; WISDOM 2007).

The 13 trials included 38,171 post-menopausal women; 19,302 randomised to receive some form of HT and 18,869 to receive either placebo or a no treatment control. WISDOM 2007 also included a further 1307 women who were randomised to a comparison of two active HT therapies, and EPHT 2006, also included 1001 women who were randomised to either open label HT, or a no treatment control, to examine the effect of blinding upon recruitment and retention rates within the trial. The data from these further 2306 women randomised into either of these trials (EPHT 2006; WISDOM 2007) are not included in this review.

The trials varied dramatically in size, ranging from 40 (HALL 1998) to 16,608 (WHI I 2002). Likewise, there was large variation in the length of follow-up within the trials ranging from 11.9 months (WISDOM 2007) to 7.1 years (WHI II 2004). Overall, three large trials (HERS I 1998; WHI I 2002; WHI II 2004) with a mean follow-up duration of 5.6 years (range: 4.1 – 7.1) randomised 30,110 women to either HT treatment or placebo, and therefore contributed approximately 79% of the data available from the 13 trials.

The majority of the trials (n = 7) had been conducted in the USA, two were international (one in USA and Canada, and one in England, New Zealand and Australia), with one trial conducted in each of the following countries: England and Wales, Norway, Sweden, and Estonia.

Six trials were stopped early (EAGAR 2006; EPHT 2006; EVTET 2000; WHI I 2002; WHI II 2004; WISDOM 2007) either as other trial results were published showing no beneficial effect, or a detrimental effect of HT on CVD outcomes, (EAGAR 2006; EPHT 2006; EVTET 2000; WISDOM 2007) or due to it being established that the overall

risks (adverse events) associated with HT use were unlikely to be outweighed by any potential benefits of HT use on CVD outcomes within the time frame of the trial (WHI I 2002; WHI II 2004).

A summary of the main characteristics of the included trials in displayed in Table 1.

Participants

All the trials included post-menopausal women, whether menses was natural or an artefact of hysterectomy or oophorectomy, with a mean age of 63.2 years (range: 42 - 91 years). In 11 out of the 13 trials the mean participant age was over 60 years at baseline. The hysterectomy status of the women in three of the trials was related to the inclusion criteria and therefore in both HERS I 1998 and WHI I 2002 was 0%, and in WHI II 2004 100%. In the other five trials reporting baseline hysterectomy status this ranged from 10% - 61% (EPAT 2001; EPHT 2006; ERA 2000; ESPRIT 2002; WEST 2001)

The trial inclusion criteria varied according to the primary study objectives. Five of the trials were designed to assess the effects of HT in the primary prevention of CVD, and therefore enrolled predominantly healthy patient populations (EPAT 2001; EPHT 2006; WHI I 2002; WHI II 2004; WISDOM 2007). Whilst eight of the trials aimed to assess the impact of HT in secondary prevention, and therefore enrolled women with established CVD (ERA 2000; HERS I 1998; WAVE 2002) or after a designated specific CVD event of interest, namely coronary artery by-pass graft (CABG) (EAGAR 2006), angina (HALL 1998) myocardial infarction (MI) or transient ischaemic attack (TIA) (ESPRIT 2002; WEST 2001), or pulmonary embolism (PE) or deep vein thrombosis (DVT) (EVTET 2000).

Primary prevention trials

Five studies enrolled relatively healthy women (EPAT 2001; EPHT 2006; WHI I 2002; WHI II 2004; WISDOM 2007). Although one of the studies enrolled women with one CVD risk factor, namely hypercholesterolaemia (EPAT 2001) and a small minority (approximately ≤ 5%) of women within all trials had a history of CVD, the trial participants were representative of population samples of fit women in this age group without overt disease. Four of these trials (EPHT 2006; WHI I 2002; WHI II 2004; WISDOM 2007) assessed the impact of HT on both CVD, as well as a wide range of other endpoints, including cancer, osteoporosis and gallbladder disease, and therefore reported detailed lists of participant inclusion and exclusion criteria.

The two biggest primary prevention trials (WHI I 2002 and WHI II 2004) both set enrolment targets to establish set fractions for baseline age categories and to achieve racial and ethnic group representation within participant groups in the proportions recorded in the USA census for the 50 - 79 year old age group. This was achieved, with it being noted that baseline cardiovascular risk factors in the trial participants in both WHI I 2002 and WHI II 2004 were low and consistent with those observed in a generally healthy population of post-menopausal women (Manson 2003; Stefanick 2003). WISDOM 2007 recruited women with no major health problems from general practice registers in England, Australia and New Zealand, whilst EPHT 2006 included healthy women with no major health problems drawn from population samples in Estonia. In both trials participant baseline cardiovascular risk factors were low and consistent with those observed in the general population of postmenopausal women within this age group.

Secondary prevention trials

Eight studies included women with established CVD (EAGAR 2006; ERA 2000; ESPRIT 2002; EVTET 2000; HALL 1998; HERS I 19988; WAVE 2002; WEST 2001). Both ERA 2000 and WAVE 2002 included women who had coronary artery stenosis evidenced by angiogram. HERS I 1998 and EAGAR 2006 both included women who had undergone a revascularization procedure [CABG or percutaneous coronary intervention (PCI)], whilst ESPRIT 2002 and WEST 2001 included women who had had a previous MI or TIA. HALL 1998 included women previously hospitalised with angina, and EVTET 2000 included women who had suffered a thrombo-embolic event, PE or DVT.

The largest of the eight trials (HERS I 1998) compared the baseline characteristics of the trial participants with a similar group of women presumed to have coronary heart disease who were participants in a survey designed to produce nationally representative data. The HERS I 1998 participants had significantly fewer smokers, women with hypertension and diabetics than the comparison group but were comparable with respect to blood pressure, body mass index, physical activity and cholesterol levels (Grady 1998).

Interventions

A number of different oestrogen alone or oestrogen and progestogen combinations had been assessed in the different trials. One trial (ERA 2000) was a three armed trial, and therefore assessed both oestrogen alone and in combination with a progestogen versus placebo. Most of the included comparisons used a moderate does of oestrogen, for example, oestradiol 1 mg or conjugated equine oestrogen (CEE) 0.625 mg daily. The following interventions assessed were:

Estrogen-alone HT

1 mg 17-ß oestradiol (EAGAR 2006; EPAT 2001; WEST 2001).

2 mg oestradiol valerate (ESPRIT 2002).

0.625 mg conjugated equine oestrogen (ERA 2000; WAVE 2002; WHI II 2004).

Three of the trials assessing oestrogen alone (WAVE 2002; WEST 2001; WHI II 2004) did not randomise women to this comparison unless they had had a hysterectomy.

Combined HT regimes

Combined HT regimens included one of the above types of oestrogen in combination with one of the two progestogens:

- medroxyprogesterone acetate (MPA)norethisterone
- (norethindrone)

The continuous combined regimens were composed of the following

CEE 0.625 mg with MPA 2.5 mg daily (EPHT 2006; ERA 2000; HERS I 1998; WAVE 2002; WHI I 2002; WISDOM 2007).

Oestradiol 2 mg with 1 mg norethisterone daily (EVTET 2000).

Whist the combined sequential regimes included:

Oestradiol 1 mg daily with MPA 5 mg for 12 days once a year (WEST 2001).

CEE 0.625 mg for 18 days followed by a combination with oral 5 mg MPA (HALL 1998).

The control arm in each of the trials received placebo tablets.

The duration of HT use varied widely across the trials, with follow-up duration ranging from 11.9 months (WISDOM 2007) to 7.1 years (WHI II 2004). Three trials reported outcomes after HT use for around one-year (EVTET 2000; HALL 1998; WISDOM 2007); two for 2-3 years (EPAT 2001; ESPRIT 2002), and five for approximately 3 years (EAGAR 2006; ERA 2000; EPHT 2006; WAVE 2002; WEST 2001). HERS I 1998 measured outcomes after 4.1 years, and continued the study unblinded for a further 2.7 years follow-up (HERS II) (Grady 2002). Both the WHI I 2002 and WHI II 2004 trials were planned to continue for 8.5 years, but both trials were terminated early. Outcomes in WHI I 2002 were reported at 5.2 years and subsequently for a further 4 months of follow-up (total follow-up 5.6 years) for primary and selected secondary outcome measures. WHI II 2004 reported outcomes at 6.8 years and for a subsequent further three-months of follow-up (7.1-years) for primary and selected secondary outcomes, with a median time of 5.9 and 5.8 years on treatment for the HT and placebo groups respectively.

Outcomes

The outcomes assessed in the individual trials varied according to the trial objectives. One primary prevention trial (EPAT 2001) and three secondary prevention trials (ERA 2000; ESPRIT 2002; WAVE 2002) aimed to assess the effects of HT upon intermediate outcomes, namely carotid artery intima-media thickness, and the impact on coronary atherosclerosis as measured by the minimal lumen diameter of the arteries respectively. However, all four trials also reported one or more of the clinical outcomes of interest as secondary outcomes and therefore were included in the analyses. The primary aim in the largest two trials, WHI I 2002 and WHI II 2004 was to assess the potential cardio-protective effect of HT in relatively healthy post-menopausal women, and therefore both trials reported cardiovascular clinical endpoints as the primary outcome. Invasive breast cancer was the designated primary adverse outcome in both trials, with the incidence of other cancers, fractures, gallbladder disease and death reported as secondary outcomes. Two further primary prevention trials, EPHT 2006 and WISDOM 2007 also measured similar outcomes, with CVD outcomes designated as the primary ones of interest. The remaining five secondary prevention trials aimed to examine the effects of HT in women with already established clinical disease, with the primary outcome designated according to the underlying patient pathology. Their primary outcomes were myocardial infarction or death (ESPRIT 2002; HERS I 1998), thrombo-embolism (EVTET 2000), stroke (WEST 2001), and angina (HALL 1998).

Five out of the 13 trials (EPHT 2006; HERS I 1998; WHI I 2002; WHI II 2004; WISDOM 2007) additionally reported HRQoL outcomes obtained using one or more validated measures. These outcomes focused on overall health or functional status, and the specific domains of energy/fatigue, depressive symptoms, sleep disturbance, sexual satisfaction, and psychological well being. Outcomes were reported at baseline and one- (WHI I 2002; WHI II 2004; WISDOM 2007) and three-year follow-up (HERS I 1998) in four of the trials. Whilst in EPHT 2006 no baseline scores were reported, with only follow-up scores at two- and 3.6 years presented

Funding Source

All 13 trials reported the funding source. Only one of the trials, HERS I 1998 was exclusively funded by the Pharmaceutical Industry (Wyeth-Ayerst), whilst EVTET 2000 was part funded by a grant from Novo-Nordisk Pharmaceutical. The study medication for ERA 2000 and WHI I 2002 and WHI II 2004 was provided by Wyeth-Ayerst Research, and for ESPRIT 2002 and WEST 2001, Schering AG and Mead Johnson laboratories respectively.

Excluded studies

Nineteen (as well as the HERS II study) studies were excluded. The primary reason for the exclusion were:

Fourteen studies reported no relevant outcomes of interest to this review

Two assessed a different intervention

One was not a randomised controlled trial

One was not the relevant population

One assessed a non-comparison

Risk of bias in included studies

The design and methods within the trials were generally well reported. The review authors' judgements about the risk of bias in the included studies are displayed in Figure 2 and Figure 3.

Figure 2. Figure 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

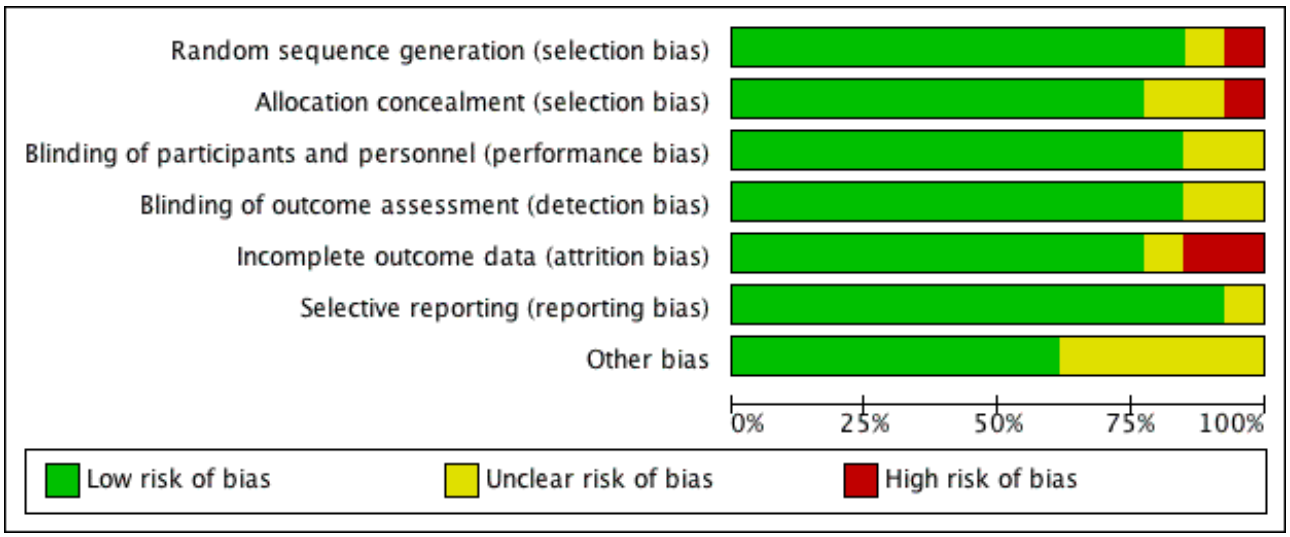


Figure 3. Figure 3: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

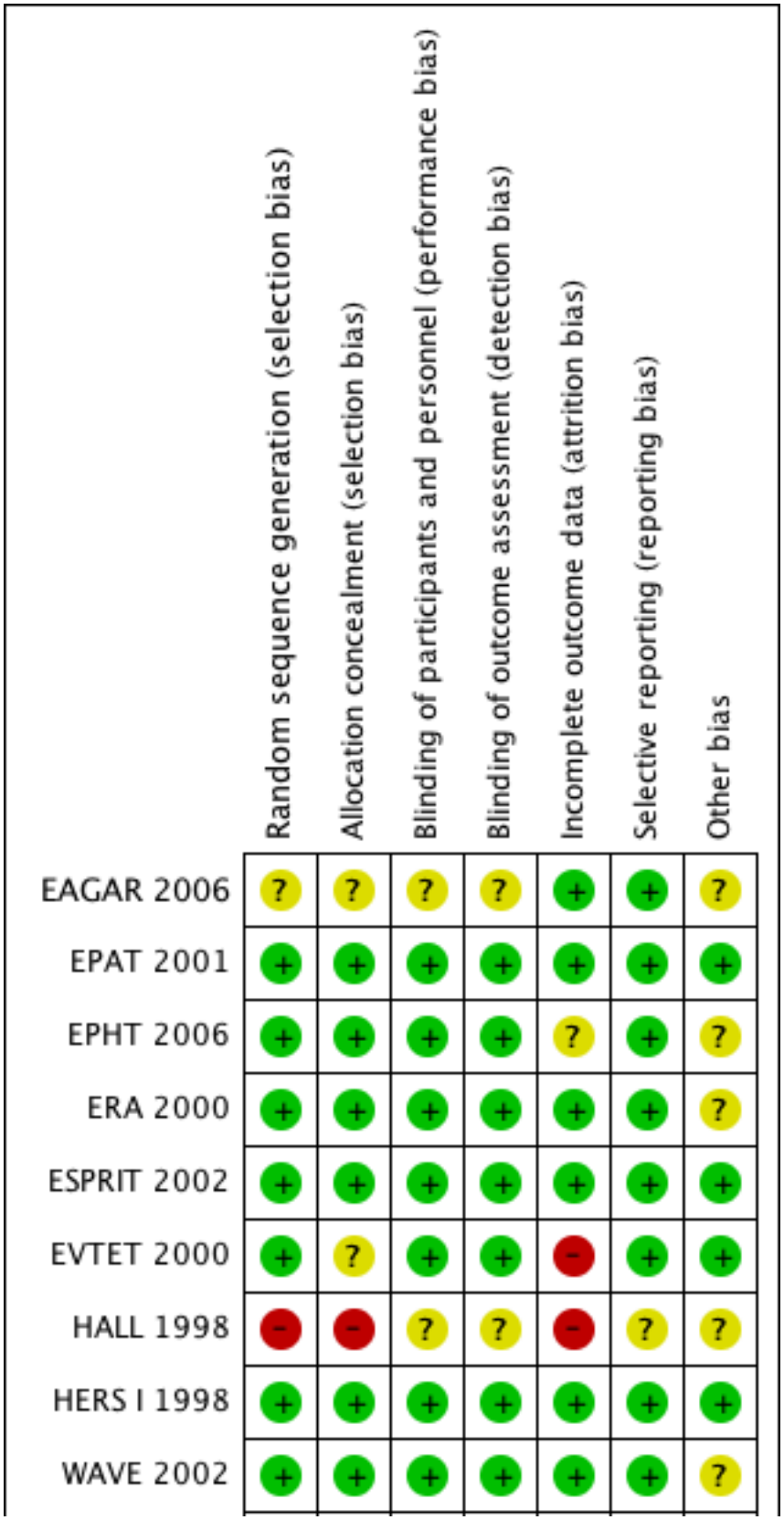
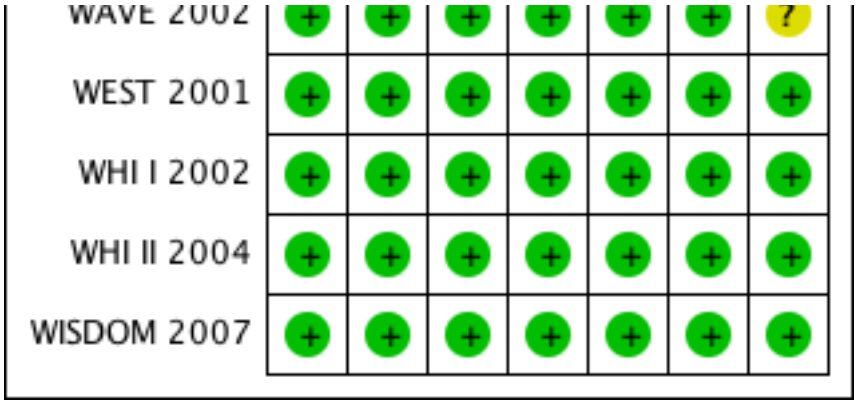


Figure 3. (Continued)



Allocation

The generation of randomised sequence was adequate in 11 out of the 13 trials; in all of these cases it was computer-generated.

Neither EAGAR 2006 or HALL 1998 reported the methods used to generate random allocation, and therefore it is unclear as to whether the method used was satisfactory. Ten trials described a satisfactory method of allocation concealment: in these trials allocation to treatment was either generated by the computer once information about an eligible participant had been entered, or was completed by remote contact between the recruiting centre and the study co-ordinating centre or pharmacy. One of these ten trials, EPHT 2006 randomised women who expressed an interest in participating, but did not open the randomisation envelope until their eligibility had been checked and they had consented. Three of the trials (EAGAR 2006; EVTET 2000; HALL 1998) did not report methods of allocation concealment.

Blinding

All the trials except HALL 1998 described themselves as double blind. Ten of the trials explicitly stated that all participants, clinical staff and outcome assessors were blinded to treatment allocation, and all 13 trials reported 'hard' outcomes; the verification of which is unlikely to be effected by blinding. Unblinding of participants occurred in 331 women initially randomised into the active single HT treatment arm in WHI II 2004, whom after a protocol change were unblinded, and changed arms into the WHI I 2002 combined therapy arm. Eight of the trials additionally described an unblinding mechanism to be used in the management of adverse events (ERA 2000; ESPRIT 2002; WAVE 2002; WEST 2001; WHI I 2002; WHI II 2004; WISDOM 2007).

Incomplete outcome data

Twelve of the trials analysed all participants on an intention-to-treat basis at least for the outcomes of interest in the present review, whilst data in WAVE 2002 were analysed on an ITT basis for over 97% of participants. Drop-out rates (medication non-compliance) were generally high, particularly in the active treatment groups, and tended to increase over time. In the 11 trials that reported data on adherence, these ranged from greater than 90% compliance rates in EPAT 2001 at two-year follow-up, to less than 40% compliance in EPHT 2006 at four-year follow-up. In the two WHI trials with the longest follow-up, 42% of the active treatment group and 38% of the placebo group were no longer taking their allocated treatment at 5.2 years in WHI I 2002, and 10.7% of the placebo group had initiated active HT treatment outside of the trial. Whilst in WHI II 2004 53% of participants overall were no longer taking their allocated treatment at 6.8 years and a further 5.7% had initiated hormone use outside the study. A summary of medication compliance within the trials is given in Table 2.

Losses to follow up were low in most of the trials, with no women lost to follow-up in six trials (EPAT 2001; ERA 2000; ESPRIT 2002; EVTET 2000; HALL 1998; WEST 2001) and between 0.1% to 5.2% lost in five other trials(EPHT 2006; HERS I 1998; WAVE 2002; WHI I 2002; WHI II 2004; WISDOM 2007).

Selective reporting

Only one trial HALL 1998 may have been subject to selective reporting. All the other 11 trials reported all expected outcomes.

Effects of interventions

See: **Summary of findings for the main comparison** HT compared to placebo for prevention of cardiovascular events in postmenopausal women

Results are reported below. In most cases details of effect measures are only reported in the text where results are statistically significant. It was not possible to conduct any analyses stratified by the participants mean age at baseline (> 60 versus < 60 years of age), as only two trials (EPHT 2006; EVTET 2000) included participants with a mean age < 60 years at baseline.

Estrogen alone versus placebo in primary prevention

This comparison was reported in two trials (EPAT 2001; WHI II 2004) with a total of 10,961 participants. No protective effects for HT on all cause mortality, or any CVD outcomes (death, non-fatal MI or angina), the number of angioplasties, or PE was observed (Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.5; Analysis 1.7; Analysis 1.8). However, at 7.1 year follow-up HT use was associated with a increased risk of stroke, RR 1.35 (95% CI 1.08 to 1.70) (Analysis 1.4), and a borderline significant increase in the number of venous thromboembolism, RR 1.32 (95% CI 1.00 to 1.74) relative to placebo (Analysis 1.6). The associated number needed-to-harm (NNH) was 121 for stroke and 197 for venous thromboembolism respectively. Due to the limited evidence for

this outcome no analyses stratified by time on treatment were conducted. However, the WHI II 2004 authors noted the excess risk in the intervention arm was due to an increased risk of ischaemic rather than haemorrhagic stroke which become apparent after four years of follow-up (Hendrix 2006). There was no significant statistical heterogeneity between the two studies for any outcome.

Combination HT versus placebo in primary prevention

Combination HT versus placebo in primary prevention was assessed in three trials, EPHT 2006, WHI I 2002 and WISDOM 2007, with a total of 21,770 participants. Results showed no significant impact on all cause mortality, CVD mortality, or angina (Analysis 2.1; Analysis 2.2; Analysis 2.5; Analysis 2.8). There was an increased risk of non-fatal MI (Analysis 2.3) and stroke (Analysis 2.4). The overall RR for non-fatal MI of 1.38 (95% CI: 1.06 to 1.78) had an associated NNH of 295, whilst the RR for stroke of 1.31 (95% CI 1.03 to 1.68) had a NNT of 231. Analysis stratified by time on treatment for stroke, indicated the excess risk was apparent after three-years on treatment and remained significant with further follow-up time until 5.6 years (Analysis 2.9). There was moderate statistical heterogeneity between the trials (I^2 = 39%) due to the low event rate observed in EPHT 2006, and the dominance of WHI I 2002 results in the analyses, accounting for 97.7% of the weighting.

The RR for venous thromboembolism and PE also increased compared to placebo: 2.29 (95% CI 1.76 to 2.97) (Analysis 2.6) and 2.29 (95% CI 1.59 to 3.31) (Analysis 2.7) respectively. The NNH for the outcome of venous thromboembolism was 100, and the NNH for PE 197. Analysis by time on treatment for venous thromboembolism indicated excess risk at each follow-up time. This was highest early on treatment (one-year follow-up) and diminished with time, but remained significantly higher at each time point (Analysis 2.10). Significant statistical heterogeneity between trials (WHI I 2002 and WISDOM 2007) with an I^2 of 75% was observed for the outcome of venous thromboembolism. This was due to the high number of event rates observed in the treatment arm in WISDOM 2007 which may inflate the relative risk reported at one-year of treatment. Analyses using a random effects model had no impact on this observed variation.

Estrogen alone versus placebo in secondary prevention

Four trials with a total of 1917 participants assessed oestrogen alone versus placebo in women with established CVD disease (EAGAR 2006; ERA 2000; ESPRIT 2002; WEST 2001). No significant differences between treatment arms were observed for mortality (all cause or CVD), any CVD outcomes (non-fatal MI, stroke, angina), or either venous thromboembolism or PE (Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4; Analysis 3.5; Analysis 3.6; Analysis 3.7). Significantly more patients on HT underwent an angioplasty, with a RR of 8.60 (95% CI 1.13 to 65.73), but this result was based on the results of one small trial (EAGAR 2006; n = 83) with a low number of event rates (n = 9). There was no statistical heterogeneity between trials for any of the outcomes.

Combination HT versus placebo in secondary prevention

Combination HT versus placebo in secondary prevention was assessed in five trials with a total of 3523 participants (ERA 2000; HALL 1998; HERS I 1998; EVTET 2000; WAVE 2002). No protective effects for combination therapy were observed for mortality (all cause or CVD), any CVD outcomes (non-fatal MI, stroke, angina), or the number of CABG or angioplasty procedures (Analysis 4.1; Analysis 4.2; Analysis 4.3; Analysis 4.4; Analysis 4.5; Analysis 4.8; Analysis 4.9). Significantly more venous thromboembolic events (including PE) occurred in the HT trial arms, with a RR of 2.59 (95% CI 1.51 to 4.42) for all venous thromboembolic events and a RR of 3.77 (95% CI 1.41 to 10.06) for PE alone (Analysis 4.6; Analysis 4.7). The associated NNH for venous thromboembolism and PE were 60 and 104 respectively. Analysis by time on treatment for venous thromboembolism indicated excess risk at each follow-up time. This was highest early on treatment (one-year follow-up) which diminished but remained significantly higher compared to placebo at each follow-up time until 6.8 years (Analysis 4.12). There was no significant heterogeneity between the trials for any of the outcomes.

Single and combination HT (oestrogen plus progestogen) in both primary and secondary prevention

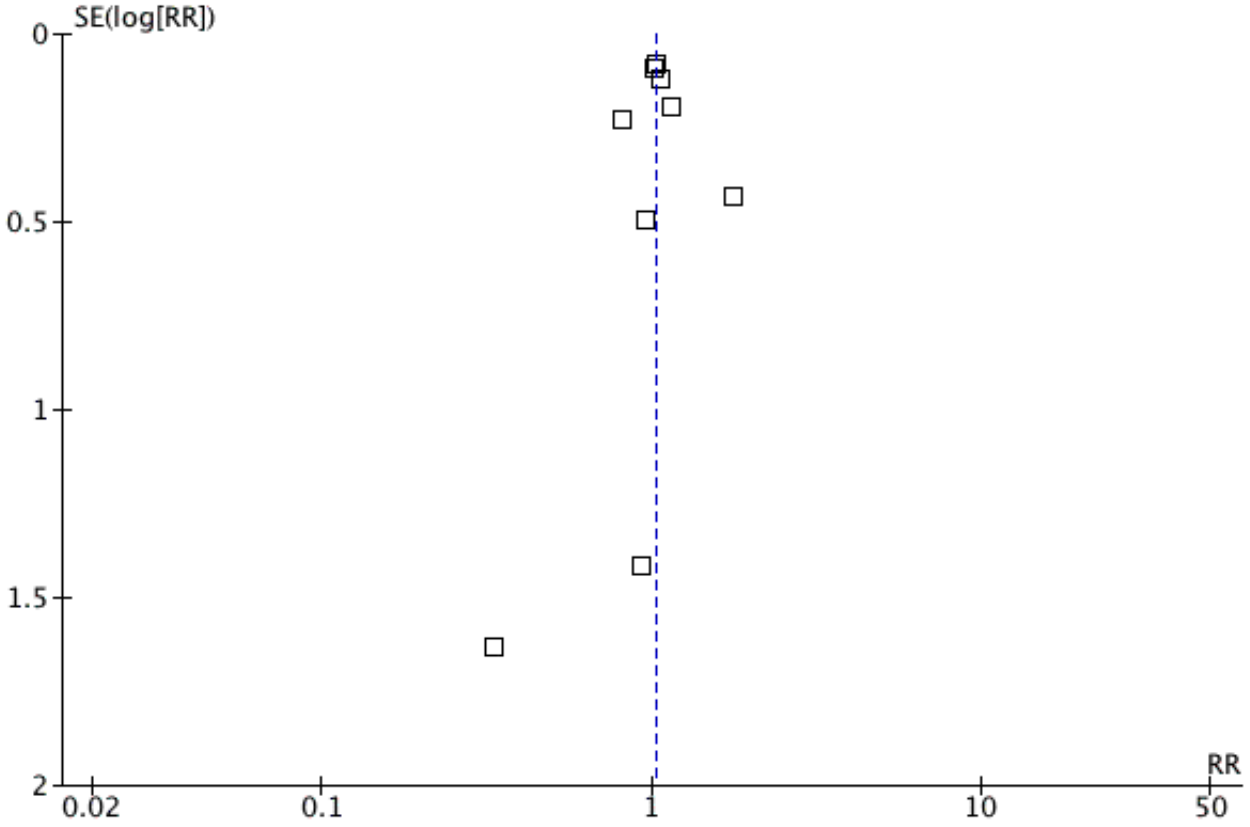
Consistent with effects observed in both primary and secondary prevention, HT overall had no protective effects for death, or any of the CVD outcomes, or CVD related surgical procedures compared to placebo (Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.8; Analysis 5.9). Again, an increased risk of stroke, RR 1.26 (95% CI 1.11 to 1.43), venous thromboembolism RR 1.89 (95% CI 1.58 to 2.26) and PE RR 1.84 (95% CI 1.42 to 2.37) relative to placebo was observed (Analysis 5.4; Analysis 5.6; Analysis 5.7). The associated NNH were 164, 109 and 243 for stroke, venous thromboembolism and PE respectively.

Analysis for stroke by time on treatment indicated that excess risk was evident from approximately three-year follow-up, and remained higher until the longest follow-up time of 7.1-years (Analysis 5.13). Whilst the analysis for time on treatment for venous thromboembolism evidenced an excess risk at all follow-up points (1 - 7.1 years), which was highest at one-year follow-up and attenuated with longer follow-up, but remained significantly higher relative to placebo (Analysis 5.15).

Significant statistical heterogeneity was present between trials for the outcome of venous thromboembolism (I^2 = 66%). Analyses using a random effects model had no impact on this observed variation.

No evidence of reporting bias was evident on examination of funnel plots (Figure 4)

Figure 4. Funnel plot of comparison: HT versus placebo in primary and secondary prevention, outcome: 5.1 Death (all causes).



Meta-regression analyses

None of the three predictor variables of length of trial follow-up, whether treatment was single (i.e.) oestrogen alone or in combination with progestogen, and whether the patient population were being treated for primary or secondary prevention of CVD were statistically significant predictors for the outcomes of (i) all cause mortality, (ii) CVD mortality, (iii) non-fatal MI, (iv) stroke, (v) angina, (vi) venous thromboembolism or (vii) PE in the trials. This was related to the fact that there was no overall substantive statistical heterogeneity in terms of the results between the trials, and stratified analyses for both stroke and venous thromboembolism indicated that effects did not vary linearly as a function of treatment time, but were likely to be curvlinear. The results of the meta-regression are presented in Table 3.

Health-related quality of life

Five out of the 13 trials (EPHT 2006; HERS I 1998; WHI I 2002; WHI II 2004; WISDOM 2007) reported validated HRQoL measures. The results are displayed in Table 4 and Table 5 . A number of different measures had been used across the trials, both generic and condition specific. HERS I 1998 (Hlatky 2002) measured physical functioning at baseline, years one, two and three-year follow-up using the 12-item Duke Activity Status Index (Hlatky 1989), energy/fatigue using a four-item RAND scale (Ware 1992), mental health using the Rand Mental Health Inventory (Stewart 1988), and depressive symptoms using an eight-item scale by Burnam and colleagues developed to screen for depression in the National Study of Medical Outcomes (Burnam 1988). Only very limited data from each scale were reported graphically, and therefore only the composite results from baseline and three-year follow-up are presented. HRQoL / functional status was assessed using the RAND 36-Item Health Survey (RAND 36) (Ware 1992) at baseline and one-year follow-up in both WHI I 2002 and WHI II 2004; depressive symptoms were assessed using the same 8-item scale by Burnam 1988 used in HERS I 1998; sleep quality was assessed using a five-item Women's Health Initiative Insomnia Rating Scale (developed and validated for use in the WHI; Levine 2003) and sexual satisfaction (either with your current partner or alone) was assessed by a single item with a four-point response scale ranging from one (worst) to four (best). In WISDOM 2007 general HRQoL and psychological well being were assessed at baseline and 11.9 month follow-up using a modified version of the Women's Health questionnaire (Hunter 1992), emotional and physical menopausal symptoms using a trial specific 28 item symptoms questionnaire, depression using the Centre for Epidemiological Studies Questionnaire (CES-D) (Radloff 1977), and generic HRQoL using the EQ-5D (EuroQol 1990) (Kind 2003). EPHT 2006 assessed generic HRQoL also using the EQ-5D at both two- and 3.6-year follow-up. However, no results were reported at baseline, so interpreting any changes in scores longitudinally is problematic.

Given the disparity and wide variation in the HRQoL outcomes used, pooling outcomes across the studies was deemed inappropriate. The HRQoL results at baseline and three-year follow-up for HERS I 1998, baseline and one-year follow-up for WHI I 2002

and WHI II 2004, WISDOM 2007 and EPHT 2006 with the between group differences are therefore presented in Table 4 and Table 5.

Overall, from HERS I 1998 (Hlatky 2002) there was no evidence that HT had any statistically significant impact on any of the four domains of HRQoL assessed (energy/fatigue, physical functioning, mental health or depressive symptoms) compared to placebo from baseline over the three-year follow-up period. Energy/fatigue, physical functioning and mental health remained relatively stable from baseline until year three in both groups. However, a minor statistically significant decline in depressive symptoms was observed in both groups across the trial period. This did not differ between the two treatment groups. Results from WHI I 2002 (Hays 2003) showed that women randomised to HT had a statistically significantly better level of functioning on four out of the eleven domains of functioning assessed, namely sleep disturbance, bodily pain, physical functioning, and related to this, role limitation due to physical problems compared to those on placebo at one-year follow-up. However, when the increment of change between the two groups was compared, the differences in effect size between the two groups was small, and therefore whilst statistically significant was not likely to be clinically meaningful. Likewise, the results from the WHI II 2004 (Brunner 2005) indicated that HT (oestrogen alone) had a statistically significant positive impact on some limited areas of functioning, namely physical functioning and sleep disturbance, but appeared to have a detrimental effect on vitality compared to placebo. Again, a statistically significant positive impact for HT use on overall HRQoL was observed for only two of the 11 domains of functioning assessed, and effect sizes were small. Results from WISDOM 2007 (Welton 2008) indicate that combination HT had a statistically significant positive impact on some areas of functioning across the 11.9 month follow-up period. Most notably, as expected, these were related to menopausal symptoms such as hot flushes, night sweats, vaginal problems (dryness and discharge), breast tenderness and bloating. However, this statistically significant effect was only observed in seven of the 28 areas of symptom related problems assessed, and may be of somewhat limited clinical impact, as no differences between the two treatment groups was observed on either the EQ-5D VAS or questionnaire which assess health impact more broadly on a wider set of functioning domains. Likewise, no significant differences in the distribution of EQ-5D scores were observed between women on HT and placebo in EPHT 2006 at either two- or 3.6-year follow-up. All scores were highly positively skewed, indicating high levels of functioning and little if any impairment, with half of the women in both trials arms having a EQ-5D score of 0.90 at the end of the second year of the trial, and 0.80 at the end of the trial.

DISCUSSION

Summary of main results

In the overall trial populations there is no evidence that HT has a role in either the prevention or the treatment of CVD. Treatment with HT had no significant impact on either overall death rates, CVD related death, non-fatal MI, angina, or the number of patients undergoing revascularization procedures. On the contrary it is associated with an increased risk of stroke, venous thromboembolism and pulmonary embolism, and combination HT in primary prevention also increased the risk of non-fatal MI. This increased risk of non-fatal MI was not observed in secondary prevention combination HT trials, and it is unclear why differential effects are observed for this outcome between these patient populations particularly given that both HERS I 1998 and WHI I 2002 used the same combination HT preparation (continuous combination CEE with MPA). In contrast to combination HT, oestrogen only HT does not appear to have any statistically significant negative effect on coronary disease.

The excess risk of coronary events in women in the HT group was observed in the first year of treatment in women taking combination HT in both HERS I 1998 and WHI I 2002. Although there was a significant trend in both WHI I 2002 and the blinded phase of HERS I 1998 for CVD risk in the HT group to diminish with time on treatment, subsequent analysis of HERS I 1998 data (including both the blinded and non-blinded follow-up phase) indicated no statistically significant variation in risk over time. The WHI I 2002 investigators suggest the apparent decline in CVD risk in later years may be due to an acceleration of events in earlier years among susceptible women in the HT group, and highlight that the trend towards a decreasing CVD risk over time with combination therapy should be interpreted with caution (Manson 2003). Results from our analyses by time on treatment for both CVD death and non-fatal MI broadly agree with the WHI I 2002 and HERS I 1998 findings. Excess risk (although not significant) was highest for both outcomes in the first year on treatment and then gradually declined. Both WHI I 2002 and WHI II 2004 undertook pre-specified sub-group analyses to evaluate whether any clinical characteristics of the trial populations may potentially moderate the effects of HT. The potential predictor variables examined included: age, time since menopause, presence or absence of vasomotor symptoms, prior hormone use, CHD risk factor status and presence or absence of pre-existing CVD (Hsia 2006; Manson 2003). None of these variables significantly effected results, although a non-significant trend for a reduction in CHD risk for women who initiated HT use within ten-years of menopause was observed.

The significant excess risk of stroke in our analyses was observed in both primary prevention analyses (i.e.) those randomised to either oestrogen alone or oestrogen in combination with progestogen compared to placebo. These findings are based on the two largest trials, WHI I 2002 and WHI II 2004 with follow-up of 5.6 and 7.1 years respectively. Whilst, no significant excess risk was observed in any of the secondary prevention trials, including the largest trial HERS I 1998, it is probable that the results from the primary prevention trials are applicable to secondary prevention populations, and that sub-group analyses of these trials were underpowered due to small trial sizes, low event rates and shorter length of follow-up to detect any statistically significant differences in stroke rates between HT and placebo treatment arms. In both WHI I 2002 and WHI II 2004 the excess risk of stroke observed with HT use was driven by an excess of ischaemic rather than haemorrhagic stroke, with 79.8% and 80.3% of strokes respectively observed within the trials being ischaemic (Hendrix 2006; Wassertheil-Smoller 2003). In our analyses increased risk of stroke was apparent after three-years on treatment in women taking combination HT, and after four-years for women randomised to oestrogen alone (Hendrix 2006). In both trials the hazard ratios for ischaemic stroke did not differ significantly in sub-groups based on age, years since menopause, prior CVD, hypertension status or diabetes mellitus, body mass index, or statin or aspirin use at baseline (Hendrix 2006; Wassertheil-Smoller 2003).

The finding of a significant increase in risk for both venous thromboembolism and PE within the overall trial populations appears in our analyses to be driven largely by the excess risk observed in both primary and secondary prevention combination HT trials. Estrogen alone use in primary prevention was associated with a marginally significantly increased risk of venous thromboembolism , and there was no significant excess risk associated with oestrogen alone use in secondary prevention; although it should be noted that in both analyses the point estimates favoured treatment with placebo, and therefore these results should be interpreted with some degree of caution. The risk of venous thromboembolism and PE in both primary and secondary prevention trials with combination HT indicated a more than two-fold risk increase of venous thromboembolism and PE on HT relative to placebo. Analyses by time on treatment showed that for both primary and secondary prevention, the risk was highest close to the initiation of treatment, and attenuated with time, but remained significantly higher on HT compared to placebo. Both WHI I 2002 and WHI II 2004 undertook further pre-specified subgroup analyses to evaluate the association between participant baseline characteristics and venous thromboembolism and PE risk. Not surprisingly, given the fact that no excess risk was observed within the trial WHI II 2004 investigators found no significant interactions between oestrogen alone use and age, body mass index, or most other venous thromboembolism risk factors. The authors did note however, the hazard ratios for combination therapy in WHI II 2004 were significantly higher than those for oestrogen alone even after adjusting for venous thromboembolism risk factors (Curb 2006). In WHI I 2002, increasing age, overweight and obesity, and having a factor V Leiden mutation (a blood coagulation disorder) were associated with a higher risk of venous thromboembolism compared to placebo (Cushman 2004).

Overall completeness and applicability of evidence

There are a number of limitations to the evidence base reviewed. Firstly, it should be highlighted that the results are based on those obtained in 13 RCTs, with the majority of statistically significant findings derived from the results of the three largest trials, HERS I 1998, WHI I 2002 and WHI II 2004 which dominated the results. These three trials all evaluated oral CEE 0.625 mg, with or without continuous methoxy progesterone (MPA 2.5 mg). Other trials evaluating different types of HT tended to be much smaller with a shorter duration of follow-up, and reported few if any major clinical events. There is some debate regarding the external validity of the findings of WHI I 2002 and WHI II 2004, and the degree to which they apply to any type of HT other than continuous combined oral CEE 0.624 mg with or without MPA 2.5 mg. The effects of HT may vary with different estrogens and progestogens, different doses, and routes of administration. However, in order to statistically pool the results of different studies we had to make assumptions regarding a ‘class effect’ of HT, which may not be warranted.

It was not possible to stratify any analyses according to the mean baseline age of trial participants in order to assess the impact of time since menopause on CVD outcomes. Only two of the trials (EPHT 2006; EVTET 2000) included participants with a mean baseline age of less than 60 years, and only WHI I 2002 and WHI II 2004 reported additional sub-group analyses to assess the relationship between both participant age and time since menopause on outcome. It therefore has not been possible within the review to assess any potential impact of the timing of HT treatment in relation to the time of menopause, and therefore contribute to the current debate regarding the 'timing hypothesis'.

The clinical outcomes of interest in the review were secondary outcomes in four of the trials (EPAT 2001; ERA 2000; ESPRIT 2002 and WAVE 2002). It can therefore be postulated that these trials may not have been sufficiently powered in order to detect differences in clinical treatment effects between the HT and placebo arms, as this was not the primary aim of the trial. Furthermore, as previously highlighted six of the trials were stopped early (EAGAR 2006; EPHT 2006; EVTET 2000; WISDOM 2007; WHI I 2002; WHI II 2004) either as other trial results were published showing no beneficial effects on CVD outcomes for HT relative to placebo, or observation of a detrimental effect either on CVD outcomes or adverse events was shown. The mean length of trial follow-up therefore ranged considerably from 11.9 months to 7.1 years, with a mean duration of follow-up of three years across the trials. The early stopping of the trials has implications both for the power to detect differences in treatment effects between the HT and placebo arms, as the sample size will have been predicated based on the original proposed length of follow-up and assumptions regarding the number of events observed, and also limits the availability of evidence on the longer term treatment effects of HT compared to placebo. A further limitation of the evidence base reviewed relates to the impact of patient medication compliance, which ranged dramatically between the trials. A high proportion of women in the trials did not receive the treatment to which they were randomised. Overall, the number of women who discontinued their medication or took less than 80% was disproportionately high in the HT trial arms, presumably due to medication side effects. The authors of WHI I 2002 noted that if discontinuation of treatment and initiation of non-study treatment occurred independently of risk factors for clinical outcomes their intention-to-treat analysis underestimates both the harms and benefits of HT among women who adhere to treatment.

Quality of the evidence

Overall study quality was high (Figure 3).

Potential biases in the review process

There are a number of potential biases in the review process, although attempts have been made to limit these. The bias of most concern is that of patient-selection bias which limits external validity. Nearly all the included trials had a mean participant age of over 60-years at baseline, and none focused on women who were either peri-menopausal or around the time of the menopause. Whilst these inclusion criteria reflected the aims of the trials, it does not reflect usual clinical practice, in which HT is prescribed for the relief of vasomotor symptoms at the time of menopause. This also limited the analyses that could be undertaken, as it was not possible to stratify trials according to the participants mean age at baseline to assess the potential impact of time since menopause on CVD outcomes.

Despite of extensive searches it is possible that we failed to identify all relevant studies. However, given the dominance of WHI I 2002 and WHI II 2004 on the results of the review, it is unlikely that we missed any trials large enough to impact substantially on the results. Additionally, as already indicated, assumptions had to be made in the analyses regarding the effects of different HT preparations in order to undertake meta-analyses. These

assumptions may not be warranted, as it is as yet unclear how different preparations and doses may differ.

Agreements and disagreements with other studies or reviews

Magliano 2006 pooled results from seven of the trials included in the current review (ERA 2000, ESPRIT 2002, HERS I 1998, WAVE 2002, WEST 2001, WHI I 2002; WHI II 2004), and concluded that there was no impact of HT compared to placebo on total mortality or non-fatal MI, but a statistically significant increase of 29% in the number of strokes observed with HT use. Likewise, a meta-analysis by Bath 2005 pooled 28 RCTs that reported stroke events. HT was associated with a statistically significant increase in the risk of stroke, particularly ischaemic stroke. Furthermore for those participants who had a stroke the HT groups appeared to have a worse outcome. However, it is unclear to what degree the results of this review are applicable to post-menopausal women, as the review had very broad inclusion criteria, pooled a wide range of trials which used different types of HT for a range of indications, some of which included male participants.

Salpeter 2006 in a second meta-analyses, aimed to examine the effect of HT on coronory heart disease events in younger and older post-menopausal women (defined as participants with a mean time from menopause of less than or greater than ten years, or mean age less than or greater than 60 years). The analyses of 23 trials (ten trials with younger women and 11 trials with older women), included the relevant WHI age-specific sub-group data in one or the other group as though they had originated from separate RCTs. The results showed that HT significantly reduced coronay heart disease events in younger women, but not in older women. Given the wide variety of different HT preparations in the 23 trials included in the analyses, the differing patient populations, and the methods of analyses it is unclear how applicable the results of this review are to the populations studied in the present review.

AUTHORS' CONCLUSIONS

Implications for practice

Treatment with HT in post-menopausal women for either primary or secondary prevention of CVD events is not effective, and causes an increase in the risk of stroke, or venous thromboembolic events. Furthermore, combination HT in primary prevention is also associated with an increased risk of non-fatal MI.

Improvements in menopausal symptoms assessed in health-related quality of life with oral HT compared with placebo are suggestive that short-term therapy could be considered for use by women seeking relief from menopausal symptoms. Short-term HT treatment should be at the lowest effective dosage with consideration of transdermal administration.

Implications for research

No trials were identified that have assessed the efficacy and safety of HT for either perimenopausal women or those seeking relief from menopausal symptoms. Currently there is a lack of evidence regarding factors that may modulate the risks involved in HT treatment, such as different oestrogen and progestogen preparations, different time-frames for the use of HT, and different doses and routes of administration (for example, skin patches and creams). The results of both ELITE 2004 (NCT00114517) and KEEPS 2005 (NCT00154180) should lay the foundation for future research in this area. There is an additional need for research on the efficacy and safety of alternative methods for the relief of menopausal symptoms for women who may wish to avoid its use.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

EAGAR 2006

Methods	**Objective:** To assess the effects in post-menopausal women of HT started after coronary artery by-pass surgery (CABG) on saphenous vein graft (SVG) disease. Multicentre randomised controlled (RCT) trial involving eight hospital sites in the United States. The trial was conducted from 1998-2002 over a 3.5 year follow-up (mean duration 33 ± 8 months). The trial was stopped early after the Women's Health Initiative (WHI 2002) reported an increased risk of breast cancer and no additional benefits for women on HT in terms of CVD risk on combined oestrogen and progestin combination therapy relative to placebo.

EAGAR 2006 *(Continued)*

	The primary outcome measure was SVG progression assessed by angiography and intravascular ultrasound (IVUS) on percent stenosis, minimal lumen diameter, and total plaque volume. Secondary outcomes (non specified a priori included death from CV disease, MI, angina and angioplasty. **Recruitment:** Not reported. **Screening:** Not reported. **Randomisation:** Not reported. **Stratification:** Not reported. Allocation: Not reported. **Baseline equality of treatment groups:** No substantive differences between study groups at baseline. **Blinding:** Not reported. **Analysis:** ITT for secondary clinical outcomes. **Funding Source:** Research Council funded.
Participants	Eight-three post-menopausal women (HT: 40; placebo: 43) with a mean age of 64 (SD: ± 8.5 years) underwent treatment with either HT or placebo within 6 months following coronary artery by-pass. Post-menopausal status was defined as > 55 years of age and amenorrhoea for ≥ 1 year or follicle stimulating hormone > 50 IU. The number of women whom had previously undergone a hysterectomy was not reported. Included women were 78% white, and 22% from an ethnic minority group. 40% had a history of diabetes, 69% hypertension, 81% hyperlipidaemia and 40% MI. In terms of smoking status: 16.5% were current smokers; 59.5% past smokers and 24.5% never smokers. 35% had prior HT use. Mean BMI among the women was 30 kg/m^2 (SD: 30 ± 6). Mean systolic blood pressure at baseline was 135 (SD: 6) mm HG and diastolic blood pressure was 72.5 (SD: 10.5) mm HG. There were no statistically significant differences between the two groups in terms of baseline demographics. **Exclusion criteria:** Current HT use (i.e.) within the three months before enrolment; contraindication to HT including a history of hormone sensitive neoplasia or severe liver disease; history of hormone idiopathic deep venous thrombosis or pulmonary embolus; symptomatic gallbladder disease; creatine of ≥ 2 mg/mL; or a life-expectancy of < 4 years.
Interventions	**HT regimen:** 1 mg unopposed 17ß-estradiol daily with or without daily 2.5mg medroxyprogesterone depending on hysterectomy status (continuous dosage regimen). **Comparator:** identical placebo capsule daily. The overall compliance with study intervention assessed by pill count at each visit exceeded 80% in both arms up to 3 - 0 months of treatment. **Follow-up times:** Six-months, angiogram (n = 83) (actual mean time of angiogram assessment 10.7 months post CABG); intravascular ultrasound assessment (IVUS) (n = 63); 42-months: angiogram (n = 45), IVUS (n = 20). Actual mean time of participant follow-up was 33 (SD: eight) months before the study drug was stopped.
Outcomes	Percent stenosis Minimal lumen diameter Total plaque volume Death from CV disease (definition not provided)

EAGAR 2006 *(Continued)*

	Angina (definition not provided) MI (definition not provided) Angioplasty (definition not provided)
Notes	Sample size calculation not reported, and therefore it is unclear whether the trial was powered to adequately detect significant differences in clinical event rates between the HT and placebo group. It is unclear how the CVD events were defined, and whether definitions may have varied between centres. Additionally it unclear how these were corroborated, locally or centrally and whether outcome assessors were blinded to patient treatment status. Patient attrition rates was high for both angiographic and intravascular ultrasound (IVUS), with only 45.6.5% of patients undergoing IVUS at trial termination [mean length of follow-up: 33 months (SD: eight months)]. However, follow-up for all clinical events was completed for all patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and study personnel not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data complete for clinical outcomes/events
Selective reporting (reporting bias)	Low risk	Paper reports main outcome measures of angiographic and intravascular ultrasound (IVUS) as well as all CVD events that occurred in the trial
Other bias	Unclear risk	It is unlikely that the trial was powered to detect differences in clinical events between the HRT and placebo treatment groups. Therefore the lack of significant differences in event rates between the two groups should be treated with caution

EPAT 2001

Methods	**Objective:** To determine the effect of estrogen-alone HT on the progression of sub-clinical atherosclerosis in healthy post-menopausal women without pre-existing cardiovascular disease, as measured by changes in thickness of carotid artery wall. University-based clinic randomised controlled (RCT) trial conducted in the United States over a two year follow-up period (1994-1998). The primary outcome measure was carotid intima-media thickness to assess the rate of progression of sub-clinical atherosclerosis; clinical outcomes were reported as secondary outcomes.

EPAT 2001 *(Continued)*

	Recruitment: Not reported. **Screening:** Interested women screened by phone for eligibility, then attended three screening visits two to four-weeks apart to determine final study eligibility. 1161 pre-screened by phone, 422 screened on site, of whom 52% randomised. **Randomisation:** Computer-generated random numbers **Stratification:** By LDL cholesterol level (threshold <4.15 mmol/L), previous duration of HRT, (threshold < 5 years), and diabetes mellitus status. **Allocation:** Blinded medication packets assigned sequentially and remotely after eligibility confirmed **Baseline equality of treatment groups:** No substantive differences between study groups at baseline apart from a significantly higher proportion of HT patients than placebo patients had undergone a complete or partial oophorectomy at baseline (p = 0.03) **Blinding:** Participants, gynaecologists, clinical staff, and image analysts. The data monitor and data analyst were blinded to treatment assignment until analyses were completed **Analysis:** ITT. **Funding Source:** National Institute on Aging.
Participants	222 post-menopausal women (HT: 111; placebo: 111) with a mean age of 62.2 years (range: 46 - 80 years) underwent treatment with either HT or placebo. Post-menopausal status was not defined in the trial. The ethnic origins of the women included in the trial were: 57% White, 11% Black, 21% Hispanic, 10% Asian and 1% Other. 38% of women had undergone a hysterectomy, and 18% an oophorectomy‡. In terms of smoking status: 53% were former smokers and 47% non-smokers. Mean BMI among the women was 29.4 kg/m^2. Systolic blood pressure at baseline was 128 mm HG and diastolic blood pressure was 76.1 mm HG. **Inclusion criteria:** Women were eligible if they were post-menopausal (serum estradiol level < 73.4 pmol/L [< 20 pg/mL], 45 years of age or older, and had a low-density lipoprotein (LDL) cholesterol level of 3.37 mmol/L or greater (≥130 mg/dL). Women with diabetes were eligible for inclusion provided their fasting blood glucose level was less than 11.1 mmol/L (< 200 mg/dL). **Exclusion criteria:** A diagnosis of breast or gynaecological cancer within the past five years or if these cancers were identified during screening; previous HT use for more than 10 years or if HT had been used within one month of the screening visit; five or more hot flushes daily that interfered with daily activity; diastolic blood pressure greater than 110 mm HG, untreated thyroid disease, life-threatening disease with a survival prognosis less than 5 years, total triglyceride level of 4.25 mmol/L or greater (≤ 400 mg/dL), high-density lipoprotein (HDL) cholesterol level less than 0.78 mmol/L (< 30 mg/dL), or serum creatinine concentration greater than 221 µmol/L (> 2.5 mg/dL), or if they were current smokers. ‡a significantly higher proportion of HT patients than placebo patients had undergone a complete or partial oophorectomy at baseline (p = 0.03)
Interventions	**HT regimen:** 1 mg unopposed micronized 17ß-estradiol daily (continuous dosage regimen). **Comparator:** identical placebo capsule daily. Overall pill adherence in the trial was 95% in the HT group and 92% in the placebo group (p = 0.08). This was maintained throughout the two year follow-up trial period. **Follow-up times:** Patients were followed-up every month for the first six-months and then every other month for two-years. Carotid artery ultrasonography in patients with a uterus was performed at baseline and then

EPAT 2001 *(Continued)*

	every six-months. Pelvic examination. Papanicolou smear, and mammography were performed annually. During the trial, mean pill adherence was 95% in the oestradiol group and 92% in the placebo group (P = 0.08). **Losses to follow up:** 33 women were not evaluable for primary study endpoints, but clinical endpoints were reported for all outcomes.
Outcomes	Carotid intima-media thickness All causes of death Death from CV disease MI Coronary artery by-pass Angioplasty
Notes	The sample size power calculation was based on potential differences in change in the intima-media thickness of the right distal common carotid artery far wall between the HT and placebo groups, and therefore it is unclear whether the trial was powered to adequately detect significant differences in clinical event rates between the HT and placebo group. It is unclear how the CVD events were defined, and whether these were corroborated locally or centrally.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Blinded medication packets assigned sequentially and remotely after eligibility confirmed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, gynaecologists, clinical staff, and image analysts. The data monitor and data analyst were blinded to treatment assignment until analyses were completed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adverse events and bleeding were assessed by the study gynaecologist who was blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	33 women were not able to be evaluated for primary (physiological) study endpoints, but clinical endpoints were reported for all by intention to treat analysis
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No obvious source of other bias

EPHT 2006

Methods	**Objective:** To ascertain harms and benefits of combined CT among healthy post-menopausal Estonian women. Multicentre four-armed randomised, placebo and non-treatment controlled trial (RCT) involving three primary care sites in Estonia. The trial was conducted from 1999 - 2001, with a mean follow-up of 3.4 years (range: 2 - 4.9). The trial was originally planned to be part of the Women's International Study of Long Duration Oestrogen After Menopause (WISDOM) trial based primarily in the United Kingdom, and therefore no individual sample size was undertaken for the Estonian component of the trial. The trial was planned for five-year duration, but was stopped early after the reports from WHI I 2002 were published. The primary aim of the trial was to assess the effects of combined oestrogen and progestin HT among healthy post-menopausal women. The trial also assessed the impact of blinding versus no blinding to treatment allocation on recruitment rates through including 4-trial arms: (1) blinded HT combination therapy; (2) blinded placebo therapy; (3) unblinded HT combination therapy, and (4) unblinded no treatment control groups. After adjustment of participant's age at recruitment and former oral contraceptive use between the blinded and non-blinded groups, the results were then combined, with HT therapy groups combined and placebo and no treatment control group combined, and the outcome data presented for both of the two groups. **Recruitment:** Invitation sent to whole female population aged 50 - 64 of two areas of Estonia **Screening:** No of women screened for eligibility: 39713 (whole female pop aged 50 - 64 of two areas of Estonia) **Randomisation:** Remotely randomised in permuted block algorithm **Stratification:** By clinical centre Allocation: Non-transparent sealed envelopes **Baseline equality of treatment groups:** More prior use of oral contraceptive in HT group 9.2% versus 6.4%; HT group older (59 versus 58.5) **Blinding:** Participants and investigators blinded **Analysis:** ITT. **Funding Source:** Academic and government grants.
Participants	1778 healthy post-menopausal women were randomised to HT, placebo or a no treatment control group. The definition of post-menopausal was at least 12 months since last menses. (1) 404 women were randomised to blinded combination HT treatment; (2) 373 to blinded placebo; (3) 494 to unblinded combination HT therapy, and (4) 507 to no treatment control. Results reported for the blinded combination HT and placebo arms (n=777) only included in the analyses. ǂ The mean age of the women was 58.8 years (SD: ± 4.0), with a mean age of menopause of 50 years (SD: ± 3.9) years. 10% of the women had previously undergone a hysterectomy. Mean BMI was 27 kg/m2. In terms of risk factors for CVD: 15% were current smokers; 13.2% were being treated for hypertension; 8.5% had a history of angina; and 1.3% had a previous MI. Mean systolic blood pressure was 137 mm Hg and mean diastolic blood pressure 86.2 mm Hg Inclusion criteria: Aged between 50 - 64 years and menopausal as defined above. **Exclusion criteria:** Use of HT during the past six-months; untreated endometrial adenomatosis of atypical hyperplasia of the endometrium; a history of breast cancer, endometrial cancer or ovarian cancer or any other cancer treated less than five-years ago; a history of meningioma; MI within the last six-moths; a history of

EPHT 2006 *(Continued)*

	hepatitis of functional liver disorders in the last three-months; a history of deep vein thrombosis; pulmonary embolism; cerebral infarction; porphyria; hypertension of more than 170/110 mm Hg despite medication; laparoscopically or histological confirmed endometriosis. ǂ Number randomised and analysed differs between clinical and HRQoL reports. 777 randomised and analysed for clinical outcomes (HT: n = 404; placebo: 373); 796 randomised and analysed for HRQoL (HT: n = 415; placebo: n = 381)
Interventions	**HT regimens :** 1) 0.625 mg conjugated equine oestrogen and 2.5 mg medroxyprogesterone acetate daily (continuous dosage regimen). For women (n = 251) within three-years of their last period 5.0 mg medroxyprogesterone acetate daily along with the standard dose of 0.625 mg conjugated equine oestrogen was prescribed. **Comparator:** 2) Placebo 3) No treatment control. Rates of medication compliance in the trial varied dramatically with adherence < 40% in HT group and < 30% in placebo group by three yrs (estimated from graph). **Follow-up times: baseline,** seven-months, and then annually. Patients underwent a Papanicolaou smear at baseline, and measurement of weight, arterial blood pressure, pelvic and breast examination annually. A Papanicolaou smear was taken every second year. Thirteen patients were lost to follow-up, so the clinical status of all participants at trial exit was known for 97% of the women.
Outcomes	**Coronary heart disease** (angina, acute MI, subsequent MI, current complications following acute MI, other acute ischaemic heart disease). **Cerebrovascular disease** (subarachnoid haemorrhage, intracerebral haemorrhage, other non-traumatic intracranial haemorrhage cerebral infarction, stroke, occlusion and stenosis of preverbal arteries, occlusion and stenosis of cerebral arteries, other cerebrovascular diseases, cerebrovascular disorders, squeal of cerebrovascular disease). Death from any cause Non-fatal MI Stroke HRQoL
Notes	No sample size calculation was performed so it is unclear whether the trial was powered to detect differences between the four treatment arms. Given the lack of patient treatment compliance which fell dramatically in the HT blinded, HT unblinded, and placebo groups from approximately 73% at baseline, to approximately 40% by one-year follow-up and 22% at four-year follow-up it is unlikely that enough clinical events associated with the use of HT relative to placebo would occur for the trial to have the power to detect any excess risks/benefits for the use of HT compared to placebo or no treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Remotely randomised in permuted blocks

EPHT 2006 *(Continued)*

Allocation concealment (selection bias)	Low risk	Non-transparent sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment blinded apart from for cancer outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Analused by intention to treat. However, stated participation rates differ across trial publications
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	EQ-5D not measured at baseline, and therefore it is unclear whether there is between group baseline imbalance. Follow-up data for EQ-5D only reported at 2- and 3.6-year follow-up.

ERA 2000

Methods	**Objective:** To evaluate the effects of HT on the progression of coronary atherosclerosis Multicentered three-armed randomised controlled (RCT) trial involving six hospital sites in the United States. The trial was conducted from January 1996 to December 1997, with a mean follow-up of 3.2 ± 0.6 years. The primary aim of the trial was to assess the effects of oestrogen replacement therapy with or without low-dose progestin on angiographic progression or regression of coronary atherosclerosis in post-menopausal women. The primary outcome was therefore change in the minimum diameter of the major epicardial segments, as assessed by quantitative coronary angiography. Clinical CVD events were all assessed as secondary outcomes. **Recruitment:** Media announcements, contact through hospital records and admissions, screening logs from other studies **Screening:** Not stated **Randomisation:** Computerised in random blocks **Stratification:** According to lipid lowering therapy at baseline and hospital where angiogram was performed Allocation: Computer displayed treatment assignment after eligible participant details entered **Baseline equality of treatment groups:** No substantive differences between study groups at baseline. **Blinding:** Participants, clinic staff and all outcomes assessment blinded. Treatment assignment available to designated member of data management staff. Questions relating to adverse effects directed to gynaecology physician and nurse not connected with study. **Analysis:** ITT. **Funding Source:** Grants from National Heart, Lung and Blood Institute and NationalCenter for Research Resources General Clinical Research Center, study medications from Wyeth-Ayerst Research

ERA 2000 *(Continued)*

Participants	Three hundred and nine post-menopausal women with angiographically verified coronary disease were randomised to receive either (1) daily conjugated oestrogen alone (n = 100), (2) daily conjugated oestrogen in combination with medroxyprogesterone acetate (n = 105), or daily placebo (n = 105). Coronary artery disease was defined as at least one stenosis of 30% in any single coronary artery. The mean age of the women was 65.8 years (range: 41.8 - 79.9), with a mean number of years since menopause of 22.5. Post-menopausal status was defined as the presence of one of the following conditions: (1) an age of at least 55 without natural menses for at least five years; (2) no natural menses for at least one year and a serum follicle-stimulating hormone level of more than 40 IU per litre; (3) documented bilateral oophorectomy; or self reported bilateral oophorectomy, a follicle-stimulating hormone level of more than 40 IU per litre, and a serum estradiol level of less than 25 pg per mm (91.1 pmol per litre). 61% of the women had undergone a hysterectomy and 30.4% an oophorectomy. At baseline 9% of women were taking oestrogen, and therefore underwent a three-month'wash out 'period prior to randomisation. Included women were 82% White, 14% Black, and 4% of Other racial origin. 49% had a history of MI and 47% a history of having undergone an angioplasty. In terms of risk factors for CVD: 28% had diabetes; 67% had hypertension; 18% were current smokers; and 57% had a BMI > 27.5 kg/m^2. The mean systolic blood pressure of the women was 130 mm Hg and the mean diastolic blood pressure 71.8 mm Hg. There were no statistically significant differences between the three treatment groups at baseline. **Inclusion criteria:** Stated above, but only women who were 80% or more medication compliant in the one-month prior to randomisation were eligible for participation in the trial. **Exclusion criteria:** Known or suspected breast cancer or endometrial carcinoma, previous or planned coronary-artery bypass surgery, a history of deep-vein thrombosis or pulmonary embolism, symptomatic gallstones, a serum aspartate aminotransferase level more than 1.5 times the normal value, a triglyceride level of more than 400 mg per decilitre (4.52 mmol per litre) while fasting, a serum creatinine level or more than 2.0 mg per decilitre (176.8 µmol per litre), more than 70% stenosis of the left main coronary artery, uncontrolled hypertension, or uncontrolled diabetes.
Interventions	**HT regimen:** 1) 0.625 mg conjugated equine oestrogen daily and a placebo tablet daily (continuous dosage regimen). 2) 0.625 mg conjugated equine oestrogen plus medroxyprogesterone acetate and placebo tablet daily (continuous dosage regimen). **Comparator:** two placebo tablets daily (continuous dosage regimen). Participants were classified as medication compliant if they took ≥ 80% of their medication throughout the trial. Medication adherences in the 248 participants evaluated was: 74% in the oestrogen alone group (measured in 79% of participants); 84% in the combination therapy group (measured in the 84% of participants) and 86% in the placebo group (measured in 80% of participants). Additionally five women in the placebo group initiated HT treatment outside the trial. **Follow-up times:** three months, six months and then every six months thereafter. Pre-treatment investigations included serum electrolytes, haemoglobin levels, hematocrit, platelet count and prothrombin, a 12-lead electrocardiogram and angiogram (if needed). Other investigations included annually included mammography and gynaecological examinations, including Papanicolaou smears and endometrial aspiration or vaginal ultrasound to detect sub-clinical hyperplasia.
Outcomes	Primary outcomes:-

ERA 2000 *(Continued)*

	Death from any cause Death from CVD disease Non-fatal MI Fatal MI Stroke Angina (hospitalisation) Any CVD event Secondary outcomes:- Venous thromboembolism
Notes	The sample size calculation was predicated on the ability to detect differences between groups in the primary outcome measure, change in the minimum diameter of the major epicardial segments, as assessed by quantitative coronary angiography. It is therefore possible that the trial was not powered to detect differences between the three treatment groups on clinical events. It is therefore not possible to state whether there is any excess risk/benefit for the use of either oestrogen alone or in combination with medroxyprogesterone acetate compared to placebo on the basis of the results reported from the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised in random blocks
Allocation concealment (selection bias)	Low risk	Computer displayed treatment assignment after eligible participant details entered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and clinicians blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up for clinical adverse events. Analysed by intention to treat
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	More in unopposed oestrogen group using nitrates at baseline, otherwise prognostic balance between groups

ESPRIT 2002

Methods	**Objective:** To assess whether unopposed oestrogen reduces the risk of further cardiac events in post-menopausal women who survive a first myocardial infarction

ESPRIT 2002 *(Continued)*

	Multicentre randomised controlled (RCT) trial involving 35 hospital sites in England and Wales. The trial was conducted over a two year follow-up period (with recruitment beginning in July 1996 and ending in February 2000). All participants had suffered a first MI and were recruited within 31 days of the index event. Myocardial infarction was defined as two or more of: typical chest pain; S1 elevation of 0.1 mV or more in at least one standard, or two precordial, leads of a 12-lead ECG; or biochemical makers indicative of MI (serum concentrations of creatinine kinase or aspartate transaminase greater than twice the normal laboratory value, or serum tropin concentration greater than the locally defined threshold for MI. The primary outcome measures were non-fatal reinfarction or cardiac death, and all-cause mortality. **Recruitment:** Research nurses checked hospital case notes, approached potentially eligible women if their family doctor agreed to collaborate. **Screening:** Not reported. Randomisation: List of random numbers generated by trial statistician in blocks of four. **Stratification:** By clinical centre site Allocation: Women assigned consecutively to numbers kept on list accessible to statistician only. **Baseline equality of treatment groups:** No substantive differences between study groups at baseline. **Blinding:** Participants, clinicians, outcome assessors. Pharmaceutical company dispensed medication/placebo in identical numbered packages. Unblinding occurred on request of family doctor or if participant withdrew from treatment (in later states of study, only if withdrawing participant had not had a hysterectomy). Outcome assessors remained blinded throughout. **Analysis:** ITT. **Funding Source:** Schering AG provided medication
Participants	1017 post-menopausal women (HT: 513; placebo: 504) after a first MI with a mean age of 62.6 years (range: 50 - 69) underwent treatment with either HT or placebo. Post-menopausal status was defined as no vaginal bleeding in the previous 12 months. The mean age at last menstrual period was 46.5 years of age. 24% of women (n = 245) had undergone a hysterectomy. In terms of ethnic origin and risk factors for a further CVD event: 97% of the women were White; 53% were smokers at the time of admission; mean BMI was 40 kg/m2; 27% had angina; 44% had high blood pressure (not defined); 7.5% had suffered a previous stroke; 15% had diabetes, and 11% had used HT> 12 months before admission to the trial. Inclusion criteria: All women aged 50 - 69 years admitted to hospital who had experienced a first MI, who were discharged alive within 31 days of admission. **Exclusion criteria:** Use of HT or vaginal bleeding in the 12 months before admission; history of breast, ovarian, or endometrial carcinoma; or active thrombophlebitis or a history of deep-vein thrombosis or pulmonary embolism, acute or chronic liver disease, Rotor syndrome, Dubin-Johnson syndrome, or severe renal disease. Both HT and placebo groups had similar baseline characteristics, including those identified a priori (and listed above) as potential confounders.
Interventions	**HT regimen:** 2 mg daily tablet of oestradiol valerate (continuous dosage regimen). **Comparator:** identical placebo capsule daily. Treatment compliance was not formally assessed, but patient reported to the treating physician at follow-up times. Medication compliance rates were poor, and were lower in the HT group than in the placebo group. At one year 51% of participants on the HT arm and 31%on the placebo arm were not taking their allocated tablets regularly. At two years, 57% of participants on the HT arm and 37% on the placebo arm were not taking their allocated tablets regularly.

ESPRIT 2002 *(Continued)*

	Drop-outs included 43 women in the HT group (8%) and 57 in the placebo group (11%) who did not take any of the trial medication. **Follow-up times:** patients were followed-up at 3, 6, 12, 18 months and at study exit at 24 months.
Outcomes	Death from CVD All causes of death Death from CVD MI (non-fatal) Stoke Deep Vein Thrombosis Pulmonary embolism
Notes	The sample size power calculation was originally based on recruiting 1700 patients to achieved 80% power with a two -sided test and a 5% significance rate predicated on HT reducing the rate of non-fatal reinforcing or cardiac death by 13%. Due to financial constraints the trial was based on a total of 1017 women being randomised, and the power to detect a difference between treatment groups with this number was calculated as 56% assuming full treatment compliance in both of the treatment groups. Due to poor treatment compliance it is likely that the trial was underpowered to detect differences between treatment groups for some outcomes, and therefore the point estimates of differences between the groups are likely to be conservative.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	List of random numbers generated by trial statistician in blocks of four
Allocation concealment (selection bias)	Low risk	Women assigned consecutively to numbers kept on list accessible to statistician only
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and clinicians blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up, analysed by intention to treat
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No apparent source of other bias

EVTET 2000

Methods	**Objective:** To determine if HT alters the risk of venous thrombo-embolism in high risk women Multicentre randomised controlled trial (RCT) with a double triangular sequential design involving four hospital sites in Norway. The trial was conducted over a 1.3 year period between February 1996 and March 1998, but stopped early as other published trial results (HERS I 1998) indicated an increased risk of Venous Thromboembolism (VTE) with use of HT. The primary outcome measure was VTE and the secondary outcome measure pulmonary embolisms. VTE was verified by objective tests (i.e.), demography or ultrasound, and pulmonary embolisms were verified by lung-scans, angiography, or helical computed tomography. At baseline all participants underwent a clinical examination including breast and pelvic examinations with cytological smear test and evaluation of the endometrium with transvaginal ultrasound. A screening mammogram was also performed, as were routine haematological and clinical chemistry screening including blood lipids. **Recruitment:** letters to family doctors, gynaecologists and hospitals, health bulletins and media. **Screening:** Not reported. **Randomisation:** computer-generated 1:1 block randomisation with fixed block sizes of ten **Stratification:** By age < 60 years or > 60 years 37 (23 HT and 14 placebo) women did not attend all visits due to premature termination of the study **Allocation:** Not reported. **Baseline equality of treatment groups:** No substantive differences between study groups at baseline. **Blinding:** Double blind **Analysis**: ITT **Funding Source:** Novo-Nordisk Pharmaceutical and research forum Ulleval University Hospital
Participants	140 post-menopausal women whom had previously had either VTE or PE (HT: 71; placebo: 69) with a mean age of 55.8 years (range: 42 - 69 years) underwent treatment with either HT or placebo. Post-menopausal status was defined as no natural menstruation for at least one year. The ethnic origin of the women included in the trial was not reported. In terms of risk factors for CVD 0.7% of women had previous/concomitant MI; 3% had angina; 1.4% had thromboembolic stroke; 3% had a transient ischaemic attack; 17% had hypertension and 2% had diabetes. The time since last DVT was four years (range: 0 - 37 years) and last PE 5 years (range: 0 - 34 years). There were no statistically significant differences between the two groups in terms of risk factors for CVD. In terms of smoking status: 39% were never smokers; 36% were previous smokers; 14% smoked between 1 - 10 cigarettes daily, whilst 10% smoked > 10 cigarettes per day. Mean BMI among the women was 27.1 kg/m2. Systolic blood pressure at baseline was 138 mm HG and diastolic blood pressure was 83 mm HG. **Inclusion criteria:** Post-menopausal women younger than 70 years who had suffered previous DVT or PE. Twenty-eight women were also enrolled into the trial without objective testing as they had a typical history and had subsequently been treated for VTE. **Exclusion criteria:** Current use or use of anti-coagulants within the last three months; familial ant thrombin deficiency; any type of malignant diseases including known, suspected or past history of breast carcinoma; acute or chronic liver disease or history of liver disease in which tests had failed to return as normal; porphyries; known drug abuse or alcoholism; life expectancy less than two years; or participation in other clinical trials within 12 weeks before study entry.

EVTET 2000 *(Continued)*

Interventions	**HT regimen:** 2 mg estradiol plus 1 mg norethisterone acetate (1 tablet) daily (continuous dosage regimen). **Comparator:** identical placebo capsule daily. Medication compliance in terms of pill counts was conducted at each follow-up visit. **Follow-up times:** patients were followed-up at three months, 12 months and 24 months. Treatment adherence was not reported. **Loss to follow-up:** Zero, but 37 (23 HT and 14 placebo) women did not attend all visits due to premature termination of the study. There were 33 dropouts, ten in HT group (two wanted be sure of being treated with oestrogen for post-menopausal symptoms, eight had adverse effects), and 23 in the placebo group (11 wanted be sure of being treated with oestrogen for post-menopausal symptoms, ten had adverse effects, two no reason stated)
Outcomes	Venous thrombosis Myocardial infarction Stroke
Notes	Study terminated early, only 140 women enrolled of 240 planned due to the results from HERS I (1998) being made available. Power calculation: At a significance level of 5% and a power of 90% the sample size was estimated to a maximum of 240 women

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated 1:1 block randomisation with fixed block sizes of ten
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and study personnel blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	The main findings were not reported by ITT, as drop-outs from the placebo group were not included in the denominator for the rate of recurrent thrombo-embolism
Selective reporting (reporting bias)	Low risk	Reports all expected outcomes
Other bias	Low risk	No apparent source of other bias

HALL 1998

Methods	**Objective:** to assess the effects of HT on angina and HRQoL in women with ischaemic heart disease. Single centre randomised controlled (RCT) trial involving one hospital site in Sweden. The trial was a three-arm trial comprising: one group who received 50 µg transdermal 17ß-estradiol daily for 18 days followed by 5 mg of combined treatment with medroxyprogesterone acetate orally; the second group who received 0.625 mg conjugated estrogens (CEE) orally for 18 days followed by a combination with oral 5 mg medroxyprogesterone acetate daily, and the third group who received placebo. Due to not confounding the results of other trials in which estrogens/progestins have been provided orally, the data presented in this trial are from the groups that received only oral medication (i.e.) groups two and three. The length of follow-up of the trial was one-year. The primary outcome was angina, with death from CVD causes, MI, and the number of angioplasties and CABG performed reported as secondary outcomes. **Recruitment:** Not reported. **Screening:** Not reported. **Randomisation:** Not reported. **Stratification:** Not reported. **Allocation:** Not reported. **Baseline equality of treatment groups:** Only limited baseline characteristics reported for the treatment groups, and no statistical comparisons made between groups. Probable baseline imbalance between treatment groups for age (placebo group older than HT group); weight (placebo group heavier than HT group); number of years since menopause (placebo group higher than of years post-menopausal compared to HT group). **Blinding:** Not reported. **Analysis:** Unclear. No statistical tests for between group differences conducted. **Funding Source:** Hospital grant funded.
Participants	Forty post-menopausal women with existing coronary artery disease (HT: 20; placebo: 20) with a mean age of 60 years (range: 44 - 75) underwent treatment with either HT or placebo for a year. No definition of what constituted post-menopausal status and whether the trial included patients with a hysterectomy was reported. The mean BMI among the 40 women included in the trial was 30 kg/m2 (range: 20.0 - 40.7 years); the mean time of menopause was 12.5 years (range: 2 - 26); 9.5% were former smokers, 5.5% were never smokers and 5.5% were present smokers. In terms of diagnosis of CVD: 55% had a previous MI; 27.5% previous bypass surgery; 22.5% previous PTCA (balloon dilation); 0% had type I diabetes; 10% had type II diabetes; 32.5% had hypertension, and 12.5% had claudication. **Inclusion criteria:** No inclusion criteria were reported. **Exclusion criteria:** No inclusion criteria were reported.
Interventions	**HT regimen:** 0.625 mg conjugated estrogens (CEE) orally for 18 days followed by a combination with oral 5 mg medroxyprogesterone acetate daily (sequential dosage regimen). **Comparator:** identical placebo capsule daily. The overall compliance with study intervention was not reported.

HALL 1998 *(Continued)*

	Follow-up times: Baseline, 3, 6, 12-months and four to six weeks after completion of the trial. Pre-treatment investigations included gynaecological history and occurrence of climacteric symptoms, Pap smear and mammography (if not performed within two-years prior to recruitment). Blood samples were analysed for estradiol, estrone, estrone sulphate and follicle stimulating hormone at baseline, 3, 6, 12 months and four to six weeks after trial completion. Additionally, a cardiac history, physical examination, and symptoms of angina pectoris were performed using the Canadian Heart Association protocol before trial entry. Minimal Health Related Quality of Life (HRQoL) data were measured at baseline and at one-year follow-up. The domains covered were: (1) well being; (2) mucous membrane changes; (3) climacteric symptoms; (4) breast tenderness; (5) negative mood changes; (6) headache, and (7) bleeding irregularities. The outcomes of these were not reported in the paper. **Withdrawals:** 20%; 10% HT and 30% placebo.
Outcomes	Death from CVD cause Angina Fatal MI Angioplasty Coronary artery by-pass
Notes	No sample size calculation was performed and it is unlikely that the trial was powered to adequately detect significant differences in clinical event rates between the HT and placebo groups. No definition of how clinical events were defined or ascertained was reported. Additionally no statistical analyses to assess differences in clinical event rates between the groups were performed. It is therefore unclear whether the groups differed significantly in the number and types of events of experienced. The length of trial follow-up (one-year) was unlikely to be long enough to ascertain either the longer term effects of HT use compared to placebo, or for other important CVD events to be assessed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods of randomisation not reported; imbalance in baseline participant characteristics between groups.
Allocation concealment (selection bias)	High risk	Methods of allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and study personnel not reported, not may not influence outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not reported, but may not influence ascertainment of outcomes.
Incomplete outcome data (attrition bias) All outcomes	High risk	Analyses do not appear to be undertaken on an ITT basis, it is unclear whether withdrawals were included in the analyses, and no statistical tests for between group differences conducted.
Selective reporting (reporting bias)	Unclear risk	The paper reports the results for the main outcome of interest, angina, but it is unclear whether any other outcomes were pre-specified but not reported. It appears that just the events that occurred in the trial were reported, rather than these being defined a priori for consideration in the trial. Additionally HRQoL was measured within the trial, but the results of the assessments were not reported.

HALL 1998 *(Continued)*

Other bias	Unclear risk	It is unlikely that the trial was powered to detect differences in clinical events between the HT and placebo treatment groups. Furthermore no statistical analyses were undertaken to assess differences in clinical event rates between the trial arms. Therefore the lack of significant differences in event rates between the two groups should be treated with caution.

HERS I 1998

Methods

Objective: To assess whether combined HT alters the risk for CHD events in post-menopausal women with established coronary disease.

Multicentre randomised placebo controlled secondary prevention trial (RCT) involving 20 primary care sites in the United States. The trial recruitment was conducted from January 1993 - September 1994, with a mean follow-up of 4.1 years. The primary aim of the trial was to assess the effects of combined oestrogen and progestin therapy compared to placebo for the prevention of recurrent coronary heart disease (CHD) events in post-menopausal women with CHD. Coronary heart disease was defined as evidenced by prior MI, coronary artery bypass graft surgery (CABG), percutaneous transluminal coronary angioplasty, or other mechanical revascularization, or at least 50% occlusion of a major coronary artery. The primary outcome was the occurrence of CHD events (CHD death or non-fatal MI). Secondary outcomes included stroke, venous thromboembolic events, angina, and breast and endometrial cancers.

Recruitment: Lists of cardiac patients, mass mailing, direct advertising

Screening: 3463 of whom 43% were excluded (ineligible, declined to participate, did not return for appointment or did not comply with placebo run-in period).

Randomisation: Computer-generated random numbers in blocks of four

Stratification: By clinical centre

Allocation: Computer displayed after participant details entered

Baseline equality of treatment groups: More women in control arm on statins at randomisation (67% versus 54%). When adjusted in analyses - made no statistically significant difference.

Blinding: Participants, clinical centre staff, outcome assessors, data analysts, funders. Unblinding could occur when required for safety or symptom control, participants reported directly to gynaecology staff who were located separately from clinical staff, did not communicate with them about breast or gynaecological problems and were not involved in outcome ascertainment

Analysis: ITT and also analysed by treatment received with inclusion limited to women with > 80% compliance.

Funding Source: Pharmaceutical (Wyeth-Ayerst).

HERS II

An unblinded, open-label observational continuation of HERS I in which 2321 women (93% of 2510 surviving HERS participants) followed up for a further 2.7 years (originally planned for additional four years but executive committee decided no further useful information likely to emerge). No analysed: 2311 for vital status. Losses to follow up: ten women (1%) not contacted at final follow up (two in HT arm; eight in control arm) of these, vital status known for five. Adherence to treatment: among women originally assigned to the HT group, 45% reported at least 80% compliance during the sixth year of follow up. Among women originally assigned to placebo, 8% reported taking HT at six years.

HERS I 1998 *(Continued)*

Participants	2763 post-menopausal women with verified CHD were randomised to receive either daily conjugated oestrogen in combination with medroxyprogesterone acetate (= 1380) or placebo (n = 1383). Post-menopausal status was defined as age at least 55 years and no natural menses for at least five years, or no natural menses for at least one year and serum follicle-stimulating hormone (FSH) level more than 40 IU/L, or documented bilateral oophorectomy, or reported bilateral oophorectomy with FSH level more than 40 IU/L and estradiol level less than 92 pmol/L (25 pg/mL). The mean age of the women was 67 years (range: 44 - 79), with a mean time of 18 years (SD: ± 8) since last menses. Included women were 89% White, 8% African-American, 2% Hispanic, < 1% Asian, and < 1% Other. In terms of risk factors for CVD: 13% were current smokers, 49% were past smokers and 38% had never smoked; 18.5% had diabetes and were on oral medication or insulin; mean systolic blood pressure was 135 (SD: ± 19) mm Hg and mean diastolic blood pressure was 73 (SD: ± 10). 56% of the women had a BMI > 27 kg/m2 and 23.5% had previous post-menopausal oestrogen use (after menopause but not within three-months of initial screenings for HERS trial). The CHD manifestations within the groups were: 9.5% had signs of congestive heart failure (presence of jugular venous distention more than 8 cm H20, S3 heart sound, rales, or pitting peripheral oedema); 17% had Q-wave MI; 45% had undergone percutaneous coronary revascularization, and 41.5% had undergone coronary artery bypass graft surgery. There were no statistically significant differences between treatment groups at baseline. **Inclusion criteria:** Stated above, plus ≤ 79 years old with uterus present. **Exclusion criteria:** CHD event within six months of randomisation; serum triglyceride level higher than 3.39 mmol/L (300 mg/dL); use of oral, parenteral, vaginal, or transdermal sex hormones within three months of the screening visit; history of deep vein thrombosis or pulmonary embolism; history of breast cancer or breast examination or mammogram suggestive of breast cancer; history of endometrial cancer; abnormal uterine bleeding, endometrial hyperplasia, or endometrium thickness greater than 5 mm on baseline evaluation; abnormal or unobtainable Papanicolaou test result; serum aspartate aminotransferase level more than 1.2 times normal; disease (other than CHD) judged likely to be fatal within four years; New York Heart Association class IV or severe class III congestive heart failure; alcoholism or other drug abuse; uncontrolled hypertension (diastolic blood pressure 105 mm Hg or systolic blood pressure 200 mm Hg); uncontrolled diabetes (fasting blood glucose level 16.7 mmol/L [300 mg/dL]); less than 80% compliance with a placebo run-in prior to randomisation; or history of intolerance to hormone therapy.
Interventions	**HT regimens:** 0.625 mg conjugated oestrogen plus 2.5 mg medroxyprogesterone acetate daily (continuous dosage regimen). **Comparator:** identical placebo tablet daily. Rates of medication compliance in the trial were reasonably high. At the end of year-one, 82% of women in the HT group and 91% in the placebo group reported taking study medication. At 3 years: 75% HT arm; 81% control arm. By pill count in HT arm: at one year: 79%; at three years: 70% HT arm. **Losses to follow up:** Vital status known for all women at end of trial. 59 women did not complete follow-up (32 in experimental arm, 27 in placebo arm). **Follow-up times:** Baseline, and then every four-months. At baseline participants had a clinical examination, including breast and pelvic examination with Papanicolaou test and endometrial evaluation, a screening mammogram and standardized 12-lead electrocardiogram (ECG). Fasting total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were also measured. Annual examinations included cardiac examination and ECG. Separate an-

HERS I 1998 *(Continued)*

	nual follow-up visits to the study gynaecologist included repeat breast and pelvic examinations with Papanicolaou smears and screening mammograms. Health Related Quality of Life (HRQoL) was measured on four scales that assessed functional capacity, emotional health, vitality and depression. These were assessed at baseline, four-months, and then follow-up at years one, two, and three. Physical function was assessed using the Duke Activity Status Index, energy/fatigue using a four-item RAND scale, mental health was measured by the RAND Mental Health Inventory, and depressive symptoms were assessed using an eight-item scale developed by Burnham et al. to screen for depression in the National Study of Medical Outcomes.
Outcomes	Primary outcomes:- Death from CVD Non-fatal MI Secondary outcomes:- Death from any cause Fatal MI Stroke Angina (necessitating hospitalisation) Pulmonary embolisms Venous thrombosis Coronary artery bypass surgery
Notes	Power calculation: 90%power to observe 24%reduction in coronary events at an average of 4.2 years (P = 0.05) follow up. Further unblinded follow up 2.7 years (HERS II) [included in original Sanchez review]

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers in blocks of four
Allocation concealment (selection bias)	Low risk	Computer displayed after participant details entered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, clinical centre staff, data analysts and funders blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Vital status known for all women at end of trial. 59 women did not complete follow-up (32 in experimental arm, 27 in placebo arm). Analysed by intention to treat

HERS I 1998 *(Continued)*

Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	More women in control arm on statins at randomisation (67% versus 54%). When adjusted in analyses - made no statistically significant difference

WAVE 2002

Methods	**Objective:** To determine whether HT or antioxidant vitamin supplements, alone or in combination, influence the progress of coronary artery disease in post-menopausal women as measured by angiography. Multicentre 2x2 randomised factorial placebo controlled (RCT) trial involving seven hospital sites; five in the United States and two in Canada. The trial recruitment was conducted from July 1997-July 1999), with a mean follow-up of 2.8 (SD: ± 0.9 years. The primary aim of the trial was to assess the effects of oestrogen and/or progestin with or without antioxidant vitamins for preventing angiographic progression of coronary artery disease. Coronary artery disease was defined as having al least one coronary segment with stenosis of ≥ 15% and 75% in a vessel ≥ 2 mm in diameter at baseline, with the angiograph conducted within four months of trial recruitment. The primary outcome was therefore change in the minimum lumen diameter (MLD) of the vessels from baseline, as assessed by quantitative coronary angiography at follow-up. Clinical CVD events and health related quality of life were all assessed as secondary outcomes. **Recruitment:** Recruited at clinical sites in USA and Canada. **Screening:** Not reported. Randomisation: Computer randomised, permuted block design with random blocks of two and four **Stratification:** Clinical centre, hysterectomy status **Allocation:** Remotely by phone call to study co-ordinating centre **Baseline equality of treatment groups:** Higher prevalence of diabetes and higher fasting blood glucose levels in the HT group **Blinding:** Participants, investigators and staff at clinical centres blinded except (when necessary) the study gynaecologist. Adverse effects managed by gynaecologist not involved in outcome assessment who had access to treatment assignment if necessary, with permission of co-ordinating centre (unblinding). **Analysis:** No (98% of women analysed by ITT). **Funding Source:** National Heart, Lung and Blood Institute contract, General Clinical Research Center grant, USA.
Participants	Four hundred and twenty-three post-menopausal women with angiographically verified coronary disease were randomised to receive either (1) daily conjugated oestrogen alone for participants who had undergone a hysterectomy; (2) daily conjugated oestrogen in combination with medroxyprogesterone acetate; (3) vitamins E and C, or (4) placebo. Post-menopausal status was defined as having bilateral oophorectomy at any age, being younger than 55 years old with a follicle-stimulating hormone level of 40 IU/ml or higher, or being older than 55 years. Included women were 66% White and 34% non-White (Black or other; specific origins not reported). In terms of risk factors for CVD: 37% had diabetes; 76% had hypertension; 39% were current smokers; 43% had suffered a previous MI, and 37.5% were current HT users. The mean BMI was 30.7 kg/m2;

WAVE 2002 *(Continued)*

	mean systolic blood pressure was 139 (SD: 21) mm Hg and the mean diastolic blood pressure 76 (SD: 10.5) mm Hg. The HT and placebo HT groups were well-balanced in terms of baseline characteristics, apart from the exception of the active HT group having a statistically significantly higher prevalence of diabetes and higher fasting blood glucose levels. **Exclusion criteria:** Exclusion criteria were no use of oestrogen replacement therapy within the past three months apart from oestrogen vaginal cream if used no more than 25% of the time; use of vitamins C and E exceeding the recommended dietary allowance and unwillingness to stop taking them; evidence of potential breast, uterine, or cervical cancer; any abnormal uterine bleeding or endometrial hyperplasia at baseline; MI less than four weeks prior to randomisation; prior or planned coronary artery bypass graft surgery; fasting triglycerides levels higher than 500 mg/dL (5.65 mmol/L); creatinine level higher than 2.0 mg/dL (176,8 µmol/L0); symptomatic gallstones; New York Heart Association class IV congestive heart failure or a left ventricular ejection fraction known to be less than 25%; history of hemorrhagic stroke, bleeding diathesis, pulmonary embolism, idiopathic deep venous thrombosis, or untreated osteoporosis.
Interventions	**HT regimens :** 1) 0.625 mg conjugated equine oestrogen daily plus placebo for women who had undergone a hysterectomy (continuous dosage regimen). 2) 0.625 mg conjugated equine oestrogen plus 2.5 mg medroxyprogesterone acetate daily plus placebo for women who had not undergone a hysterectomy (continuous dosage regimen). 3) 400 IU vitamin E twice daily (800 IU) plus 500 mg vitamin C twice daily (1 g) **Comparator:** 2 placebo tablets daily. Adherence to treatment: Evaluated for 159/211 who had angiographic follow up: HT group took 67% of medication, placebo group took 70%; 9/108 women in placebo group crossed to open-label oestrogen. **Losses to follow up:** Five (three in HT group, two in placebo group) **Follow-up times:** Baseline, three-months, and then every six-months. Patients underwent a coronary angiography at baseline and trial exit. Other investigations performed at baseline were: 12-lead electrocardiogram; breast and pelvic examinations, mammography, Papanicolaou smears and fulfilment of the five health related quality of life questionnaires (HRQoL). Baseline assays included: fasting glucose, insulin, HbA1c, fibrinogen, lipid profile, vitamins C and E and estrone. HRQoL questionnaires: Five HRQoL questionnaires were completed at baseline and at 18-months by participants. The specific questionnaires completed were: (1) the Medical Outcome Study Short Form (SF-36); (2) Centre for Epidemiological Studies-Depression Scale; (3) Seattle Angina Questionnaire; (4) Duke Activity Scale Index, and (5) The Medical Outcomes Study Sleep Questionnaire.
Outcomes	Mean change from baseline in MLD of all qualifying angiographic segments Death from any cause Death from CVD Non-fatal MI Stroke

WAVE 2002 *(Continued)*

	Secondary outcomes:- Deep vein thrombosis Health-related quality of life
Notes	The sample size calculation was predicated on the ability to detect differences between groups in the primary outcome measure, change in the minimum lumen diameter of all qualifying angiographic segments, as assessed by quantitative coronary angiography. The trial was therefore not powered to detect differences in CVD clinical events between the treatment groups. Additionally, as the factorial design revealed no interactions between treatment groups, results for the two HT versus placebo treatment groups (i.e. oestrogen alone or oestrogen in combination with progestin) were pooled and presented as aggregate numbers of events. It is therefore not possible to state whether there is any excess risk/benefit for the use of either oestrogen alone or in combination with medroxyprogesterone acetate compared to placebo on the basis of the results reported from the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomised, permuted block design with random blocks of two and four
Allocation concealment (selection bias)	Low risk	Remotely by phone call to study coordinating centre
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, investigators and staff at clinical centres blinded except (when necessary) the study gynaecologist
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators and staff at clinical centres blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up five (three in HT group, two in placebo group), 98% of women analysed by intention to treat
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	Groups balanced at baseline, apart from HT group had a higher prevalence of diabetes and higher fasting blood glucose levels

WEST 2001

Methods	**Objective:** To determine whether 17ß-oestradiol reduces the risk of recurrent stroke or death among post-menopausal women who have experienced a transient ischaemic attack or non-disabling ischaemic stroke Multicentre randomised controlled (RCT) trial involving 21 hospital sites in the United States. The trial was conducted from Dec 1993 - May1998, with a mean follow-up duration of 2.8 years ± 17 months. The primary outcome measures were the number of strokes or deaths that occurred, with further clinical events of MI, and TIA also reported.

WEST 2001 *(Continued)*

	Medical testing for patients at baseline included computerized tomography (CT) scan, clinical breast examination, electrocardiogram, and a pelvic examination including a Papanicolaou smear (in women who had not undergone a hysterectomy). Additionally neurological examination was performed by a trained nurse using the National Institutes of Health (NIH) Stroke Scale, and tests on physical and cognitive performance, including the Boston Naming Test, a test of digit span recall, category work list generation, a depression screen, the Mini-Mental Status Examination and a test of delayed spatial recognition were undertaken. **Recruitment:** Admissions to 20 largest regional hospitals in Connecticut and Massachusetts; also via contact with selected neurology groups and direct referrals from physicians **Screening:** 5296 screened for eligibility (2772 ineligible, 1843 declined to participate, 17 unable to be randomised within protocol time frame) **Randomisation:** Computer generated at pharmacy, in blocks of four **Stratification:** By trial centre and risk level (three levels) **Allocation:** By remote contact with trial pharmacy **Baseline equality of treatment groups**: No substantive differences between study groups at baseline. **Blinding:** Participants, investigators and endpoint assessors blinded. Study internist unblinded in the case of overriding concern about a woman's clinical care **Analysis:** ITT. **Funding Source:** National Institute of Neurological Disorders and Stroke grant, Medical Research Council of Canada grant. Mead Johnson laboratories provided support and study drug.
Participants	664 post-menopausal women (HT: n = 337; placebo: n = 327) with a mean age of 71.5 (SD: ± 10 years) who had undergone either a non-disabling ischaemic stroke or a transient ischaemic attack in the previous 90 days prior to recruitment. Post-menopausal status was defined as amenorrhoea for at least 12 months or for women who had undergone a hysterectomy without oophorectomy an estradiol level less than 40 pg/mL and a follicle-stimulating hormone level over 40 mIU/mL. The number of women whom had previously undergone a hysterectomy was 44.5%. 29.5% of the women had previously used estrogen-replacement therapy. In terms of ethnic background included women were: 83.5% White; 13% Black; and 3.5% Other (unspecified). 24% had a previous MI; 14.5% congestive heart failure; 7% atrial fibrillation; 73.5% hypertension; and 28% diabetes. 12.5% were current cigarette smokers, and the mean BMI among the women was 28 kg/m2 (SD: ± 6). In terms of neurological characteristics: 18.5% had a history of stroke before the index (ischaemic or TIA) event, and 75% had a stroke as the index event. In relation to summary risk stratum of the occurrence of another event [based on a validated instrument that included the five clinical features of age, blood pressure, diabetes, cardiac disease, and index event (stroke versus TIA)] 12.5% of women were classified as low risk, 67% as medium risk, and 20.5% as high risk. **Inclusion criteria:** Age over 45 years, post-menopausal (at least 12 months since cessation of menstrual periods), and a qualifying neurological event of TIA or non-disabling ischaemic stroke within 90 days of randomisation. **Exclusion criteria:** estimated survival less than five years, history of breast or uterine cancer, an identical twin with breast cancer, or severe psychiatric illness. Temporary exclusion criteria that had to be resolved by the time of randomisation were moderate-severe neurological disability, or clinical suspicion of breast or uterine cancer.
Interventions	**HT regimen:** 1 mg 17ß-estradiol daily (plus a course of 5 mg medroxyprogesterone acetate once a year for 12 days for women with a uterus) plus standard care (continuous dosage regimen). **Comparator:** identical placebo capsule daily plus standard care.

WEST 2001 *(Continued)*

	The overall compliance with study intervention assessed by pill count at each visit (including women who discontinued treatment) was 60% (56% in the HT group and 64% in the placebo group). Compliance among women who did not discontinue the study drug was 90% in both treatment groups. **Dropouts:** 34% of the HT group and 24% of the placebo group. **Losses to follow-up:** Zero. **Follow-up times:** Baseline and then every three-months.
Outcomes	Death Stroke Death from CVD cause Non-fatal MI Secondary outcomes:- Venous thromboembolism Pulmonary embolism
Notes	Sample size calculations and recruitment of participants was adequate to allow for drop outs, and still to provide the power to detect any statistically significant differences between the HT and placebo group in terms of the primary outcomes of interest. The clinical events of interest were defined according to standard criteria and verified by a neurologist blinded to treatment allocation, or by objective measures of disease such as positive results on a duplex ultrasonogram or venogram for the diagnosis of VTE. All events were centrally corroborated, and sensitivity analyses undertaken to examine the effect of including only medication compliant patients in the analyses. Study publication pools results for women on unopposed and combined therapies. Vital status was confirmed for all women at the conclusion of the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated at pharmacy, in blocks of four
Allocation concealment (selection bias)	Low risk	By remote contact with trial pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoint assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow up, analysed by intention to treat
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No apparent source of other bias

WHI I 2002

Methods	**Objective:** To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States. Multicentre randomised placebo controlled primary prevention trial (RCT) involving 40 primary care sites in the United States. The trial recruitment was conducted from January 1993 – September 1998, with a mean follow-up of 5.2 years (range: 3.5 – 8.5); planned duration 8.5 years. The primary aim of the trial was to assess the effects of oestrogen in combination with progestin compared to placebo on disease incident rates of CHD, hip fractures and deaths from all causes. The primary outcome measure was CHD events (defined as non-fatal MI and CHD death), with invasive breast cancer as the primary adverse outcome. Secondary outcomes included stroke (both fatal and non-fatal), pulmonary embolism, DVT, angina (both hospitalisation due to and confirmed), revascularization (CABG or PCI combined), death from all causes, as well as a global index of risks and benefits defined as time to the first event among CHD, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture or death due to other causes to summarise overall effects. Late in 1999, the National Institute for Health data and safety monitoring board (DSMB) observed small but consistent early adverse effects in cardiovascular outcomes and in the global index. However, none of the disease specific monitoring boundaries had been crossed. These adverse CV effects continued throughout 2000 and 2001, but the trial continued because the balance of risks and benefits remained uncertain. The trial was finally stopped early after a mean follow-up of 5.2 years in May 2002, when the DSMB found that the adverse effects in CVD persisted, although these remained within the monitoring boundaries, but the weighted log-rank test statistic for breast cancer had cross the designated stopping boundary, and the global index was supportive of a finding of overall harm. The trial was therefore terminated at the end of May 2002. **Recruitment:** Letter of invitation in conjunction with media awareness programme. Sampling method gave women from minority groups six-fold higher odds for selection than Caucasian women and resulted in sample with 84% racially/ethnically designated “white”, 16% non-“white”. **Screening:** Interested women screened by phone or mail for eligibility, then attended three screening visits for history, clinical exam and tests. Three month washout period before baseline evaluation of women using post-menopausal hormones at baseline screening. Lead-in placebo pills given for at least four weeks during screening process to establish compliance with pill taking. **Randomisation:** Centrally randomised by permuted block algorithm **Stratification:** By clinical centre site and age group **Allocation:** By local access to remote study database **Baseline equality of treatment groups:** No substantive differences between study groups at baseline. **Blinding:** All participants, clinic staff, and outcome assessors blinded, with the exception of 331 participants who were unblinded from the unopposed oestrogen arm and reassigned to combined HT arm due to change in protocol. **Analysis:** ITT. **Funding Source:** The National Heart, Lund, and Blood Institute. Wyeth-Ayerst Research provided the study medication.
Participants	16, 608 healthy post-menopausal women were randomised to receive either daily conjugated equine oestrogen in combination with progestin (n = 8506) or placebo (n = 8102). Post-menopausal was defined as no vaginal bleeding for six months (12 months for 50- to 54- years), or having ever used post-menopausal hormones. The mean age of the women was 63.25 years [(SD: 7.1) (range: 50 - 79]. Age ra-

WHI I 2002 *(Continued)*

	tio of 33%:45%:21% for the baseline age categories of 50 - 59, 60 - 69, 70 - 79 respectively (enrolment targeted to achieve ratio of 30: 45: 25). Included women were 84% White, 7% Black, 5% Hispanic, 0.4% American Indian, 2.2% Asian/Pacific Islander, and 1.4 % unknown. In terms of previous hormone use: 74% were 'never' HRT users, 20% were past users and 6% were current users (therefore requiring a three-month washout period prior to randomization). 70% of women had used HRT < five years, 18% for five to < ten years, and 12% for ≥ 10 years. In terms of risk factors for CVD: 50% were never smokers, 39.5% were past smokers, and 10.5% were current smokers. The mean BMI among the women was 28.5 kg/m^2; mean systolic blood pressure was 128 (SD: ± 17.5) mm Hg and mean diastolic blood pressure was 75.7 (SD: ± 9.1). The CHD manifestations within the groups were: 4.4% were being treated for diabetes, 36% for hypertension or BP≥ 140/90 mm Hg, 1.8% had a previous MI, 2.9% had angina, 1.3% had undergone either CABG/PTCA surgery, 0.9% had suffered a previous stroke, and 0.9% had DVT or PE.†; 12.7% had elevated cholesterol levels requiring medication, 6.7% were using statins at baseline, and 19.6% aspirin. **Inclusion criteria:** Age 50 - 79 years at initial screening, post-menopausal, likelihood of residence in the area for three-years, and provision or written informed consent. **Exclusion criteria:** Invasive cancer in the past ten years; breast cancer at any time or suspicion of breast cancer at baseline screening; endometrial cancer or endometrial hyperplasia at baseline; malignant melanoma; acute MI, stroke, TIA or pulmonary embolism or deep vein thrombosis that was non-traumatic or that had occurred in the previous six months †; known chronic active hepatitis or severe cirrhosis, blood counts indicative of disease; bleeding disorder; lipaemic serum and hypertriglyceridaemia diagnosis; current use of anticoagulants or tamoxifen; or PAP smear or pelvic abnormalities severe hypertension; or currently use of oral corticosteroids; bleeding disorder; lipaemic serum and hypertriglyceridaemia diagnosis; current use of anticoagulants or tamoxifen; or Papanicolaou smear or pelvic abnormalities (2) for reasons of adherence or retention: severe menopausal symptoms inconsistent with assignment to placebo; inability or unwillingness to discontinue current HRT use or oral testosterone use; inadequate adherence with placebo run-in; unwillingness to have baseline or follow-up endometrial aspirations; alcoholism, drug dependency, mental illness, dementia. † Prior to the publication of the results of HERS I in 1997, (which led to a change in the inclusion criteria) women with a history of venous thromboembolism (VTE) were eligible for inclusion. From this point onwards women with indicated prior VTE were excluded. At this point 171 women with a history of VTE had been enrolled into the trial.
Interventions	**HRT regimens :** 0.625 mg conjugated equine oestrogen plus 2.5 mg medroxyprogesterone acetate (MPA) daily. **Comaparator:** identical placebo tablet daily. Medication adherence was defined as participants taking > 80 study pills, and was monitored by weighing medication bottles at each clinic visit. Medication adherence data for each trial year were not reported, but by the time of study termination 40% of women had stopped taking study medication (HRT: 42%; placebo: 38%). Therefore only 60% of women remained medication compliant. At 5.2 years follow-up 6.2% of women in the HT arm had initiated hormone use through their own physician and 10.7% of women in the placebo arm had also initiated hormone use (drop-in).

WHI I 2002 *(Continued)*

	Follow-up times: baseline, and then every six-months. At baseline participants had a clinical examination, including breast and pelvic examination with Papanicolaou test and endometrial evaluation, a screening mammogram and standardized 12-lead electrocardiogram (ECG).Fasting total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured in a sub-sample of participants. Annual examinations included mammograms and clinical breast examinations. ECG results were collected and three- and six-year follow-up. Participant attrition rates were low. Over the 5.2 year follow-up 3.5% [total n = 583; (HRT: n = 307; placebo: n = 276)] women withdrew, were considered lost to follow-up, or stopped providing outcome data for more than 18-months. Vital status at the end of the trial was therefore known for 15,576 (96.5%) of randomised participants, including 580 (2.7%) known to be deceased.
Outcomes	**Primary outcomes:-** CHD (defined as acute MI requiring overnight hospitalisation, silent MI, or CHD death) Death from CVD Non-fatal MI (defined as acute MI requiring overnight hospitalisation, silent MI) **Secondary outcomes:-** Death from any cause Stroke (fatal and non-fatal combined) Angina (confirmed) Revascularisation (CABG or PCI combined) Pulmonary embolisms Venous thrombosis (pulmonary embolism plus DVT combined) HRQoL not included in the analyses; length of follow-up: 5.6 years
Notes	The sample size calculation was adequate so the trial was powered to detect differences between the HRT and placebo groups in terms of CVD events, and adverse events. All outcomes were pre-specified and defined *a prior,* and reported in the trial results. All study personnel, bar the study gynaecologist were 'blinded'. The gynaecologist was 'unblinded' if necessary to treatment group, but separate from the rest of the trial team, and therefore 'blinding' is likely to have been maintained. Participant attrition rates were very low at 3.5%. However, medication compliance rates were low, with only 60% of women still medication compliant at 5.2 year follow-up. This is likely to have 'diluted' the true effects, both positive and negative, of the HRT combination therapy compared to placebo relative to what might be observed with full medication adherence. Additionally the trial was stopped early which would have further decreased the power to detect differences between the two trial arms, and reduced the precision of the estimated effects for the outcomes assessed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally randomised by permuted block algorithm
Allocation concealment (selection bias)	Low risk	By local access to remote study database
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants and clinic staff blinded, with the exception of 331 participants

WHI I 2002 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	583 participants (3.5%) withdrew, were lost to follow-up, or stopped providing outcome information for more than 18 months. Analysis conducted on ITT basis
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No apparent source of other bias

WHI II 2004

Methods	**Objective:** To assess the effects on major disease incidence rates of the most commonly used post-menopausal HT in the United States. **Trial type:** Multicentre randomised placebo controlled primary prevention trial (RCT) involving 40 primary care sites in the United States. The trial recruitment was conducted from January 1993 - September 1998, with a mean follow-up of 6.8 years (range: 5.7 - 10.7). The primary aim of the trial was to assess the effects of oestrogen therapy compared to placebo on disease incident rates of CHD, hip fractures and deaths from all causes. The primary outcome measure was CHD events (defined as acute MI requiring overnight hospitalisation, silent MI, or CHD death), with invasive breast cancer as the primary adverse outcome. Secondary outcomes included stroke (both fatal and non-fatal), pulmonary embolism, DVT, angina (both hospitalisation due to and confirmed), revascularization (CABG or PCI combined), death from all causes, as well as a global index of risks and benefits defined as time to the first event among CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, hip fracture or death due to other causes to summarise overall effects. The trial was stopped early after a mean follow-up of 6.8 years when the National Institute for Health (NIH) concluded that CEE alone did not to appear to effect the risk of heart disease, but was associated with a significant increase in the risk of stroke, and given the likelihood that neither cardio-protection or breast cancer risk would be demonstrated in the remaining intervention period terminated the trial on March 1, 2004. **Recruitment:** Letter of invitation in conjunction with media awareness programme. Sampling method gave women from minority groups six-fold higher odds for selection than Caucasian women and resulted in sample with 84% racially/ethnically designated “white”, 16% non-“white”. **Screening:** Interested women screened by phone or mail for eligibility, then attended three screening visits for history, clinical exam and tests. Three month washout period before baseline evaluation of women using post-menopausal hormones at baseline screening. Lead-in placebo pills given for at least four weeks during screening process to establish compliance with pill taking. **Randomisation:** Centrally randomised by permuted block algorithm **Stratification:** By clinical centre site and age group **Allocation:** By local access to remote study database **Baseline equality of treatment groups:** No substantive differences between study groups at baseline. **Blinding:** All participants, clinic staff, and outcome assessors blinded, with the exception of 331 participants who were unblinded from the unopposed oestrogen arm and reassigned to combined HT arm due to change in protocol. **Analysis:** ITT.

WHI II 2004 *(Continued)*

	Funding Source: The National Heart, Lund, and Blood Institute. Wyeth-Ayerst Research provided the study medication.
Participants	10,739 healthy post-menopausal women who had previously undergone hysterectomy with or without an oophorectomy (including 248 in experimental arm, 183 in placebo arm who joined this study after randomisation to corresponding arms in WHI 2002 having subsequently had a hysterectomy for reasons other than cancer) were randomised to receive either daily conjugated equine oestrogen (n = 5310) or placebo (n = 5429). The mean age of the women was 63.6 years [(SD: ± 7.3; range: 50 - 79)] (Age ratio of 33%: 45%: 21% for the baseline age categories of 50 - 59, 60 - 69, 70 - 79 respectively). Included women were 75% White, 15% Black, 6% Hispanic, 1% American Indian, 1.5% Asian/Pacific Islander, and 1.5% unknown. In terms of previous hormone use: 74% were 'never' HT users, 20% were past users and 6% were current users (therefore requiring a three-month washout period prior to randomisation). 53% of women had used HRT < 5 years, 19% for 5 - < 10 years, and 18% for ≥ 10 years.ǂ In terms of risk factors for CVD: 51% were never smokers, 38.5% were past smokers, and 10.5% were current smokers. The mean BMI among the women was 28.5 kg/m^2 (SD: ± 5.85); mean systolic blood pressure was 127.5 (SD: ±17.55) mm Hg and mean diastolic blood pressure was 75.7 (SD: ± 9.1). The CHD manifestations within the groups were: 4.4% were being treated for diabetes, 36% for hypertension or BP ≥ 140/90 mm Hg, 1.6% had a previous MI, 2.9% had a history of angina, 1.3% had undergone either CABG/PTCA surgery, 0.85% had suffered a previous stroke, and 0.85% had a history of DVT or PE. **Inclusion criteria:** Women age 50 - 79 years of age at initial screening, who had undergone a hysterectomy (thereby considered menopausal for enrolment purposes). **Exclusion criteria:** Invasive cancer in the past ten years; breast cancer at any time or suspicion of breast cancer at baseline screening; endometrial cancer or endometrial hyperplasia at baseline; malignant melanoma; acute MI, stroke, TIA or pulmonary embolism or deep vein thrombosis that was non-traumatic or that had occurred in the previous six months; known chronic active hepatitis or severe cirrhosis, blood counts indicative of disease; bleeding disorder; lipaemic serum and hypertriglyceridaemia diagnosis; current use of anticoagulants or tamoxifen; or Papanicolaou smear or pelvic abnormalities; severe hypertension; or current use of oral corticosteroids; bleeding disorder; lipaemic serum and hypertriglyceridaemia diagnosis; current use of anticoagulants or tamoxifen; (2) for reasons of adherence or retention: severe menopausal symptoms inconsistent with assignment to placebo; inability or unwillingness to discontinue current HT use or oral testosterone use; inadequate adherence with placebo run-in; unwillingness to have baseline or follow-up endometrial aspirations; alcoholism, drug dependency, mental illness, dementia. ǂ among women reporting hormone use (data do not sum to 100%)
Interventions	**HT regimens :** 0.625 mg conjugated equine oestrogen daily (CEE) (continuous dosage regimen). **Comparator:** identical placebo tablet daily. Medication adherence was defined as participants taking > 80 study pills, and was monitored by weighing medication bottles at each clinic visit. Medication adherence data for each trial year were not reported, but by the time of study termination 53.8% of women had stopped taking study medication. Therefore only 46.2% of women remained medication compliant. Compliance rates did not differ significantly between the two trial arms. At 6.8 years follow-up 5.7% of women in the HT arm had initiated hormone use through their own physician and 9.1% of women in the placebo arm had also initiated hormone use (drop-in). **Follow-up times:** Baseline, and then every six-month, with an annual clinic visit. At baseline participants completed a medical, reproductive history and psychosocial questionnaire; ECG, and underwent breast examination and gynaecological examination. Mammograms and breast examinations were repeated annually and ECGs were repeated at visit years three and six. Participant attrition rates were low. Over the 6.8 year follow-up 5.2% [total n = 563; (HT: n = 262; placebo: n = 301)] women withdrew [n = 321 (HT: n = 136; placebo: n = 185)] were considered lost to follow-up [n = 142 (HT: n = 126; placebo: n = 116)], or stopped providing outcome data for more than 18-

WHI II 2004 *(Continued)*

	months. Vital status at the end of the trial was therefore known for 10,176 (94.8%) of randomised participants, including 580 (5.4%) known to be deceased.
Outcomes	**Primary outcomes:-** CHD (defined as acute MI requiring overnight hospitalisation, silent MI, or CHD death) Death from CVD Non-fatal MI (defined as acute MI requiring overnight hospitalisation, silent MI) **Secondary outcomes:-** Death from any cause Stroke (fatal and non-fatal combined) Angina (confirmed) Revascularisation (CABG or PCI combined) Pulmonary embolisms Venous thrombosis (pulmonary embolism plus DVT combined) HRQoL **n**ot included in the analyses; length of follow-up: 7.1 years
Notes	The sample size calculation was adequate so the trial was powered to detect differences between the HT and placebo groups in terms of CVD events. All outcomes were pre-specified and defined *a prior,* and reported in the trial results. All study personnel, bar the study gynaecologist were 'blinded'. The gynaecologist was 'unblinded' if necessary to treatment group, but separate from the rest of the trial team, and therefore 'blinding' is likely to have been maintained. Participant attrition rates were low at 5.2%. However, medication compliance rates were low, with only 46.2% of women still medication compliant at 6.8 year follow-up. This is likely to have 'diluted' the true effects, both positive and negative, of estrogens relative to placebo relative to what might be observed with full medication adherence. Additionally the trial was stopped early which would have further decreased the power to detect differences between the two trial arms, and reduced the precision of the estimated effects for the outcomes assessed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally randomised by permuted block algorithm
Allocation concealment (selection bias)	Low risk	By local access to remote study database
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants and clinic staff blinded, with the exception of 331 participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	563 participants (5.2%) withdrew, were lost to follow-up, or stopped providing outcome information for more than 18 months. Analysis conducted on ITT basis

WHI II 2004 *(Continued)*

Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No apparent source of other bias

WISDOM 2007

Methods	**Objective:** To assess the long term benefits and risks of HT Multicentre three-armed randomised controlled (RCT) trial involving 499 general practices; (n = 385 UK); (n = 91 Australia) and (n = 24) New Zealand. The trial was conducted between 1999 - 2002, with an intended follow-up period of ten-years. The trial was halted early after the publication of the results from WHI I 2002 trial showed no statistically significant benefit for treatment with HT compared with placebo. The median follow-up time was 11.9 months (interquartile range: 7.1 - 19.6) for the entire trial participants and 12.8 months (range: 7.5 -20 -4) months for participants randomised to combination therapy. The trial was composed of 3 different strata: Strata 1: Women with an intact uterus or sub-total hysterectomy not taking HT randomised to combined oestrogen and progesterone therapy or placebo. Strata 2: Hysterectomised women taking HT and randomised to oestrogen only HT or combined HT. Stratum 3: Hysterectomised women not taking HT randomised to oestrogen only HT or combined HT or placebo. The design therefore allowed for two main comparisons to be made: (1) combined oestrogen and progestogen therapy versus placebo, and in women who had a hysterectomy, (2) oestrogen alone versus combination oestrogen and progestogen therapy. Only the baseline demographic data and results from strata 1 are reported within this report, as this was the only comparison of HT versus placebo within the trial. **Recruitment:** Practice registries **Screening:** 14,203 screened for eligibility (4385 randomised) All women took placebo medication during run in: those who achieved 80% compliance were randomised **Randomisation:** Remote computer-generated **Stratification:** By hysterectomy status and intended use of HT: women with no uterus and unwilling to take placebo randomised to CEE or combined HT. Equal probability of any treatment within each stratum. **Allocation:** Remote computer-generated **Baseline equality of treatment groups:** No substantive differences at baseline **Blinding:** All participants, clinic staff, and outcome assessors blinded except when vaginal bleeding triggered a code break **Analysis:** ITT. **Funding Source:** Non-commercial medical research funding
Participants	4385 healthy women in strata one (out of a total of 5692 women randomised) were randomised to either combined HT or placebo.

WISDOM 2007 *(Continued)*

	The mean age of the women was 63.3 years (SD: 4.7), with a mean of 14.7 years (SD: 7.1) years since menopause. Post-menopausal status was defined as the presence of no menses in the past 12 months or having undergone a hysterectomy. Women taking HT at baseline screening who were prepared to enter the placebo controlled strata of the study ceased therapy for three-months before the run-in phase. During run-in they took placebo so that at randomisation they had not taken HT for six-months. At baseline 9% of women were taking oestrogen, and therefore underwent a three-month 'wash out 'period prior to randomisation. 2% of the included women were of non-white ethnic status; 18% were using HT at screening and 86% had previously used HT. In terms of risk factors for CVD: mean BMI was 28.0 kg/m^2; mean systolic blood pressure was 136.5 mm Hg and mean diastolic blood pressure 73 mm Hg; 24% were current smokers; 55% were former smokers; 10% had previous angina; 3% had a previous MI; 3% had a previous stroke and 7% had diabetes. Inclusion criteria: Stated above, but only women who were 80% or more medication compliant in the run-in period were eligible for participation in the trial. **Exclusion criteria:** For the placebo controlled group oral transdermal HT use in the last six months; ever use of HT implant in women with a uterus, HT implant inserted in last eight months in women with a hysterectomy; history of endometriosis or endometrial hyperplasia in a woman with a uterus; history of invasive breast cancer, lobular carcinoma in situ (LCIS), ductal carcinoma in-situ (DCIS), Paget's disease of the nipple or atypical hyperplasia of the breast; BRCA1 or BRCA2 mutation carrier; history of melanoma; invasive cancer at any other site apart from basal and squamous cell skin cancer within the last ten years; history of meningioma; myocardial infarction, cerebrovascular accident, subarachnoid haemorrhage or transient ischaemic attack within the last six months; history of currently active liver disease or chronic liver disease but excluding Hepatitis A unless currently active; severe renal impairment; gall bladder disease in a woman who had not had a cholecystectomy or of gallstones following a cholecystectomy; deep vein thrombosis, pulmonary embolism or retinal vein occlusion; positive thrombophilia screen (Factor V Leiden or prothrombin mutations, Protein C, Protein S or antithrombin III deficiencies, APC resistance, dysfibrinogenaemia or antiphospholipid antibodies); Otosclerosis; Porphyria; currently pregnant or taking contraceptive drugs in the last 12 months; current triglyceride level (fasting) > 5.5 mmol/l; active participant in any other intervention trial likely to affect trial outcomes; taking tamoxifen, toremifene, raloxifene or any other selective oestrogen receptor modulator (SERM). History of hepatitis B, hepatitis C or HIV (not an exclusion criteria in New Zealand).
Interventions	**HT regimen:** 0.625 mg conjugated equine oestrogen in combination with 2.5 mg medroxyprogesterone acetate (MPA) daily (continuous dosage regimen). **Comaparator:** placebo tablet daily. Participants were classified as medication compliant if they took ≥ 80% of their medication throughout the trial. Trial treatment delivered 73% of time to women in combined HT arm and 86% of time to women on placebo. **Follow-up times:** 4, 14, 27, 40 and 52-weeks and then at six-month intervals. At baseline recent cervical screening and mammography were checked and then at each follow-up visit information was collected on all outcomes (none of the outcomes were defined), adverse events and patients other medical history. **Losses to follow up:** five **Dropouts:** 615 (14%) had withdrawn from randomised treatment by trial closure
Outcomes	Primary outcomes:- Death from CVD Angina Non-fatal MI

WISDOM 2007 *(Continued)*

	Fatal MI Secondary outcomes:- Pulmonary embolism Venous thromboembolism Health-related quality of life
Notes	Powered in protocol to detect 25% reduction in CHD over ten years. This assumed an 18,000 sample size but trial stopped early with 26% of target A further 1307 women were in comparison of combined therapy vs oestrogen only and not included in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Remote computer-generated
Allocation concealment (selection bias)	Low risk	Remote computer-generated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants and clinic staff blinded except when vaginal bleeding triggered a code break
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All outcome assessors blinded except when vaginal bleeding triggered a code break
Incomplete outcome data (attrition bias) All outcomes	Low risk	615 (14%) had withdrawn from randomised treatment by trial closure. Analysed by intention to treat
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	No apparent source of other bias

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Angerer 2001	No relevant clinical outcomes
Clarke 2002	Wrong intervention. Transdermal patches used
Davidson 1997	Abstract only; did not report relevant clinical outcomes.
HERS II	This trial was the long-term open label follow-up phase of HERS I 1998, and therefore not included as a separate trial, as done in the original review.

Study	Reason for exclusion
Holmberg 2004	Wrong patient population: trial is of women with breast cancer
Hsia 2003	Did not report relevant clinical outcomes
Hsia 2004	WHI: combination trial with 5.6 year follow-up; reports peripheral arterial disease outcomes only. No relevant clinical outcomes
Huang 2009	No clinically relevant data reported. Reports number of hot flushes by year and treatment group in the HERS 1 trial
Karim 2008	No relevant clinical outcomes reported
Lamon-Fava 2009	No relevant clinical outcomes reported
Marsden 2002	Abstract for a trial to be undertaken
Moriyama 2008	Wrong comparison. HT compared with either being physically active or sedentary, and being active or sedentary compared to placebo
Mosca 2009	Wrong intervention (Raloxifene) and outside the scope of the review
Nair 2005	No relevant clinical outcomes reported. Examination of relationship between baseline brachial pulse pressure and CV outcomes in HERS I
Neuhouser 2009	Does not report results for HT or placebo users separately from all women randomised to take vitamins
Pinkerton 2009	No relevant clinical outcomes reported
Prentice 2008	WHI: outcomes for breast cancer for both the oestrogen alone and combination trials. No relevant outcomes reported
Prentice 2009	No relevant clinical outcomes reported. WHI: outcomes for breast cancer for both the oestrogen alone and combination trials
Toh 2010	Effect of HT in WHI compared with The Nurses Health Study. The outcome is not clear and defined, just stated as CHD risk
Yeboah 2008	No relevant clinical outcomes reported.

Characteristics of ongoing studies *[ordered by study ID]*

ELITE 2004 (NCT00114517)

Trial name or title	Early versus Late Intervention Trial with Estradiol (ELITE)
Methods	Randomised placebo controlled trial
Participants	Post-menopausal healthy women
Interventions	17β-estradiol versus placebo
Outcomes	Atherosclerotic progression and cognition

ELITE 2004 (NCT00114517) *(Continued)*

Starting date	2005- 2013
Contact information	Principal Investigator: Howard N. Hodis, MD; University of Southern California, Atherosclerosis Research Unit, Division of Cardiovascular Medicine, Department of Medicine
Notes	Additional information: USC Atherosclerosis Research Unit ELITE Trial

KEEPS 2005 (NCT00154180)

Trial name or title	The Kronos Early Estrogen Prevention Study; Effects of Estrogen Replacement on Atherosclerosis Progression in Recently Menopausal Women
Methods	Randomised placebo controlled trial
Participants	Recently menopausal healthy women (within 36 months of menses)
Interventions	0.45 mg oral oestrogen weekly with 200 mg cyclic oral, micronized progesterone for 12 days each month
Outcomes	Rate of change of carotid intimal medial thickness by ultrasound; Cognitive and Affective scores; HRQoL
Starting date	2005- 2012
Contact information	Principal Investigators: Michael Mendelsohn, MD, Tufts Medical Center; Howard Hodis, MD, University of Southern California; Matthew Budoff, MD, University of California, Los Angeles; Sanjay Asthana, MD, University of Wisconsin, Madison; Dennis M Black, PhD, University of California, San Francisco
Notes	Sponsor: Kronos Longevity Research Institute

DATA AND ANALYSES

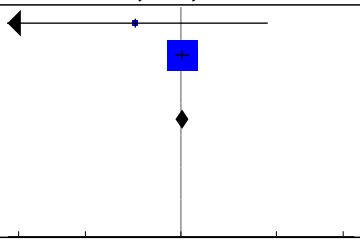
Comparison 1. Estrogen vs placebo in primary prevention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	2	10961	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.88, 1.20]
2 Death (CV causes)	2	10961	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.70, 1.40]
3 Non-fatal MI	2	10961	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.73, 1.13]
4 Stroke	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.08, 1.70]
5 Angina	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.79, 1.20]
6 Venous thromboembolism	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.00, 1.74]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Pulmonary embolism	1	10739	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.90, 2.06]
8 Angioplasty	1	222	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.43]

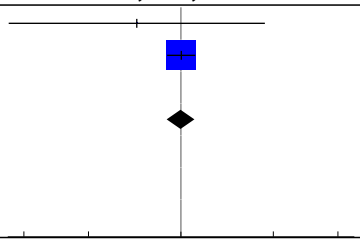
Analysis 1.1. Comparison 1 Estrogen vs placebo in primary prevention, Outcome 1 Death (all causes).

Study or subgroup	Estrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
EPAT 2001	0/111	1/111		0.52%	0.33[0.01,8.1]
WHI II 2004	291/5310	289/5429		99.48%	1.03[0.88,1.21]
Total (95% CI)	**5421**	**5540**		**100%**	**1.03[0.88,1.2]**
Total events: 291 (Estrogen), 290 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.48, df=1(P=0.49); I^2=0%					
Test for overall effect: Z=0.32(P=0.75)					



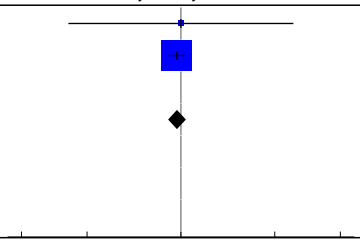
Analysis 1.2. Comparison 1 Estrogen vs placebo in primary prevention, Outcome 2 Death (CV causes).

Study or subgroup	Estrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
EPAT 2001	0/111	1/111		2.35%	0.33[0.01,8.1]
WHI II 2004	62/5310	63/5429		97.65%	1.01[0.71,1.43]
Total (95% CI)	**5421**	**5540**		**100%**	**0.99[0.7,1.4]**
Total events: 62 (Estrogen), 64 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.46, df=1(P=0.5); I^2=0%					
Test for overall effect: Z=0.05(P=0.96)					



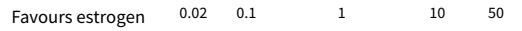
Analysis 1.3. Comparison 1 Estrogen vs placebo in primary prevention, Outcome 3 Non-fatal MI.

Study or subgroup	Estrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
EPAT 2001	1/111	1/111		0.6%	1[0.06,15.79]
WHI II 2004	149/5310	168/5429		99.4%	0.91[0.73,1.13]
Total (95% CI)	**5421**	**5540**		**100%**	**0.91[0.73,1.13]**
Total events: 150 (Estrogen), 169 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.94); I^2=0%					
Test for overall effect: Z=0.88(P=0.38)					



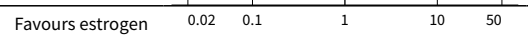
Analysis 1.4. Comparison 1 Estrogen vs placebo in primary prevention, Outcome 4 Stroke.

Study or subgroup	Estrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
WHI II 2004	168/5310	127/5429		100%	1.35[1.08,1.7]
Total (95% CI)	**5310**	**5429**		**100%**	**1.35[1.08,1.7]**
Total events: 168 (Estrogen), 127 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.6(P=0.01)					



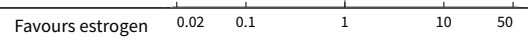
Analysis 1.5. Comparison 1 Estrogen vs placebo in primary prevention, Outcome 5 Angina.

Study or subgroup	Estrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
WHI II 2004	163/5310	171/5429		100%	0.97[0.79,1.2]
Total (95% CI)	**5310**	**5429**		**100%**	**0.97[0.79,1.2]**
Total events: 163 (Estrogen), 171 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.24(P=0.81)					



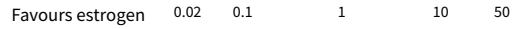
Analysis 1.6. Comparison 1 Estrogen vs placebo in primary prevention, Outcome 6 Venous thromboembolism.

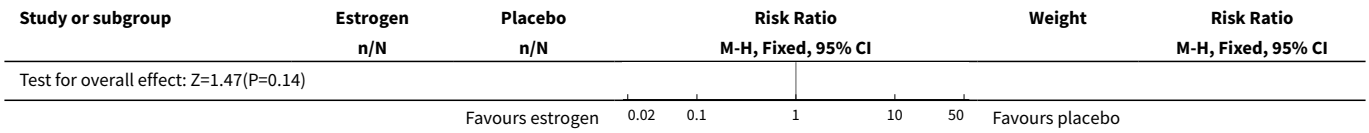
Study or subgroup	Estrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
WHI II 2004	111/5310	86/5429		100%	1.32[1,1.74]
Total (95% CI)	**5310**	**5429**		**100%**	**1.32[1,1.74]**
Total events: 111 (Estrogen), 86 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.95(P=0.05)					



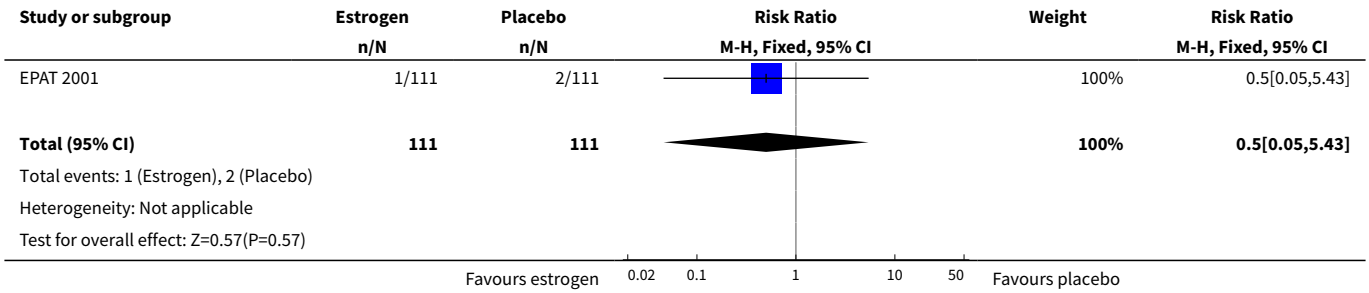
Analysis 1.7. Comparison 1 Estrogen vs placebo in primary prevention, Outcome 7 Pulmonary embolism.

Study or subgroup	Estrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
WHI II 2004	52/5310	39/5429		100%	1.36[0.9,2.06]
Total (95% CI)	**5310**	**5429**		**100%**	**1.36[0.9,2.06]**
Total events: 52 (Estrogen), 39 (Placebo)					
Heterogeneity: Not applicable					





Analysis 1.8. Comparison 1 Estrogen vs placebo in primary prevention, Outcome 8 Angioplasty.



Comparison 2. Combination HT vs placebo in primary prevention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	3	21770	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.85, 1.22]
2 Death (CV causes)	2	20993	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.71, 1.76]
3 Non-fatal MI	3	21770	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.06, 1.78]
4 Stroke	2	17385	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.03, 1.68]
5 Angina	2	20993	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.64, 1.06]
6 Venous thromboembolism	2	20993	Risk Ratio (M-H, Fixed, 95% CI)	2.29 [1.76, 2.97]
7 Pulmonary embolism	2	20993	Risk Ratio (M-H, Fixed, 95% CI)	2.29 [1.59, 3.31]
8 Death (all causes): time on treatment	3	54986	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.21]
8.1 1-year follow-up	2	20993	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.76, 2.27]
8.2 3-year follow-up	2	17385	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.79, 1.42]
8.3 5.6 year follow-up	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.84, 1.21]
9 Stroke: time on treatment	2	67209	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.11, 1.58]
9.1 1-year follow-up	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.49, 1.86]
9.2 2-year follow-up	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.83, 2.06]

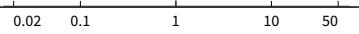
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.3 3-year follow-up	2	17385	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.98, 2.00]
9.4 5.6 year follow-up	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [1.05, 1.72]
10 Venous thromboembolism: time on treatment	2	70817	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [2.13, 3.09]
10.1 1-year follow-up	2	20993	Risk Ratio (M-H, Fixed, 95% CI)	4.28 [2.49, 7.34]
10.2 2-year follow-up	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	2.98 [1.88, 4.71]
10.3 3-year follow-up	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	2.54 [1.73, 3.72]
10.4 5.6 year follow-up	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [1.60, 2.74]
11 Non-fatal MI: time on treatment	3	21770	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.06, 1.78]
11.1 1-year follow-up	1	4385	Risk Ratio (M-H, Fixed, 95% CI)	8.97 [0.48, 166.53]
11.2 3-year follow-up	1	777	Risk Ratio (M-H, Fixed, 95% CI)	4.62 [0.22, 95.86]
11.3 5.6 year follow-up	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.02, 1.71]

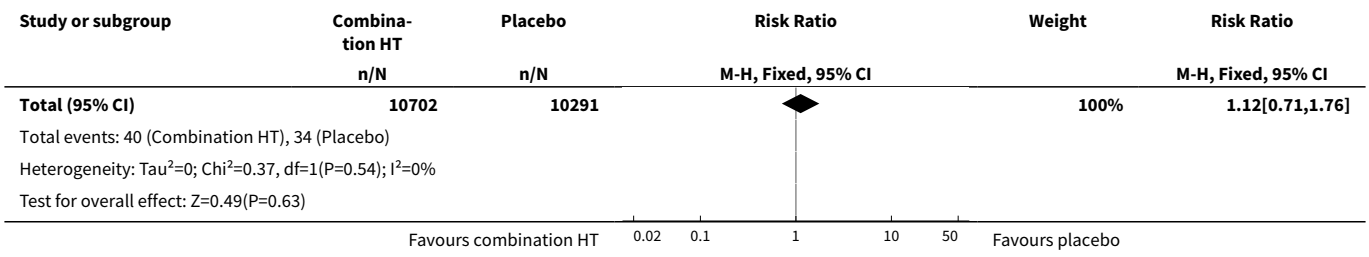
Analysis 2.1. Comparison 2 Combination HT vs placebo in primary prevention, Outcome 1 Death (all causes).

Study or subgroup	Combination HT n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
EPHT 2006	1/404	1/373		0.45%	0.92[0.06,14.71]
WHI I 2002	231/8506	218/8102		97.36%	1.01[0.84,1.21]
WISDOM 2007	8/2196	5/2189		2.18%	1.59[0.52,4.87]
Total (95% CI)	**11106**	**10664**		**100%**	**1.02[0.85,1.22]**
Total events: 240 (Combination HT), 224 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.63, df=2(P=0.73); I^2=0%					
Test for overall effect: Z=0.23(P=0.81)					

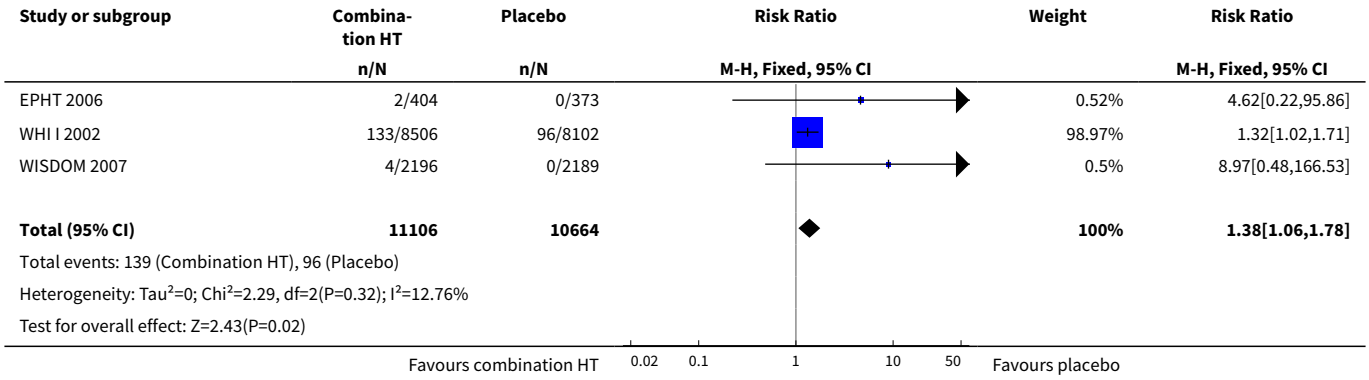
Analysis 2.2. Comparison 2 Combination HT vs placebo in primary prevention, Outcome 2 Death (CV causes).

Study or subgroup	Combination HT n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
WHI I 2002	39/8506	34/8102		98.58%	1.09[0.69,1.73]
WISDOM 2007	1/2196	0/2189		1.42%	2.99[0.12,73.37]

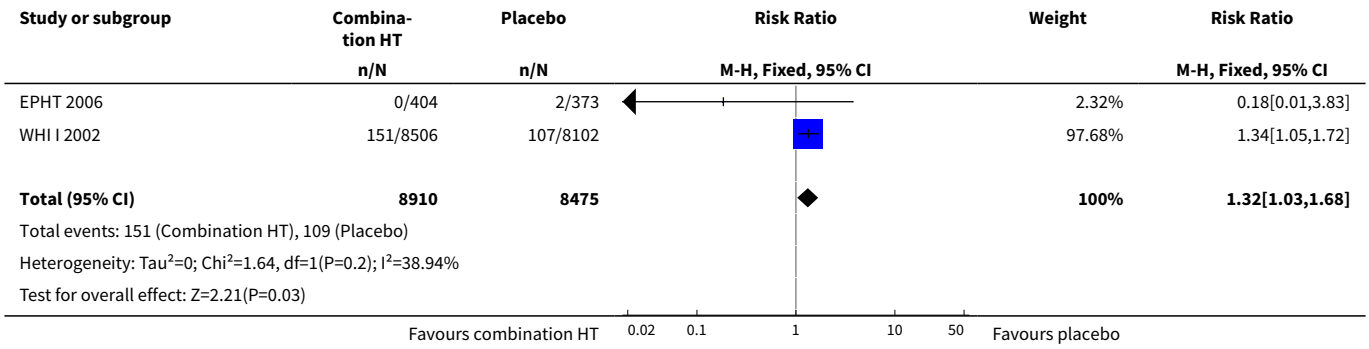




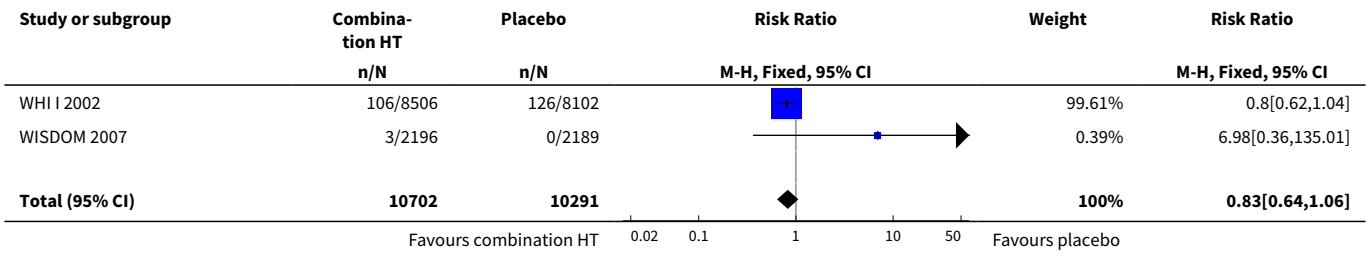
Analysis 2.3. Comparison 2 Combination HT vs placebo in primary prevention, Outcome 3 Non-fatal MI.

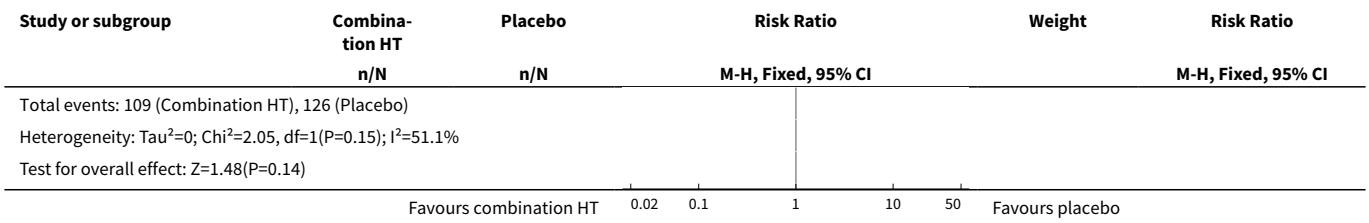


Analysis 2.4. Comparison 2 Combination HT vs placebo in primary prevention, Outcome 4 Stroke.

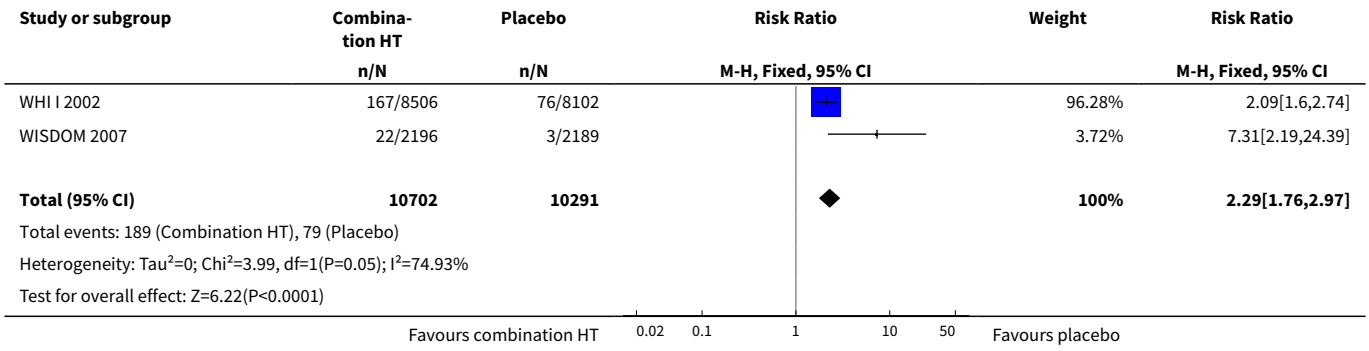


Analysis 2.5. Comparison 2 Combination HT vs placebo in primary prevention, Outcome 5 Angina.

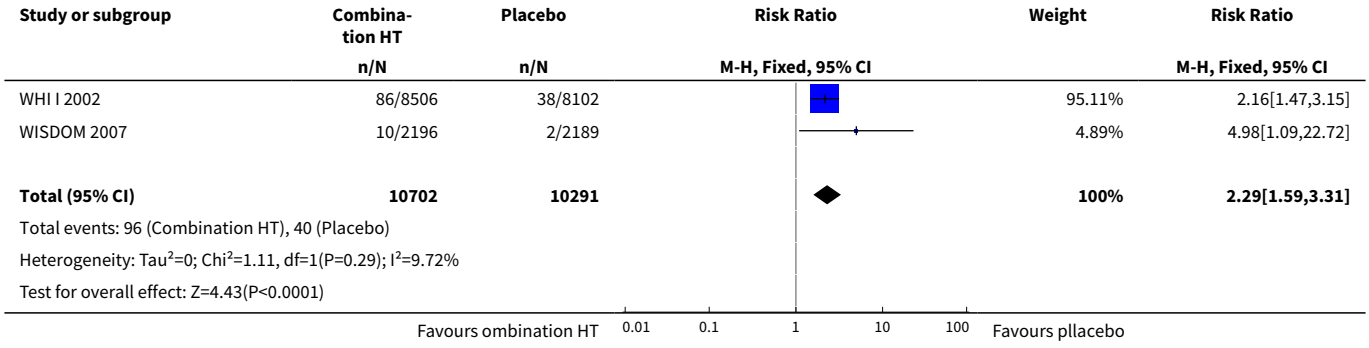




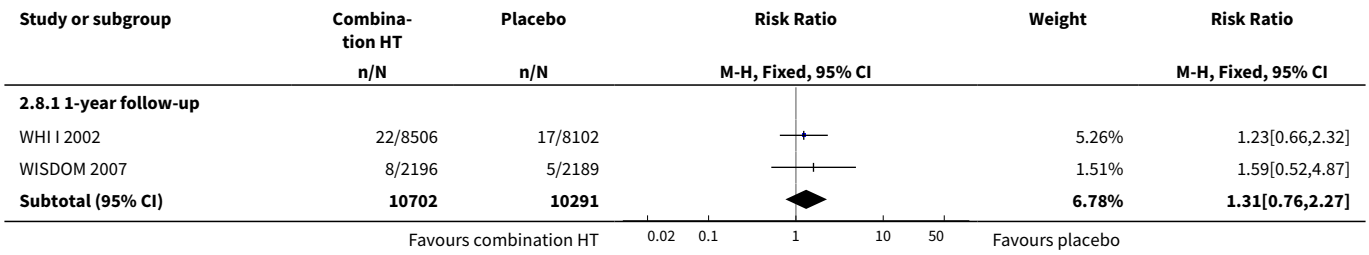
Analysis 2.6. Comparison 2 Combination HT vs placebo in primary prevention, Outcome 6 Venous thromboembolism.

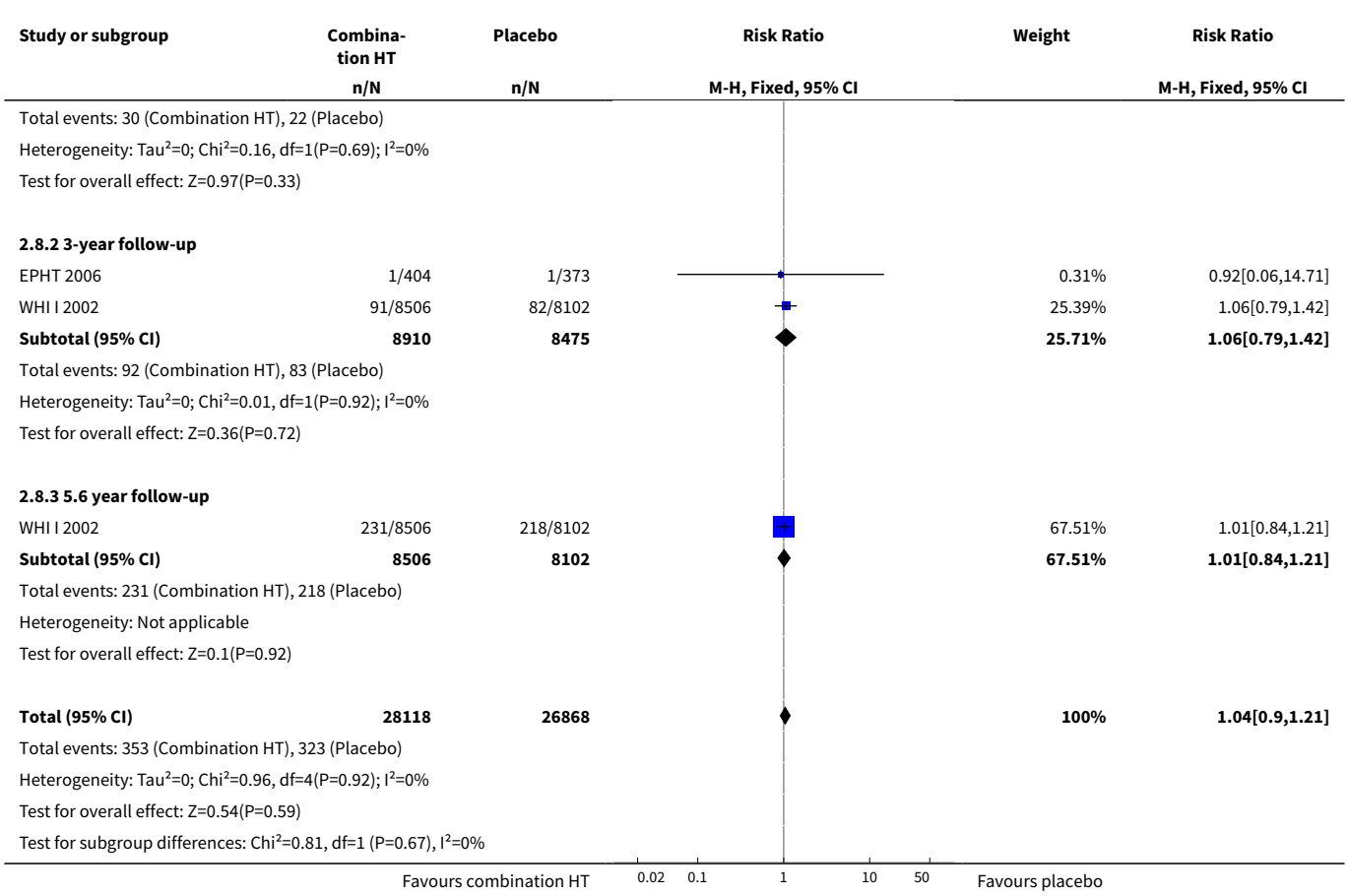


Analysis 2.7. Comparison 2 Combination HT vs placebo in primary prevention, Outcome 7 Pulmonary embolism.

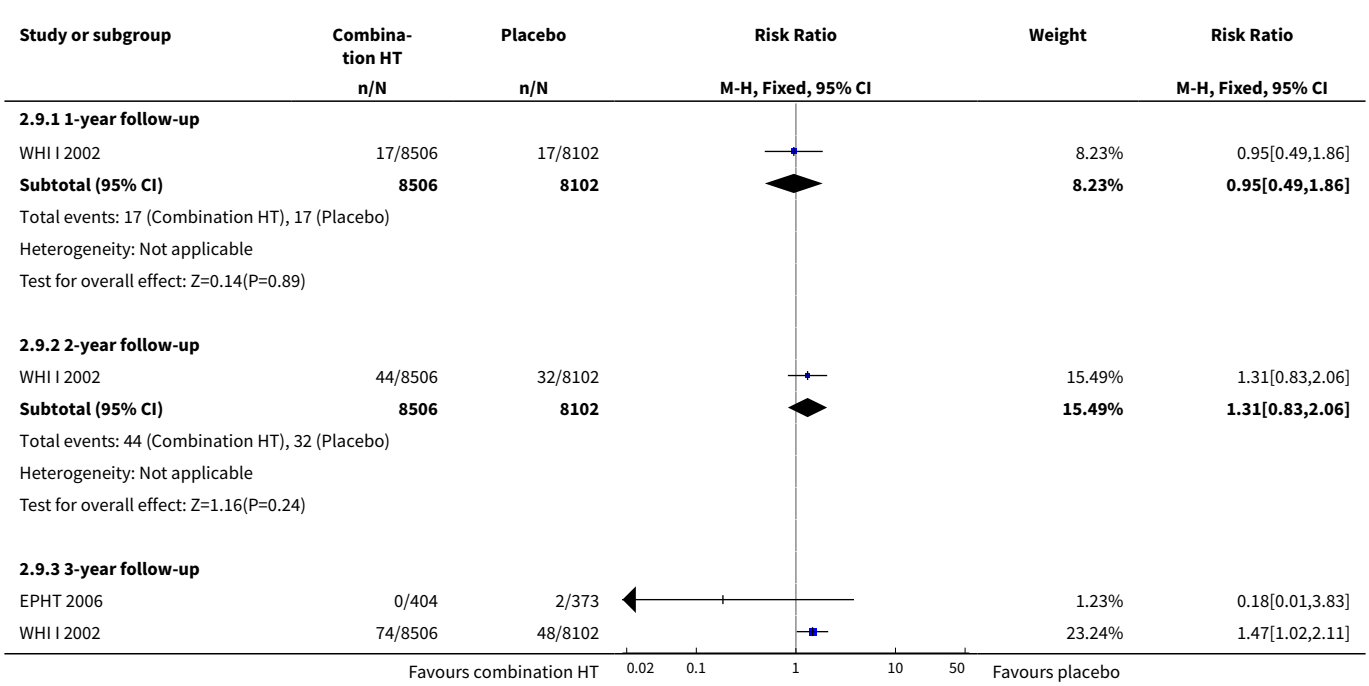


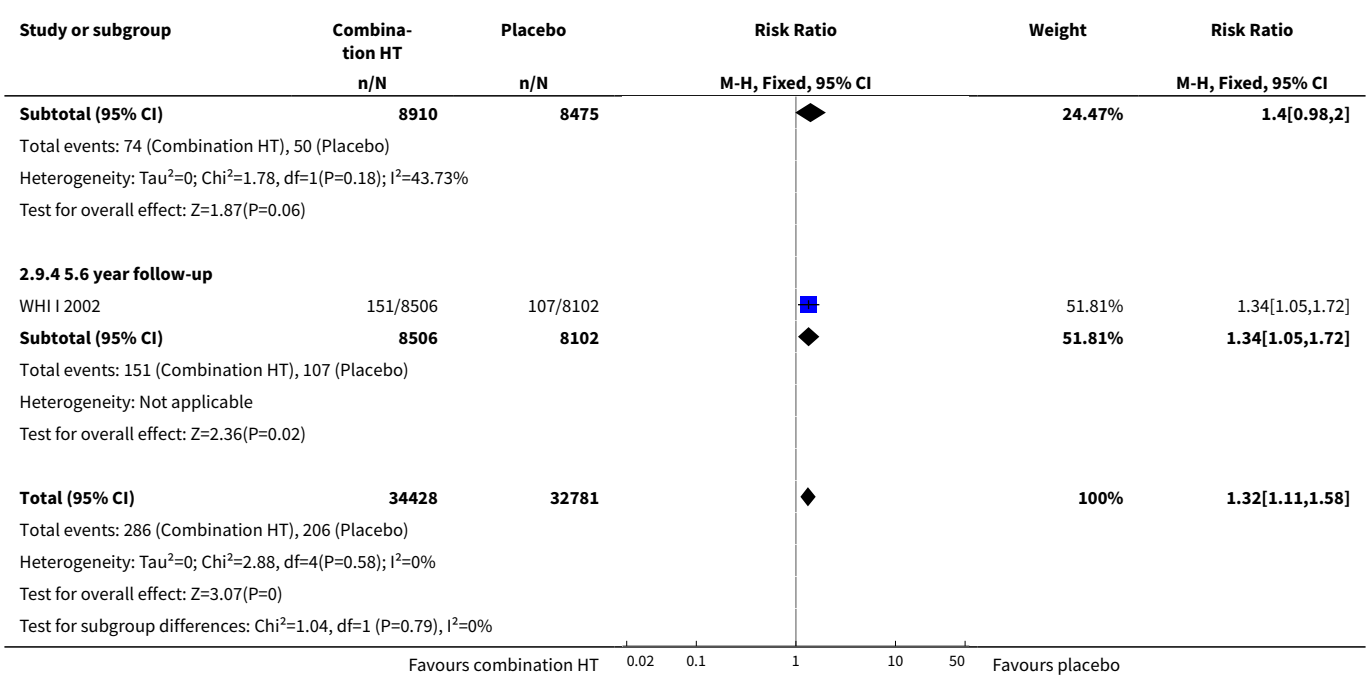
Analysis 2.8. Comparison 2 Combination HT vs placebo in primary prevention, Outcome 8 Death (all causes): time on treatment.



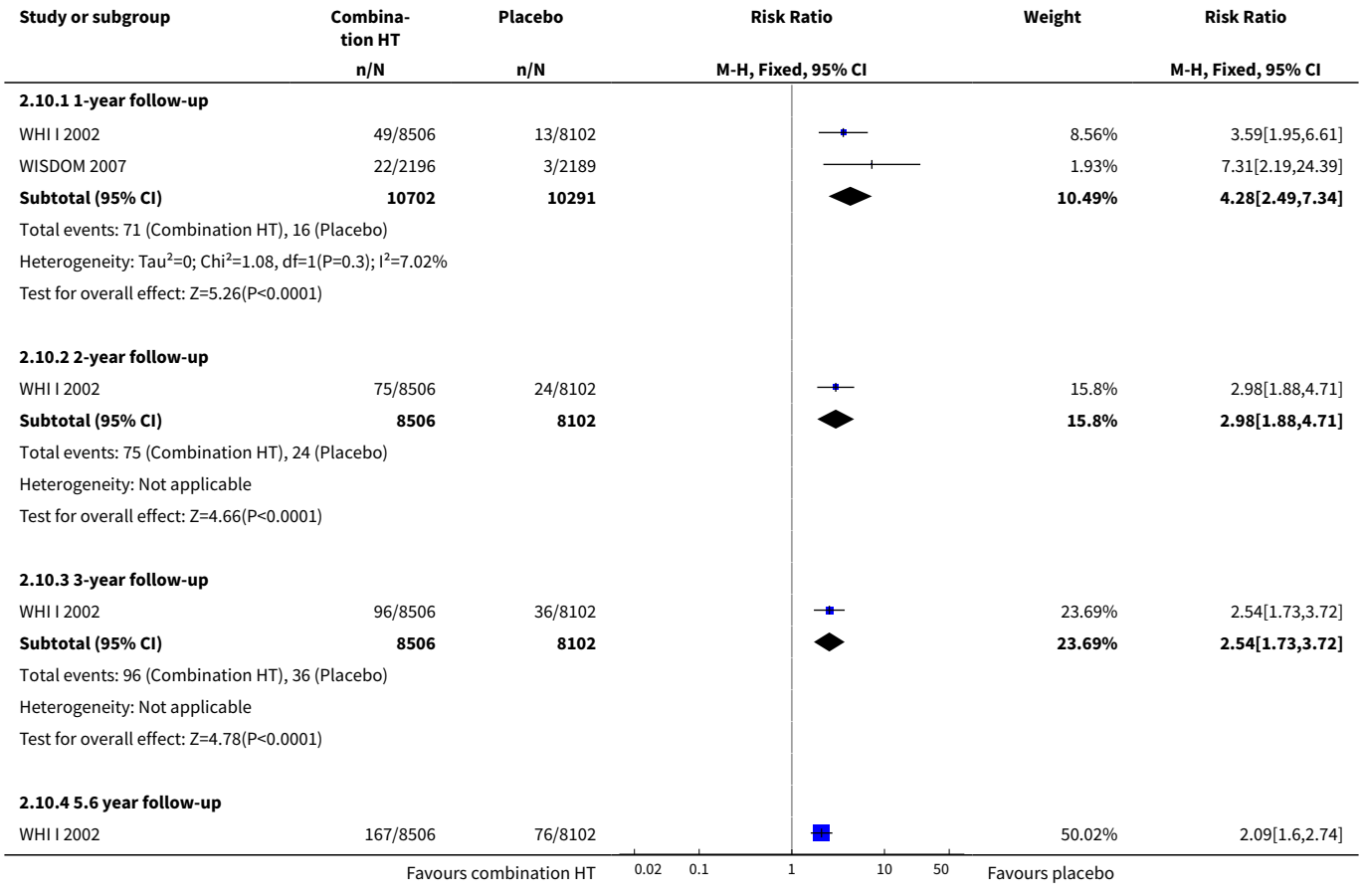


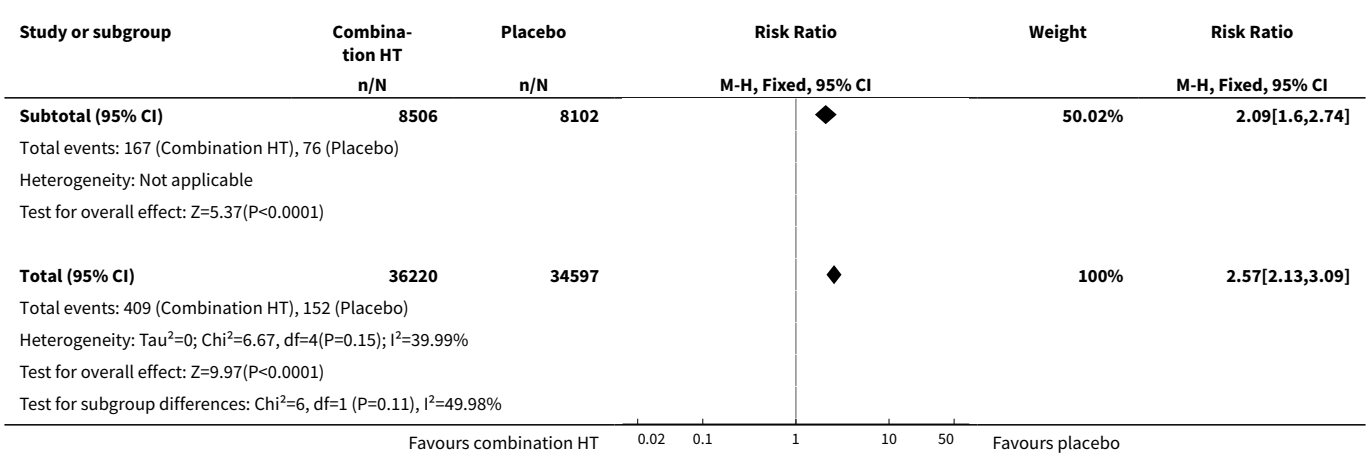
Analysis 2.9. Comparison 2 Combination HT vs placebo in primary prevention, Outcome 9 Stroke: time on treatment.



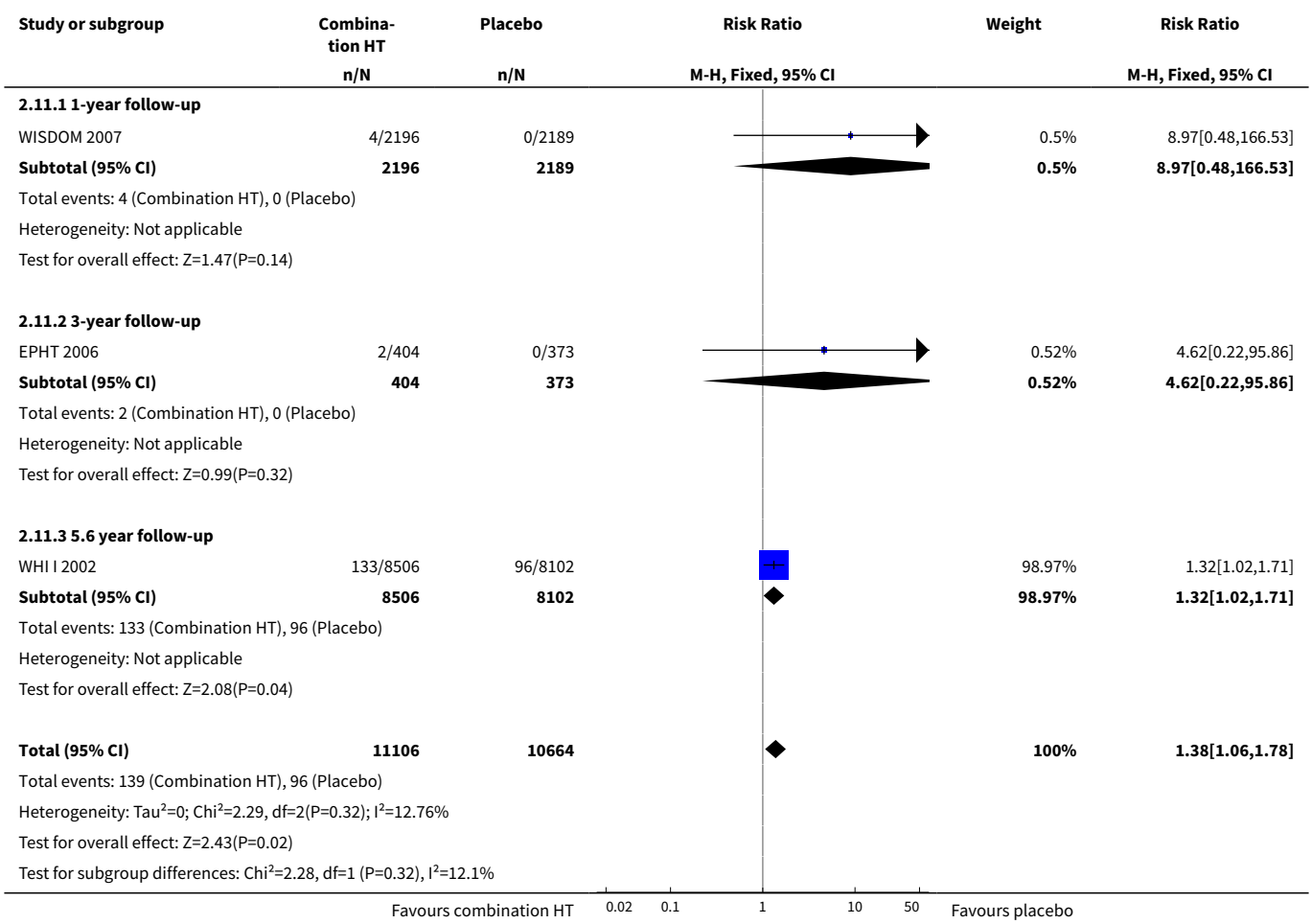


Analysis 2.10. Comparison 2 Combination HT vs placebo in primary prevention, Outcome 10 Venous thromboembolism: time on treatment.





Analysis 2.11. Comparison 2 Combination HT vs placebo in primary prevention, Outcome 11 Non-fatal MI: time on treatment.

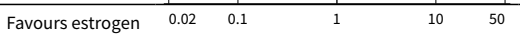


Comparison 3. Estrogen vs placebo in secondary prevention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	3	1834	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.75, 1.33]
2 Death (CV causes)	4	1917	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.48, 1.11]
3 Non-fatal MI	4	1917	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.84, 1.72]
4 Stroke	3	1834	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.73, 1.40]
5 Angina	2	236	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.64, 1.69]
6 Venous thromboembolism	2	817	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.37, 3.84]
7 Pulmonary embolism	1	1017	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.20, 4.84]
8 Angioplasty	1	83	Risk Ratio (M-H, Fixed, 95% CI)	8.6 [1.13, 65.73]

Analysis 3.1. Comparison 3 Estrogen vs placebo in secondary prevention, Outcome 1 Death (all causes).

Study or subgroup	Estrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ERA 2000	8/100	3/53		4.62%	1.41[0.39,5.11]
ESPRIT 2002	32/513	39/504		46.35%	0.81[0.51,1.27]
WEST 2001	48/337	41/327		49.03%	1.14[0.77,1.67]
Total (95% CI)	**950**	**884**		**100%**	**1[0.75,1.33]**
Total events: 88 (Estrogen), 83 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.57, df=2(P=0.46); I^2=0%					
Test for overall effect: Z=0.03(P=0.98)					



Analysis 3.2. Comparison 3 Estrogen vs placebo in secondary prevention, Outcome 2 Death (CV causes).

Study or subgroup	Estrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
EAGAR 2006	2/40	4/43		7.72%	0.54[0.1,2.78]
ERA 2000	4/100	2/53		5.24%	1.06[0.2,5.6]
ESPRIT 2002	21/513	30/504		60.61%	0.69[0.4,1.18]
WEST 2001	11/337	13/327		26.43%	0.82[0.37,1.81]
Total (95% CI)	**990**	**927**		**100%**	**0.73[0.48,1.11]**
Total events: 38 (Estrogen), 49 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.46, df=3(P=0.93); I^2=0%					
Test for overall effect: Z=1.47(P=0.14)					

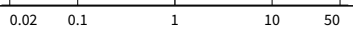
Analysis 3.3. Comparison 3 Estrogen vs placebo in secondary prevention, Outcome 3 Non-fatal MI.

Study or subgroup	Estrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
EAGAR 2006	2/40	2/43		3.81%	1.08[0.16,7.27]
ERA 2000	6/100	4/53		10.33%	0.8[0.23,2.69]
ESPRIT 2002	41/513	31/504		61.79%	1.3[0.83,2.04]
WEST 2001	14/337	12/327		24.07%	1.13[0.53,2.41]
Total (95% CI)	**990**	**927**		**100%**	**1.2[0.84,1.72]**
Total events: 63 (Estrogen), 49 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.59, df=3(P=0.9); I^2=0%					
Test for overall effect: Z=0.98(P=0.33)					

Favours estrogen — Favours placebo

Analysis 3.4. Comparison 3 Estrogen vs placebo in secondary prevention, Outcome 4 Stroke.

Study or subgroup	Estrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ERA 2000	5/100	3/53		6.25%	0.88[0.22,3.55]
ESPRIT 2002	10/513	6/504		9.65%	1.64[0.6,4.47]
WEST 2001	51/337	52/327		84.11%	0.95[0.67,1.36]
Total (95% CI)	**950**	**884**		**100%**	**1.01[0.73,1.4]**
Total events: 66 (Estrogen), 61 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.03, df=2(P=0.6); I^2=0%					
Test for overall effect: Z=0.08(P=0.94)					



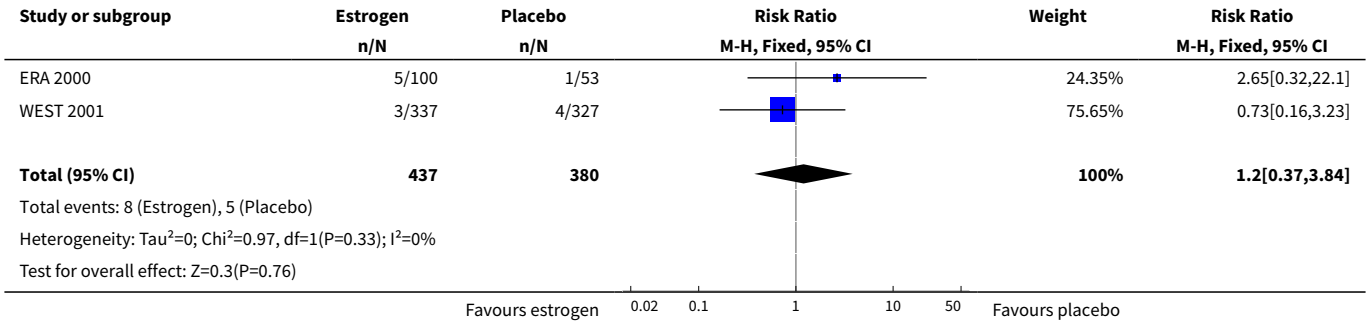
Favours estrogen — Favours placebo

Analysis 3.5. Comparison 3 Estrogen vs placebo in secondary prevention, Outcome 5 Angina.

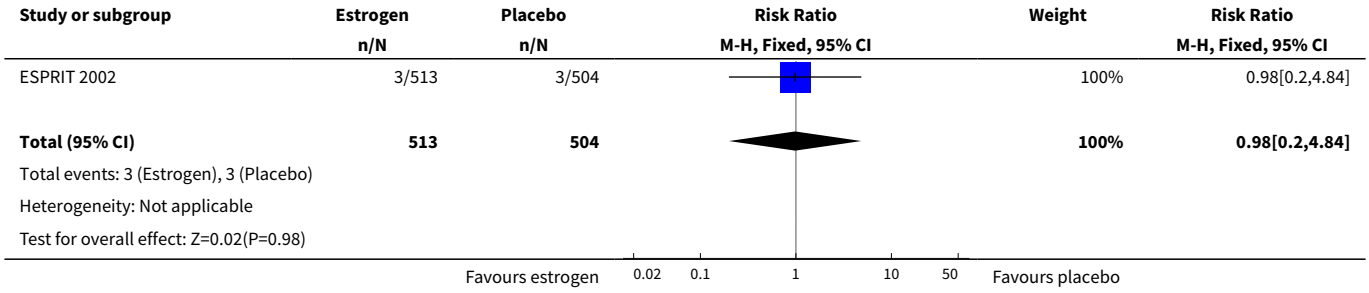
Study or subgroup	Estrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
EAGAR 2006	12/40	10/43		40.13%	1.29[0.63,2.65]
ERA 2000	18/100	11/53		59.87%	0.87[0.44,1.7]
Total (95% CI)	**140**	**96**		**100%**	**1.04[0.64,1.69]**
Total events: 30 (Estrogen), 21 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.62, df=1(P=0.43); I^2=0%					
Test for overall effect: Z=0.15(P=0.88)					

Favours estrogen — Favours placebo

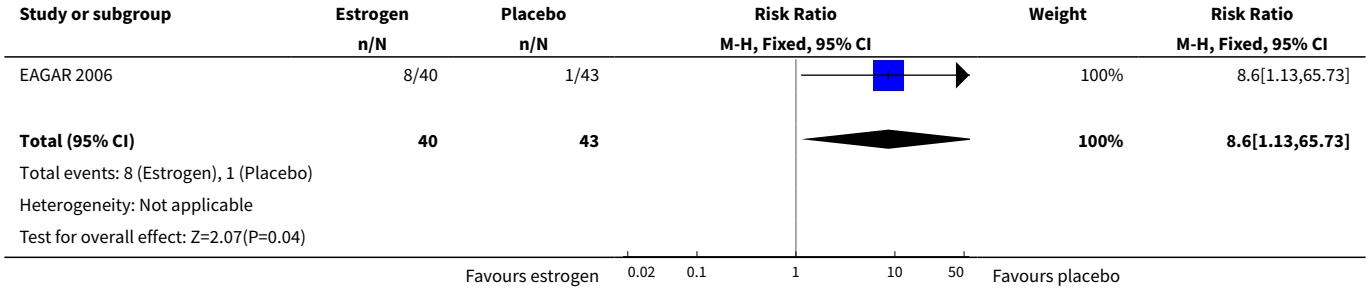
Analysis 3.6. Comparison 3 Estrogen vs placebo in secondary prevention, Outcome 6 Venous thromboembolism.



Analysis 3.7. Comparison 3 Estrogen vs placebo in secondary prevention, Outcome 7 Pulmonary embolism.



Analysis 3.8. Comparison 3 Estrogen vs placebo in secondary prevention, Outcome 8 Angioplasty.



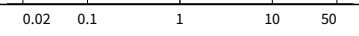
Comparison 4. Combination HT vs placebo in secondary prevention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	3	3343	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.87, 1.36]
2 Death (CV causes)	4	3383	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.85, 1.59]
3 Non-fatal MI	4	3483	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.71, 1.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Stroke	3	3339	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.89, 1.47]
5 Angina	3	2960	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.69, 1.11]
6 Venous thromboembolism	4	3483	Risk Ratio (M-H, Fixed, 95% CI)	2.59 [1.51, 4.42]
7 Pulmonary embolism	2	2903	Risk Ratio (M-H, Fixed, 95% CI)	3.77 [1.41, 10.06]
8 Coronary artery by-pass surgery	2	2803	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.67, 1.16]
9 Angioplasty	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.60]
10 Death (CV causes): time on treatment	4	13993	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.01, 1.45]
10.1 1-year follow-up	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.73, 3.29]
10.2 2-year follow-up	2	2803	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.87, 2.37]
10.3 3-year follow-up	3	3343	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.93, 1.94]
10.4 4-year follow-up	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.85, 1.67]
10.5 4 – 6.8-year follow-up	1	2321	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.71, 1.39]
11 Non-fatal MI: time on treatment	4	5804	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.78, 1.15]
11.1 1-year follow-up	1	140	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.82]
11.2 3-year follow-up	2	580	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.56, 5.90]
11.3 4-year follow-up	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.71, 1.14]
11.4 4-6.8 year follow-up	1	2321	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.70, 1.40]
12 Venous thromboembolism: time on treatment	4	14093	Risk Ratio (M-H, Fixed, 95% CI)	2.62 [1.88, 3.66]
12.1 1-year follow-up	2	2903	Risk Ratio (M-H, Fixed, 95% CI)	4.17 [1.58, 11.01]
12.2 2-year follow-up	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	3.51 [1.42, 8.66]
12.3 3-year follow-up	3	3343	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [1.32, 4.64]
12.4 4-year follow-up	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	2.84 [1.48, 5.46]
12.5 4-6.8 year follow-up	1	2321	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.63, 2.98]

Analysis 4.1. Comparison 4 Combination HT vs placebo in secondary prevention, Outcome 1 Death (all causes).

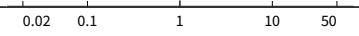
Study or subgroup	Combination HT n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ERA 2000	3/104	3/53		2.95%	0.51[0.11,2.44]
HERS I 1998	130/1380	123/1383		91.16%	1.06[0.84,1.34]
WAVE 2002	14/210	8/213		5.89%	1.78[0.76,4.14]
Total (95% CI)	**1694**	**1649**		**100%**	**1.09[0.87,1.36]**
Total events: 147 (Combination HT), 134 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=2.23$, df=2(P=0.33); $I^2=10.35\%$					
Test for overall effect: Z=0.72(P=0.47)					



Favours combination HT — Favours placebo

Analysis 4.2. Comparison 4 Combination HT vs placebo in secondary prevention, Outcome 2 Death (CV causes).

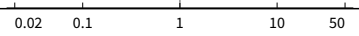
Study or subgroup	Combination HT n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ERA 2000	2/104	2/53		3.84%	0.51[0.07,3.52]
HALL 1998	0/20	1/20		2.17%	0.33[0.01,7.72]
HERS I 1998	70/1380	59/1383		85.36%	1.19[0.85,1.67]
WAVE 2002	8/210	6/213		8.63%	1.35[0.48,3.83]
Total (95% CI)	**1714**	**1669**		**100%**	**1.16[0.85,1.59]**
Total events: 80 (Combination HT), 68 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=1.41$, df=3(P=0.7); $I^2=0\%$					
Test for overall effect: Z=0.92(P=0.36)					



Favours combination HT — Favours placebo

Analysis 4.3. Comparison 4 Combination HT vs placebo in secondary prevention, Outcome 3 Non-fatal MI.

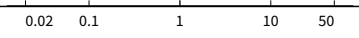
Study or subgroup	Combination HT n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ERA 2000	6/104	4/53		3.79%	0.76[0.23,2.59]
EVTET 2000	0/71	1/69		1.09%	0.32[0.01,7.82]
HERS I 1998	116/1380	129/1383		92.27%	0.9[0.71,1.14]
WAVE 2002	4/210	4/213		2.84%	1.01[0.26,4]
Total (95% CI)	**1765**	**1718**		**100%**	**0.89[0.71,1.12]**
Total events: 126 (Combination HT), 138 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.49$, df=3(P=0.92); $I^2=0\%$					
Test for overall effect: Z=0.96(P=0.34)					



Favours combination HT — Favours placebo

Analysis 4.4. Comparison 4 Combination HT vs placebo in secondary prevention, Outcome 4 Stroke.

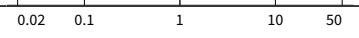
Study or subgroup	Combination HT n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ERA 2000	5/100	3/53		3.78%	0.88[0.22,3.55]
HERS I 1998	106/1380	96/1383		92.39%	1.11[0.85,1.44]
WAVE 2002	9/210	4/213		3.83%	2.28[0.71,7.3]
Total (95% CI)	**1690**	**1649**		**100%**	**1.14[0.89,1.47]**
Total events: 120 (Combination HT), 103 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=1.55$, df=2(P=0.46); $I^2=0\%$					
Test for overall effect: Z=1.03(P=0.3)					



Favours combination HT — Favours placebo

Analysis 4.5. Comparison 4 Combination HT vs placebo in secondary prevention, Outcome 5 Angina.

Study or subgroup	Combination HT n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ERA 2000	15/104	11/53		11.04%	0.69[0.34,1.41]
HALL 1998	2/20	0/20		0.38%	5[0.26,98]
HERS I 1998	103/1380	117/1383		88.58%	0.88[0.68,1.14]
Total (95% CI)	**1504**	**1456**		**100%**	**0.88[0.69,1.11]**
Total events: 120 (Combination HT), 128 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=1.74$, df=2(P=0.42); $I^2=0\%$					
Test for overall effect: Z=1.08(P=0.28)					



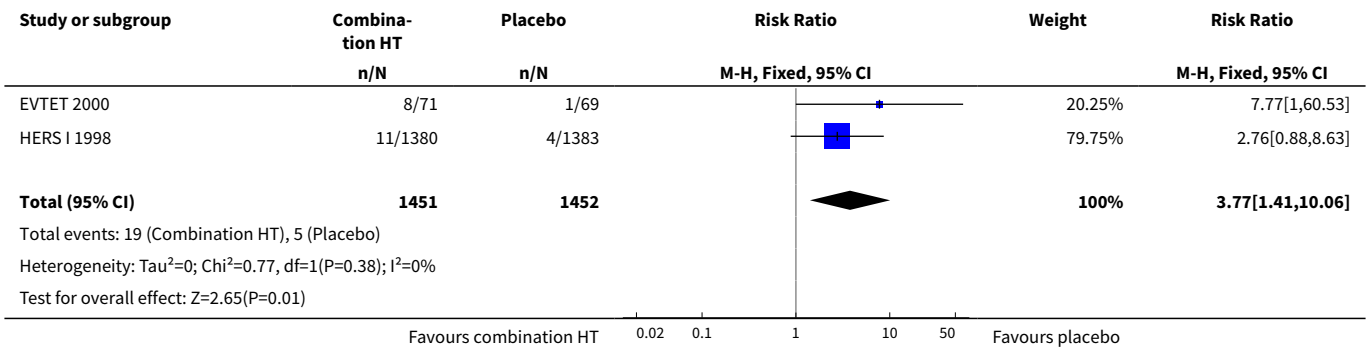
Favours combination HT — Favours placebo

Analysis 4.6. Comparison 4 Combination HT vs placebo in secondary prevention, Outcome 6 Venous thromboembolism.

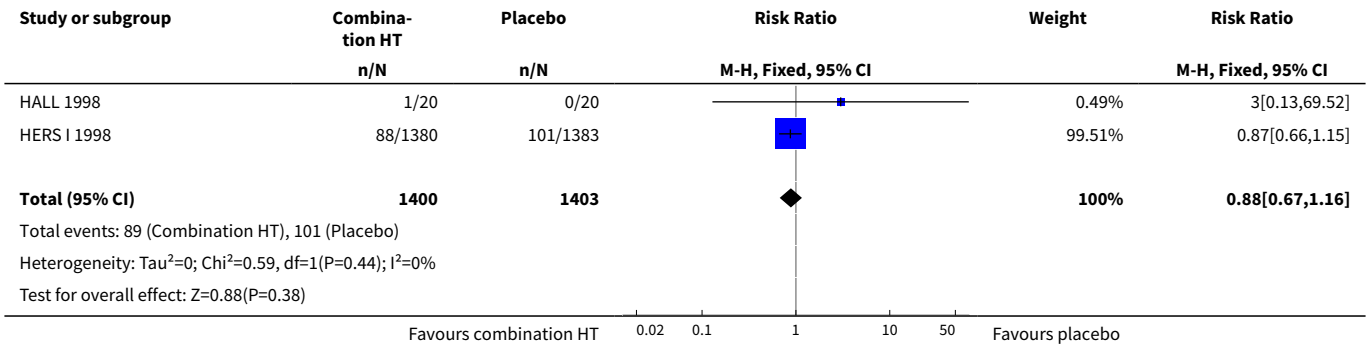
Study or subgroup	Combination HT n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ERA 2000	2/104	1/53		7.24%	1.02[0.09,10.99]
EVTET 2000	8/71	1/69		5.54%	7.77[1,60.53]
HERS I 1998	34/1380	12/1383		65.51%	2.84[1.48,5.46]
WAVE 2002	4/210	4/213		21.71%	1.01[0.26,4]
Total (95% CI)	**1765**	**1718**		**100%**	**2.59[1.51,4.42]**
Total events: 48 (Combination HT), 18 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=3.56$, df=3(P=0.31); $I^2=15.68\%$					
Test for overall effect: Z=3.47(P=0)					

Favours combination HT — Favours placebo

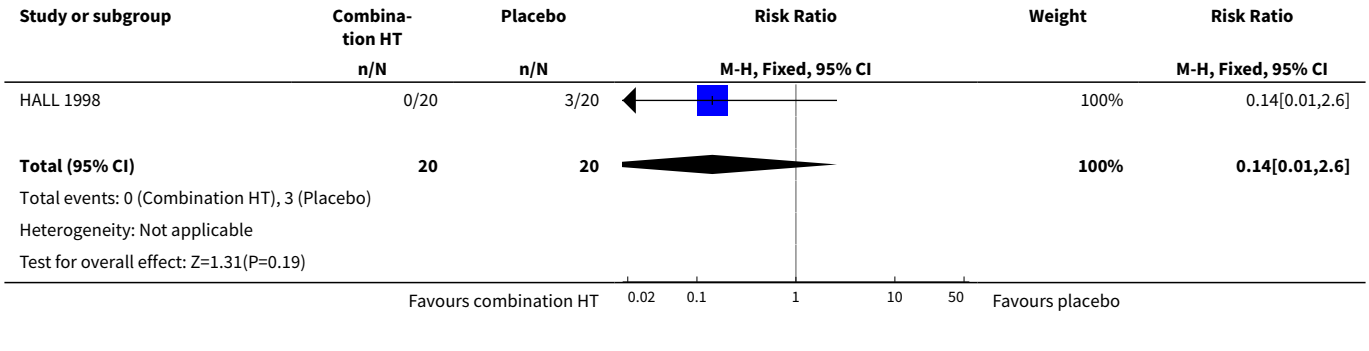
Analysis 4.7. Comparison 4 Combination HT vs placebo in secondary prevention, Outcome 7 Pulmonary embolism.



Analysis 4.8. Comparison 4 Combination HT vs placebo in secondary prevention, Outcome 8 Coronary artery by-pass surgery.

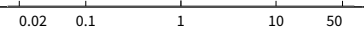


Analysis 4.9. Comparison 4 Combination HT vs placebo in secondary prevention, Outcome 9 Angioplasty.

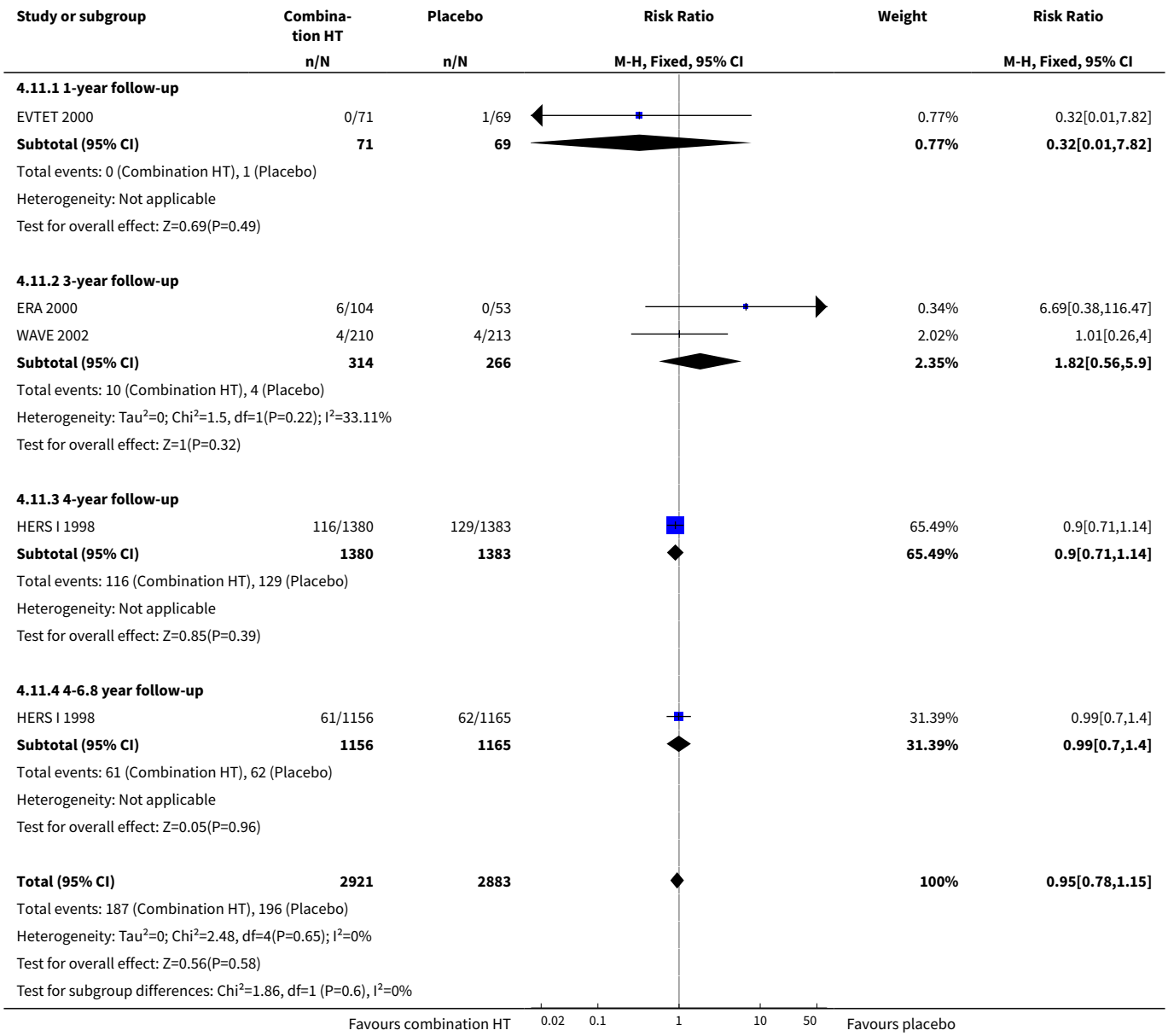


Analysis 4.10. Comparison 4 Combination HT vs placebo in secondary prevention, Outcome 10 Death (CV causes): time on treatment.

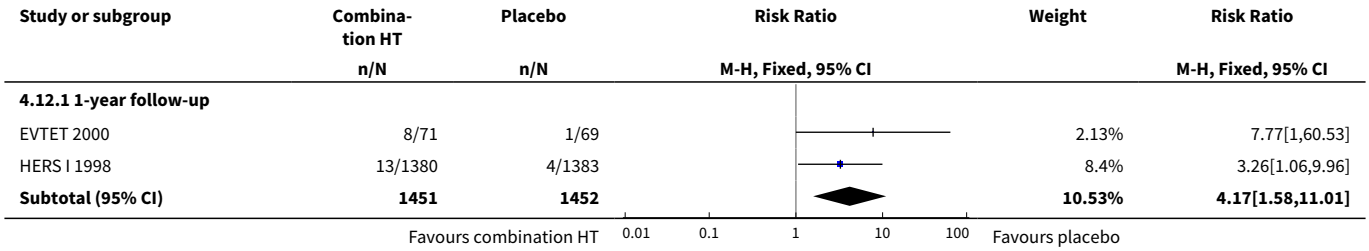
Study or subgroup	Combination HT n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.10.1 1-year follow-up					
HERS I 1998	17/1380	11/1383		5.34%	1.55[0.73,3.29]
Subtotal (95% CI)	**1380**	**1383**		**5.34%**	**1.55[0.73,3.29]**
Total events: 17 (Combination HT), 11 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.14(P=0.26)					
4.10.2 2-year follow-up					
HALL 1998	0/20	1/20		0.73%	0.33[0.01,7.72]
HERS I 1998	36/1380	24/1383		11.65%	1.5[0.9,2.51]
Subtotal (95% CI)	**1400**	**1403**		**12.38%**	**1.43[0.87,2.37]**
Total events: 36 (Combination HT), 25 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.86$, df=1(P=0.35); $I^2=0\%$					
Test for overall effect: Z=1.41(P=0.16)					
4.10.3 3-year follow-up					
ERA 2000	2/104	0/53		0.32%	2.57[0.13,52.62]
HERS I 1998	54/1380	41/1383		19.91%	1.32[0.89,1.97]
WAVE 2002	8/210	6/213		2.9%	1.35[0.48,3.83]
Subtotal (95% CI)	**1694**	**1649**		**23.12%**	**1.34[0.93,1.94]**
Total events: 64 (Combination HT), 47 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.19$, df=2(P=0.91); $I^2=0\%$					
Test for overall effect: Z=1.56(P=0.12)					
4.10.4 4-year follow-up					
HERS I 1998	70/1380	59/1383		28.65%	1.19[0.85,1.67]
Subtotal (95% CI)	**1380**	**1383**		**28.65%**	**1.19[0.85,1.67]**
Total events: 70 (Combination HT), 59 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=0$, df=0(P<0.0001); $I^2=100\%$					
Test for overall effect: Z=1(P=0.32)					
4.10.5 4 – 6.8-year follow-up					
HERS I 1998	62/1156	63/1165		30.5%	0.99[0.71,1.39]
Subtotal (95% CI)	**1156**	**1165**		**30.5%**	**0.99[0.71,1.39]**
Total events: 62 (Combination HT), 63 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.05(P=0.96)					
Total (95% CI)	**7010**	**6983**		**100%**	**1.21[1.01,1.45]**
Total events: 249 (Combination HT), 205 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=3.53$, df=7(P=0.83); $I^2=0\%$					
Test for overall effect: Z=2.1(P=0.04)					
Test for subgroup differences: $Chi^2=2.47$, df=1 (P=0.65), $I^2=0\%$					

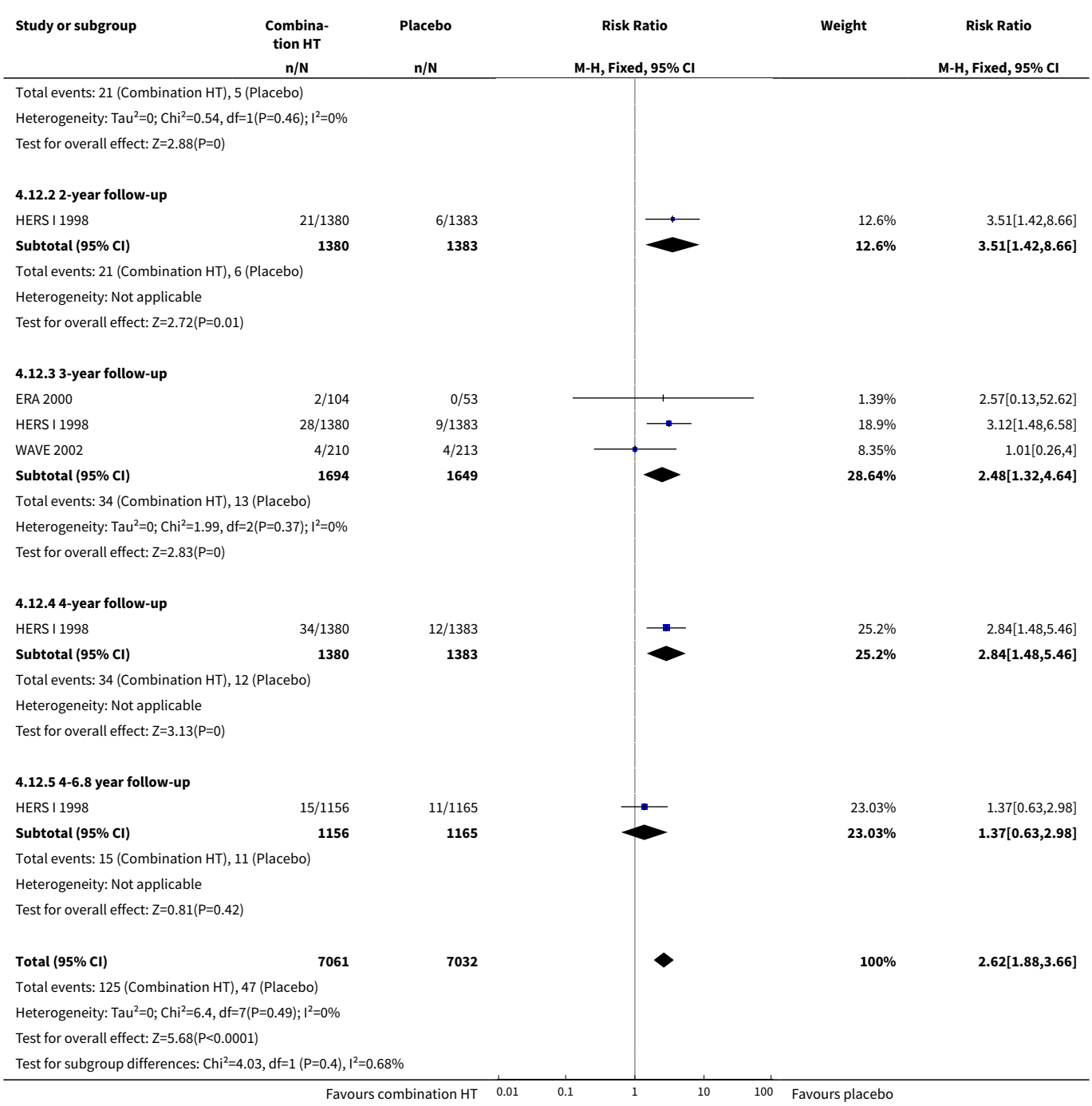


Analysis 4.11. Comparison 4 Combination HT vs placebo in secondary prevention, Outcome 11 Non-fatal MI: time on treatment.



Analysis 4.12. Comparison 4 Combination HT vs placebo in secondary prevention, Outcome 12 Venous thromboembolism: time on treatment.





Comparison 5. HT vs placebo in primary and secondary prevention

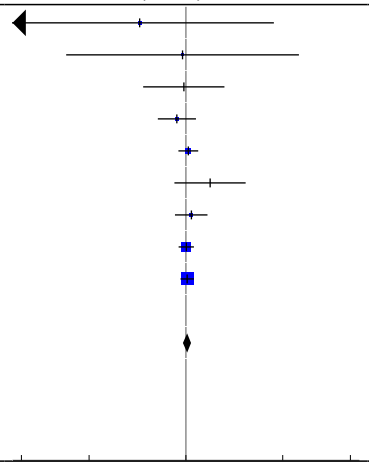
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	9	33523	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.93, 1.13]
2 Death (CV causes)	11	37254	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.86, 1.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Non-fatal MI	12	38125	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.18]
4 Stroke	8	33197	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.11, 1.43]
5 Angina	7	34928	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.80, 1.03]
6 Venous thromboembolism	7	35609	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [1.58, 2.26]
7 Pulmonary embolism	7	36316	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [1.42, 2.37]
8 Coronary artery by-pass surgery	2	2803	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.67, 1.16]
9 Angioplasty	3	345	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.09, 11.54]
10 Death (all causes): time on treatment	10	73445	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.96, 1.15]
10.1 1-year follow-up	2	20993	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.76, 2.27]
10.2 2-year follow-up	2	1239	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.51, 1.23]
10.3 3-year follow-up	5	18782	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.89, 1.39]
10.4 4-year follow-up	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.84, 1.34]
10.5 5.6 year follow-up	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.84, 1.21]
10.6 6.7 year follow-up	2	13060	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.93, 1.21]
11 Death (CV causes): time on treatment	10	47781	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.96, 1.27]
11.1 1-year follow-up	2	7148	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [0.87, 3.66]
11.2 2-year follow-up	4	4042	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.75, 1.44]
11.3 3-year follow-up	4	4160	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.87, 1.67]
11.4 4-year follow-up	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.85, 1.67]
11.5 5.6 year follow-up	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.69, 1.73]
11.6 7.1 year follow-up	2	13060	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.78, 1.27]
12 Non-fatal MI: time on treatment	12	40446	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.17]
12.1 1-year follow-up	2	4525	Odds Ratio (M-H, Fixed, 95% CI)	2.47 [0.48, 12.78]
12.2 2-year follow-up	2	1239	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.82, 2.12]
12.3 3-year follow-up	5	2251	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.68, 1.96]
12.4 4-year follow-up	1	2763	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.69, 1.16]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
12.5 5.6 year follow-up	1	16608	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.99, 1.62]
12.6 7.1 year follow-up	2	13060	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.77, 1.12]
13 Stroke: time on treatment	8	85342	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.13, 1.40]
13.1 1-year follow-up	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.49, 1.86]
13.2 2-year follow-up	2	17625	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.90, 2.06]
13.3 3-year follow-up	5	18678	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.04, 1.64]
13.4 4-year follow-up	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.85, 1.44]
13.5 5.6 year follow-up	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [1.05, 1.72]
13.6 7.1-year follow-up	2	13060	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.05, 1.54]
14 Angina: time on treatment	7	37249	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.79, 1.02]
14.1 1-year follow-up	1	4385	Risk Ratio (M-H, Fixed, 95% CI)	6.98 [0.36, 135.01]
14.2 2-year follow-up	1	40	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 98.00]
14.3 3 year follow-up	2	393	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.61, 1.35]
14.4 4-year follow-up	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.68, 1.14]
14.5 5.6 year follow-up	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.62, 1.04]
14.6 7.1 year follow-up	2	13060	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.77, 1.14]
15 Venous thromboembolism: time on treatment	7	96043	Risk Ratio (M-H, Fixed, 95% CI)	2.22 [1.93, 2.54]
15.1 1-year follow-up	4	23896	Risk Ratio (M-H, Fixed, 95% CI)	4.38 [2.72, 7.06]
15.2 2-year follow-up	2	19371	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [2.05, 4.64]
15.3 3-year follow-up	4	20345	Risk Ratio (M-H, Fixed, 95% CI)	2.53 [1.83, 3.49]
15.4 4-year follow-up	1	2763	Risk Ratio (M-H, Fixed, 95% CI)	2.84 [1.48, 5.46]
15.5 5.6-year follow-up	1	16608	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [1.60, 2.74]
15.6 7.1-year follow-up	2	13060	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.02, 1.72]

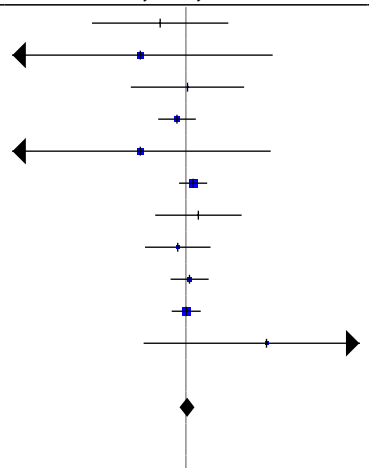
Analysis 5.1. Comparison 5 HT vs placebo in primary and secondary prevention, Outcome 1 Death (all causes).

Study or subgroup	HT n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
EPAT 2001	0/111	1/111		0.21%	0.33[0.01,8.1]
EPHT 2006	1/404	1/373		0.14%	0.92[0.06,14.71]
ERA 2000	11/204	6/106		1.08%	0.95[0.36,2.5]
ESPRIT 2002	32/513	39/504		5.38%	0.81[0.51,1.27]
HERS I 1998	130/1380	123/1383		16.8%	1.06[0.84,1.34]
WAVE 2002	14/210	8/213		1.09%	1.78[0.76,4.14]
WEST 2001	48/337	41/327		5.69%	1.14[0.77,1.67]
WHI I 2002	231/8506	218/8102		30.53%	1.01[0.84,1.21]
WHI II 2004	291/5310	289/5429		39.08%	1.03[0.88,1.21]
Total (95% CI)	**16975**	**16548**		**100%**	**1.03[0.93,1.13]**
Total events: 758 (HT), 726 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.58, df=8(P=0.89); I^2=0%					
Test for overall effect: Z=0.55(P=0.58)					



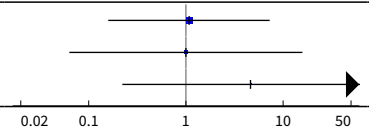
Analysis 5.2. Comparison 5 HT vs placebo in primary and secondary prevention, Outcome 2 Death (CV causes).

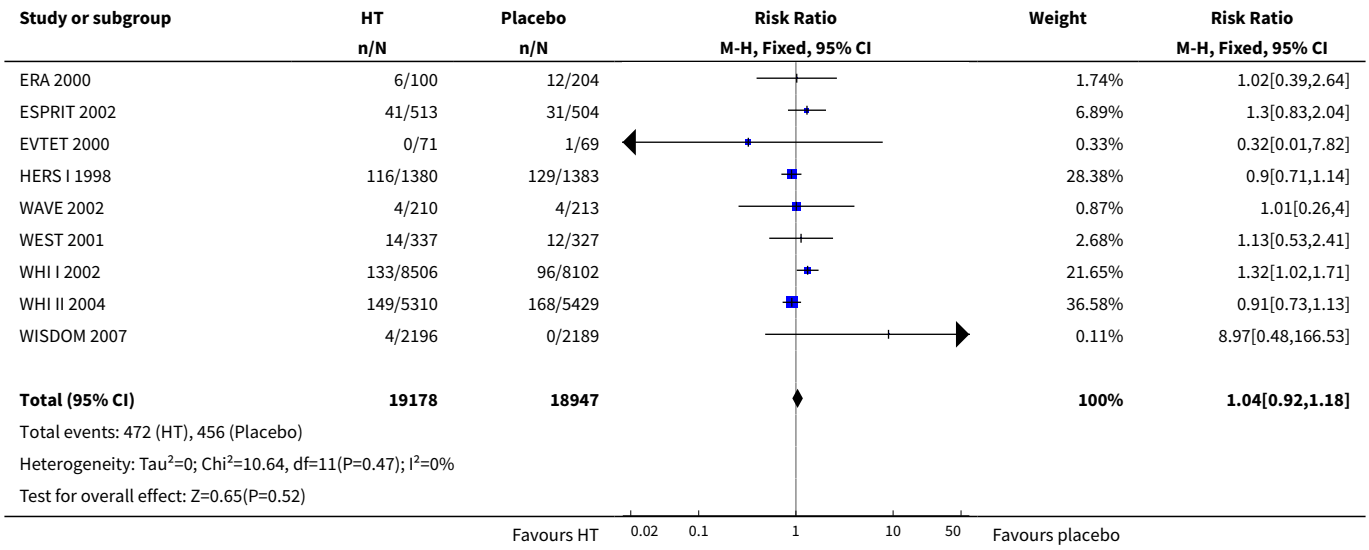
Study or subgroup	HT n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
EAGAR 2006	2/40	4/43		1.71%	0.54[0.1,2.78]
EPAT 2001	0/111	1/111		0.66%	0.33[0.01,8.1]
ERA 2000	6/204	3/106		1.75%	1.04[0.27,4.07]
ESPRIT 2002	32/513	39/504		17.42%	0.81[0.51,1.27]
HALL 1998	0/20	1/20		0.66%	0.33[0.01,7.72]
HERS I 1998	70/1380	59/1383		26.09%	1.19[0.85,1.67]
WAVE 2002	8/210	6/213		2.64%	1.35[0.48,3.83]
WEST 2001	11/337	13/327		5.84%	0.82[0.37,1.81]
WHI I 2002	39/8506	34/8102		15.42%	1.09[0.69,1.73]
WHI II 2004	62/5310	63/5429		27.58%	1.01[0.71,1.43]
WISDOM 2007	3/2196	0/2189		0.22%	6.98[0.36,135.01]
Total (95% CI)	**18827**	**18427**		**100%**	**1.03[0.86,1.23]**
Total events: 233 (HT), 223 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.66, df=10(P=0.84); I^2=0%					
Test for overall effect: Z=0.3(P=0.77)					



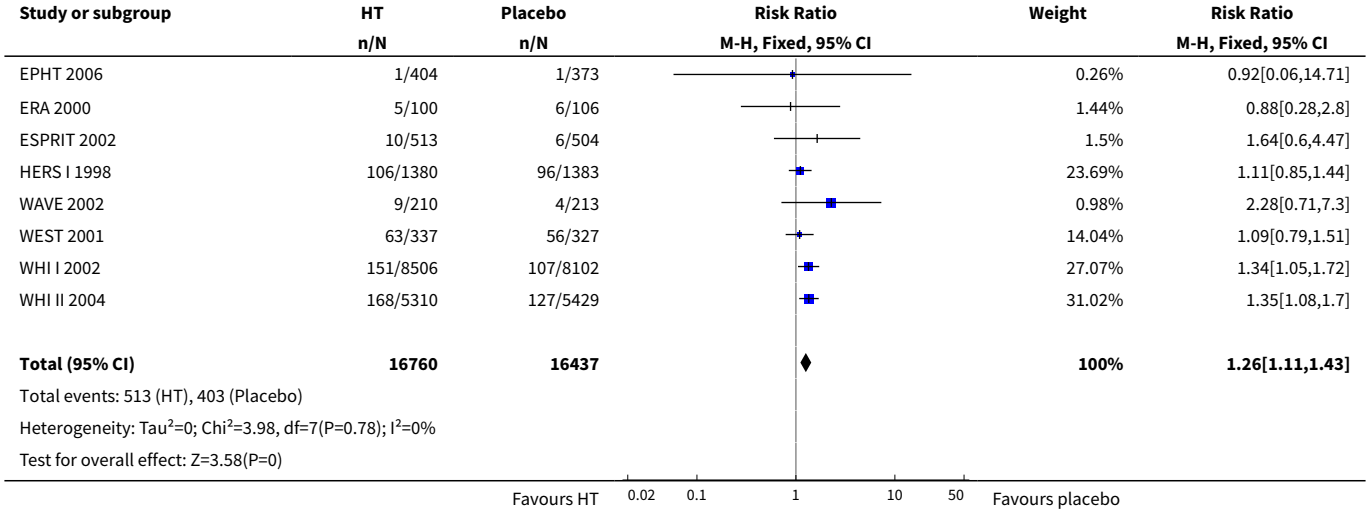
Analysis 5.3. Comparison 5 HT vs placebo in primary and secondary prevention, Outcome 3 Non-fatal MI.

Study or subgroup	HT n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
EAGAR 2006	2/40	2/43		0.42%	1.08[0.16,7.27]
EPAT 2001	1/111	1/111		0.22%	1[0.06,15.79]
EPHT 2006	2/404	0/373		0.11%	4.62[0.22,95.86]

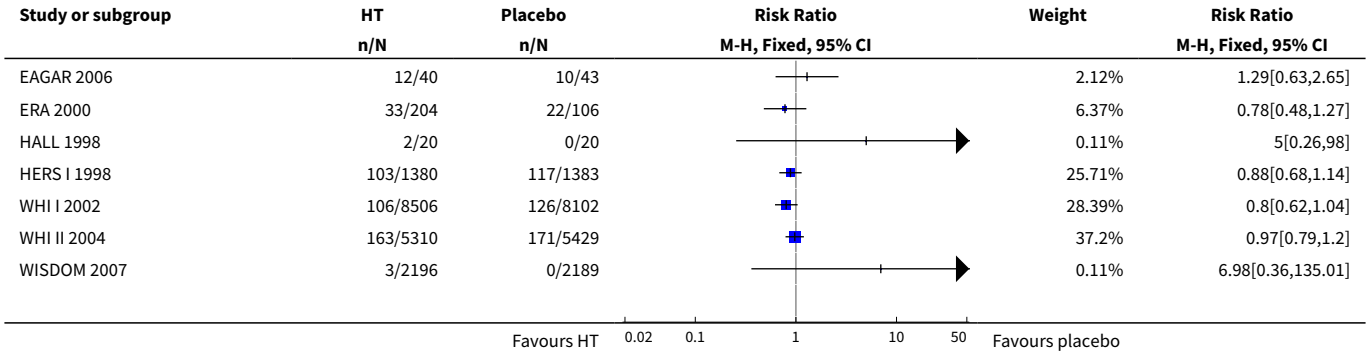


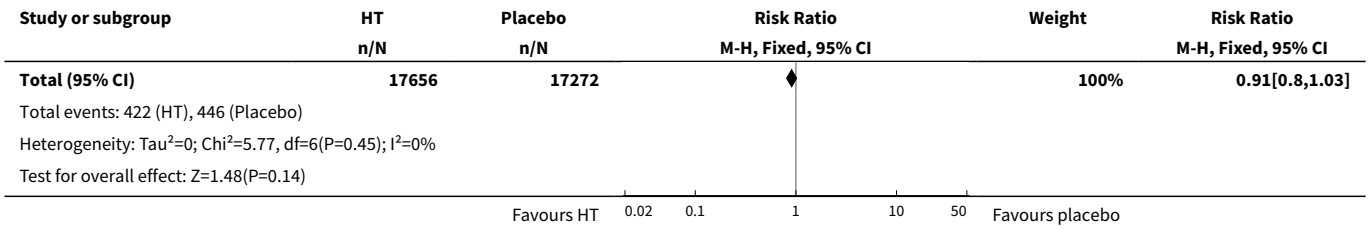


Analysis 5.4. Comparison 5 HT vs placebo in primary and secondary prevention, Outcome 4 Stroke.

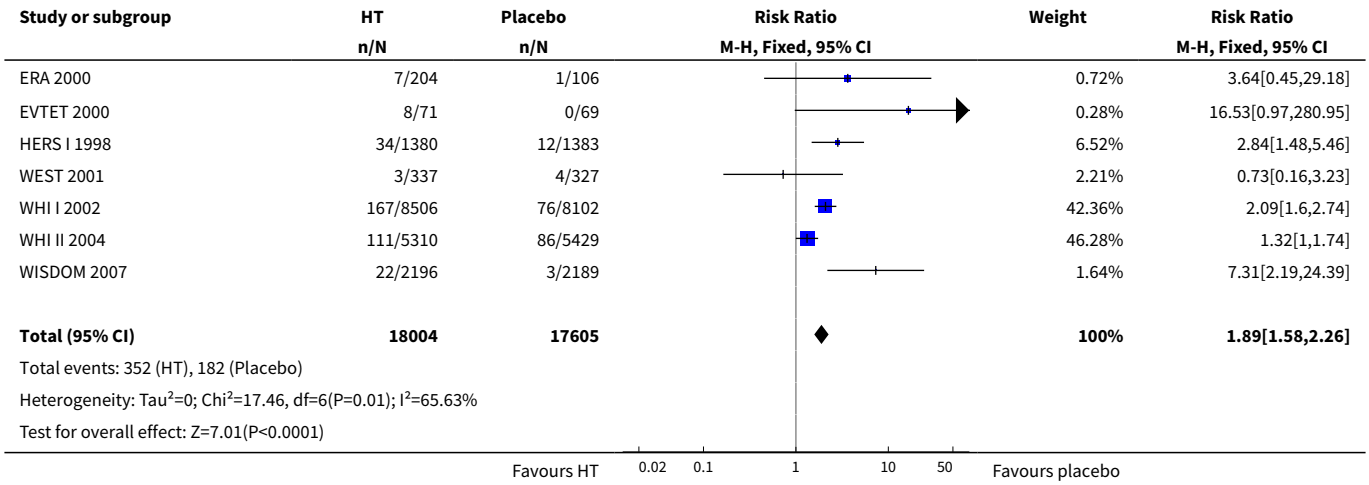


Analysis 5.5. Comparison 5 HT vs placebo in primary and secondary prevention, Outcome 5 Angina.

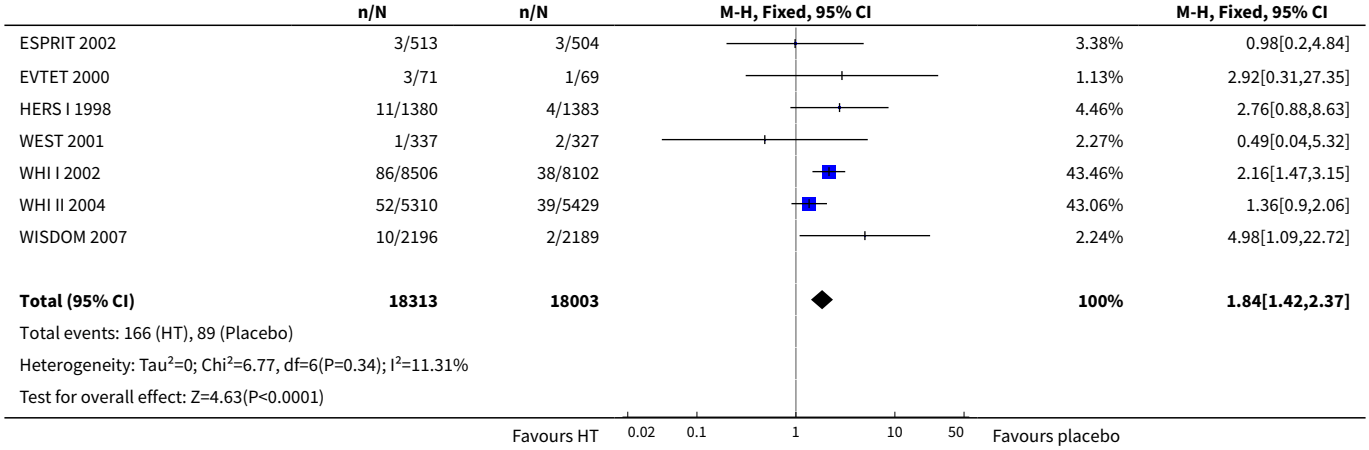




Analysis 5.6. Comparison 5 HT vs placebo in primary and secondary prevention, Outcome 6 Venous thromboembolism.



Analysis 5.7. Comparison 5 HT vs placebo in primary and secondary prevention, Outcome 7 Pulmonary embolism.



Analysis 5.8. Comparison 5 HT vs placebo in primary and secondary prevention, Outcome 8 Coronary artery by-pass surgery.

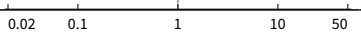
Study or subgroup	HT n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
HALL 1998	1/20	0/20		0.49%	3[0.13,69.52]
HERS I 1998	88/1380	101/1383		99.51%	0.87[0.66,1.15]
Total (95% CI)	**1400**	**1403**		**100%**	**0.88[0.67,1.16]**
Total events: 89 (HT), 101 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.59, df=1(P=0.44); I^2=0%					
Test for overall effect: Z=0.88(P=0.38)					

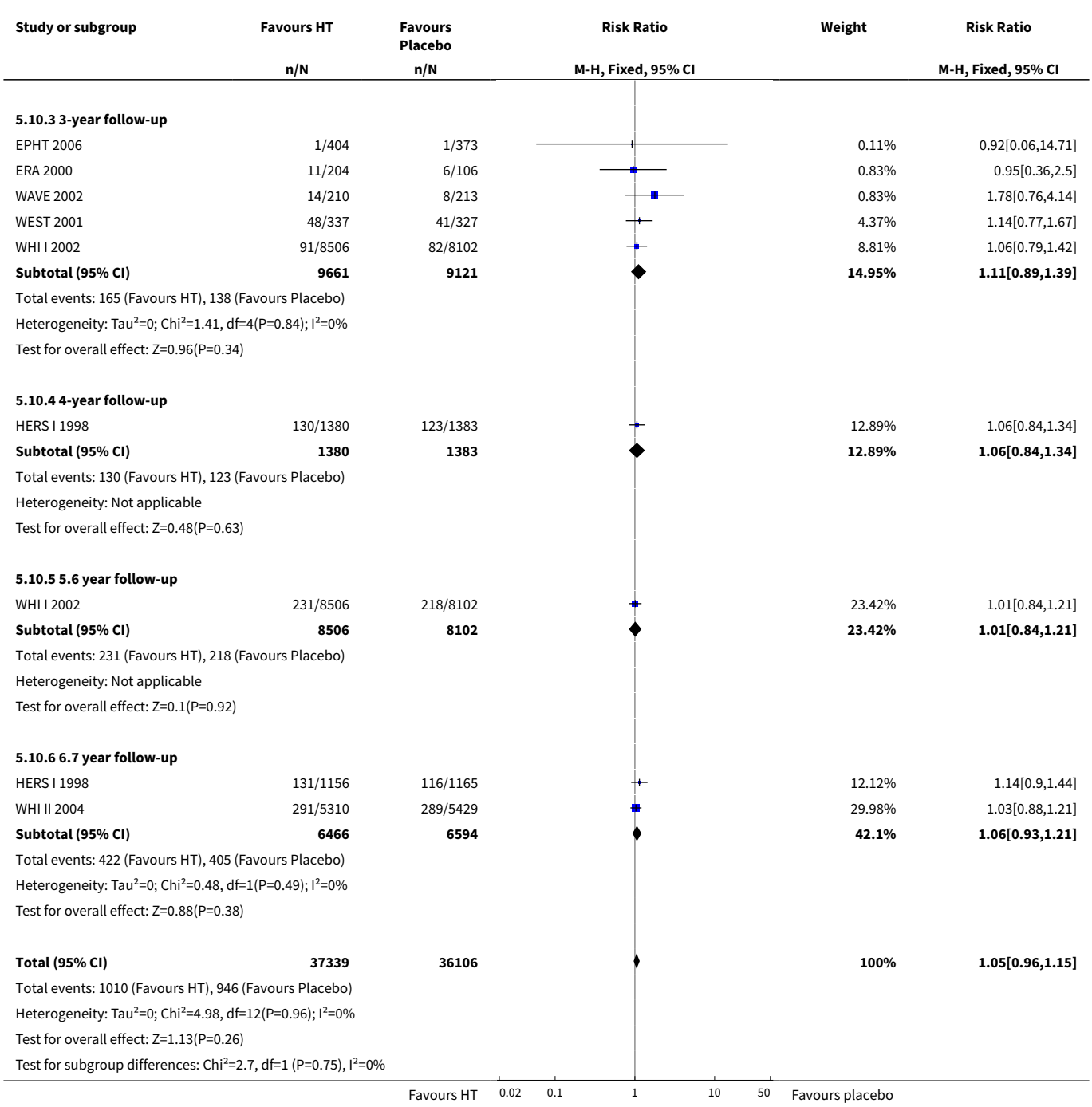
Analysis 5.9. Comparison 5 HT vs placebo in primary and secondary prevention, Outcome 9 Angioplasty.

Study or subgroup	HT n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
EAGAR 2006	8/40	1/43		36.97%	8.6[1.13,65.73]
EPAT 2001	1/111	2/111		33.75%	0.5[0.05,5.43]
HALL 1998	0/20	3/20		29.28%	0.14[0.01,2.6]
Total (95% CI)	**171**	**174**		**100%**	**0.99[0.09,11.54]**
Total events: 9 (HT), 6 (Placebo)					
Heterogeneity: Tau^2=3.16; Chi^2=6.17, df=2(P=0.05); I^2=67.61%					
Test for overall effect: Z=0.01(P=0.99)					

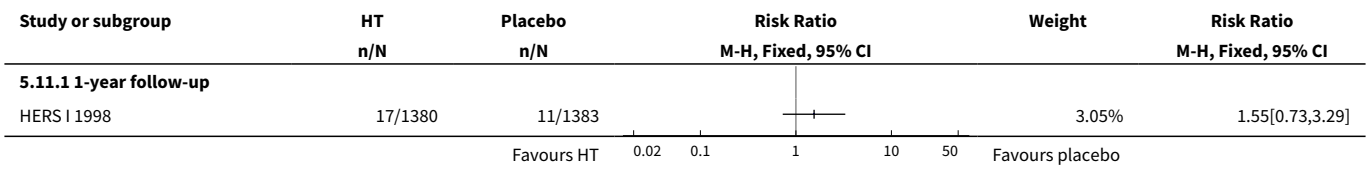
Analysis 5.10. Comparison 5 HT vs placebo in primary and secondary prevention, Outcome 10 Death (all causes): time on treatment.

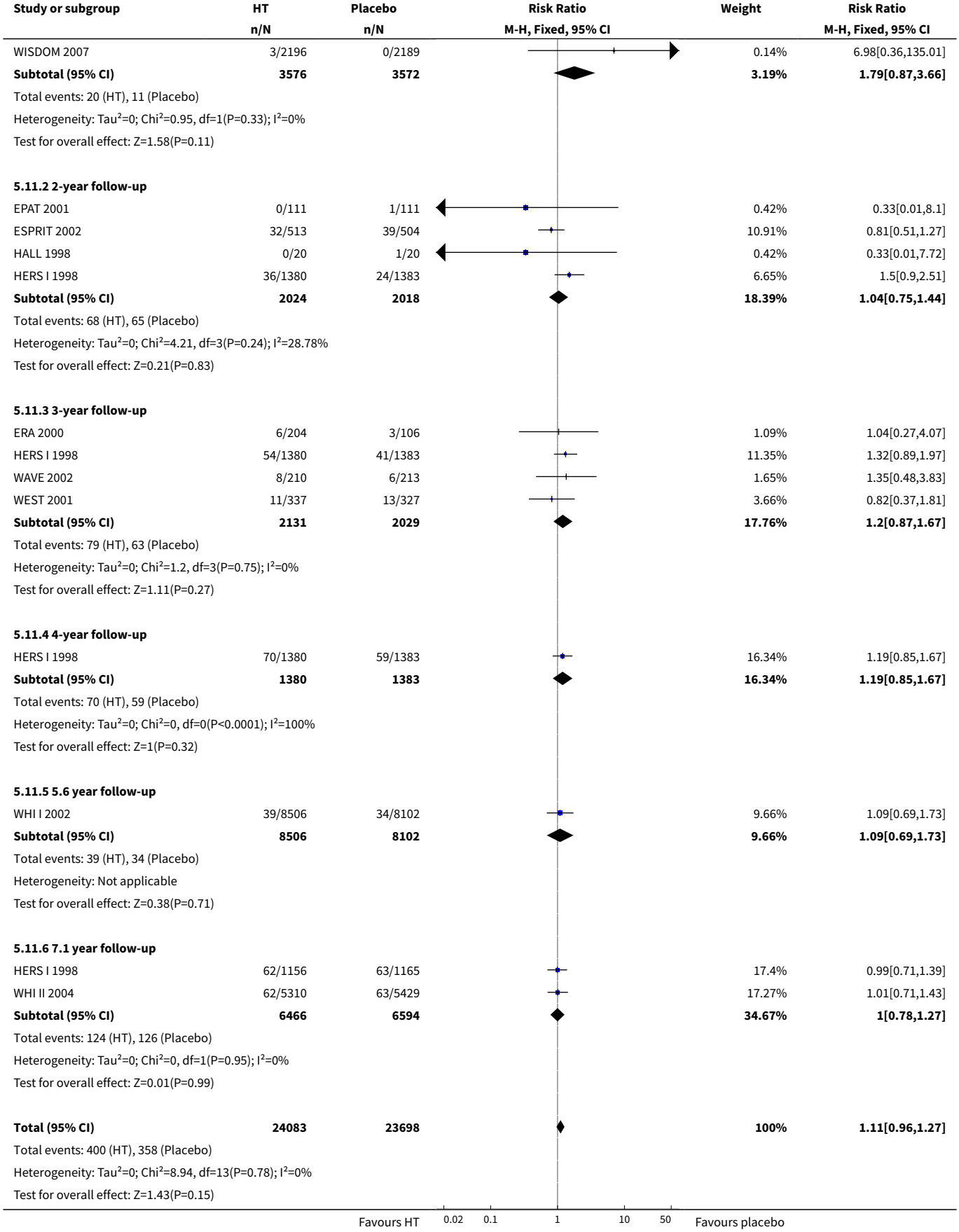
Study or subgroup	Favours HT n/N	Favours Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.10.1 1-year follow-up					
WHI I 2002	22/8506	17/8102		1.83%	1.23[0.66,2.32]
WISDOM 2007	8/2196	5/2189		0.53%	1.59[0.52,4.87]
Subtotal (95% CI)	**10702**	**10291**		**2.35%**	**1.31[0.76,2.27]**
Total events: 30 (Favours HT), 22 (Favours Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.16, df=1(P=0.69); I^2=0%					
Test for overall effect: Z=0.97(P=0.33)					
5.10.2 2-year follow-up					
EPAT 2001	0/111	1/111		0.16%	0.33[0.01,8.1]
ESPRIT 2002	32/513	39/504		4.13%	0.81[0.51,1.27]
Subtotal (95% CI)	**624**	**615**		**4.28%**	**0.79[0.51,1.23]**
Total events: 32 (Favours HT), 40 (Favours Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=1.04(P=0.3)					

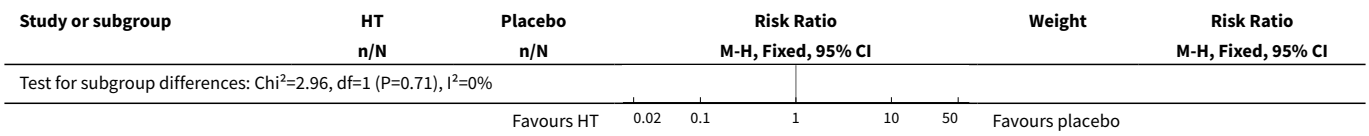




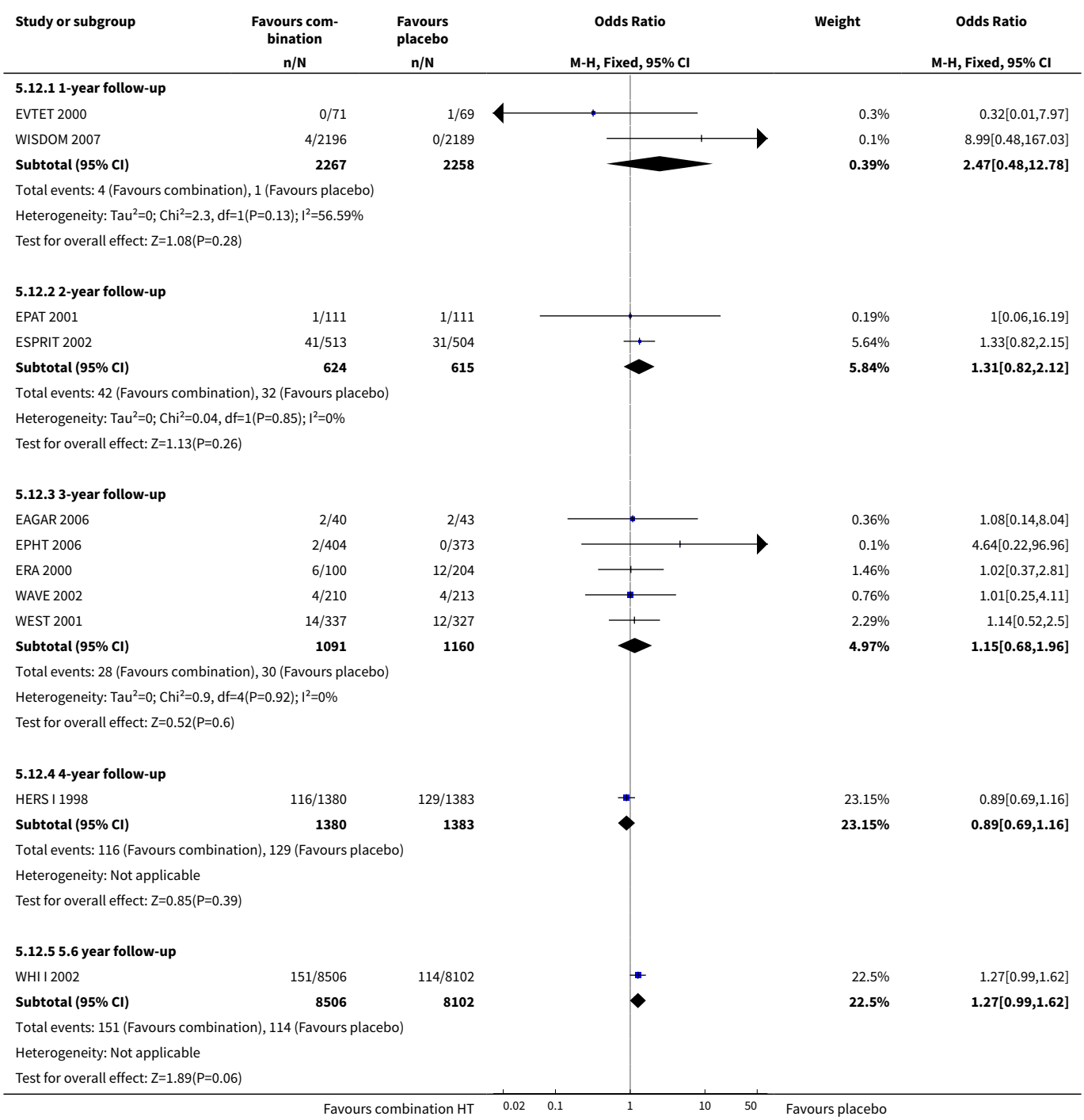
Analysis 5.11. Comparison 5 HT vs placebo in primary and secondary prevention, Outcome 11 Death (CV causes): time on treatment.

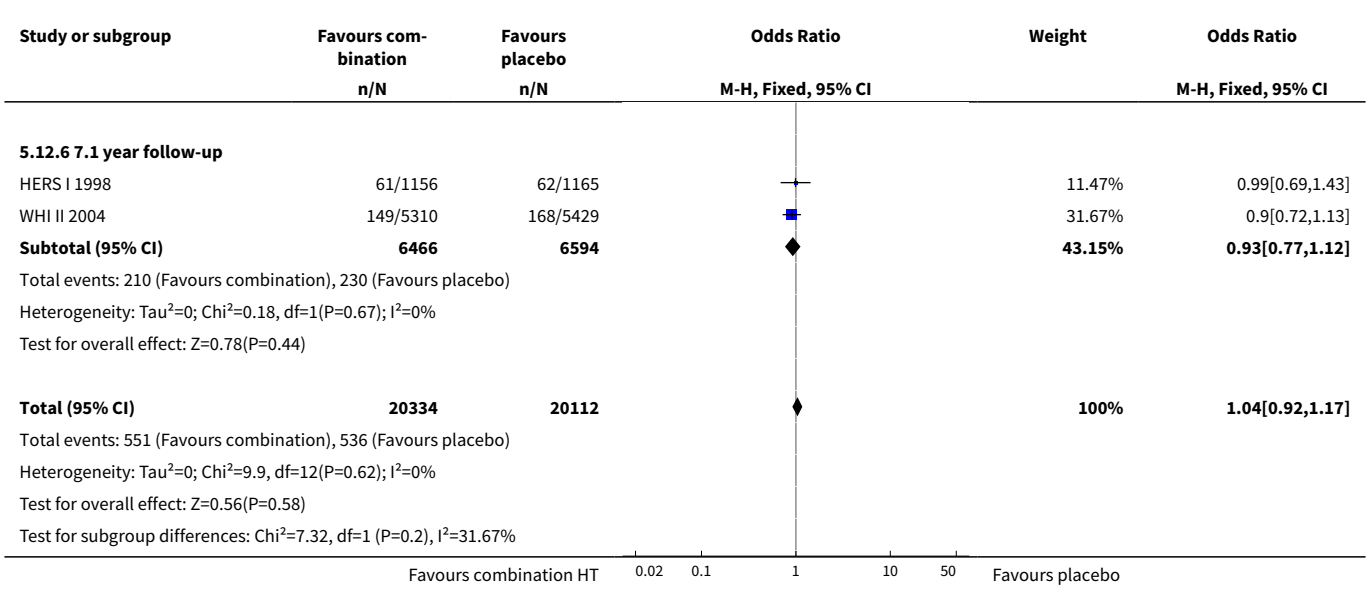




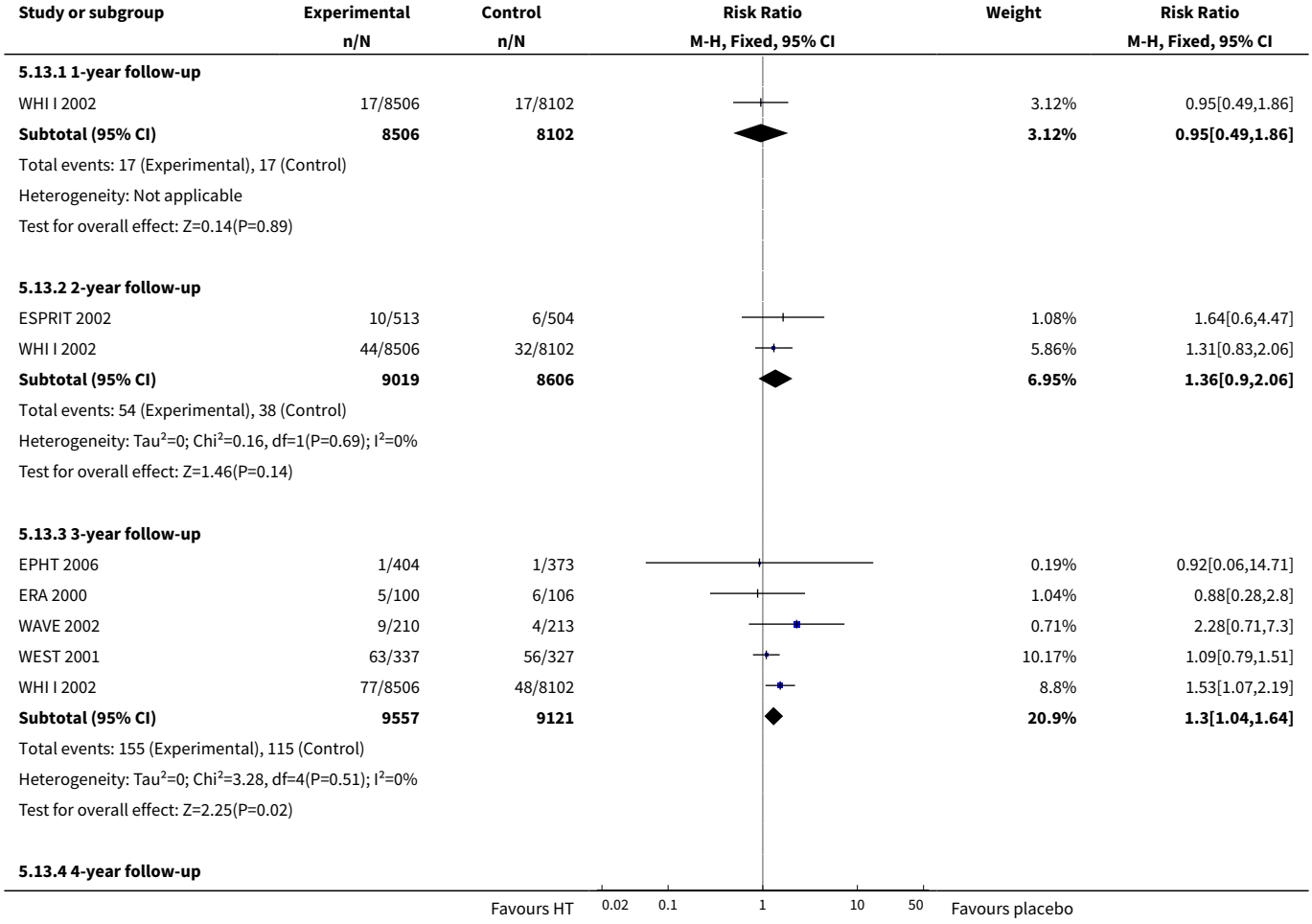


Analysis 5.12. Comparison 5 HT vs placebo in primary and secondary prevention, Outcome 12 Non-fatal MI: time on treatment.

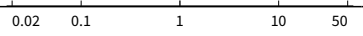




Analysis 5.13. Comparison 5 HT vs placebo in primary and secondary prevention, Outcome 13 Stroke: time on treatment.

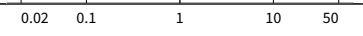


Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
HERS I 1998	106/1380	96/1383		17.16%	1.11[0.85,1.44]
Subtotal (95% CI)	**1380**	**1383**		**17.16%**	**1.11[0.85,1.44]**
Total events: 106 (Experimental), 96 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.75(P=0.46)					
5.13.5 5.6 year follow-up					
WHI I 2002	151/8506	107/8102		19.61%	1.34[1.05,1.72]
Subtotal (95% CI)	**8506**	**8102**		**19.61%**	**1.34[1.05,1.72]**
Total events: 151 (Experimental), 107 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.36(P=0.02)					
5.13.6 7.1-year follow-up					
HERS I 1998	59/1156	55/1165		9.8%	1.08[0.76,1.55]
WHI II 2004	168/5310	127/5429		22.47%	1.35[1.08,1.7]
Subtotal (95% CI)	**6466**	**6594**		**32.27%**	**1.27[1.05,1.54]**
Total events: 227 (Experimental), 182 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.07, df=1(P=0.3); I^2=6.61%					
Test for overall effect: Z=2.44(P=0.01)					
Total (95% CI)	**43434**	**41908**		**100%**	**1.26[1.13,1.4]**
Total events: 710 (Experimental), 555 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.48, df=11(P=0.84); I^2=0%					
Test for overall effect: Z=4.17(P<0.0001)					
Test for subgroup differences: Chi^2=2.07, df=1 (P=0.84), I^2=0%					

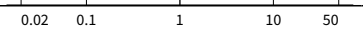


Analysis 5.14. Comparison 5 HT vs placebo in primary and secondary prevention, Outcome 14 Angina: time on treatment.

Study or subgroup	HT n/N	Placebol n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.14.1 1-year follow-up					
WISDOM 2007	3/2196	0/2189		0.1%	6.98[0.36,135.01]
Subtotal (95% CI)	**2196**	**2189**		**0.1%**	**6.98[0.36,135.01]**
Total events: 3 (HT), 0 (Placebol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.29(P=0.2)					
5.14.2 2-year follow-up					
HALL 1998	2/20	0/20		0.1%	5[0.26,98]
Subtotal (95% CI)	**20**	**20**		**0.1%**	**5[0.26,98]**
Total events: 2 (HT), 0 (Placebol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.06(P=0.29)					
5.14.3 3 year follow-up					
EAGAR 2006	12/40	10/43		1.96%	1.29[0.63,2.65]

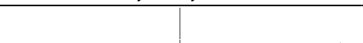


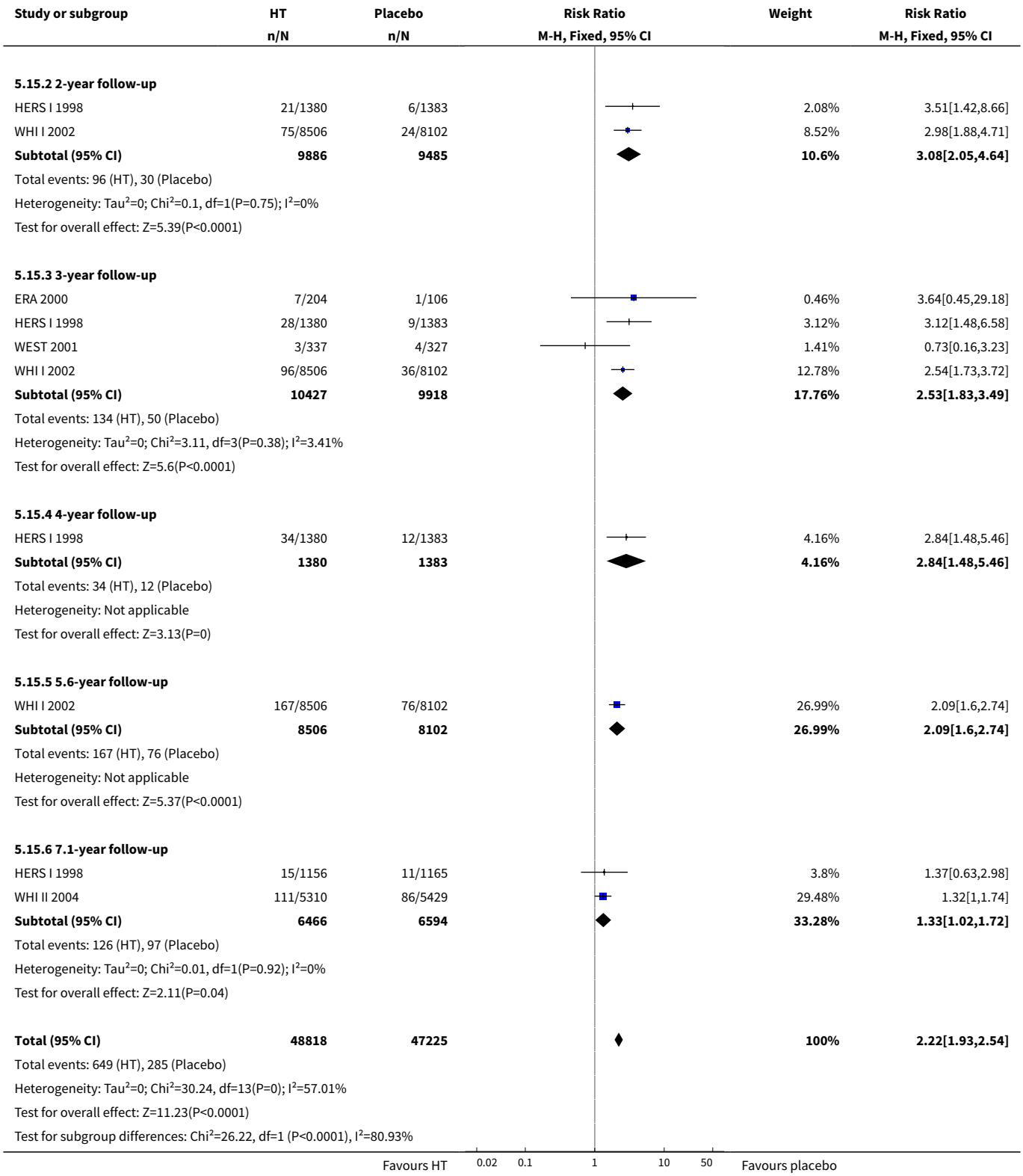
Study or subgroup	HT n/N	Placebol n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ERA 2000	33/204	22/106		5.89%	0.78[0.48,1.27]
Subtotal (95% CI)	**244**	**149**		**7.85%**	**0.91[0.61,1.35]**
Total events: 45 (HT), 32 (Placebol)					
Heterogeneity: Tau²=0; Chi²=1.29, df=1(P=0.26); I²=22.65%					
Test for overall effect: Z=0.48(P=0.63)					
5.14.4 4-year follow-up					
HERS I 1998	103/1380	117/1383		23.78%	0.88[0.68,1.14]
Subtotal (95% CI)	**1380**	**1383**		**23.78%**	**0.88[0.68,1.14]**
Total events: 103 (HT), 117 (Placebol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.97(P=0.33)					
5.14.5 5.6 year follow-up					
WHI I 2002	106/8506	126/8102		26.26%	0.8[0.62,1.04]
Subtotal (95% CI)	**8506**	**8102**		**26.26%**	**0.8[0.62,1.04]**
Total events: 106 (HT), 126 (Placebol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.69(P=0.09)					
5.14.6 7.1 year follow-up					
HERS I 1998	28/1156	37/1165		7.5%	0.76[0.47,1.24]
WHI II 2004	163/5310	171/5429		34.41%	0.97[0.79,1.2]
Subtotal (95% CI)	**6466**	**6594**		**41.91%**	**0.94[0.77,1.14]**
Total events: 191 (HT), 208 (Placebol)					
Heterogeneity: Tau²=0; Chi²=0.83, df=1(P=0.36); I²=0%					
Test for overall effect: Z=0.66(P=0.51)					
Total (95% CI)	**18812**	**18437**		**100%**	**0.9[0.79,1.02]**
Total events: 450 (HT), 483 (Placebol)					
Heterogeneity: Tau²=0; Chi²=6.2, df=7(P=0.52); I²=0%					
Test for overall effect: Z=1.72(P=0.09)					
Test for subgroup differences: Chi²=4.07, df=1 (P=0.54), I²=0%					



Analysis 5.15. Comparison 5 HT vs placebo in primary and secondary prevention, Outcome 15 Venous thromboembolism: time on treatment.

Study or subgroup	HT n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.15.1 1-year follow-up					
EVTET 2000	8/71	0/69		0.18%	16.53[0.97,280.95]
HERS I 1998	13/1380	4/1383		1.39%	3.26[1.06,9.96]
WHI I 2002	49/8506	13/8102		4.62%	3.59[1.95,6.61]
WISDOM 2007	22/2196	3/2189		1.04%	7.31[2.19,24.39]
Subtotal (95% CI)	**12153**	**11743**		**7.22%**	**4.38[2.72,7.06]**
Total events: 92 (HT), 20 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.21, df=3(P=0.53); I²=0%					
Test for overall effect: Z=6.06(P<0.0001)					





ADDITIONAL TABLES

Table 1. Summary of trial characteristics

Trial (year)	Country	Length of follow-up (years)	No. participants	Mean age of participants (years)	% hysterectomy	Primary or secondary prevention	HT type	Participant previous indication
EAGAR (2006)[1]	USA	2.8	83	64	NR	Secondary	single	CAGB
EPAT (2001)	USA	2	222	62	38	Primary	single	None
EPHT (2006)[1]	Estonia	3.4	1178	59	10	Primary	combination	None
ERA (2000)	USA	3.2	309	66	61	Secondary	single & combination	CD
ESPRIT (2002)	UK	2 .0	1017	63	25	Secondary	single	MI or TIA
EVTET (2000)[2]	Norway	1.3	140	56	NR	Secondary	combination	DVT or PE
HALL (1998)	Sweden	1.0	40	60	NR	Secondary	combination	CD
HERS I (1998)	USA	4.1	2763	67	0	Secondary	combination	CD
WAVE (2002)	International	2.8	423	66	NR	Secondary	combination	CD
WEST (2001)	USA	2.8	664	72	45	Secondary	single	MI or TIA
WHI I (2002)[3]	USA	5.6	16,606	63	0	Primary	combination	None
WHI II (2004)[4]	USA	7.1	10,739	64	100	Primary	single	None
WISDOM (2007)[1]	International	11.9 months	4385	63	NR	Primary	combination	None

Key: 1: trial stopped early due to publication of WHI I 2002 results; (2): trial stopped early due to publication of HER I 1998 results; (3) trial stopped early as the weighted log-rank test statistic for breast cancer crossed designated stopping boundary, and global index supportive of finding of overall harm; (4) trial stopped early as National Institute for Health (NIH) concluded that CEE alone did not to appear to effect the risk of heart disease, but was associated with a significant increase in the risk of stroke; NR: Not reported; CABG: Coronary-artery bypass graft; CD: Coronary disease; MI: myocardial infarction; TIA: Transient ischemic attack; DVT: Deep vein thrombosis; PE: Pulmonary embolism

Table 2. Medication adherence in the trials

Trial	Adherence Definition	Assessment method	HR arm	Placebo arm
EAGAR (2006)	% study medication taken	Pill counts	>80% up to 30 months of treatment	>80% up to 30 months of treatment
EPAT (2001)	% study medication taken	Pill counts	Level of adherence 95% (87% of participants evaluated)	Level of adherence 92% (92% of participants evaluated)
EPHT (2006)	> 80% of prescribed treatment taken	Number of collected/ returned drugs & clinic reports	< 40% compliant at 3 yrs (estimated from graph)	< 30% compliant at 3 yrs (estimated from graph)
ERA (2000)	% study medication taken	Pill counts	Level of adherence at 3.2 years: Women on single therapy (measured in 79% of participants): 74%; women on combination therapy (measured in 82% of participants): 84%	Level of adherence at 3.2 years: (measured in 80% of participants): 86% 5 women initiated treatment outside study
ESPRIT (2002)	"Regular tablet use"	Self-report to family doctor. Self-report to study nurse at 6 weeks and whenever in contact with trial staff	Number non-adherent: 51% at 12 months 57% at 24 months	Number non-adherent: 31% at 12 months 37% at 24 months
EVTET (2000)	Not reported			
HALL (1998)	Not reported			
HERS 1 (1998)	Taking at least 80% of study medication	Pill counts	82% adherent at 1 year; 75% adherent at 3 yrs 3% initiated treatment outside study	91% adherent at 1 yr; 81% adherent at 3 yrs Under 10% used HRT during un-blinded follow-

Table 2. Medication adherence in the trials *(Continued)*

			About 50% continued to use open-label HT during un-blinded follow up (4.2 - 6.8 yrs)	up (4.2 - 6.8 yrs)
WAVE (2002)	% study medication taken	Pill counts	At 2.8 yrs: Adherence 67% in the 78% of women analysed	At 2.8 yrs: Adherence 70% in the 81% of women analysed
WEST (2001)	% study medication taken	Self-report to study nurse 3 monthly Computer chip in medication bottle records opening date and time Pill counts	At 2.8 yrs: Mean adherence including drop-outs: 70% Mean adherence excluding dropouts: 90% 35% discontinued medication by 2.8 yrs, of whom 1% initiated treatment outside study	At 2.8 yrs: Mean adherence including dropouts: 74% over 2.8 yrs Mean adherence excluding dropouts: 90% 24% discontinued medication 2% initiated treatment outside study
WHI I (2002)	Taking at least 80% of study medication. Temporary discontinuation (e.g. during surgery) permitted	Weighing medication bottles	42% non-adherent by 5.2 yrs Of these 6.2% initiated HRT outside study	38% non-adherent by 5.2 yrs Of these 10.7% initiated HRT outside study
WHI II (2004)	Taking at least 80% of study medication. Temporary discontinuation (e.	Weighing medication bottles	At 6.8 years, about 53.8% of women were non-adherent In addition 5.7% of women had initiated	At 6.8 years, about 53.8% of women were non-adherent In addition 9.1% of women had initiated

Table 2. Medication adherence in the trials *(Continued)*

	g. during surgery) permitted		hormone use through their own physician	hormone use through their own physician
WISDOM (2007)	Supply of study medication	Time at risk minus temporary interruptions and time after withdrawal from treatment	73% of time	86% of time

Table 3. Results of meta-regression analyses

Outcome	Predictor	Exp (β)	Standard error (SE)	p-value
Death (all causes)	Length of follow-up	0.999	0.002	0.644
	Single or combination therapy	1.079	0.104	0.457
	Primary or secondary prevention	1.069	0.101	0.499
Death (CV causes)	Length of follow-up	1.002	0.004	0.72
	Single or combination therapy	1.247	0.221	0.241
	Primary or secondary prevention	0.977	0.177	0.899
Non-fatal MI	Length of follow-up	0.9970	0.0043	0.510
	Single or combination therapy	1.0637	0.1941	0.741
	Primary or secondary prevention	0.9292	0.1646	0.686
Stroke	Length of follow-up	1.0045	0.0033	0.216
	Single or combination therapy	0.8649	0.1199	0.330
	Primary or secondary prevention	0.8070	0.1019	0.133
Angina	Length of follow-up	0.993	0.013	0.622
	Single or combination therapy	Not calculable	Not calculation	Not calculable
	Primary or secondary prevention	Not calculable	Not calculation	Not calculable
Venous thromboembolism	Length of follow-up	0.993	0.011	0.549
	Single or combination therapy	1.610	0.361	0.087
	Primary or secondary prevention	1.231	0.541	0.656

Table 3. Results of meta-regression analyses *(Continued)*

Pulmonary embolism	Length of follow-up	0.989	0.008	0.184
	Single or combination therapy	1.765	0.495	0.089
	Primary or secondary prevention	1.05	0.470	0.917

Table 4. Summary of HRQoL scores for HT versus placebo for HERS I

Trial **First author (year)**	**Length of follow-up**	**HRQoL measure**	**N**	**Outcome values at follow up** **Mean (SD)** **HT vs. Placebo, between group p-value**
HERS I (1998) **Hlatky (2002)**	**3 years**	**Duke Activity Status Index**	HT: 1380 Placebo: 1383	
		Physical function‡		Baseline: 25.5 vs 25.2 Follow-up: 51.2 vs 52.3 (p > 0.5) **HT = placebo**
		Energy/fatigue‡		Baseline: 55.8 vs 55.3 Follow-up: 51.2 vs 52.3 (p > 0.5) **HT = placebo**
		Mental Health‡		Baseline: 55.8 vs 55.3 Follow-up: 75.7 vs 74.8 (p > 0.5) **HT = placebo**
		Depressive symptoms†		Baseline: - 5.5 vs - 5.5 Follow-up: - 5.8 vs – 5.7 (p > 0.5) **HT = placebo**

Scale scoring: ‡ higher score = better functioning; †lower score = better functioning

Table 5. Summary of HRQoL scores for HT versus placebo for WHI I, WHI II, WISDOM 2007 and EPHT 2006

Trial First author (year)	Length of follow-up	HRQoL measures	N	Outcome values at follow up Mean (SD) HT vs. Placebo, between group p-value
WHI I (2002) **Hays (2003)**	1 year	RAND 36-Item Health Survey; Women's Health Initiative Insomnia Rating Scale; Satisfaction with sex questionnaire General health*	HT: 7722 Placebo: 7381 HT: 7638 Placebo: 7287	Baseline: 76.7 vs 76.5 Follow-up change: - 0.4 vs - 0.7; (p = 0.08)
			HT: 7735 Placebo: 7395	**HT = placebo**
		Physical functioning*	HT: 7825 Placebo: 7487	Baseline: 82.8 vs 82.9 Follow-up change: - 0.6 vs - 1.4; (p < 0.001)†
			HT: 7733 Placebo: 7379	**HT > placebo**
		Role physical*	HT: 7782 Placebo: 7459	Baseline: 70.49 vs 70.22 Follow-up change: - 2.04 vs - 1.81; (p = 0.77)
		Bodily pain*	HT: 7720 Placebo: 7399	**HT = placebo**
		Vitality*	HT: 7731 Placebo: 7370	Baseline: 77.3 vs 77.2 Follow-up change: 0.1 vs - 1.8; (p < 0.001)†
			HT: 7591	**HT > placebo**
		Social functioning*	Placebo: 7286	Baseline: 64.8 vs 64.8
		Role emotional*	HT: 7642	Follow-up change: 0.2 vs 0.0; (p = 0.31)
		Mental health*	Placebo: 7307	**HT = placebo**
		Depressive symptoms‡	HT: 6223	Baseline: 91.5 vs 91.5
		Sleep disturbance§		

Table 5. Summary of HRQoL scores for HT versus placebo for WHI I, WHI II, WISDOM 2007 and EPHT 2006 *(Continued)*

		Satisfaction with sex‖	Placebo: 5849	Follow-up change: - 3.09 vs - 1.77; (p = 0.003)† **HT > placebo**
				Baseline: 85.6 vs 85.3 Follow-up change: - 0.7 vs - 0.5; (p = 0.68) **HT = placebo**
				Baseline: 79.8 vs 79.8 Follow-up change: 0.6 vs 0.7; (p= 0.81) **HT = placebo**
				Baseline: - 5.5 vs - 5.5 Follow-up change: - 0.1 vs - 0.1; (p = 0.72) **HT = placebo**
				Baseline: 13.4 vs 13.3 Follow-up change: 0.5 vs 0.1; (p < 0.001)† **HT > placebo**
				Baseline: 2.9vs 2.9 Follow-up change: 0.0 vs 0.0; (p = 0.48) **HT = placebo**

Trial **First author (year)**	**Length of follow-up**	**HRQoL measures**	**N**	**Outcome values at follow up** **Mean (SD)** **HT vs. Placebo, between group p-value**

Table 5. Summary of HRQoL scores for HT versus placebo for WHI I, WHI II, WISDOM 2007 and EPHT 2006 *(Continued)*

WHI II (2004) **Brunner (2005)**	1-year	RAND 36-Item Health Survey; Women's Health Initiative Insomnia Rating Scale; Satisfaction with sex questionnaire.	HT: 4654 Placebo: 4767	Baseline: 71.95 vs 72.38 Follow-up change: - 0.31 vs - 0.37; (p = 0.82) **HT = placebo**
		General health*	HT: 4580 Placebo: 4678	
		Physical functioning*	HT: 4664 Placebo: 4783	Baseline: 76.7 vs 76.5 Follow-up change: - 0.4 vs - 0.7; (p = 0.08) **HT = placebo**
		Role physical*	HT: 4764 Placebo: 4885	Baseline: 82.8 vs 82.9 Follow-up change: - 0.6 vs - 1.4; (p < 0.001)† **HT > placebo**
		Bodily pain*	HT: 4764 Placebo: 4885	Baseline: 70.49 vs 70.22 Follow-up change: - 2.04 vs - 1.81; (p = 0.77) **HT = placebo**
		Vitality*	HT: 4736 Placebo: 4836	Baseline: 77.3 vs 77.2 Follow-up change:0.1 vs - 1.8; (p < 0.001)† **HT > placebo**
		Social functioning*	HT: 4682 Placebo: 4801	Baseline: 64.8 vs 64.8 Follow-up change: 0.2 vs 0.0; (p = 0.31) **HT = placebo**
		Role emotional*	HT: 4651 Placebo: 4750	Baseline: 91.5 vs 91.5 Follow-up change: - 3.09 vs - 1.77; (p = 0.003)† **HT < placebo**
		Mental health*	HT: 4465 Placebo: 4599	
		Depressive symptoms‡	HT: 4574 Placebo: 4670	
		Sleep disturbance§	HT:3314 Placebo:3368	
		Satisfaction with sex‖		

Table 5. Summary of HRQoL scores for HT versus placebo for WHI I, WHI II, WISDOM 2007 and EPHT 2006 *(Continued)*

				Baseline: 85.6 vs 85.3 Follow-up change: - 0.7 vs - 0.5; (p = 0.68) **HT = placebo**
				Baseline: 79.8 vs 79.8 Follow-up change: 0.6 vs 0.7; (p = 0.81) **HT = placebo**
				Baseline: - 5.5 vs - 5.5 Follow-up change: - 0.1 vs - 0.1; (p = 0.72) **HT = placebo**
				Baseline: 13.4 vs 13.3 Follow-up change: 0.5 vs 0.1; (p < 0.001)† **HT > placebo**

Key: * Scored from 0 (worst) to 100 (best);‡Scored from 4.0 (worst) to -8.1 (best); § Scored from 0 (worst) to 20 (best);|| Scored from 0 (worst) to 4 (best); † p value is statistically significant at Bonferroni corrected α level of 0.001; actual unadjusted p values presented.

WISDOM (2007) **Welton (2008)**	**Length of follow-up**	**Prevalence of symptoms related to the menopause**	**N**	**Outcome values at follow up** **Mean (SD)** **HT vs. Placebo, between group p-value**
	1 year		HT: 1043 Placebo: 1087	
		Hot flushes		Baseline: 317 vs 311 Follow-up: 98 vs 269 (p < 0.001)‡ **HT > placebo**

Table 5. Summary of HRQoL scores for HT versus placebo for WHI I, WHI II, WISDOM 2007 and EPHT 2006 *(Continued)*

Night sweats	
	Baseline: 283 vs 281
	Follow-up: 145 vs 252
	(p < 0.001)‡
Insomnia	**HT > placebo**
	Baseline: 471 vs 472
	Follow-up: 367 vs 450
Feeling depressed	(p < 0.001)‡
	HT > placebo
Feeling anxious	Baseline: 195 vs 207
	Follow-up: 234 vs 256 (p = 0.6)
	HT = placebo
Dizziness	Baseline: 293 vs 284
	Follow-up: 300 vs 313 (p = 0.7)
	HT = placebo
Aching joints or muscles	Baseline: 117 vs 137
	Follow-up: 117 vs 137 (p = 1)
	HT = placebo
Tiredness	Baseline: 659 vs 680
	Follow-up: 592 vs 688 (p < 0.001)‡
	HT > placebo
Headache	Baseline: 523 vs 516
	Follow-up: 556 vs 554 (p = 0.5)
	HT = placebo

Table 5. Summary of HRQoL scores for HT versus placebo for WHI I, WHI II, WISDOM 2007 and EPHT 2006 *(Continued)*

Migraine	Baseline: 264 vs 288 Follow-up: 268 vs 273 (p = 0.6) **HT = placebo**
Irritability/mood swings	Baseline: 44 vs 56 Follow-up: 51 vs 60 (p = 0.8) **HT = placebo**
Heart racing or skipping beats	Baseline: 181 vs 183 Follow-up:186 vs 220 (p = 0.1) **HT = placebo**
Dry skin or scaling	Baseline: 114 vs 112 Follow-up: 149 vs 128 (p = 0.1) **HT = placebo**
Vaginal or genital dryness	Baseline: 319 vs 332 Follow-up: 304 vs 326 (p = 0.6) **HT = placebo**
Vaginal or genital itching	Baseline: 249 vs 244 Follow-up: 150 vs 211(p < 0.001)‡ **HT > placebo**
Vaginal or genital discharge	Baseline: 115 vs 101 Follow-up: 121 vs 118 (p = 0.9) **HT = placebo**
Pain or burning while urinating	Baseline: 58 vs 48
Breast tenderness	
Leg cramps in one leg	

Table 5. Summary of HRQoL scores for HT versus placebo for WHI I, WHI II, WISDOM 2007 and EPHT 2006 *(Continued)*

Leg cramps in both legs	Follow-up: 151 vs 55 (p < 0.001)‡ **HT > placebo**
Swelling in one leg	Baseline: 31 vs 31 Follow-up: 36 vs 39 (p = 0.8)
Swelling in both legs	**HT = placebo**
Nausea	Baseline: 65 vs 69 Follow-up: 164 vs 76 (p < 0.001)‡
Abdominal cramps	Baseline: 96 vs 108 Follow-up: 122 vs 113 (p = 0.3)
Bloating	**HT = placebo** Baseline: 169 vs 167 Follow-up: 227 vs 205 (p = 0.1)
Skin rash/itching	**HT = placebo**
Crawling feelings under skin	Baseline: 45 vs 35 Follow-up: 44 vs 31 (p = 0.2) **HT = placebo**
Trouble seeing not corrected by glasses / contact lenses	Baseline: 96 vs 80 Follow-up: 82 vs 98 (p = 0.07) **HT = placebo**
	Baseline: 85 vs 87 Follow-up: 84 vs 91 (p = 0.8)

Table 5. Summary of HRQoL scores for HT versus placebo for WHI I, WHI II, WISDOM 2007 and EPHT 2006 *(Continued)*

				HT = placebo Baseline: 70 vs 76 Follow-up: 81 vs 95 (p = 0.4) **HT = placebo** Baseline: 235 vs 217 Follow-up: 215 vs 260 (p = 0.005) **HT > placebo** Baseline: 185 vs 166 Follow-up: 187 vs 177 (p = 0.6) **HT = placebo** Baseline: 83 vs 81 Follow-up: 77 vs 76 (p = 0.8) **HT = placebo** Baseline: 46 vs 54 Follow-up: 51 vs 64 (p = 0.4) **HT = placebo**

Key: ‡ Significant at Bonferroni corrected α level of 0.001; actual unadjusted p values presented.

WISDOM (2007) **Welton (2008)**	**Length of follow-up**	**EQ-5D**	**N**	**Outcome values at follow up** **Mean (SD)**

Table 5. Summary of HRQoL scores for HT versus placebo for WHI I, WHI II, WISDOM 2007 and EPHT 2006 *(Continued)*

				HT vs. Placebo, between group p-value
	1 year		HT: 1043 Placebo: 1087	
EQ-VAS				Baseline: 79.2 (0.4) vs 79.4 (0.4) Follow-up: 77.9 (0.5) vs 78.5 (0.4) (p = 0.28)
EQ-5D				Baseline: 0.88 (0.005) vs 0.87 (0.005) Follow-up: 0.89 (0.005) vs 0.87 (0.005) (p = 0.02)
EPHT Trial (2006) **Veerus (2008)**				
EQ-5D				
2-year	**EQ-5D Score**			
	Minimum	**1st quartile**	**Median**	**3rd quartile**
HT: N = 295	0.30	0.80	0.90	1.0
Placebo: N = 254	0.30	0.80	0.90	1.0
3.6-year				
HT: N = 329	0.30	0.70	0.80	0.9-
Placebo: N = 308	0.10	0.70	0.80	0.90

APPENDICES

Appendix 1. Search strategies

Original Review

#1 CARDIOVASCULAR-DISEASES*:ME
#2 CEREBROVASCULAR-DISORDERS*:ME
#3 CHOLESTEROL*:ME
#4 BLOOD-COAGULATION-FACTORS*:ME
#5 CARDIOVASCULAR
#6 CORONARY
#7 ANGINA*
#8 MYOCARDIAL
#9 STROKE
#10 HYPERTENSION
#11 CHOLESTEROL
#12 EMBOLI*
#13 THROMBO*
#14 CEREBROVASCULAR
#15 ATHEROSCLERO*
#16 ARTERIOSCLERO*
#17 LIPIDS*:ME
#18 LIPID*
#19 HYPERLIPIDEMIA*:ME
#20 (HYPERLIPIDEMIA or HYPERLIPIDAEMIA)
#21 FIBRIN*
#22 (((((((#1 or #2) or #3) or #4) or #5) or #6) or #7) or #8) or #9)
#23 ((((((((((#10 or #11 or #12) or #13) or #14) or #15) or #16) or #17) or #18) or #19) or #20) or #21)
#24 (#22 or #23)
#25 ESTROGEN-REPLACEMENT-THERAPY*:ME
#26 HRT
#27 (HORMONE near REPLAC*)
#28 (OESTROGEN near REPLAC*)
#29 (ESTROGEN near REPLAC*)
#30 ((MENOPAUS* or POSTMENOPAUS*) or POSTMENOPAUS*)
#31 OESTROGEN
#32 ESTROGEN
#33 (#31 or #32)
#34 (#30 and #33)
#35 ((((#25 or #26) or #27) or #28) or #29)
#36 (#34 or #35)
#37 (#24 and #36)

Up-date Review

Cochrane Controlled Trial Register, Issue 1, April 2010 (search date: 20/04/2010)

#1. MeSH descriptor Cardiovascular Diseases explode all trees
#2. MeSH descriptor Cerebrovascular Disorders explode all trees
#3. CARDIOVASCULAR*
#4. CORONARY
#5. ANGINA*
#6. MYOCARD*
#7. HEART NEAR/3 ATTACK
#8. STROKE*
#9. MeSH descriptor Embolism and Thrombosis explode all trees
#10. EMBOL*
#11. THROMBO*
#12. CEREBROVASCULAR
#13. MeSH descriptor Hypertension explode all trees
#14. HYPERTENSION
#15. MeSH descriptor Arteriosclerosis explode all trees

#16. ARTERIOSCLER* OR ARTHEROSCLER*
#17. ISCHAEMIC OR ISCHEMIC
#18. MeSH descriptor Hyperlipidemias explode all trees
#19. HYPERLIPIDEMIA* OR HYPERLIPIDAEMIA*
#20. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21. MeSH descriptor Hormone Replacement Therapy explode all trees
#22. HRT OR ERT OR ORT
#23. HORMONE NEAR/4 (REPLAC* OR THERAP* OR SUPPLEMENT*)
#24. ESTROGEN NEAR/4 (REPLAC* OR THERAP* OR SUPPLEMENT*)
#25. OESTROGEN NEAR/4 (REPLAC* OR THERAP* OR SUPPLEMENT*)
#26. (#21 OR #22 OR #23 OR #24 OR #25)
#27. (menopaus* OR postmenopaus* OR post-menopaus*)
#28. MeSH descriptor Postmenopause, this term only
#29. (#27 OR #28)
#30. oestrogen OR estrogen
#31. (#29 AND #30)
#32. (#26 OR #31)
#33. (#20 AND #32)

MEDLINE search 20/04/2010

1. CARDIOVASCULAR-DISEASES#.DE.
2. CEREBROVASCULAR-DISORDERS#.DE.
3. CARDIOVASCULAR.TI,AB.
4. CORONARY.TI,AB.
5. ANGINA$2.TI,AB.
6. (MYOCARDIAL OR HEART NEAR ATTACK).TI,AB.
7. STROKE$4.TI,AB.
8. EMBOLISM-AND-THROMBOSIS#.DE.
9. EMBOL$5.TI,AB.
10. THROMBO$6.TI,AB.
11. CEREBROVASCULAR.TI,AB.
12. HYPERTENSION.W..DE.
13. HYPERTENSION.TI,AB.
14. ARTERIOSCLEROSIS#.W..DE.
15. (ARTERIOSCLERO$5 OR ARTHEROSCLERO$5).TI,AB.
16. (ISCHAEMIC OR ISCHEMIC).TI,AB.
17. HYPERLIPIDEMIAS#.W..DE.
18. (HYPERLIPIDEMIA$4 OR HYPERLIPIDAEMIA$4).TI,AB.
19. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10
20. 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18
21. 19 OR 20
22. HORMONE-REPLACEMENT-THERAPY#.DE.
23. (HRT OR ERT OR ORT).TI,AB.
24. HORMONE NEAR (REPLAC$6 OR THERAP$4 OR SUPPLEMENT$6)
25. ESTROGEN NEAR (REPLAC$6 OR THERAP$4 OR SUPPLEMENT$6)
26. OESTROGEN NEAR (REPLAC$6 OR THERAP$4 OR SUPPLEMENT$6)
27. 22 OR 23 OR 24 OR 25 OR 26
28. MENOPAUS$4 OR POSTMENOPAUS$4 OR POST-MENOPAUS$4
29. POSTMENOPAUSE.W..DE.
30. 28 OR 29
31. (ESTROGEN OR OESTROGEN).TI,AB.
32. 30 AND 31
33. 27 OR 32
34. PT=RANDOMIZED-CONTROLLED-TRIAL
35. PT=CONTROLLED-CLINICAL-TRIAL
36. (SINGL$4 OR DOUBLE$4 OR TRIPLE$4 OR TREBLE$4) AND (BLIND$4 OR MASK$4)
37. RANDOM$5 OR PLACEBO$2
38. RANDOM-ALLOCATION.DE.
39. DOUBLE-BLIND-METHOD.DE.
40. SINGLE-BLIND-METHOD.DE.
41. (CLINIC$3 NEAR TRIAL$2).TI,AB.

42. RETRACT$5 NEAR PUBLICATION
43. 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42
44. ANIMAL=YES NOT HUMAN=YES
45. 21 AND 33 AND 43
46. 45 NOT 44

EMBASE search 20/04/2010

1. CARDIOVASCULAR-DISEASE#.DE.
2. CEREBROVASCULAR-DISEASE#.DE.
3. CARDIOVASCULAR.TI,AB.
4. CORONARY.TI,AB.
5. ANGINA$2.TI,AB.
6. MYOCARDIAL.TI,AB. OR (HEART NEAR ATTACK).TI,AB.
7. STROKE$4.TI,AB.
8. EMBOL$5.TI,AB.
9. THROMBO$6.TI,AB.
10. CEREBROVASCULAR.TI,AB.
11. HYPERTENSION.W..DE.
12. HYPERTENSION.TI,AB.
13. ARTERIOSCLEROSIS#.W..DE.
14. (ARTERIOSCLERO$5 OR ARTHEROSCLERO$5).TI,AB.
15. (ISCHAEMIC OR ISCHEMIC).TI,AB.
16. (HYPERLIPIDEMIA$4 OR HYPERLIPIDAEMIA$4).TI,AB.
17. HYPERLIPIDEMIA#.W..DE.
18. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
19. Hormone-Substitution#.DE.
20. (HRT OR ERT OR ORT).TI,AB.
21. HORMONE NEAR (REPLAC$6 OR THERAP$4 OR SUPPLEMENT$6).TI,AB.
22. ESTROGEN NEAR (REPLAC$6 OR THERAP$4 OR SUPPLEMENT$6).TI,AB.
23. OESTROGEN NEAR (REPLAC$6 OR THERAP$4 OR SUPPLEMENT$6).TI,AB.
24. (menopaus$4 OR postmenopaus$4 OR post-menopaus$4).TI,AB.
25. Postmenopause.W..DE.
26. 39 OR 40
27. (oestrogen OR estrogen).TI,AB.
28. 41 AND 42
29. 19 OR 20 OR 34 OR 37 OR 38 OR 43
30. 44 AND 18
31. factorial$
32. crossover$2 OR cross ADJ over$2
34. (RANDOM$ OR PLACEBO$).DE,TI,AB.

LILACS search conducted 20/04/2010

Search 1:

"HORMONE REPLACEMENT THERAPY" OR

((hormone OR oestrogen OR oestrogen) AND (replac$ or therap$ or supplement$)) or (hrt OR ert OR ort) AND ("clinical trials, RANDOMIZED" or "controlled clinical trials, RANDOMIZED" OR ((trial$ or ensa$ or estud$) AND (clin$)) OR ((singl$ or doubl$ or doble$ or duplo$ or trebl$ or trip$) AND (blind$ or cego$ or ciego$ or mask$ or mascar$)) OR (random$ or randon$ or casual$ or acaso$ or azar or aleator$)) = 318

Search 2:

(("POSTMENOPAUSE" OR menopaus$ or postmenopaus$ or post-menopause) AND (oestrogen or estrogen))

F E E D B A C K

Question from Jim Thornton, 18 October 2013

Summary

This review does not include any of the 22 studies identified in the paper "Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials" (Hemminki E, McPherson K BMJ 1997;315:149-153).

We recognise that some of them may not have included relevant endpoints, but we were surprised not to see them in the list of excluded studies.

We also recognise that most were not initiated with the aim of cardioprotection. However since the Hemminki-McPherson paper identified cardiac events, they surely are informative to he question addressed in the present review.

Finally, since most of these studies included relatively young women they are relevant to the timing hypothesis.

Reply

Having assessed the review by Hemminki-McPherson the authors note that the methods section describes 22 studies including 4124 women, but table 1 (included studies) provides details of 23 studies on 4164 women. It is therefore unclear which of the 22 studies were included in the review. The response therefore pertains to all 23 studies listed in table 1.

As Thornton et al, may be aware, this review was an up-date of the original Cochrane review on Hormone replacement therapy for preventing cardiovascular disease in post-menopausal women (Gabriel-Sanchez 2005). All 23 of the studies identified in the Hemminki-McPherson review were listed in the excluded studies section of the original Gabriel-Sanchez 2005 review, but were excluded as they did not meet the inclusion criteria. Likewise, all 23 studies were identified in the searches for the up-date review, but were excluded on the basis of title and abstract, as they clearly did not meet the inclusion criteria specified for the up-date review. It is worth noting that the inclusion criteria for the Hemminki-McPherson review differed considerably from those for the up-date Cochrane review, in terms of study design, intervention, and outcome measures. Therefore the Hemminki-McPherson review includes studies of transdermal HT, a cross-over trial, and studies of less than 6-months duration, all of which were criteria that clearly did not meet the inclusion criteria for the present up-date review, and readers would probably not expect to see listed in the excluded studies section. In terms of outcome measures, the Hemminki-McPherson review included studies in which the primary aim was not to assess the effects of HT on CVD, and therefore only seven of the 23 studies reported any CV outcomes, with a total of 17 events identified. Data on CV events in the review “were given incidentally”, mostly as “reasons for dropping out”. As the aim of the up-dated Cochrane review was to assess the effects of HT on specific types of CV events, as well as death from CV causes, CV events needed to be specified a priori in the trial and reported as either primary or secondary outcome measures. Therefore the review did not include trials in which CV events were reported only as adverse events or reasons for withdrawals.

Contributors

James Hitchin, Klim McPherson, Jim Thornton

Caroline Main, responded to the feedback.

WHAT'S NEW

Date	Event	Description
19 November 2013	Feedback has been incorporated	Jim Thornton submitted feedback on 18th October 2013

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 2, 2005

Date	Event	Description
20 June 2012	New citation required but conclusions have not changed	The searches were updated to April 2010, and the cardiovascular outcomes of angina, coronary artery by-pass graft (CABG), angioplasty, and health-related quality of life (HRQoL) included as further relevant additional outcomes.
20 June 2012	New search has been performed	Four new trials, with a total of 15984 participants were included in the review update. One trial included in the previous review, the open-label long-term follow-up of another trial was excluded. The review update therefore included 13 RCTs with a total

Date	Event	Description
		of 38171 women randomised to either HT or placebo. Five trials were primary prevention and eight secondary prevention trials.
20 February 2012	Amended	The results and conclusion of the update review have not changed from those of the original review. However, there is further substantive evidence that treatment with HT in post-menopausal women for either primary or secondary prevention of CVD events is not effective, and causes an increase in the risk of stroke, and venous thromboembolic events.

CONTRIBUTIONS OF AUTHORS

Tiffany Moxham developed and ran the search strategies. Study selection, quality assessment and data extraction were performed by Caroline Main and Beatrice Knight. Caroline Main wrote the first draft of the review, and all co-authors commented on this and contributed to the final draft of the review. All authors have approved the manuscript.

DECLARATIONS OF INTEREST

None known.

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External sources

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INDEX TERMS

Medical Subject Headings (MeSH)

Cardiovascular Diseases [mortality] [*prevention & control]; Cause of Death; Estrogen Replacement Therapy [adverse effects] [methods]; Hormone Replacement Therapy [adverse effects] [*methods]; Postmenopause; Primary Prevention; Secondary Prevention; Stroke [chemically induced]; Venous Thromboembolism [chemically induced]

MeSH check words

Adult; Aged; Aged, 80 and over; Female; Humans; Middle Aged