UK Public Assessment Report

Hormone-replacement therapy: safety update

Executive summary

Hormone-replacement therapy (HRT) with small doses of oestrogen (and progestogen for women with an intact uterus) can help relieve menopausal symptoms that result from hormonal deficiency as a result of natural menopause or surgical menopause.

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency that is responsible for ensuring that medicines and medical devices work and are acceptably safe. Evidence-based judgments underpin the Agency's work to ensure that the benefits to patients and the public justify the potential risks.

The Commission on Human Medicines advises ministers on the quality, safety, and efficacy of medicines. The UK's Medicines for Women's Health Expert Advisory Group (MWHEAG) of the Commission on Human Medicines (CHM) regularly reviews important new data that are published on the safety of HRT; their most recent assessment took place in July, 2007.

A core Summary of Product Characteristics (SPC) for HRT was developed on a European-wide basis in 2000–01 to provide consistent safety information between similar products. Since then, several long-term studies of HRT have ended, and the core SPC has undergone two major revisions as a result—first in December, 2002, and then in February, 2004.

Since then further important data on HRT safety have become available, including re-analyses of results from the Women's Health Initiative trial and Nurses' Health Study on the risk of cardiovascular disease. These new data have given rise to the hypothesis that the effect of HRT on risk of coronary heart disease (CHD) differs according to the state of the underlying vasculature when treatment is started. Since the state of the vasculature is generally regarded as being age-dependent, it has been suggested that HRT is cardioprotective in younger women with a healthy vasculature, but can trigger a coronary event in older women with complicated atherosclerotic lesions.

However, as yet there is no evidence to support a cardioprotective effect of HRT, and further research is needed before any firm conclusions can be drawn about the effect of HRT on CHD risk in younger women.

In addition to CHD, HRT is associated with other important risks:

- **Stroke:** Oestrogen-only HRT and combined HRT each increase stroke risk by about 1·3-times.
- **Venous thromboembolism (VTE):** Oral oestrogens increase VTE risk by about 1·3-times, and oral progestogens increase risk by about 2·4-times. The risk is highest in early use. The level of risk may be lower with transdermal HRT, although this has not been clearly established.
- **Breast cancer:** Oestrogens may slightly increase the risk of having breast cancer diagnosed. Combined HRT increases the risk by about 1·6-times after 5 years of use and 2·3-times after 10 years of use. Risk decreases within a few years of stopping HRT.
- **Ovarian cancer:** Risk of ovarian cancer may be slightly increased by long-term use of oestrogen-only HRT and combined HRT. Risk falls within a few years of stopping HRT.

- **Endometrial cancer:** Oestrogen-only HRT increases risk of endometrial cancer about 3-times after 5 years of use and about 9-times after 10 years of use. In women with a uterus, progestogen should be added for at least 10 days per cycle to reduce or eliminate the effect of oestrogen on the endometrium.

Generally the much lower baseline risk of CHD and other adverse events in healthy younger women who use HRT to relieve menopausal symptoms means that their overall risk from HRT is very low. With increasing age, however, their baseline risk for all cardiovascular events increases substantially, and so older HRT users have a much greater overall risk of these events. Furthermore, risk of breast cancer, ovarian cancer, and endometrial cancer due to HRT increases with longer duration of use.

The balance of risks and benefits of HRT therefore differs for every woman according to her need for treatment, age at starting HRT, duration of use and type of HRT—ie, oestrogen-only or oestrogen plus progestogen.

No single recommendation for optimum duration of treatment or safe upper-age limit for use of HRT is therefore possible because they will be specific to every woman's circumstances. For most women, short-term treatment will be sufficient to relieve vasomotor symptoms; for others, HRT may need to be continued for longer. For all women, the lowest effective dose should be used for the shortest possible time, and the need to continue HRT should be reviewed at least yearly, taking into consideration the change in balance of risks and benefits.

This Public Assessment Report summarises the key evidence reviewed by MWHEAG and their recommendations. The September issue of the MHRA's *Drug Safety Update* bulletin included updated advice for healthcare professionals on the use of HRT in women (see http://www.mhra.gov.uk/mhra/drugsafetyupdate).

1. Introduction

Hormone-replacement therapy (HRT) with small doses of oestrogen (and progestogen for women with an intact uterus) can help relieve menopausal symptoms that result from hormonal deficiency as a result of natural menopause or surgical menopause.

A core Summary of Product Characteristics (SPC) for HRT was developed on a European-wide basis in 2000–01 to provide consistent safety information between similar products. Since then, several long-term studies of HRT have ended, and the core SPC has undergone two major revisions—first in December, 2002, and the second in February, 2004.

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency that is responsible for ensuring that medicines and medical devices work and are acceptably safe. Evidence-based judgments underpin the Agency's work to ensure that the benefits to patients and the public justify the potential risks.

The Commission on Human Medicines advises ministers on the quality, safety, and efficacy of medicines. The UK's Medicines for Women's Health Expert Advisory Group (MWHEAG) of the Commission on Human Medicines (CHM) regularly reviews important new data that are published on the safety of HRT; their most recent assessment took place in July, 2007.

This Public Assessment Report summarises the evidence reviewed by the Group in July and their recommendations. It discusses key evidence considered by the Group for the risks associated with HRT use, and summarises the overall balance of risks and benefits of HRT. The September issue of the MHRA's *Drug Safety Update* bulletin included updated advice for healthcare professionals on the use of HRT in women (see http://www.mhra.gov.uk/mhra/drugsafetyupdate).

2. Coronary heart disease (CHD)

2.1 Key data previously considered by the Group

Two large randomised controlled trials, the Heart and Estrogen-Progestin Replacement Study (HERS)[1] and the Women's Health Initiative (WHI) trial[2] have assessed oral conjugated equine oestrogens (CEE, 0·625 mg) plus medroxyprogesterone (2·5 mg). The HERS study[1] analysed this treatment for the secondary prevention of heart disease, whereas the WHI trial[2] studied its effects in women who were mostly healthy. Both trials[1,2] found that HRT gave no overall benefit for prevention of CHD in the women studied and slightly increased the risk of CHD in the first year of use.

Two randomised controlled secondary-prevention trials broadly support the findings of HERS and WHI: the Papworth HRT Atherosclerosis Study (PHASE)[3] trial of transdermal 17β-oestradiol (with or without norethisterone), and the Estrogen in Prevention of Reinfarction Trial (ESPRIT)[4] trial of oral oestradiol.

In April, 2004, the group who were assigned oestrogen only (ie, CEE, 0·625 mg) in the WHI study had their treatment terminated prematurely.[5]

2.2 New evidence

Subgroup analyses of data from the women who were assigned CEE and medroxyprogesterone in the WHI trial[2] identified a non-significant interaction between increasing time since menopause at starting HRT and greater CHD risk.[6] This finding has stimulated further re-analysis of data from WHI, re-analysis of data from the Nurses Health Study (NHS), systematic reviews and meta-analyses and revision of prescribing guidelines in Europe[7] and North America.[8]

2.2.1 Randomised controlled trials

WHI trial—final results of CEE arm[9]

The primary outcome of this analysis was non-fatal myocardial infarction (clinical or silent) or coronary death; secondary outcomes included 26 prespecified subgroup analyses.

At a mean follow-up of 7·1 years, 54% of CEE users and 53·5% of placebo users had discontinued treatment. At baseline, mean age of participants was 63·6 years, 30% had treated hypertension, 15% had hypercholesterolaemia, 10·5% were smokers, 10% had untreated hypertension, 8% had diabetes, and 5% had a history of myocardial infarction or coronary revascularisation.

After 1 year of treatment, women assigned CEE had greater increases from baseline in high density lipoprotein (HDL) and triglyceride levels, and had greater reductions in total cholesterol, low density lipoprotein (LDL), glucose, and insulin levels compared with women assigned placebo. The use of statins throughout the trial significantly increased in the CEE group compared with the placebo group.

After 7·1 years, no overall effect of CEE on CHD compared with placebo was observed (hazard ratio [HR] 0·95 [95% CI 0·79–1·16]); findings were similar in those who adhered to study treatment (HR 0·91). For women who adhered to treatment, a non-significant trend towards lower risk of CHD in younger women was observed (p=0·35). Hazard ratios were not significant in any subgroup analyses. Risk of CHD was not associated with duration of use (p=0·14), and no increase in risk was identified during any year of treatment.

The final results of the CEE-only group of the WHI trial differ little from those published in 2004.[5] Although subgroup analyses showed a trend towards a lower risk of CHD in younger women, the number of women in the younger age categories is small and the results were statistically non-significant.

WHI trial—combined analyses of CEE and CEE plus medroxyprogesterone arms[10]

The number of events in individual arms of the WHI trial was too small to give definitive answers about the effect of age at starting HRT on CHD risk. The study investigators therefore pooled data from the CEE-only and the CEE plus medroxyprogesterone arms.

These data showed an increased risk of CHD with increasing time since menopause at starting treatment (p=0·02; table 1) becoming significant in women who started HRT more than 20 years since menopause.

Table 1: Effect of CEE and CEE plus medroxyprogesterone on CHD by age and time since menopause (WHI trial)

AGE (years)								
50–59			60-69			70–79		
HRT (n cases)	Placebo (n cases)	HR (95% CI)	HRT (n cases)	Placebo (n cases)	HR (95% CI)	HRT (n cases)	Placebo (n cases)	HR (95% CI)
59	61	0·93 (0·65-1·33)	174	178	0·98 (0·79-1·21)	163	131	1·26 (1·00-1·59)
TIME SINCE MENOPAUSE (years)								
Less than 10			10-19			At least 20		
HRT (n cases)	Placebo (n cases)	HR (95% CI)	HRT (n cases)	Placebo (n cases)	HR (95% CI)	HRT (n cases)	Placebo (n cases)	HR (95% CI)
39	51	0·76 (0·50-1·16)	113	103	1·10 (0·84-1·45)	194	158	1·28 (1·03-1·58)

Similar to the individual arms, a non-significant, trend was observed when data were analysed according to age at starting HRT (p=0·16).

In HRT users who were age 50–59 years, ten fewer deaths from any cause occurred per 10 000 in a year compared with placebo, and in women aged 70–79 years 16 additional deaths occurred per 10 000 in a year compared with placebo (p=0·03 for difference between the two age-groups).

In individual arms of the WHI trial, a trend for increasing risk of CHD with increasing time since menopause was recorded, which became significant when the data were pooled. Significantly increased risk of CHD was observed in women aged 70–79 years and in those who were more than 20 years' postmenopause in the group assigned CEE plus medroxyprogesterone and in the pooled arms. No evidence for cardioprotection was noted in any subgroup.

Few firm conclusions can be drawn from the data. The pooled subgroup analyses were not specified beforehand, and can therefore be viewed only as hypothesis-generating. Furthermore, the substantial number of analyses makes it likely that at least some results would be significant based on 95% confidence intervals.

Further evidence is needed to substantiate these observations; however, the low incidence of CHD in younger women is likely to preclude further randomised trials. Independent meta-analysis of the available data from all randomised controlled trials, stratified by age, may provide further information.

2.2.2 Observational studies

Group Health Cooperative (GHC) study[11]

This study tracked changes to the formula of standard postmenopausal oestrogen in a US health maintenance organisation (HMO), from CEE to esterified oestrogen (EE) and back again, to assess the effects of these different oestrogens on incident myocardial infarction and stroke (for stroke data, see section 3.3.2). All participants were postmenopausal and aged between 30 years and

79 years. Cases of myocardial infarction were identified by hospital diagnosis codes and death records. Controls were sampled at random from GHC and were matched by age, treated hypertension, and calendar year of identification. Cases were excluded if the myocardial infarction or stroke was a complication of a procedure or surgery.

Only current users of oestrogen were analysed in this study. Data for current smoking, angina, or systolic blood pressure was missing in only 1% of women. The mean age of cases and controls for myocardial infarction was 68 years.

A total of 1644 cases of myocardial infarction occurred within the designated period. Compared with non-use of hormones, there was little difference in the adjusted risk of myocardial infarction associated with the use of either CEE or EE, with or without progestogen. However, a suggestion of an increased risk of myocardial infarction was identified for high dose CEE (ie, >0·625 mg, odds ratio [OR] 2·22 [95% CI 0·82–5·97]) and for recent users of CEE (ie, use in <6 months, 2·33 [0·93–5·82]) compared with EE.

This study eliminates prescribing bias because the choice of oestrogen was guided by changes in formulary rather than patient characteristics. Furthermore, the main analyses were restricted to current users of CEE and EE to avoid potential biases of inclusion of ever-users of HRT. A lack of increase in risk of myocardial infarction for current use of CEE versus non-use is consistent with the WHI trial. In the UK, oestradiol is the most commonly used oestrogen.

Nurses Health Study[12]

Information on HRT use in this prospective cohort study was updated via a questionnaire every 2 years between 1976 and 2000. Classification of participants as current HRT users was based on the information given in the questionnaire before an event.

First cases of non-fatal myocardial infarction and fatal coronary disease were identified for the period of interest. Non-fatal myocardial infarctions were confirmed by hospital records. Deaths were reported by participants' families and the National Death Index. Follow-up was more than 98% complete.

Risk estimates adjusted only for age suggested a decrease in CHD events in users of oestrogen-only HRT (RR 0·57) and combined HRT (RR 0·49). Further adjustment for various cardiovascular variables increased these estimates to 0·71 (95% CI 0·61–0·83) and 0·68 (0·55–0·83), respectively.

Compared with non-users, CHD risk significantly decreased in women who started HRT within 4 years of menopause (table 2). In women who started HRT more than 10 years after menopause, no significant effect of HRT on CHD risk was observed. Inclusion or exclusion of women with pre-existing CHD (6% of participants) had no significant effect on risk.

Table 2: Effect of time since menopause at starting HRT on CHD risk (Nurses Health study)

Subgroup	Cases (n)	Adjusted RR (95% CI) versus non-use
Oestrogen only		
<4 years since menopause	116	0·66 (0·54-0·80)

>10 years since menopause	59	0·76 (0·57–1·00)
Oestrogen plus progestogen		
<4 years since menopause	78	0·72 (0·56–0·92)
>10 years since menopause	23	0·80 (0·53–1·23)

Significant results are highlighted in bold.

In all cases, the risks associated with oestrogen-only HRT were slightly lower than those associated with combined HRT.

No cardioprotective effect was observed in the subgroup of women that is demographically most similar to the CEE group of the WHI trial—ie, older than 60 years at starting HRT and including a low proportion with known CHD (RR 1·03 [0·65–1·64]). By contrast, in the subgroup that is aligned most closely to most observational studies (ie, women aged 50–59 years with no known CHD), significant cardioprotection was observed (RR = 0·51 [0·32–0·82]).

Sensitivity analyses suggested that any incomplete capture of early clinical events due to possible misclassification of current-users was unlikely to have substantially affected risk estimates. Prentice obtained similar results in comparisons of data from the WHI randomised controlled trial and the WHI observational study.[13,14]

The recognised limitations of observational studies for assessment of cardiovascular risks in HRT users have previously been used to explain the lower CHD risk recorded in observational studies compared with randomised controlled trials. In these analyses, the Nurses Health study investigators attempted to assess the effect of these limitations. While adjusting for all common potential confounding factors for CHD attenuated the observed cardioprotective effect, the researchers suggest that further adjustment for as-yet unidentified risk factors is unlikely to cause further attenuation. Therefore, confounding alone may not explain fully the differences between observational and randomised studies.

In the Nurses Health study, the greatest effect on risk estimates was obtained by restricting the women who were included in analyses: when limited to women who started HRT at older than 60 years, risk estimates for CHD were similar to those of the WHI trial; when restricted to women who started HRT before age 59 years, risk estimates were similar those of other observational studies.

These findings are suggestive of an effect of age at starting HRT on risk of NHD, but are inconclusive because of the small numbers of events in each subgroup.

2.2.3 Meta-analyses and reviews

Salpeter, 2006[15]

This study included randomised trials of at least 6 months' duration that compared HRT use with non-use or with placebo and that were published between 1966 and 2004. 23 trials with 39 049 participants and a mean trial duration of 4·9 years (range 0·5–10) met the inclusion criteria. CHD was measured as myocardial infarction or death from cardiac causes.

Overall, HRT had no effect on CHD events (OR 0·99 [95% CI 0·88–1·11]). In 12 trials of women with a mean age younger than 60 years at study baseline or who were less than 10 years since menopause, HRT significantly reduced CHD events (0·68 [0·48–0·96]). Analyses that were restricted to studies that included only younger women (about 70 000 women-years of exposure) showed a similar but non-significant observation (0·70 [0·49–1·0]). In 13 trials of women with a mean age older than 60 years at baseline or who were more than 10 years since menopause, HRT had no effect on CHD risk (1·03 [0·91–1·16])—a finding that changed little when analyses were restricted to studies that included only older women (1·08 [0·91–1·27]). When directly compared, risk of CHD in younger HRT users was significantly lower than in older women (0·66 [0·46–0·95]).

In the first year of treatment, HRT had no effect on CHD in younger women (0·22 [0·02–2·26]), but in older women it significantly increased incidence of CHD events (1·47 [1·12–1·92]). After 2 years, the risk in older women was significantly reduced (0·79 [0·67–0·93]), resulting in a neutral effect over time. There was a significant trend for increased numbers of events in early use followed by decreased numbers in later use (p=0·02). There was no evidence of heterogeneity in any of the analyses.

It is unclear what trials were included in this meta-analysis, and there are few details on their quality and endpoints. There are also few methodological details of the meta-analysis itself. The author states that limitations of the analyses include the wide range of study sizes, HRT formulations, and routes of administration, and the fact that in many trials CHD was not a primary outcome but was an adverse event. A further limitation is that age at starting HRT was defined according to the study average at baseline rather than the age of individual study participants.

Magliano, 2006[16]

This analysis included all trials that: were considered to be of 'high quality'; lasted at least 1 year; compared HRT with placebo; and measured so-called hard cardiovascular outcomes, including non-fatal acute myocardial infarction, stroke, death due to CHD, and all-cause mortality. Studies that assessed surrogate cardiovascular outcomes were specifically excluded.

Seven trials that included about 32 000 women met all inclusion criteria[i]. For oestrogen-only HRT and combined HRT, no significant difference in all-cause mortality over a 2–6·8-year treatment period was identified compared with placebo (RR 1·02 [95% CI 0·93–1·13]). Similarly, no significant difference in CHD death (0·99 [0·82–1·21]) or non-fatal acute myocardial infarction (1·00 [0·88–1·14]) due to HRT was observed.

Stratification according to the mean age of women younger or older than 65 years at study baseline had no effect on any outcome for CHD. Thus, the risk of non-fatal acute myocardial infarction in studies of women with a mean age younger than 65 years was 1·04 (0·79–1·38) compared with 0·94 (0·75–1·17) in studies of women with a mean age older than 65 years.

The relative strictness of Magliano's study-inclusion criteria means that only seven trials were included in the analyses.

[i] Estrogen Replacement and Atherosclerosis (ERA) trial; Estrogen in the Prevention of Re-Infarction Trial (ESPRIT); Heart and Estrogen Replacement Study (HERS); Women's Angiographic Vitamin and Estrogen (WAVE); Women's Estrogen for Stroke Trial (WEST); Women's Health Initiative (WHI)—CEE and CEE medoxyprogesterone groups.

No difference in CHD risk was observed in women older or younger than age 65 years, although analyses were again based on mean age at study baseline rather than individual age. The threshold for investigation of the effect of age at starting HRT on CHD risk was older, at 65 years, and thus the WHI trial (mean age of participants 63 years) was considered as a trial in younger women.

2.3 Discussion—CHD

Randomised controlled trials versus observational studies

In general, randomised controlled trials have found no cardioprotective effect for HRT. In the HERS[1] and WHI[2] trials, a slight increase in risk was observed with early use of CEE and medroxyprogesterone. By contrast, observational studies have historically observed a protective effect of HRT on CHD.[17]

For study of cardiovascular outcomes, observational studies may be subject to certain systematic biases that make direct comparison of their results with those from randomised controlled trials difficult. Recent analyses of the Nurses Health study that have attempted to correct for these limitations have shown that such biases may be partly responsible for the observed differences.[12]

Another key difference between these two study types is the participants. Observational studies include mostly women who are around the time of their menopause, whereas many of the women who participate in randomised controlled trials that have cardiovascular endpoints are at least 10 years' postmenopause to increase the power of the trial.

Age at initiating HRT

On the basis of recent re-analyses, there is growing speculation that exogenous oestrogens may have a different effect on CHD risk according to the age or time since menopause at which HRT is started. While there is now little doubt that HRT increases CHD risk in older women, there are currently insufficient data to draw conclusions about its effect in younger women.

There is also no direct scientific evidence to support a differential effect of HRT on CHD with age, but exogenous oestrogen has been proposed to trigger acute events in the presence of pre-existing advanced atherosclerotic lesions (through its procoagulant and inflammatory mechanisms) and slow the early stages of atherosclerosis in women with no pre-existing disease (through its beneficial effects on endothelial function and blood lipids). According to this theory, a woman's underlying atherosclerotic state, which generally depends on her age, dictates what effect HRT has on her risk of having a coronary event.

2.4 Conclusion

At present, there are only limited data about the effect of HRT on CHD risk in younger women. However, even if the relative risk of CHD that has been identified in randomised controlled trials in older women was the same in younger women, the much lower baseline risk of these events in healthy younger women means that their overall risk of CHD is very low.

It is unlikely that observational studies for cardiovascular endpoints will ever be completely free from bias, or that randomised controlled trials will be large enough to give significant results in younger women. Independent meta-analysis of all existing data from randomised controlled trials with

stratification by age of individual participants may be the only way to obtain more robust data about the risk of CHD due to HRT in younger users.

Every woman's risk of CHD should be assessed carefully before starting HRT, irrespective of age.

3. Stroke

3.1 Key data previously assessed by the Group

Estimated risk of ischaemic and haemorrhagic stroke for the CEE plus medroxyprogesterone group of the WHI trial was HR 1·31 (95% CI 1·02–1·68) compared with non-use; ischaemic stroke accounted for 80% of all cases.[18]

Preliminary results from the oestrogen-only group of the WHI trial showed that the risk of stroke in users of CEE alone was broadly similar to the risk for CEE plus medroxyprogesterone (HR 1·39 [95% CI 1·10–1·77]).[5]

A systematic review of 28 randomised controlled trials that compared stroke events in HRT users with controls[19] identified a significantly increased risk of stroke for HRT users (OR 1·29 [1·13–1·47]). About 88% of strokes were ischaemic in origin.

3.2 New evidence

3.2.1 Randomised controlled trials

WHI trial—final results of CEE only arm[20]

During the 7·1 years of follow-up, 168 strokes occurred in the CEE group versus 127 in the placebo group (HR by intention-to-treat analyses 1·37 [95% CI 1·09–1·73]) for all strokes. Risk of ischaemic stroke (1·55 [1·19–2·01], 80% of all strokes) was greater than risk of haemorrhagic stroke (0·64 [0·35–1.18], 15% of all strokes). On adjustment for treatment adherence, risk of ischaemic stroke increased to 1·93 [1·34–2·78]). No significant differences in the distribution of stroke subtypes or severity, including fatal strokes, were observed between the CEE and placebo groups.

Risk of ischaemic stroke was lower in women with a previous history of cardiovascular disease (HR 1·01 [95% CI 0·58–1·75]) compared with those without (1·73 [1·28–2·33], p=0·09 for comparison), but was not affected by the increased blood pressure that occurred in CEE users throughout the trial, by the differential use of statins throughout the study, or by use of aspirin. Furthermore, stroke risk was independent of the severity of vasomotor symptoms or previous hormone use.

These data confirm a significant increase in risk of ischaemic stroke in postmenopausal women, which seems to be independent of age or time since menopause at starting treatment.

Rossouw and colleagues, 2007[10]

Stroke data from both arms of the WHI trial were combined to assess the effect of age and time since menopause at starting HRT on risk of stroke.

Age or time since menopause at starting therapy did not affect stroke risk (table 3).

Table 3: Effect of CEE and CEE plus medroxyprogesterone on CHD by age and time since menopause at starting (WHI trial)

AGE (years)								
50–59			60-69			70–79		
HRT (n cases)	Placebo (n cases)	HR (95% CI)	HRT (n cases)	Placebo (n cases)	HR (95% CI)	HRT (n cases)	Placebo (n cases)	HR (95% CI)
44	37	1·13 (0·73–1·76)	156	102	1·50 (1·17–1·92)	127	100	1·21 (0·93–1·58)
TIME SINCE MENOPAUSE (years)								
Less than 10			10-19			At least 20		
HRT (n cases)	Placebo (n cases)	HR (95% CI)	HRT (n cases)	Placebo (n cases)	HR (95% CI)	HRT (n cases)	Placebo (n cases)	HR (95% CI)
41	23	1·77 (1·05–2·98)	100	79	1·23 (0·92–1·66)	142	113	1·26 (0·98–1·62)

3.2.2 Observational studies

Group Health Cooperative (GHC) study[11]

See section 2.2.2 for study design and methods.

1080 cases of stroke occurred within the designated study periods. Mean age of cases and controls was 70 years for ischaemic stroke and 67 years for haemorrhagic stroke.

Compared with non-use of HRT, there was little difference in the adjusted risk of ischaemic or haemorrhagic stroke associated with the use of either CEE or EE.

Risk of stroke did not differ between current use of CEE and current use of EE (both with or without added progestogen). However, subgroup analyses found a non-significant increase in risk of ischaemic stroke in users of CEE alone (OR 1·57 [95% CI 0·98–2·53]) and high-dose CEE (2·59 [0·83–8·07]) compared with EE. Recency of starting hormone use had no detectable effect on stroke risk.

The finding of no increased risk of stroke for current use of CEE versus non-use is inconsistent with findings from the WHI study. A significant proportion of women in this study may have been existing HRT users: cardiovascular risk may be highest in early HRT use and thus early adverse effects may have been missed or susceptible women may have had an event associated with the first type of oestrogen they used and were therefore unlikely to have another on switching. Neither of these types of oestrogen are used commonly in the UK.

Nurses Health study, unpublished data, 2007

Data presented at the 5th Amsterdam Menopause Symposium in June, 2007, suggested that age at starting HRT had no effect on risk of stroke, which remained consistently elevated in all age subgroups. This finding is consistent with that of the WHI trial.

3.3 Conclusions

Most randomised controlled trials and observational studies have identified an increased risk of stroke in HRT users. Evidence suggests that risk is similar for both oestrogen-only HRT and combined HRT, and is independent of age at starting HRT. Available data suggest that risk may be limited to ischaemic stroke, but data for haemorrhagic strokes are limited and therefore less robust.

There is some suggestion for increased stroke risk with increasing dose of oestrogen. However, the numbers of women were small and no firm conclusions can be made.

4. Venous thromboembolism

4.1 Key data previously considered by the Group

In 1996, several observational studies suggested that HRT users have a risk of venous thromboembolism (VTE) that is 2–3 times that of non-users.[21–23] The HERS[1] and WHI trials[2] subsequently confirmed the magnitude of this risk, but showed that the absolute risks are higher than previously estimated due to a higher baseline incidence for postmenopausal women. The risk of VTE is greatest in the first year of HRT use.

Preliminary results from the oestrogen-only arm of the WHI trial identified a non-statistically significant increased risk of VTE in women assigned to CEE (HR 1·33 [95% CI 0·99–1·79]). Risk of deep vein thrombosis (DVT) was significant (1·47 [1·04–2·08]).[5]

Final results from the CEE plus medroxyprogesterone arm of the WHI trial confirmed a doubling of VTE risk (HR 2·06 [1·57–2·70]).[24]

Two case-control studies have assessed the effect of route of HRT administration and oestrogen type on the risk of VTE, but neither provide sufficiently robust data to draw firm conclusions.[25,26] Several other studies have analysed the effect of different doses and types of oestrogens or progestogens, or route of administration, but in most cases this was by post hoc analysis of data not specifically gathered for this purpose.[21–23,26]

4.2 New evidence

4.2.1 Randomised controlled trials

WHI trial—final results of CEE-only group[27]

Consistent with preliminary findings, CEE increased the risk of VTE versus placebo (HR 1·32 [95% CI 0·99–1·75]), which was significant only for deep vein thrombosis (1·47 [1·06–2·06]).

Previous venous thrombosis, increasing age, and body mass index (BMI) did not significantly affect VTE risk due to HRT. Kaplan Meier plots show that the risk of venous thrombosis increased during the first 2 years of treatment and remained relatively constant thereafter. Factor V Leiden and past use of CEE did not seem to have a synergistic effect on VTE risk.

These data confirm a significant increase in risk of DVT and a non-significant increase in risk of VTE. The researchers suggest that poor compliance in the WHI trial may have resulted in an

underestimation of the true effect of CEE and CEE plus medroxyprogesterone on VTE. Because compliance was equally poor in both groups of the trial, the difference in risk observed between the CEE group (HR 1·32) and the CEE plus medroxyprogesterone group (HR 2·06) remains valid.

4.2.2 Observational data

ESTHER study—final results[28]

The EStrogen and THromboEmbolism Risk (ESTHER) study previously found a higher risk of VTE in users of oral oestrogen compared with users of transdermal oestrogen (OR 4·0 [95% CI 1·9–8·3]).[26] Final results from this French multicentre case-control study in postmenopausal women aged 45–70 years include a further 104 cases of first-documented, medically confirmed idiopathic VTE (total number of participants=271). Patients were excluded if they reported personal history of VTE, a contraindication for HRT, a predisposing factor for VTE, a referral for oestrogen advice, or known thrombophilia. Women were interviewed by questionnaire and classified as current HRT users if they had used oestrogen at any time in the 3 months before the index date.

Cases were more likely to have a higher BMI, older age at menopause, family history of VTE, and varicose veins than were controls, and thus crude ORs were adjusted for these factors.

Most women in this study used transdermal HRT (29%) compared with oral (10%), and most used 17β oestradiol. Users of transdermal oestrogens tended to be older and had used HRT for longer than had users of oral oestrogens. Adjusted risk estimates confirm the previous finding of an increased risk of VTE associated with oral HRT, but not with transdermal HRT (table 4).

Table 4: Risk of VTE by route of administration and progestogen type

HRT type	Cases (n=259)	Controls (n=603)	Adjusted OR (95% CI)
Non-use	146	384	1
Route of administration			
Oral oestrogen	45	39	4·0 (1·6–10·1)
Transdermal oestrogen	67	180	0·8 (0·4–1·8)
Type of progestogen			
Micronised progesterone	19	63	0·9 (0·4–2·2)
Pregnane derivatives*	39	79	0·9 (0·4–2·2)
Nor-pregnane derivatives†	40	37	4·0 (1·7–9·4)

*Dydrogesterone, medrogestone, chlormadinone, cyproterone, medroxyprogesterone. †Normegestrol, promegestrone.

Products that contain nor-pregnane derivatives (see table footnotes) were associated with a significant increase in VTE risk compared with micronised progesterone and pregnane derivatives, which had no effect on risk.

Analyses stratified by dose of oestrogen and duration of exposure or analyses restricted to women who used the most common doses found that these did not significantly affect results. There was no interaction between oestrogens by route of administration and progestogen type.

This study suggests a lower risk of VTE associated with transdermal HRT compared with oral HRT. However, based on the upper 95% CI, a 1·8-times increased risk of VTE in transdermal HRT users cannot be excluded.

Several key factors differed between transdermal users and oral users, including older age and longer use associated with transdermal HRT compared with oral HRT, which may reflect differential prescribing decisions for women who have different baseline risks for VTE. However, older women would be expected to have a higher, not lower, baseline risk of VTE.

In the UK the testosterone-derived progestogens norethisterone and levonorgestrel are most commonly used.

4.3 Conclusions

Randomised controlled trials and observational studies have identified an elevated risk of VTE that is greatest in early HRT use. In most studies, the risk is lower in users of oestrogen-only HRT compared with combined HRT. There are limited data to suggest that transdermal administration is associated with a lower VTE risk than the oral route.

5. Breast cancer

5.1 Key data previously considered by the Group

Re-analysis of data from 51 studies[29] identified a small increased risk of breast cancer in users of mainly oestrogen-only HRT. The increase was related to the duration of HRT use and disappeared within about 5 years of stopping treatment.

The WHI study showed that 0·625 mg CEE plus 2·5 mg medroxyprogesterone significantly increased the incidence of breast cancer compared with placebo in a duration-dependent way within 3 years of starting (frequency of breast cancer was lower in the treatment group than in the placebo group for the first 2–3 years of treatment and higher thereafter).[30] The frequency of abnormal mammograms that needed medical evaluation increased after 1 year of therapy.

The type of cancers that were diagnosed was similar in the CEE plus medroxyprogesterone group and placebo group, but invasive tumours were slightly larger in size in the CEE plus medroxyprogesterone group and were diagnosed at a significantly more advanced stage than in the placebo group. It is possible, although not proven, that this occurrence may be related to the effect of combined HRT on mammographic density.

Subgroup analyses found that the risk increase seemed to be related to cumulative HRT use. Thus, women with no past use of HRT had a lower risk (HR 1·09) compared with those who had up to 5 years' (HR 1·70) and more than 5 years' (HR 2·27) previous use. The effect of cumulative exposure was not significant (p=0·15).

The Million Women Study subsequently confirmed a small increase in risk associated with current use of oestrogen-only HRT (RR 1·30), but found that the risk associated with combined HRT was substantially higher than previously thought (RR 2·00).[31]

5.2 New evidence

5.2.1 Randomised controlled trial data

WHI trial—final results of CEE arm [32]

All women had baseline mammograms and clinical breast examinations to exclude breast abnormalities, which were repeated yearly after enrolment. Before enrolment, 52% of women had never taken HRT, less than 5% had taken combined HRT, and about 43% had previously used oestrogen-only HRT. Previous HRT users differed from never-users in several ways, but there was no significant difference by treatment assignment. By the end of the study, 54% of women had stopped taking their study medication, but discontinuation frequency was similar between treatment groups.

At study end, 237 invasive breast cancers and 55 in-situ centrally adjudicated breast cancers had been reported.

CEE non-significantly reduced the risk of invasive breast cancer (HR 0·80 [0·62–1·04]) in intention-to-treat analyses. When adjusted for non-adherence to treatment, the reduction in risk became significant (HR 0·67 [0·47–0·97]).

Past use of oestrogen-only HRT for more than 5 years had no significant effect on breast-cancer risk (HR 1·28 [0·73–2·24]), but in women who had previously used combined HRT the risk was nominally significant (2·35 [0·60–9·14], p=0·05).

Invasive breast cancers diagnosed in women who received CEE were larger (mean size 1·8 cm) than in those who received placebo (mean size 1·5 cm) and a higher proportion were lymph-node positive. In subgroup analyses, significant reductions in risk of ductal, but not lobular, tumours were observed.

From the second year of treatment, the frequency of abnormal mammograms that needed follow-up was substantially higher in the CEE group than in the placebo group (36% *vs* 28% over study course). By the second year, more women who received CEE needed breast biopsies compared with placebo, and by study end 198 more biopsies without a subsequent cancer diagnosis had been taken from CEE users compared with placebo.

The finding of a possible reduction in risk of breast cancer in CEE users is difficult to explain in view of: preclinical observations; the findings of many other studies; and the rationale for use of anti-oestrogens or oestrogen-receptor antagonists for the treatment of breast cancer. In women who had previously used oestrogen-only HRT for 5 years or more, no reduction in risk was observed. A clinically significant effect on biopsy requirement was observed in CEE users.

WHI mammography study—CEE plus medroxyprogesterone[33]

In the CEE plus medroxyprogesterone arm of the WHI trial, 413 women randomly assigned active therapy and 211 women randomly assigned placebo took part in a 2-year ancillary mammography study, in which all mammograms were digitalised to calculate the proportion of density. After 1 year of treatment, mean mammographic density increased by 6% in users of CEE plus medroxyprogesterone and reduced by 0·9% in the placebo group. 75% of users of CEE plus medroxyprogesterone had increased mammographic density. The effect of active treatment continued into the second year, but was not progressive. The greatest increase in density occurred in older women (ie, age 70–79 years) and in those with the lowest baseline densities.

After 1 year of follow-up, women who received CEE plus medroxyprogesterone were four times more likely than those who received placebo to have an abnormal mammogram—a finding that could not be explained by the increase in mammogram density alone. Too few cases of breast cancer occurred to assess the relation between breast cancer and mammographic density.

WHI trial—re-analysis of CEE arm[34]

Further data evaluation confirmed that the observed increase in breast-cancer risk in users of CEE plus medroxyprogesterone was restricted to women who had previously used exogenous hormones (even after adjustment of HR for differences in baseline characteristics between those with and without previous hormone exposure: adjusted HR 1·96 [95% CI 1·17–3·27] for past users compared with 1·02 [0·77–1·36]) for naive users; p=0·03). Kaplan-Meier estimates of cumulative incidence over time showed that women with no past hormone use who took CEE plus medroxyprogesterone had a lower incidence of breast cancer than those who took placebo for the first 5 years, but a higher incidence thereafter. In women with previous hormone exposure the incidence of breast cancer in the CEE plus medroxyprogesterone group was higher than placebo after 3 years. No interaction was observed with duration or recency of past hormone use. The increase in abnormal mammograms was not affected by past use of hormones.

The effect of past hormone use in this study is consistent with the idea that longer exposure to hormones increases breast-cancer risk. However, data are currently insufficient to estimate how long HRT can be taken before risk starts to increase. Consistent with other studies, Kaplan Meier plots for women with no previous hormone use support a lag-time between starting HRT and increasing risk of breast-cancer diagnosis. Further follow-up of women in both groups of the WHI trial is ongoing and should provide more information about the long-term effects of CEE and CEE plus medroxyprogesterone in women with and without past exposure.

5.2.2 Observational studies

Million Women Study[34]

This study incorporates another year's follow-up information from the Million Women investigators, and it assesses the effect of HRT on histological type of cancer. Information about current and past use of HRT, type of HRT preparation last used, and total duration of use were updated, where possible, with information from a follow-up questionnaire that was mailed to all participants about

3 years after recruitment. For current users of HRT, duration of current use at the time of diagnosis of breast cancer was estimated from the duration of current use reported at the time of last contact plus the time to diagnosis—ie, the expectation was that women remained on HRT after completing their questionnaire.

Compared with the previous analysis,[31] a further 688 cases of breast cancer were diagnosed in current users of oestrogen-only HRT (total cases=1679) and a further 1498 cases were diagnosed in current users of combined HRT (total cases=3432). The risk estimates for breast cancer with both types of HRT were marginally increased compared with previous estimates at 1·32 (95% CI 1·24–1·39) for oestrogen-only HRT and 2·14 (2·04–2·24) for combined HRT.

The risk of having an invasive lobular or tubular cancer diagnosed was higher than the risk for diagnosis of ductal cancers in users of both types of HRT.

The risks recorded in the Million Women Study remain markedly higher than the overall risks estimated in the WHI trial.[30,32] However, in women with more than 5 years of previous hormone use in the CEE plus medroxyprogesterone group of the WHI trial a similar 2-times increased risk was noted (HR 2·27). Several European studies[36-38] have identified a higher risk of breast cancer than that have North American studies,[39,40] which may be related to the progestogens used. The observation of less effect of HRT on breast-cancer risk with increasing BMI suggests that the greater proportion of obese women in the WHI trial compared with the Million Women Study (45% *vs* 18%, respectively) may also account for the discrepancy.[31]

The Million Women Study has previously been criticised for classifying current users on the basis of a questionnaire that had been completed up to 3 years before diagnosis. This updated analysis assessed the pattern of HRT use in current users who did not develop breast cancer but who completed a follow-up questionnaire. In the 38% of women with follow-up information, 84% reported no change in their HRT use since the last questionnaire; an estimated 7% of oestrogen-only HRT users and 9% of combined HRT users stopped therapy (ie, ceased to be current users every year). The researchers consider that this degree of misclassification is unlikely to have significantly affected overall results.

5.2.3 Meta-analysis by Shah and colleagues, 2005[41]

Shah and colleagues included observational or interventional studies if they had: a comparator group; longitudinal ascertainment of exposure to HRT and disease; reported frequencies in never HRT users and current users and if they differentiated between use of oestrogens for oral contraception or hormone replacement. Results from observational studies and randomised trials were assessed separately because of their different potentials for bias and, where possible, adjusted estimates were used. Publication bias was assessed. Studies done in the 1970s or earlier were presumed to have exposed women to oestrogen-only therapy unless stated otherwise. All studies other than the Million Women Study were done in the USA.

Eight cohort and five case-control studies that fulfilled the criteria investigated the effect of oestrogen-only therapy on breast-cancer risk (n=701 160). A small but significant increase in risk was observed (OR 1·16 [95% CI 1·06–1·28]), which was unaffected by duration of use. The WHI

study was the only randomised trial of oestrogen-only HRT that met all inclusion criteria (HR 0·80 [0·62–1·04]).

For combined HRT, the findings from four cohort and four case-control studies (n=655 559) gave a pooled OR of 1·39 (95% CI 1·13–1·72). Assessment of heterogeneity showed that the type of progestogen (medroxyprogesterone *vs* other), study location (Europe *vs* USA), and study size had a relation with the OR, and thus the risk was recalculated in the absence of data from the Million Women Study. The revised OR was 1·32 (1·19–1·46). The risk associated with less than 5 years' HRT use was 1·35 (1·16–1·57) and increased to 1·63 (1·22–2·18) with more than 5 years' use. The HERS[1] (HR 1·30 [0·77–2·19]) and WHI[2] studies (HR 1·26 [0·83–1·92]) were the only randomised controlled trials of combined HRT to meet all inclusion criteria.

Meta-analysis of observational studies shows a higher risk of breast cancer for combined HRT compared with oestrogen-only HRT.

5.3 Conclusions

Most studies show a greater increase in the risk of breast cancer for combined HRT than for oestrogen-only HRT. The risk due to HRT increases with duration of use and returns to baseline within a few years of stopping. European studies have generally identified a higher risk of breast cancer than have North American studies, which may be due to the type of progestogen in combined HRT products or the higher level of obesity in the USA, or both.

By contrast with most data, the WHI trial found a non-significant reduction in breast-cancer risk in the CEE-only group.

HRT, particularly combined HRT, increases mammographic density. CEE and CEE plus medroxyprogesterone increase the risk of having an abnormal mammogram.

6. Endometrial cancer

6.1 Key data previously considered by the Group

Increased risk of endometrial hyperplasia and carcinoma with prolonged use of unopposed oestrogen-replacement therapy is well established. Unopposed oestrogen treatment adversely affects the endometrium in a dose-dependent and duration-dependent way.[42–44] Addition of progestogens reduces, but may not necessarily eliminate, this risk.[45,46]

In 2005, the Million Women Study found that addition of a progestogen to oestrogen for 10 days or more every month effectively removed the risk to the endometrium (RR 1·05 [95% CI 0·91–1·22])[47] This study also found that addition of a progestogen to oestrogen on a daily basis reduced the risk to the endometrium compared with never-use of HRT (0·71 [0·56–0·90]).

6.2 New evidence

6.2.1 Observational data

Strom and colleagues, 2006[48]

A population-based case-control study of 511 cases and 1412 controls in the USA found no difference in the risk of endometrial cancer in users of sequential combined HRT, with progestogen added for between 5 days and 14 days per cycle, compared with no HRT use (adjusted OR 0·9 [95% CI 0·4–2·0]), and found a non-significant risk reduction in users of continuous combined HRT with progestogen added daily (0·7 [0·5–1·0]). The use of unopposed oestrogens was a significant risk factor for endometrial cancer (adjusted OR for more than 3 years' use 3·4 [1·4–8·3]), particularly in those with lower BMI.

Previous studies have shown that progestogen needs to be added for at least 10 days per cycle to fully oppose the effect of oestrogens on the endometrium.[45] Because most combination products add progestogen for 10 days or more per cycle and prescribing guidelines recommend this practice, it is likely that the number of women who report fewer than 10 days of use is a very small proportion of the study population.

US National Institutes of Health-AARP Diet and Health Study[49]

This US cohort study of 433 incident endometrial cancers in 51 312 women found that 5 or more years' use of sequential HRT (10–14 days of progestogen per cycle) or continuous combined HRT did not increase the risk of endometrial cancer (RR 0·79 [95% CI 0·38–1·66] and 0·85 [0·53–1·36], respectively).

6.3 Conclusions

Addition of progestogen for at least 10 days per cycle reduces, but may not completely eliminate, the increased incidence of endometrial cancer caused by unopposed oestrogens. Combined continuous HRT does not increase the risk of endometrial cancer, and there is some evidence that it may slightly reduce the risk relative to non-HRT users.

7. Ovarian cancer

7.1 Key data previously considered by the Group

Epidemiological studies have shown that long-term (ie, at least 5–10 years') use of oestrogen-only HRT in women who have had a hysterectomy is associated with an increased risk of ovarian cancer.[50-54]

7.2 New evidence

7.2.1 Observational data

Million Women Study[55]

The effect of HRT on incident and fatal ovarian cancer has been assessed in 948 576 postmenopausal women. A third of women were current users of HRT at the time of last contact,

and a further 20% were past users. Women whose hysterectomy status was unknown were excluded from analyses, as were those with bilateral oophorectomy. All analyses were stratified by age and previous hysterectomy status reported at baseline, and were adjusted for several risk factors. Information on HRT use was taken either from the baseline questionnaire or the follow-up questionnaire, which was available for two-thirds of women who returned it. Current users were classified by duration of use last reported and type of HRT; past users were classified by time since last use and duration of use. Sensitivity analyses examined the effect of a lack of updated information about HRT use on the results.

After an average of 5·3 years of follow-up, 740 incident ovarian cancers were reported in current HRT users compared with 1142 in never-users (RR 1·20 [95% CI 1·09–1·32]). Risk of ovarian cancer did not differ significantly between women who used oestrogen-only or combined HRT preparations. In all cases, risk was raised only in women who used HRT for more than 5 years. The estimated duration of use of HRT by current users at diagnosis was 7·7 years. No significant differences in risk were observed between different oestrogens and progestogens, oral and transdermal preparations, or between combined products given sequentially or continuously. Sensitivity analyses to examine the effect of potential misclassification of HRT user status yielded little difference in risk estimates in current users. Past use of HRT was not associated with an increased risk of ovarian cancer (RR 0·98 [95% CI 0·88–1·11).

Most tumours were epithelial, of which a significantly higher proportion were serous (RR 1·53 [1·31–1·79]).

The likelihood of dying from ovarian cancer was slightly increased in current HRT users (RR 1·23 [1·09–1·38] compared with never-users; 497 deaths in current users over an average 6·9 years' follow-up). Risk did not differ between different HRT preparations.

Standardised rates of incident cancer and fatal cancer are 2·2 (95% CI 2·1–2·3) and 1·3 (1·2–1·4), respectively, per 1000 never-users of HRT over 5 years. This compares with rates of 2·6 (2·4–2·9) and 1·6 (1·4–1·8) for incident and fatal ovarian cancer per 1000 current HRT users of HRT over 5 years.

5 years' use of HRT may therefore cause one extra case of ovarian cancer in every 2500 users, and one extra death from ovarian cancer in every 3300 users.

Nurses Health Study[56]

This prospective observational study of 89 905 postmenopausal women had a follow-up rate of 93·7% of potential women-years between 1976 and 2002. 389 incident ovarian cancers were reported for 966 017 women-years of follow-up, including 134 epithelial cancers in 16 831 current HRT users.

Neither current nor past use of HRT had a significant effect on the risk of all ovarian cancers (RR 1·24 [95% CI 0·97–1·59] and 1·00 [0·77–1·31], respectively), but current use significantly increased the risk of serous tumours (1·43 [1·04–1·96]) compared with never use.

Stratification of all tumours by duration of HRT use identified a higher risk in current users (1·41 [1·07–1·86]) or those who had previously used HRT for more than 5 years (1·52 [1·01–2·27]). Subanalyses in past users showed that the increase in risk due to HRT fell with increasing time

since last use (ie, >3 years) and with shorter duration of use (ie, <5 years); however, numbers of participants for these analyses were small.

Exclusive use of unopposed oestrogens for 5 years or more was associated with a significantly increased risk (RR 2·04 [95% CI 1·41–2·97]). Too few cases occurred in exclusive long-term users of combined HRT to enable statistical analyses.

7.3 Conclusions

Long-term use of HRT is associated with a small increased risk of ovarian cancer, particularly epithelial serous tumours. Risk is similar for oestrogen-only and combined HRT.

Risk of ovarian cancer falls with increasing time since stopping HRT, and with shorter duration of use.

A meta-analysis of nine recent studies that compared current use versus never use showed an overall significant 1·3-times increase in risk (95% CI 1·20–1·36).[55]

8. Prevention of osteoporosis

The incidence of hip fractures in women younger than age 60 years is very low. It does not increase significantly until age 70 years, and peaks in over those older than age 85 years. If women stop using HRT by the time they reach age 60 years, its effect on bone density will wear off within a few years and is unlikely to provide benefit when most needed. If HRT is continued beyond age 60 years for the sole purpose of preventing osteoporosis, many women will likely be exposed to an unacceptable level of risk due to marked increase in baseline risk of cardiovascular events and the increasing risk of breast cancer and ovarian cancer with long-term HRT use.

The current second line indication of HRT for prevention of osteoporosis in women at high risk of future fractures who are unable to use other medicines approved for this purpose remains appropriate.

9. Benefit-risk balance of HRT

A crude estimate of the overall balance of risks and benefits for HRT has been calculated by adding the number of extra cases of breast cancer, endometrial cancer, ovarian cancer, stroke, CHD, and VTE caused by HRT, and subtracting the number of fractures and colorectal cancers prevented by HRT in 1000 women aged between 50–59 years and 60–69 years over 5 years and 10 years of use (tables 6–10). Calculations are based on risk estimates from meta-analyses of published data (for Forrest plots of these data, see Annex) and compared with placebo or non-HRT use (table 5).

Table 5: Risks and benefits of HRT

Age range (yrs)	Time (yrs)	Background incidence per 1000 women in Europe*	Oestrogen-only HRT		Oestrogen-progestogen HRT	
			Additional cases per 1000 HRT users†	Risk ratio (95% CI)‡	Additional cases per 1000 HRT users†	Risk ratio (95% CI)‡
CANCER RISK						
Breast						
50–59	5	10	2 (1–4)	1·2 (1·1–1·4)	6 (5–7)	1·6 (1·5–1·7)
60–69	5	15	3 (2–6)		9 (8–11)	
50–59	10	20	6 (4–10)	1·3 (1·2–1·5)	24 (20–28)	2·2 (2·0–2.4)
60–69	10	30	9 (6–15)		36 (30–42)	
Endometrial						
50–59	5	2	4 (3–5)	3·0 (2·5–3·6)	NS	1·0 (0·8–1·2)§
60–69	5	3	6 (5–8)		NS	
50–59	10	4	32 (21–48)	9·0 (6·3–12·9)	NS	1·1 (0·9–1·2)§
60–69	10	6	48 (32–71)		NS	
Ovarian						
50–59	5	2	<1	1·1 (1·0–1·3)	<1	1·1 (1·0–1·3)
60–69	5	3	<1		<1	
50–59	10	4	1 (1–2)	1·3 (1·1–1·5)	1 (1–2)	1·3 (1·1–1·5)
60–69	10	6	2 (1–3)		2 (1–3)	
CARDIOVASCULAR RISK						
Venous thromboembolism (VTE)						
50–59	5	5	2 (0–4)	1·3 (1·0–1·7)	7 (5–10)	2·3 (1·8–3·0)
60–69	5	8	2 (0–6)		10 (7–16)	
50–59	10$	10	3 (0-7)	1·3 (1·0–1·7)	13 (8-20)	2·3 (1·8–3·0)
60–69	10	16	5 (0-11)		21 (13-32)	
Stroke						
50–59	5	4	1 (1–2)	1·3 (1·1– 1·4)	1 (1–2)	1·3 (1·1– 1·4)
60–69	5	9	3 (1–4)		3 (1–4)	
50–59	10$	8	2 (1-3)	1·3 (1·1– 1·4)	2 (1-3)	1·3 (1·1– 1·4)
60–69	10	18	5 (2-7)		5 (2-7)	
Coronary Heart Disease (CHD)						
		Oestrogen‖	**O+P‖**			
50–59	5	14	9	NS	0·6 (0·4–1·1)	NS	1·3 (0·8–2·1)
60–69	5	31	18	NS	0·9 (0·7–1·2)	NS	1·0 (0·7–1·4)
70–79	5	44	29	NS	1·1 (0·8–1·5)	15 (1–32)	1·5 (1·0–2·1)
50–59	10$	28	18	NS	0·6 (0·4–1·1)	NS	1·3 (0·8–2·1)
60–69	10	62	36	NS	0·9 (0·7–1·2)	NS	1·0 (0·7–1·4)
70–79	10	88	58	NS	1·1 (0·8–1·5)	29 (0-64)	1·5 (1·0–2·1)
BENEFITS¶						
Colorectal cancer						
		Oestrogen‖	**O+P‖**			
50–59	5	6	3	NS	0·9 (0·7–1·1)	NS	0·9 (0·7–1·1)
60–69	5	10	8	NS		NS	
50–59	10	12	6	NS	0·9 (0·7–1·1)	NS	0·9 (0·7–1·1
60–69	10	20	16	NS		NS	
Fracture of femur						
		Oestrogen‖	**O+P‖**			
50–59	5	0·5	1·5	0 (0–0)	0·6 (0·4–0·9)	NS	0·7 (0·5–1·0)
60–69	5	5·5	5·5	–2 (–3 to –1)		NS	
50–59	10	1.0	3	0 (–1 to 0)	0·6 (0·4–0·9)	NS	0·7 (0·5–1·0)
60–69	10	11	11	–4 (–7 to –1)		NS	

*Background incidence from: Hospital Admissions in England (HES) for stroke and VTE; WHI trial for CHD; the International Agency for Research on Cancer (IARC) for ovarian cancer and endometrial cancer; and from never-users in the Million Women Study for breast

cancer. †Best estimate and range based on relative risk and 95% CI. ‡Risk ratios and 95% CI from: meta-analyses of randomised controlled trials (RCTs) for stroke; meta-analyses of RCTs and observational studies for VTE, endometrial cancer, and ovarian cancer; meta-analysis of RCTs and observational studies in Europe only for breast cancer; and from Women's Health Initiative (WHI) trial for CHD. §Progestogen added for 10 days or more per 28-day cycle. $ Assumes the relative risk for cardiovascular events due to HRT remains constant over time ||Estimates from placebo groups of CEE and CEE plus medroxyprogesterone arms of WHI trial.[2] ¶Menopausal symptom relief is not included in this table, but is a key benefit of HRT and will play a major part in the decision to prescribe HRT. NS=non-significant difference. O+P=oestrogen-progestogen.

A key drawback of this approach is that the benefits of vasomotor symptom relief—the main indication for HRT—are difficult to quantify and have been not taken into consideration. Because the efficacy of oestrogen-only HRT and combined HRT in relief of vasomotor symptoms is similar, however, the safety profile of these two types of HRT can justifiably be compared.

Although not recommended in practice, the risks and benefits associated with use of oestrogen-only HRT in women with a uterus have been included for completeness:

Table 6: Comparison of overall balance of benefits and risks associated with oestrogen-only and combined HRT in different prescribing scenarios

i) 5 years' HRT use in women younger than age 60 years

Type of HRT	Baseline risk per 1000 women*	Absolute risk in 1000 HRT users†	Attributable risk in 1000 HRT users‡
Oestrogen-only (women without uterus)	42	47 (44–52)	5 (2–10)
Oestrogen-only (women with uterus)	44	53 (49–59)	9 (5–15)
Combined HRT	37	51 (48–56)	14 (11–19)

*Obtained by adding the baseline rates for breast cancer, endometrial cancer (in women with a uterus), ovarian cancer, colorectal cancer, venous thromboembolism, CHD, stroke and fracture of femur in non-HRT users. †Obtained by subtracting the number of cases of colorectal cancer and fracture prevented from the total number of cases of breast cancer, endometrial cancer (in women with a uterus), ovarian cancer, venous thromboembolism, CHD, stroke in HRT users. ‡ Obtained by subtracting the baseline risk in non-HRT users from the absolute risk in HRT users.

ii) 5 years' use in women aged 60–69 years

Type of HRT	Baseline risk per 1000 women	Absolute risk in 1000 HRT users	Attributable risk in 1000 HRT users
Oestrogen-only (women without uterus)	82	88 (82–97)	6 (0–15)
Oestrogen-only (women with uterus)	85	97 (90–108)	12 (5–23)
Combined HRT	70	92 (86–101)	22 (16–31)

iii) 10 years' use in women aged 50–59 years

Type of HRT	Baseline risk per 1000 women	Absolute risk in 1000 HRT users	Attributable risk in 1000 HRT users
Oestrogen-only (women without uterus)	83	95 (88–105)	12 (5–22)
Oestrogen-only (women with uterus)	87	131 (113–157)	44 (26–70)
Combined HRT	73	113 (103–126)	40 (30–53)

iv) 10 years' use in women aged 60–69 years

Type of HRT	Baseline risk per 1000 women	Absolute risk in 1000 HRT users	Attributable risk in 1000 HRT users
Oestrogen-only (women without uterus)	163	181 (165–198)	17 (2–35)
Oestrogen-only (women with uterus)	169	235 (203–275)	65 (34–106)
Combined HRT	139	203 (185–223)	64 (46–84)

Though crude estimates only, general these figures demonstrate that for most women without a uterus, the balance of benefits and risks of using oestrogen-only HRT is likely to be favourable. For most women with a uterus, the balance of risks and benefits is likely to be less favourable, particularly for those older than 60 years and those who have used HRT for a long time.

10. Conclusions

Important new data for HRT safety have recently become available, including re-analyses of data from the WHI trial and Nurses Health study on the risk of cardiovascular disease and age or time at starting HRT. These analyses have given rise to the suggestion that the effect of HRT on risk of coronary heart disease (CHD) differs according to the state of the underlying vasculature when treatment is started. Because the condition of the vasculature is generally related to age, it has been suggested that HRT may: have a cardioprotective effect in women with a healthy vasculature; have no adverse effect in women whose vessels have mild to moderate atherosclerosis; and may trigger a coronary event in women with complicated atherosclerotic lesions.

However, randomised controlled trials have typically recruited older women, and so there are few robust data about the effect of CHD in younger women, and no evidence to support a cardioprotective effect. Further research is needed before any firm conclusions can be drawn about the effect of HRT on CHD risk in younger women.

In addition to CHD, HRT is associated with other important risks:

- **Stroke:** Oestrogen-only HRT and combined HRT each increase stroke risk by about 1·3-times.
- **Venous thromboembolism (VTE):** Oral oestrogens increase VTE risk by about 1·3-times, and oral progestogens increase risk by about 2·4-times. The risk is highest in early use. The level of risk may be lower with transdermal HRT, although this has not been clearly established.
- **Breast cancer:** Oestrogens may slightly increase the risk of having breast cancer diagnosed. Combined HRT increases this risk by about 1·6-times after 5 years of use and 2·3-times after 10 years of use. Risk decreases within a few years of stopping HRT.
- **Ovarian cancer:** Risk of ovarian cancer may be slightly increased by long-term use of oestrogen-only HRT and combined HRT. Risk falls after stopping HRT.
- **Endometrial cancer:** Oestrogen-only HRT increases risk of endometrial cancer about 3-times after 5 years of use and about 9-times after 10 years of use. In women with a uterus, progestogen should be added for at least 10 days per cycle to reduce or eliminate the effect of oestrogen.

Generally, the much lower baseline risk of CHD and other adverse events in healthy younger women who use HRT to relieve menopausal symptoms means that their overall risk from HRT is very low. With increasing age, however, their baseline risk for all cardiovascular events increases substantially, and so older HRT users have a much greater overall risk of these events. Furthermore, risk of breast cancer, ovarian cancer, and endometrial cancer due to HRT increases with longer duration of use.

Evidence for the risks of HRT in women who have premature menopause is limited. However, the baseline risk of adverse events in these younger women is very low, and the balance of benefits and risks may therefore be more favourable than in older women.

The balance of risks and benefits of HRT therefore differs for every woman according to her need for treatment, age at starting HRT, duration of use, and type of HRT—ie, oestrogen-only or oestrogen plus progestogen.

No single recommendation for optimum duration of treatment or safe upper-age limit for use of HRT is therefore possible because they will be specific to every woman’s circumstances. For most women, short-term treatment will be sufficient to relieve vasomotor symptoms; for others, HRT may need to be continued for longer. For all women, the lowest effective dose should be used for the shortest possible time, and the need to continue HRT should be reviewed at least yearly, taking into consideration the change in balance of risks and benefits.

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Glossary

Active therapy

A medicine that patients receive in a study setting such as a **randomised controlled trial**; contrast with **placebo**

Acute

Short-term

Adjusted risk

An estimate of risk after taking into consideration other features of the patient or their lifestyle (see **confounding factors**) that may bias the risk calculation

Angina

Pain in the chest

Anti-oestrogens/oestrogen-receptor antagonists

Drugs that block the action of the hormone oestrogen in the body

Atherosclerotic lesions

Plaques of fatty material that are deposited in heart valves

Baseline

The beginning of a study

Bilateral oophorectomy

Removal of the ovaries

Biopsies

The removal and sampling of a small piece of tissue from the body

Blood lipids

Fats present in the circulatory system

Body mass index

The weight of a person (in kg) divided by the square of their height in (m); the index is used to assess whether someone is underweight or overweight

Carcinoma

A type of cancer, one that arises in **epithelial** tissue

Cholesterol

A fatty-like substance

Compliance

The extent to which a patient takes their medicine according to the dosing guidelines

Confounding factors

Features of a patient or of a study that may influence or bias the outcome

Conjugated equine oestrogens

A type of hormone-replacement therapy that contains multiple types of oestrogens, including those not produced by human ovaries

Contraindication

A feature of a patient that makes it unsuitable for them to receive a particular medicine

Coronary death

Death as a result of a heart defect

Coronary revascularisation

A treatment for heart disease

Deep vein thrombosis

A blood clot in the calf of the leg

Endometrial hyperplasia

Excessive growth of cells in the **endometrium**

Endometrium

The lining of the womb

Endothelial

Of cells that line closed spaces of the body such as blood vessels and the heart

Epidemiological studies

The study of disease in populations

Epithelial

Of cells that line open surfaces of the body such as the skin

Esterified oestrogen

A mixture of related oestrogens that is found in some hormone-replacement products

Exogenous

Originating outside the body

Factor V Leiden

An inherited error in genetic material that leads to a susceptibility for people to have blood clots in veins

Follow-up

The tracking and assessment of participants during a study

Glucose

A sugar that is an important source of energy for the body

Hazard ratio (95% CI)

A method of measuring the risk of an event. A hazard ratio of more than 1 suggests an increased risk; a hazard ratio of less than 1 suggests decreased risk. Hazard ratios are usually accompanied by a 95% CI (confidence interval)—a statistical method of assessing the true difference between two groups: the range covered by this interval gives a 95% chance that the real difference between the two groups lies within this interval. If the 95% CI does not cross 1, then the hazard ratio is regarded as statistically significant

Heterogeneity

The extent of difference between two or more comparisons

Histological

Relating to the study of the structure of tissue

Hormone

A substance produced by one part of the body and passes via the bloodstream to another part of the body where it modifies functions

Hypercholesterolaemia

A high level of **cholesterol** in the blood

Hypertension

High blood pressure

Hysterectomy

Surgical removal of the womb

Idiopathic

Of unknown cause

Index date

The date of diagnosis

In-situ centrally adjudicated breast cancers

Diagnosis of non-invasive breast cancer within a clinical trial by the experts who have been appointed to diagnose all possible cases of breast cancer that arise during the trial, thus maintaining consistency

Insulin

A hormone produced by the pancreas that controls the level of sugar in the blood

Intention-to-treat analyses

A method of analysing patients in a **randomised controlled trial**, who are assessed according to the treatment they were randomly allocated to receive irrespective of whether they actually received this treatment. Such a method of analysis is thought to reflect findings that would occur with the treatment under investigation in real life

Interventional

Circumstances in which study participants are not only observed but are exposed to a measurable factor called an intervention (eg, a treatment, a diet, or a change in lifestyle)

Kaplan Meier plots

Graphs that show the proportion of patients being followed-up, and their outcome, during a **randomised controlled trial**

Lipoprotein

A substance found in the blood that is important for the transport of fats around the body

Longitudinal

A type of study that tracks two or more groups from exposure to outcome

Lymph-node positive

The presence of cancerous cells in the lymph nodes of the body. Lymph nodes are part of the lymphatic system that help prevent foreign bodies and infection from entering the bloodstream

Mammographic density

The appearance of an X-ray examination of the breast

Mean

An average, calculated by dividing the sum of all values by the total number of values

Menopause/menopausal symptoms

The time at which a woman no longer produces eggs from the ovaries. This change can lead to symptoms such as hot flushes, palpitations, vaginal dryness, and emotional disturbance

Meta-analyses

A study that combines the results from several similar clinical trials that asked the same study question and applies new statistical analysis

Micronised progesterone

A component of some types of hormone-replacement therapy, in which the hormone progesterone is broken down to enable the body to metabolise it more easily

Myocardial infarction

Irreversible injury to heart muscle, also known as a heart attack

Non-significant interaction

A relationship between two factors in a study (eg, treatment and patient outcome) that is not statistically significant

Nor-pregnane derivatives [of progesterone]

Metabolites (breakdown products) of progesterone

Odds ratio

A method of measuring the risk of an event. An odds ratio of more than 1 suggests an increased risk; an odds ratio of less than 1 suggests decreased risk.

Oestrogen

A hormone that controls female sexual development and function

p

A measure of the statistical probability of an event occurring by chance. Usually, a p value of less than 0·5 suggests the event is statistically significant and did not occur by chance, whereas a p value of more than 0.5 suggests the event is not statistically significant and arose by chance

Placebo

A dummy treatment (eg, a sugar pill) given to a group of patients in a **randomised controlled trial**

Post hoc

Data analyses that are done after the experiment, but which were not defined or planned before the experiment started

Pregnane derivatives

Metabolites (breakdown products) of progesterone.

Primary outcome
The main question that a **randomised controlled trial** aims to answer

Procoagulant

An agent that promotes the clotting of blood

Progesterone

A steroid hormone involved in menstruation, pregnancy, and formation of an embryo.

Progestogens

Synthetic hormones with similar effects to **progesterone**. In HRT its main effect is to oppose the action of oestrogen on the **endometrium.**

Prospective cohort study

A study that tracks two or more groups forward from the present time

Randomised controlled trial

A study technique, regarded as robust, in which participants are enrolled onto the study and randomly assigned a treatment or treatment technique. In a **placebo** controlled trial, some patients are allocated the drug or technique of interest, whereas some are allocated **placebo** as a control group to identify the effects of the drug of interest. In a double-blind study, neither the trial participants nor the trial investigators are aware of who has been assigned to a particular treatment group, thus minimising bias

Second line indication

A medicine that can be given to a patient as a second option when other, first-line, options have not been effective or are not suitable

Secondary prevention

A method to protect against an event re-occurring

Serous

Relating to serum

Stratified

A method of separating analyses of different patients to avoid bias (eg, separate analysis of smokers versus non-smokers)

Stroke

Arises as a result of a decreased blood supply and therefore lack of oxygen to the brain, which can cause paralysis, coma, speech problems, or dementia. **Ischaemic stroke** occurs when a clot blocks blood flow; **haemorrhagic stroke** occurs when an artery wall ruptures

Summary of Product Characteristics (SPC)

Detailed information that accompanies any licensed medicine. The **Summary of Product Characteristics** details the composition, clinical characteristics, pharmacological properties, pharmaceutical characteristics

Surrogate

A measure or event occurring in the body that can be assessed to give a picture of another event that is not easy to assess

Systematic review

An overview and appraisal of the current literature on a topic

Systolic blood pressure

Maximum blood pressure in the arteries during contraction of left ventricle (lower chamber) of the heart, which supplies blood to the general circulation

Thrombophilia

A condition that predisposes people to blood clots

Transdermal

Administration of a medicine by a skin patch

Triglyceride

A type of fat

Unopposed oestrogen-replacement therapy

Administration of oestrogens without a progestogen to women with a uterus

Uterus

The womb

Vasomotor symptoms

Menopausal symptoms that include flushing, sweating, and raised heart rate

Venous thromboembolism

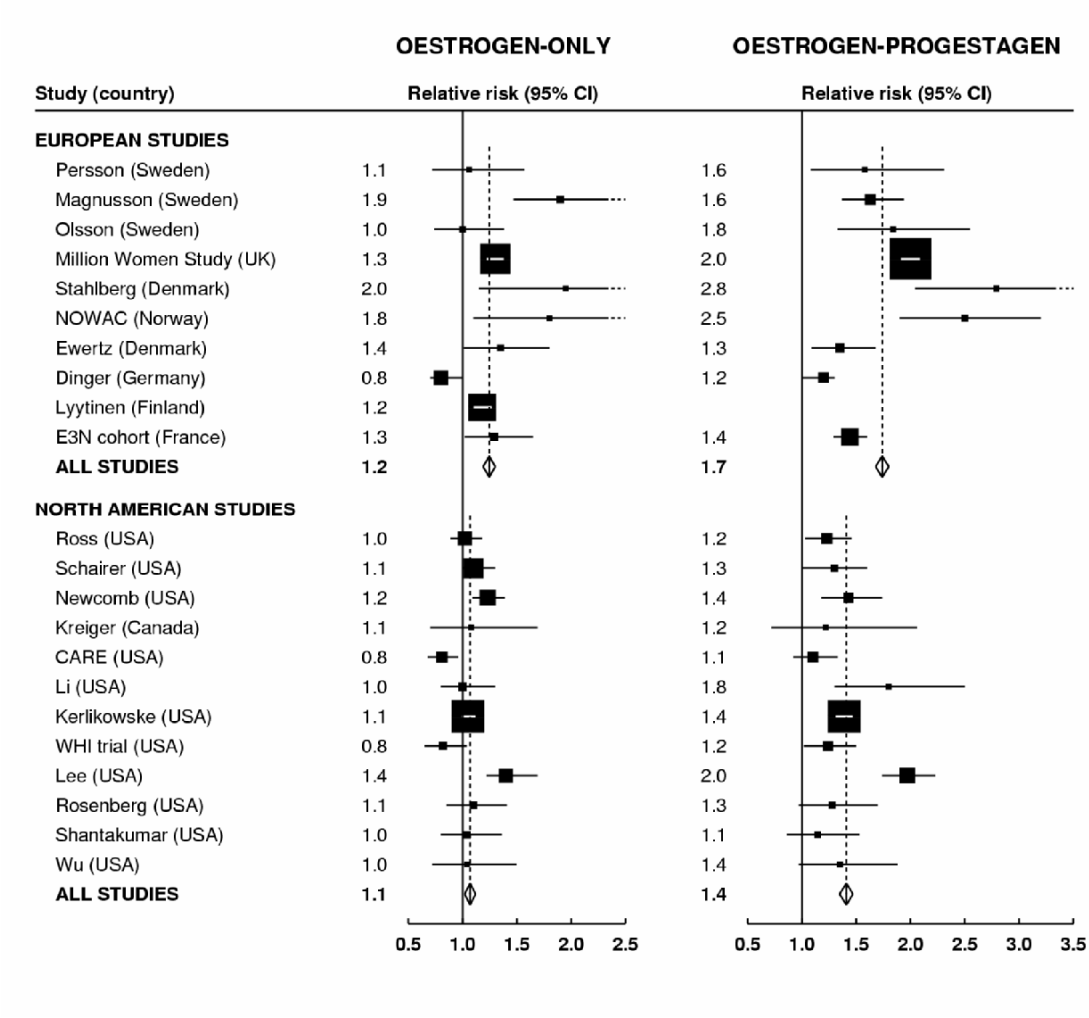
A blood clot in a vein

Annex

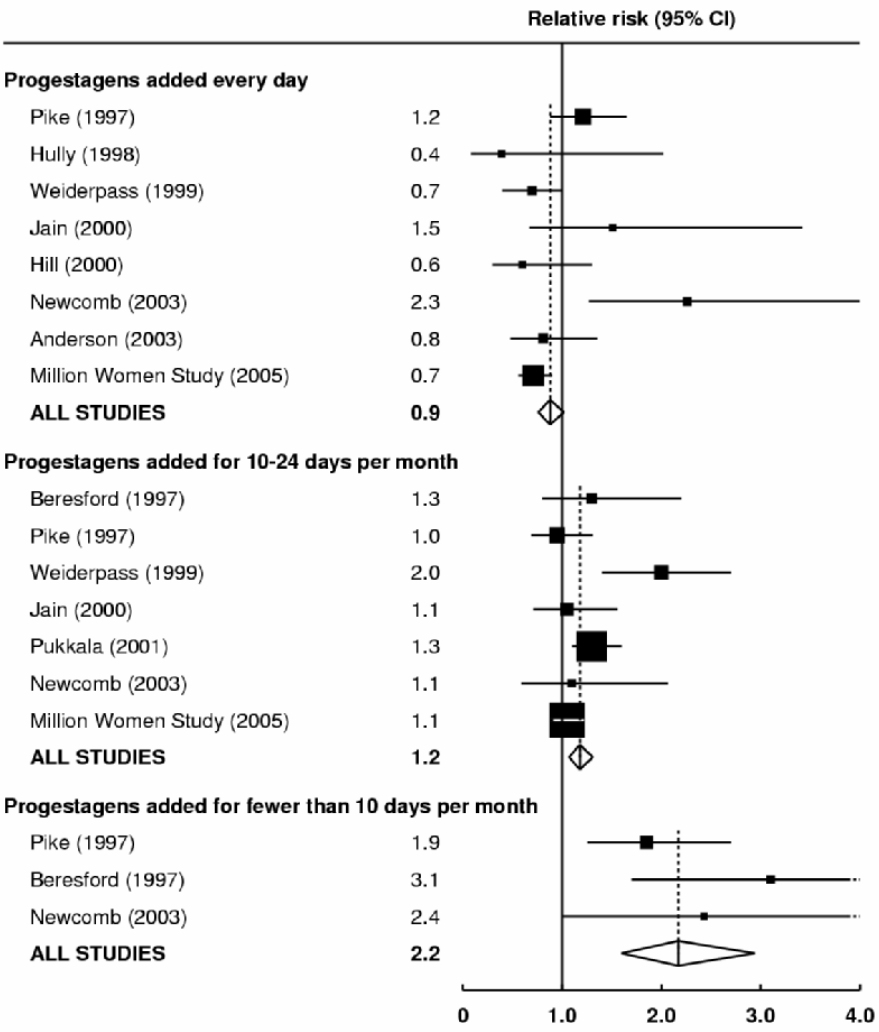
Risk estimates from meta-analyses of published data

Comparison is with placebo or non-HRT use.

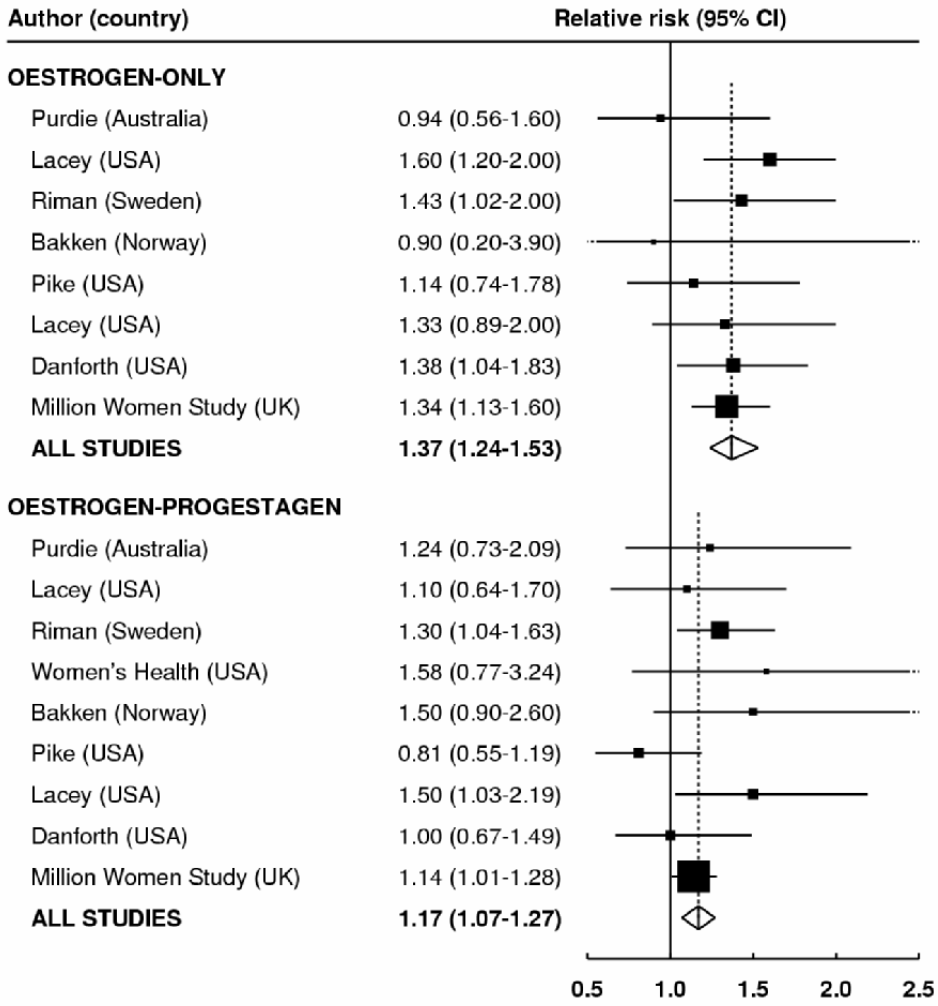
a) Breast cancer (European *vs* North American studies by HRT type)



b) Endometrial cancer—by duration of added progestogen

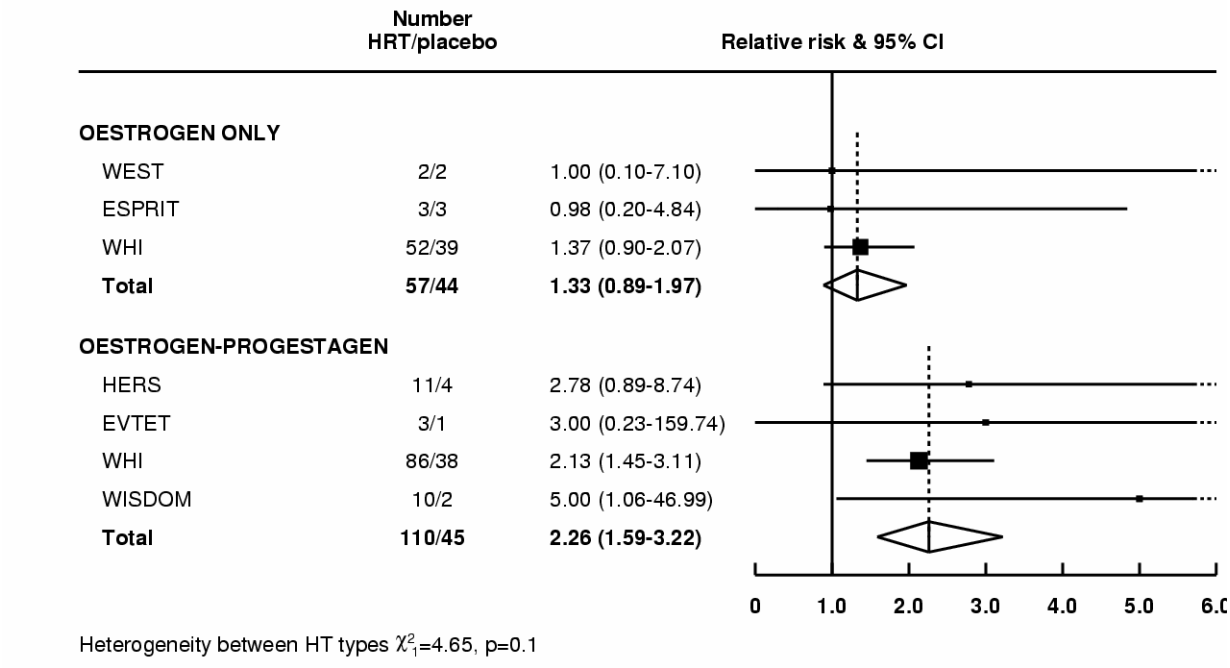


c) Ovarian cancer—by HRT type



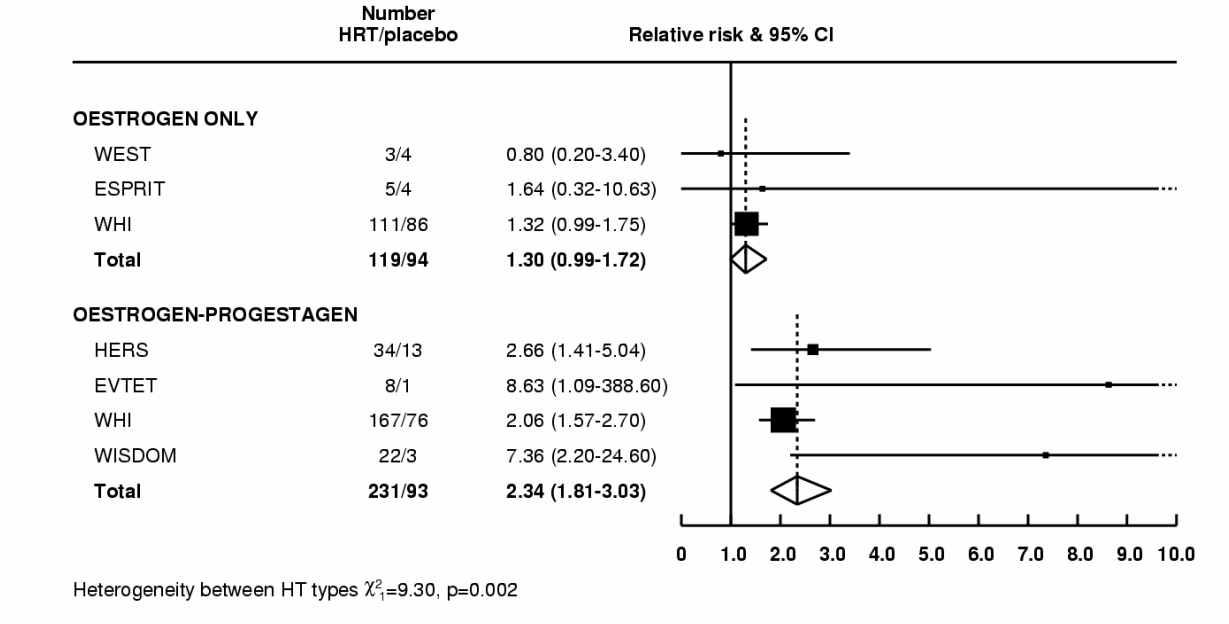
d) Venous thromboembolism (VTE)—by HRT type

i) Pulmonary embolism (PE)



Heterogeneity between HT types χ^2_1=4.65, p=0.1

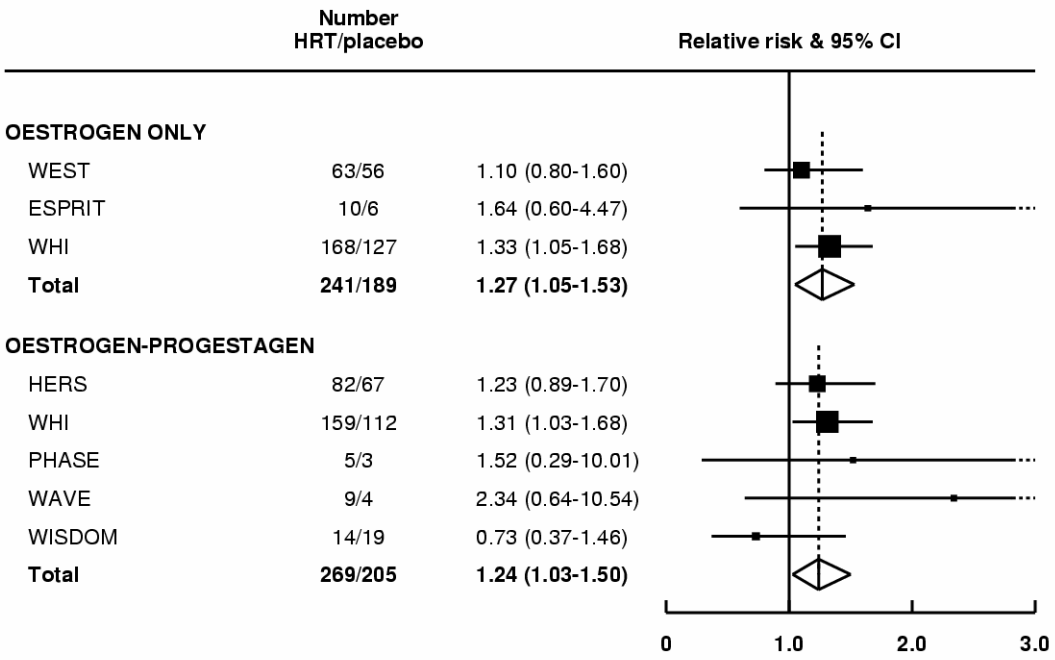
ii) Deep vein thrombosis (DVT)



Heterogeneity between HT types χ^2_1=9.30, p=0.002

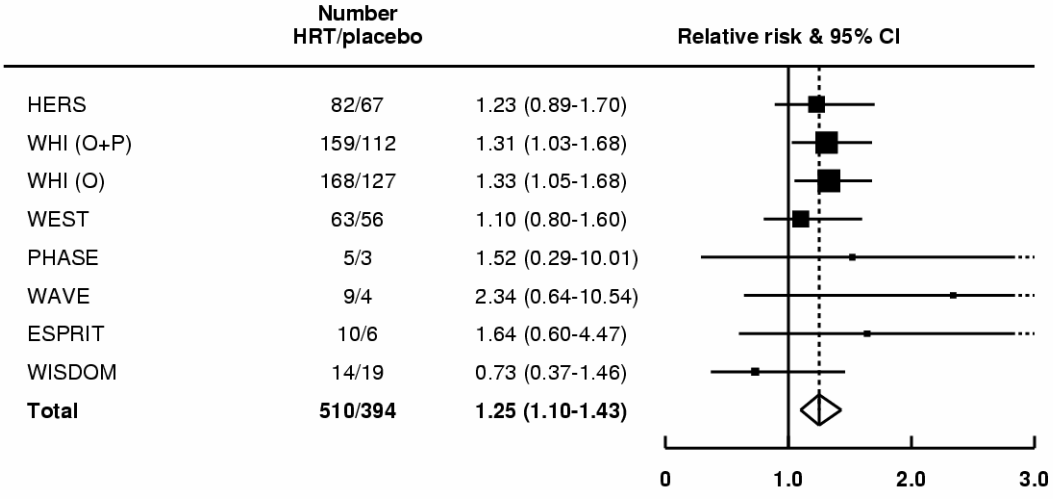
e) Stroke

i) By HRT type

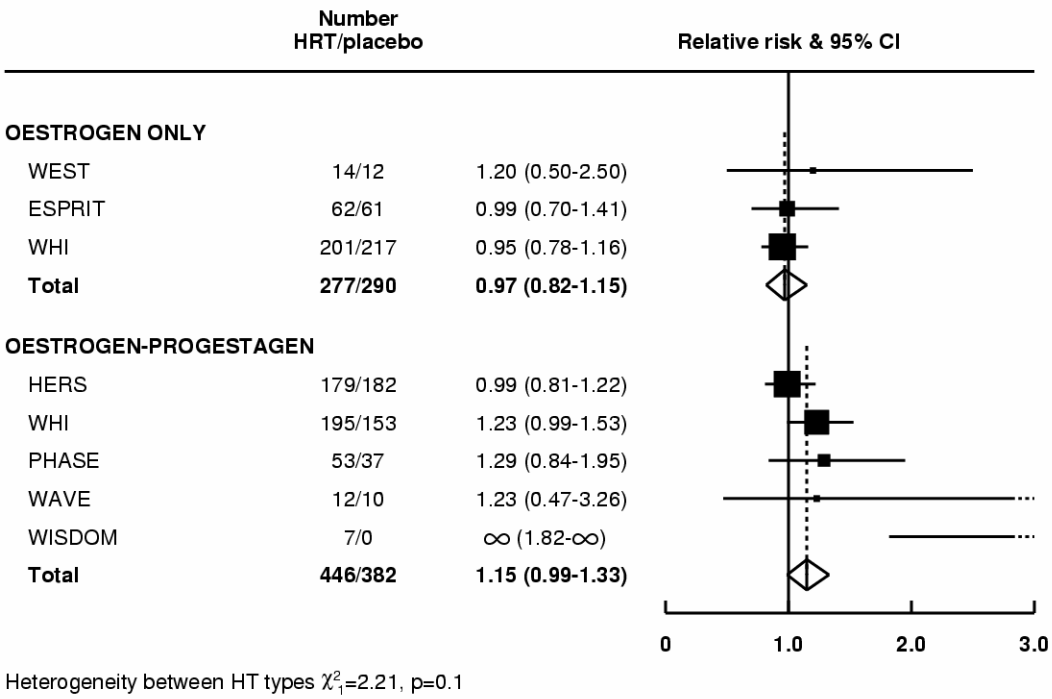


Heterogeneity between HT types χ^2_1=0.03, p=0.9

ii) All HRT

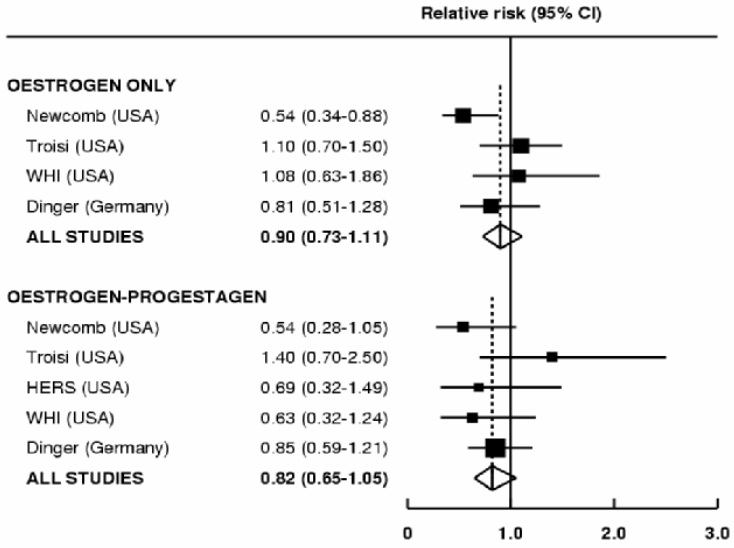


f) Coronary heart disease (CHD)—by HRT type

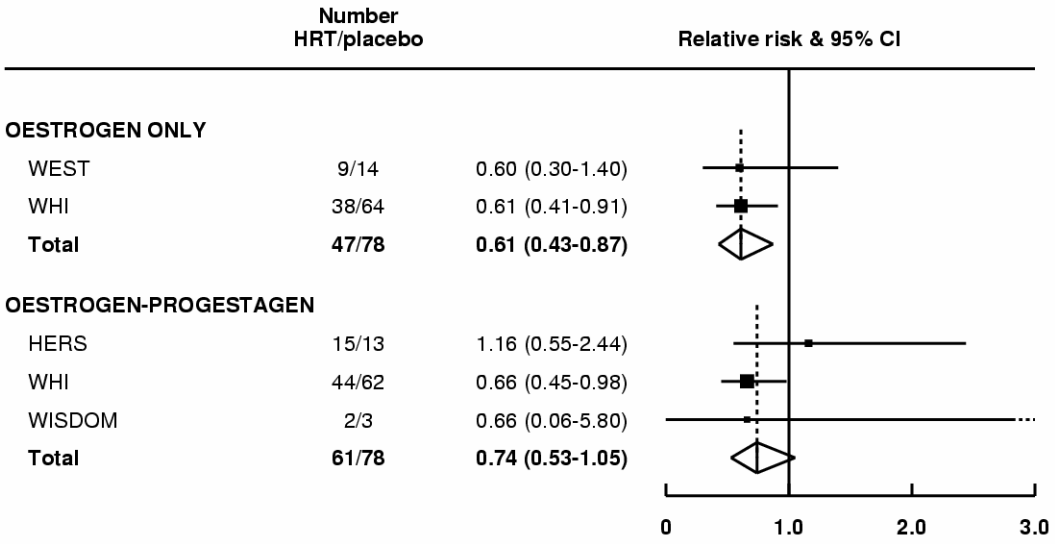


Heterogeneity between HT types χ^2_1=2.21, p=0.1

g) Colorectal cancer—by HRT type



h) Hip fracture—by HRT type



Heterogeneity between HT types χ^2_1=0.84, p=0.7