# 8 Benefits and risks of hormone replacement therapy

## At a glance

- HRT dosage, regimen and duration should be individualised, with annual evaluation of advantages and disadvantages.
- Estrogen replacement remains the most effective treatment for menopausal symptom control.
- Arbitrary limits should not be placed on the duration of usage of HRT.
- Transdermal administration of estradiol is unlikely to increase the risk of venous thrombosis or stroke and should be considered the first-choice route of estradiol administration for women with risk factors.
- Cochrane analysis suggests that HRT (estrogen with or without progestogen) started before the age of 60 years or within 10 years of the menopause is associated with a reduction in atherosclerosis progression, coronary heart disease and death from cardiovascular causes as well as all-cause mortality.
- Cochrane data also show no increase in cardiovascular events, cardiovascular mortality or all-cause mortality in women who initiated HRT more than 10 years after the menopause.
- Women should be informed that HRT is unlikely to have an adverse cardiovascular effect and may be associated with lowering of the risk of cardiovascular disease when initiated before the age of 60 or within 10 years of the menopause.
- Short-term use of estrogen-alone HRT regimens (up to five years) are unlikely to increase the risk of invasive breast cancer. Combined estrogen and progestogen can be associated with a small increase in the risk of invasive breast cancer. However, this risk is low in both medical and statistical terms and should be taken in the context of the overall benefits obtained from using HRT.
- Low-dose vaginal estrogen preparations can be used in symptomatic women and continued for as long as required.

- There is no requirement to combine vaginal estrogens with systemic progestogen treatment for endometrial protection, as low-dose vaginal estrogen preparations do not result in significant systemic absorption or endometrial hyperplasia.
- Estrogen replacement, systemic or topical, can result in significant improvement in sexual function. The addition of systemic testosterone may also result in improvement in sexual function.
- Evidence suggests that micronised progesterone is associated with a lower risk of venous thromboembolism and cardiovascular disease, and may be associated with a lower risk of breast cancer compared with synthetic progestogens.

## Introduction

The recommendations on the role of hormone replacement therapy (HRT) in managing menopausal symptoms and the risks associated with its use have been heavily based on the findings of the Women's Health Initiative Study (WHI), since the publication of the study's early findings in 2002 and up to the early part of the 21st century. Most guidance documents and media reports that followed sent a cautious if not negative message on HRT and caused confusion among clinical practitioners, as well as the public regarding the adverse effects and risks associated with HRT. This chapter explores the changes in clinical practice post-WHI, including the cardiovascular 'timing hypothesis' and 'window of opportunity', the role of transdermal administration of estradiol, as well as that of micronised progesterone in this context. In addition, we discuss the evidence assessing the benefits of HRT and its role in the management of menopausal symptoms, as well as the risks associated with the use of HRT. The chapter also discusses the changing position with the publication of the cumulative long-term follow up outcomes from the WHI trial reported in 2013 and their practical implications.

In November 2015, the National Institute for Health and Care Excellence (NICE) published its guideline on the diagnosis and management of the menopause, which provided evidence-based recommendations on the management of the menopause to guide healthcare professionals, as well as providing information to the public. The main recommendations from the NICE guidance document have been referred to in the relevant sections of this chapter.

## Background

The WHI included a set of randomised controlled trials (RCTs) and an observational study, all of which aimed to address strategies for preventing cardiovascular disease, breast cancer, colorectal cancer and osteoporotic fractures in postmenopausal women. The study was funded by the National Institutes of Health in the United States and was initiated in 1991.

The WHI trial assessed oral conjugated estrogen (Premarin®, Pfizer, 0.625 mg) alone (in women with no uterus) or with the synthetic progestogen medroxyprogesterone acetate at a dose of 2.5 mg compared with placebo. A higher incidence of stroke was reported with the use of HRT (estrogen alone or combined estrogen and progestogen), as well as a higher incidence of breast cancer (only noted in the combined estrogen and progestogen arm). The early reports from the study indicated an increased risk of cardiovascular events in the combined estrogen and progestogen arm. However, subsequent publications by the study group reported on the long-term follow-up outcomes for the same study cohort and showed no significant increase in cardiovascular events nor cardiovascular mortality in both intervention arms (estrogen alone or combined estrogen and progestogen) compared with placebo, and this neutral effect was noted in all age groups (50–59, 60–69 and 70–79 years).

In addition, the long-term follow up data, reported by the WHI study group in 2013, showed no detrimental effect with combined estrogen and progestogen replacement. This neutral cardiovascular effect was the same regardless of the age women initiated combined HRT.[1]

There are a number of limitations in the WHI trial design that need to be taken into consideration when interpreting, and for that matter applying, the findings to our current practice. The study was designed as a prevention trial that included asymptomatic women aged 50–79 years and randomised them to a relatively high dose of oral conjugated estrogen (0.625 mg) and a synthetic progestogen (the pregnane derivative medroxyprogesterone acetate 2.5 mg) in women who had a uterus. In addition, the study population included an older age group of women (average age 63 years), who largely started HRT many years after the onset of the menopause (average 10 years after the onset of the menopause) and had a high mean body mass index. It would be unusual in clinical practice to prescribe HRT for the first time so long after the onset of the menopause, and by only addressing asymptomatic women the trial did not include the population that is commonly prescribed HRT. The trial, however, remains one of the largest randomised studies in this context and, where relevant, provides useful information to guide our clinical practice.

Most of the recommendations and conclusions drawn following the WHI generally viewed HRT as one intervention and with one group of risks that applied to all. It is important to highlight that the risks of HRT reported in the WHI overall were low. Furthermore, a number of studies have since demonstrated that the risk profile associated with HRT could vary depending on the route of estradiol administration, type of progestogen and also the time of initiation of HRT in relation to the time of onset of the menopause. The clinical implications of these three areas are discussed in more detail below.

## Changes in clinical practice post-WHI

### Route of estradiol administration

The different routes of administration of estradiol follow different metabolic pathways and, as a result, may be associated with different risk profiles. Oral estrogen follows a first-pass liver metabolism pathway and, as a result, has a prothrombotic effect on the coagulation cascade and adversely effects proinflammatory markers, including C-reactive protein, compared with transdermal estradiol. Women receiving oral estrogen have alteration in all parameters of thrombin generation compared to women not using HRT, while no such alterations are noted in women receiving transdermal estrogen.

Two large nested case–control studies reviewed the UK's General Practice Research Database and reported on the risk of stroke and venous thromboembolism with transdermal estrogen replacement compared with oral administration and non-use of HRT in women aged 50–79 years.[2,3] The first study included 15,710 cases of stroke, matched with 59,958 control cases. The use of low-dose transdermal estrogen (up to 50 μg/day) was not associated with an increased risk of stroke compared with women not using HRT (odds ratio, OR, 0.81; 95% confidence interval, CI, 0.62–1.05). This effect was noted when transdermal estradiol was given alone (OR 1.02; 95% CI 0.78–1.34), or in combination with progestogens (OR 0.76; 95% CI 0.47–1.22) compared with non-use of HRT. However, the risk was increased with high-dose transdermal application (more than 50 μg/day; OR 1.89; 95% CI 1.15–3.11). Women taking oral HRT were noted to have a higher risk of stroke compared with those not taking HRT (OR 1.28; 95% CI 1.15–1.42). This effect was noted both with low-dose (estradiol up to 2 mg or conjugated estrogen up to 0.625 mg) and high-dose (> 2 mg estradiol or conjugated estrogen > 0.625 mg) of HRT. The second report by the same group included 23,505 women with venous thrombosis,

matched with 231,562 controls. The risk of venous thrombosis was not increased when transdermal estrogen was used alone (OR 1.01; 95% CI 0.89–1.16) or in combination with progestogens (OR 0.96; 95% CI 0.77–1.20), compared with non-use of HRT. However, the risk was increased with current use of oral estrogen (OR 1.49; 95% CI 1.37–1.63) and oral estrogen/progestogen (OR 1.54; 95% CI 1.44–1.65) and also increased with estrogen dosage.

The lower risk associated with transdermal estradiol compared with that with oral estrogen has now been incorporated in most international consensus statements, including those by the British Menopause Society, as well as the NICE guidance on the management of the menopause.

## Micronised progesterone versus synthetic progestogens

Micronised progesterone selectively binds to the progesterone receptors and has fewer adverse effects on the androgenic, mineral corticoid and glucocorticoid receptors than synthetic progestogens. Studies have demonstrated that micronised progesterone appears to have a better safety profile when compared with synthetic progestogens and may result in a different risk profile. Studies have suggested that androgenic progestogens appear to partly reverse the beneficial arterial effects of estrogens, while such an effect was noted to be lower with micronised progesterone. Reports have also demonstrated a neutral effect on vasculature and therefore, a lower risk of venous thromboembolism and cardiovascular disease, as well as a lower risk of breast cancer with micronised progesterone compared with synthetic progestogens. These findings have now been incorporated into most international consensus statements, acknowledging the lower risk profile associated with micronised progesterone compared with that of synthetic progestogens.

## Cardiovascular 'timing hypothesis'

Studies have reported on the concept of a 'window of opportunity' for the reduction of cardiovascular disease when HRT treatment is initiated before the age of 60 years. A Danish RCT included over 1000 women aged 45–58 years and showed that HRT commenced within 10 years of the onset of the menopause reduced the incidence of coronary heart disease by 50% and reduced overall mortality with no apparent increase in the risk of stroke or venous thrombosis.[4] The Kronos Early Oestrogen Prevention Study – a large multicentre randomised study – reported on the cardiovascular effects of HRT taken in the early menopause. It included 727 participants, randomised into three groups.[5] One group

received oral conjugated estrogen 0.45 mg/day. The second group received transdermal estradiol 50 mg/day and the third group was given a placebo. Women prescribed active estrogens received micronised progesterone 200 mg for 12 days each month, whereas women in the control group received placebo capsules. The study showed a neutral impact on cardiovascular risk markers such as coronary calcium scores and intima media thickness, with no negative effect on blood pressure, lipid and insulin resistance, suggesting that micronised progesterone given with transdermal estradiol or with oral conjugated estrogen did not reverse the beneficial effects of estrogen in this group of women.

Hodis et al. (2016)[6] reported on the cardiovascular effects of HRT in relation to the timing of initiation of treatment; 643 postmenopausal women were randomised to either oral estrogen (estradiol 1 mg), plus micronised progesterone vaginal gel for women with a uterus, or to receive placebo. Women were stratified according to the duration of time since their menopause. 'Early' was defined as less than six years since the menopause, while 'late' was defined as 10 or more years since the menopause. The primary outcome evaluated was atherosclerosis progression, assessed by ultrasound measurement of carotid artery intima and media thickness. Estrogen treatment (with or without progesterone) resulted in a significantly lower rate of atherosclerosis progression in early postmenopausal women but this effect was not noted in the late postmenopausal group.

These findings support the 'window of opportunity' theory for the primary prevention of cardiovascular disease that is influenced by the timing of initiation of HRT. This would suggest a beneficial cardiovascular effect and reduction in atherosclerosis progression with estrogen replacement commenced in the early menopause.

## HRT for menopausal symptoms

### Vasomotor symptoms

Relief of vasomotor symptoms is the most common indication for prescribing HRT in postmenopausal women. The median duration of vasomotor symptoms is 7.4 years and estrogen replacement remains the most effective treatment in this context. A Cochrane systematic review included 24 placebo-controlled randomised trials and demonstrated a clear beneficial effect compared with placebo.[7] Consensus statements, including those from the British Menopause Society, recommend offering HRT for this indication after counselling women about the risks and benefits and individualisation of regimen, dose of HRT and the duration of treatment followed by annual reviews. The statements also emphasise

that the duration of HRT usage should be decided based on the menopausal symptoms experienced by the woman and should not be subject to arbitrary age or duration limits.

The NICE menopause guidance also recommends the use of HRT for vasomotor symptom control after discussing short-term benefits (up to five years) and long-term effects.

## Urogenital symptoms

Estrogen has a proliferative effect on the lower genital tract as well as the bladder and urethral epithelium. Estrogen replacement is effective in treating symptoms related to urogenital atrophy, such as vaginal dryness and superficial dyspareunia. It may also help relieve symptoms of urinary frequency, urgency and reduce the risk of recurrent urinary tract infections in women with urogenital atrophy. Vaginal and systemic preparations are equally effective, so in the absence of other indications the vaginal route is the preferred option.

Vaginal estrogen preparations do not result in significant systemic absorption of estradiol and all topical estrogen preparations are effective. Studies have demonstrated the safety of topical vaginal estradiol preparations in the short term, although there is limited evidence assessing safety beyond one year of use. Clinicians should therefore use the lowest effective dose for symptom control and should counsel women regarding this. Consensus statements, including a guidance document from the International Menopause Society, on the management of urogenital atrophy have indicated that vaginal estrogen preparations can be used long-term in symptomatic women. The NICE menopause guidance recommends offering vaginal estrogen to women with urogenital atrophy, including those on systemic HRT and to continue treatment for as long as required to relieve symptoms. It also concluded that there is no need to offer routine monitoring of endometrial thickness with estrogen replacement for urogenital atrophy.

## Sexual function

There is a decline in sexual function with age and after the menopause. Estrogen treatment, systemic or topical, has been shown to improve sexual function in postmenopausal women. Systemic HRT may improve sexual function through its action on the arousal centres in the brain. In addition, estrogen has a proliferative effect on the vulval and vaginal epithelium and topical preparations have been shown to improve dyspareunia secondary to vaginal atrophy.

The administration of systemic testosterone has been shown to result in significant improvement in sexual function, including sexual desire, and orgasm. The NICE menopause guidance recommends that testosterone supplementation should be considered for the treatment of low sexual desire in menopausal women if HRT alone is not effective.

There is accumulating evidence on the safety and efficacy of testosterone replacement although long-term safety data are lacking. At present, there is limited availability of licensed female androgenic options. Testosterone implants and patches have been withdrawn by pharmaceutical companies for commercial, not safety reasons. Testosterone gels licensed for use in men are available and unlicensed prescribing by specialists at a reduced dosage is an option for female androgen replacement. In addition, tibolone has a weak androgenic effect, which can have a beneficial effect on sexual function and libido.

## Mood

Evidence from observational studies suggests that HRT may improve low mood, anxiety and depressive symptoms during the menopausal transition and in the early menopause. However, HRT is unlikely to be beneficial in treating menopausal women with chronic depression, and should therefore not be considered as an alternative to antidepressants in this group of women who may need specialist help. The NICE menopause guidance recommends the use of HRT or cognitive behavioural therapy for the relief of low mood arising as a result of the menopause. It also concludes that there was no clear evidence that selective serotonin reuptake inhibitors or serotonin and noradrenaline reuptake inhibitors ease low mood in menopausal women not diagnosed with depression and should not be considered as first-line therapy.

## Cognition

Evidence from well-designed randomised studies, including WHI, shows no significant improvement in memory or cognitive function with the use of HRT in older postmenopausal women. There is a reported increase in the risk of dementia in women who commence HRT for the first time at the age of 65–79 years, although in clinical practice it is very unlikely that HRT treatment would be first started at that age. Based on current evidence, HRT should not be initiated for the sole purpose of improving cognitive function or reducing the risk of dementia in postmenopausal women.

Observational data suggest an improvement in cognitive function and a possible reduction in the risk of Alzheimer's disease with the use of

HRT in women with premature ovarian insufficiency and those with early menopause. These findings have not been demonstrated in randomised trials and further evidence is needed to evaluate this.

The NICE menopause guidance concluded that there is no clear indication of risk or benefit for dementia with HRT treatment in naturally menopausal women commencing HRT before the age of 65 years. The guidance document indicated, however, that some large cohort studies have shown that the risk of dementia may be lower with HRT use in long follow-up studies.

## Musculoskeletal effects

Estrogen deficiency after the menopause has been reported to have a negative effect on various types of connective tissue in the body, including bone, skin, intervertebral discs, arterial media layer and other connective tissues in the body. Observational data suggest that estrogen treatment has a protective effect against connective tissue degeneration and may possibly reverse this process in menopausal women receiving HRT.

The NICE menopause guidance concluded that there is limited evidence to suggest that estrogen replacement could improve muscle strength or muscle mass. It also concluded joint and muscle aches and pains are often reported by women after the menopause and these frequently improve with HRT.

## Osteoporosis prevention

Osteoporosis is a systemic skeletal disorder caused by low bone mass and microarchitectural weakening. This results in increased bone fragility and susceptibility to fractures. The risk of osteoporotic fractures in postmenopausal women under the age of 60 years is low. However, this risk significantly increases in women beyond the age of 70 years.

Estrogen replacement has been shown to be effective in preserving bone density, preventing osteoporosis and reducing osteoporosis-related fractures in both spine and hip. Most international guidance documents have recommended estrogen replacement as one of the first-line therapy measures for the prevention and treatment of osteoporosis in menopausal women under the age of 60 years, especially in the presence of menopausal symptoms.

The bone-preserving effect of estrogen on bone mineral density declines after discontinuation of treatment. However, studies have demonstrated that the use of HRT for a few years around the menopause may provide a long-term protective effect many years after discontinuing HRT.

The NICE menopause guidance concluded that the risk of fragility fracture is reduced while taking HRT. The bone protective effect of HRT decreases once treatment is discontinued, although the benefit may persist longer in women who take HRT for a longer duration of time. The assessment and management of osteoporosis, including the role of HRT in this context, are discussed in more detail in Chapter 11.

### Colorectal cancer

Published data suggest a reduced risk of colorectal cancer with the use of oral combined HRT. The WHI trial showed that the risk of colorectal cancer was reduced in the combined estrogen and progestogen arm but there was a neutral effect in the estrogen-alone group. There is no clear understanding of a mechanism that might explain this reduction and HRT should not be used for this purpose. There is lack of evidence on the effect of transdermal HRT and risk of colorectal cancer.

## Risks associated with the use of HRT

### Breast cancer

The WHI study reported a small increase in the risk of breast cancer diagnosis with combined estrogen and progestogen, which begins to emerge after three years of exposure. Based on these data, for women aged between 50 and 59 years, it is estimated that use of combined estrogen and progestogen for five years probably accounts for three extra breast cancers being diagnosed per 1000 women exposed. On the other hand, the estrogen-alone arm of the study had a lower but statistically insignificant decrease in risk of breast cancer diagnosis compared with placebo when estrogen was taken for just under five years. It is uncertain whether the risk of diagnosis is increased with a longer duration of use (that is, over five years). The summary of the published literature within the NICE menopause guidance concluded that estrogen alone was associated with little or no change in the risk of breast cancer, while combined estrogen and progestogen can be associated with an increased risk of breast cancer. However, this risk is low in both medical and statistical terms and should be taken in the context of the overall benefits obtained from using HRT (Figure 8.1).

Observational evidence suggests micronised progesterone and dydrogesterone may be associated with a lower risk of invasive breast cancer compared with other synthetic progestogens, but these data are insufficient at present to conclude that they are 'breast safe' and therefore

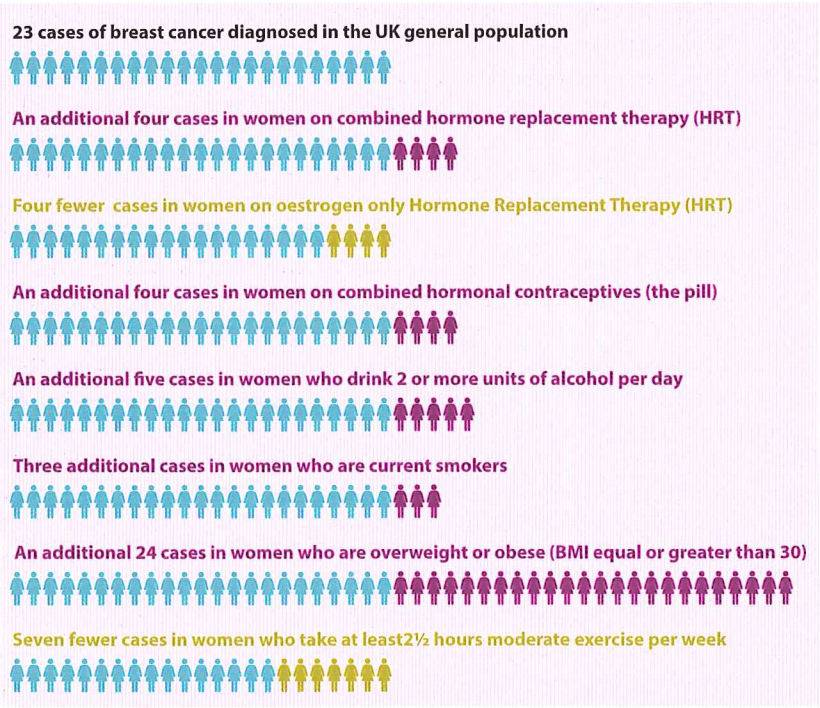


**Figure 8.1** A comparison of the risk of breast cancer with lifestyle risk factors versus hormone replacement therapy (HRT) treatment per 1000 women aged 50–59 years; approximate number of women developing breast cancer over the next five years (reproduced with permission from Women's Health Concern)

to recommend their preferential use in combined preparations. The NICE guidance also concluded from its review of available evidence about HRT and breast cancer that this risk is duration dependent and the risk falls after stopping HRT. Five years following cessation of HRT, the risk of breast cancer diagnosis in previous HRT users is the same as women who have never been exposed to HRT. Finally, there was no conclusive evidence of an increased risk of death from breast cancer in women diagnosed while taking HRT. The risk of breast cancer with HRT in those with an increased risk is discussed further in Chapter 14.

## Cardiovascular disease

There have been significant changes in our understanding of the role that estrogen replacement plays in relation to postmenopausal cardiovascular

health. Observational data prior to the publication of the WHI findings in 2002 suggested a reduction in cardiovascular disease with postmenopausal hormone replacement, with a number of retrospective reports showing up to 50% reduction in the risk. This prompted the concept of a cardiovascular timing hypothesis and suggested a cardiovascular protective role for HRT. The design of WHI was largely based on this theory. The early reports of the WHI, which included all age groups in the study combined (50–79 years of age), suggested an increase in the risk of cardiovascular disease and possible 'early harm' in women who received combined estrogen and progestogen. The long-term WHI follow-up data reported in 2013, however, showed a neutral cardiovascular effect with combined estrogen and progestogen replacement with no detrimental effect with combined hormonal replacement. This effect was the same regardless of the age women started combined HRT and was noted for all age groups (50–59 years, 60–69 years and 70–79 years). Women in the age group 50–59 years who received conjugated estrogen only (without medroxyprogesterone acetate) had a 40% reduction in the risk of coronary heart disease compared with placebo, although this did not reach statistical significance.

Studies have suggested a lower risk of cardiovascular disease when HRT is initiated in the early menopause. The effect of the time of initiation of HRT referred to as the 'window of opportunity' or 'timing hypothesis' is discussed in more detail earlier in this chapter. A Cochrane review in 2015 assessed the effects of HRT in the context of prevention of cardiovascular disease in postmenopausal women.[8] Those who started HRT within 10 years of their menopause had lower mortality (relative risk, RR, 0.70; 95% CI 0.52–0.95) and coronary heart disease, including death from cardiovascular causes and non-fatal myocardial infarction (RR 0.52; 95% CI 0.29–0.96) compared with placebo or no treatment. On the other hand, a neutral effect was noted in women who started HRT more than 10 years after the menopause, with no difference in mortality or coronary heart disease compared with placebo or no treatment. In addition, studies have reported a lower incidence of cardiovascular disease with micronised progesterone compared with synthetic progestogens, although overall there is limited evidence available on the effect of dose, preparation and route of HRT administration on the risk of cardiovascular disease.

The NICE menopause guidance concluded that there is no convincing evidence that HRT increases the risk of coronary heart disease in women under the age of 65 years, and that the presence of cardiovascular risk factors is not a contraindication to HRT as long as these are adequately managed.

Further research is also required to assess the effect of the different doses of HRT, preparations of estrogen (estradiol versus conjugated estrogens) and progesterones (micronised progesterone versus synthetic progestogens) as well as those with the different routes of administration of estradiol.

## Stroke

While the WHI study reported an overall increased risk of stroke in women in both the estrogen-alone arm and those on combined estrogen and progestogen, the effect was age related. Long-term cumulative follow-up data from the WHI showed an increased risk of stroke for the entire study group (age: 50–79 years), in both the estrogen-alone and the combined estrogen and progestogen arms. However, the 13-year cumulative follow-up data from the WHI showed no significant increase in the risk of stroke in women aged 50–59 years with estrogen-alone treatment or with combined estrogen and progestogen.

More recently, a Cochrane analysis showed no significant increase in the risk of stroke in women who commenced HRT before the age of 60 years or within 10 years of the onset of the menopause.[9] However, the review, noted an increase in the risk of stroke in women who commenced HRT more than 10 years after the menopause. Based on current evidence, HRT should not be recommended for the primary or secondary prevention of stroke.

Evidence from large observational studies has shown that transdermal administration of estradiol is unlikely to increase the risk of stroke above that in non-users and is associated with a lower risk of stroke compared with oral administration of estradiol. The lower risk of stroke associated with transdermal estradiol compared with that with oral estrogen has now been incorporated in most international consensus statements, as well as the NICE menopause guidance, which concluded that oral (but not transdermal) estrogen is associated with a small increase in the risk of stroke.

The type of progesterone used within HRT may also have an effect on the risk of developing ischaemic stroke. A large French cohort study looked at 3144 women aged 51–62 years who were hospitalised for ischaemic stroke between 2009 and 2011; the women were matched for age and postcode to 12,158 controls.[10] There was no association of ischaemic stroke with use of progesterone (OR 0.78; 95% CI 0.49–1.26), pregnanes (OR 1.00; 95% CI 0.60–1.67), and nortestosterones (OR 1.26; 95% CI 0.62–2.58), while norpregnanes (e.g. norethisterone, norgestrel) were associated with an increased risk of ischaemic stroke (OR 2.25; 95% CI 1.05–4.81).

### *Tibolone*

Evidence suggests that the risk of cerebrovascular events and other long-term adverse events with tibolone is similar to those noted with HRT.

## Venous thromboembolism

Evidence from RCTs, including the WHI as well as large observational studies, has shown that oral estrogens increase the risk of VTE two- to four-fold, with the highest risk being in the first year of use. On the other hand, transdermal administration of estradiol has been shown to have a lower risk of VTE compared with that noted with oral administration and no increased risk above that noted with non-users of HRT. VTE risk is further increased in those with a personal or family history of VTE, advanced age, particularly beyond the age of 60 years, obesity and other risk factors such as surgery or hospitalisation. Individuals requiring HRT should be risk assessed and counselled regarding their VTE risk.

The lower risk of VTE associated with transdermal estradiol compared with that with oral estrogen has now been incorporated in most international consensus statements and the NICE guidance document recommends considering transdermal rather than oral HRT for postmenopausal women at increased risk of VTE including those with a body mass index over 30.

The risk of VTE may also be affected by the type of progesterone used within HRT. There is increasing evidence that the risk is greater with certain progestogens such as norpregnane derivatives and medroxyprogesterone acetate. Evidence from observational studies suggests that micronised progesterone and pregnane derivatives such as dydrogesterone may be associated with a lower risk of VTE compared with other progestogens.

## Ovarian cancer

The WHI is the only placebo RCT that has studied the incidence of ovarian cancer and HRT and showed no increased risk with the use of HRT. A recent meta-analysis included individual data from 52 epidemiological studies, in which approximately 50% of the postmenopausal women with ovarian cancer had used HRT.[11] Ovarian cancer risk was significantly increased in current users receiving up to five years of HRT (RR 1.43; 95% CI 1.31–1.56). In past users, the risk decreased the longer the duration of time was after discontinuation of

HRT. However, the continuing risk remained slightly elevated (hazard ratio 1.37; 95% CI 1.29–1.46). The risk did not differ significantly between users of estrogen alone and combined estrogen and progestogen preparations. In addition, the increased risk was only noted for serous and endometrioid cancers. The meta-analysis concluded that women who used HRT for five years, starting approximately at the age of 50 years had an additional risk of developing ovarian cancer of approximately one extra case per 1000 users (which equates to one extra case per 5000 women per year) and a risk of having one extra death related to ovarian cancer per 1700 users. Current evidence would therefore suggest that there may be a slight increase in the risk of developing ovarian cancer associated with HRT use. However, this risk is small in both medical and statistical terms and should be taken in the context of the overall benefit and risk balance for the individual woman.

### Endometrial cancer

Current evidence suggests that long-term use of sequential combined HRT for more than five years may be associated with a small increase in risk of endometrial cancer, while continuous combined regimens are associated with a significantly lower risk of endometrial cancer than an untreated population. It is therefore common practice to recommend switching to a continuous combined HRT preparation when a woman reaches the age of 54 years (Chapter 7).

Women with a uterus require progestogen replacement for 12–14 days per month to minimise the risk of endometrial hyperplasia and endometrial cancer associated with unopposed estrogen exposure. Most published literature assessing the safety of sequential HRT regimens has assessed this in regimens that provided progestogen replacement for a minimum of 10–14 days a month. There is little evidence assessing the long-term safety of shorter duration or frequency of intake of progesterone within HRT regimens including durations less than 10 days a month.

### Lung cancer

Published literature does not show a clear association between the use of the HRT and the risk of lung cancer. Observational data and an earlier meta-analysis have suggested that the use of HRT may be associated with an increased risk of lung cancer.[12] A more recent adaptive meta-analysis, however, showed that the use of HRT had no effect on the risk of lung cancer.[13] In addition, both the WHI clinical trials and the California Teachers Study – a prospective cohort that included 60,592

postmenopausal women – showed no significant association between the use of HRT and the risk of lung cancer.[14]

## Summary

Women should be informed that the risks associated with HRT use are low overall, and these may be further lowered through individualised selection of the appropriate regimen and route of administration. Evidence from large observational series suggests that the use of transdermal estrogen replacement does not increase this risk of stroke or venous thrombosis above that noted in non-users of HRT and this should be considered when counselling patients to minimise this risk. There is a need for further research to assess the optimal regimen of HRT, including the dose and route of estradiol administration and type of progesterone.

HRT should therefore not be viewed as one intervention with a set risk profile that applies to all. Starting HRT in women in their early to mid-50s, using transdermal estradiol in combination with micronised progesterone, is likely to have a lower risk profile to that reported in the WHI study. The age of the woman at the time of starting HRT, the route of administration of estradiol and the dose of HRT used, as well as the type of progesterone, may all have a significant impact on the risk profile of HRT, and this message should be given to women to help them make an informed choice.

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