Hormone-replacement therapy: current thinking

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Abstract | For several decades, the role of hormone-replacement therapy (HRT) has been debated. Early observational data on HRT showed many benefits, including a reduction in coronary heart disease (CHD) and mortality. More recently, randomized trials, including the Women's Health Initiative (WHI), studying mostly women many years after the the onset of menopause, showed no such benefit and, indeed, an increased risk of CHD and breast cancer, which led to an abrupt decrease in the use of HRT. Subsequent reanalyzes of data from the WHI with age stratification, newer randomized and observational data and several meta-analyses now consistently show reductions in CHD and mortality when HRT is initiated soon after menopause. HRT also significantly decreases the incidence of various symptoms of menopause and the risk of osteoporotic fractures, and improves quality of life. In younger healthy women (aged 50–60 years), the risk–benefit balance is positive for using HRT, with risks considered rare. As no validated primary prevention strategies are available for younger women (<60 years of age), other than lifestyle management, some consideration might be given to HRT as a prevention strategy as treatment can reduce CHD and all-cause mortality. Although HRT should be primarily oestrogen-based, no particular HRT regimen can be advocated.

Clinical practice regarding the use of hormone-replacement therapy (HRT) has undergone many changes since it was first introduced in the 1940s. At present, the pendulum seems to be swinging back to more acceptance of use, following a marked reduction in prescriptions after the initial results of the Women's Health Initiative (WHI) study were published in the early 2000s. Following these reports, the term 'HRT' was replaced in the USA with 'hormone therapy' or 'menopausal hormone therapy'. In this Review, I focus on what frames the current thinking on use of HRT in postmenopausal women, beginning with a historical perspective and then discussing how the interpretation of HRT data has changed over time.

Hormone-replacement therapy

Historical perspective

Conjugated equine oestrogens (CEE) were first approved for use in the USA in 1942 (REF. 1). Use of oestrogen after menopause became popularized in the late 1960s with the erroneous concept that it would render women 'feminine forever'[2] and then increased further after 1988 when its use was approved by the FDA for the prevention of osteoporosis[3]. With increasing use, various observational cohorts were examined, and use of oestrogen therapy further increased during the 1990s, when these observational data suggested a decrease not only in osteoporosis but also in coronary artery disease and mortality, as well as risk of Alzheimer disease[4–6]. In the mid 1970s, unopposed oestrogen therapy in women with a uterus was recognized to increase the risk of uterine cancer; however, the addition of progestogen to the hormone regimen was subsequently shown to minimize or eliminate this risk[7]. Breast cancer risk was suggested, but was never convincingly shown to be increased with HRT, at that time. The risk of stroke with oestrogen therapy was also uncertain, with some possible small increase, but contradicted by studies showing benefit in older women, 15 or more years from menopause onset[8]. As coronary heart disease (CHD) has the highest case fatality rate, the reduction in CHD with HRT was thought to have the greatest effect on mortality; all-cause mortality was shown to be decreased by 20–40% with HRT in observational studies[9,10]. These findings were an important driver of the decision for women to use HRT after menopause. Meta-analyses carried out at the time suggested HRT would result in one or more additional years of life[10], a large benefit in epidemiological terms (FIG. 1).

So strong was the conviction that oestrogen was 'cardioprotective', as a result of the possible attenuating effects of added progestogens, an International Progestogen Consensus meeting was convened in 1988 (REF. 11) to increase understanding of the role of

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Key points

- The use of hormone-replacement therapy (HRT) has been vigorously debated
- Earlier observational data showed many benefits of HRT, which include reduced coronary heart disease (CHD) and mortality
- Randomized trials in older women (aged >60 years) have shown no benefit and increased harm
- Reassessment of clinical trials in women initiating treatment close to the onset of menopause and newer studies and meta-analyses now show benefit and rare risks
- More studies show benefit with oestrogen alone than with oestrogen plus progestogen
- The effects of reduced CHD and mortality in women initiating therapy around menopause suggest a possible role for HRT in primary prevention

progestogens in protecting the uterus, yet minimizing the attenuating effect on the cardiovascular system. The FDA also held an advisory meeting to consider an 'indication' for the cardioprotective effects of oestrogen, and although there was strong support for this effect[12], the FDA ultimately decided that randomized clinical trial data were needed.

Randomized clinical trials

As cardiovascular events are rare in young women and accrue over many years, randomized clinical trials in women with established coronary disease (also known as secondary prevention trials) were deemed to be the most efficient way to assess the efficacy of HRT. Several trials were carried out in women in their sixties with established disease[13–15]. In these short duration trials (averaging 3 years), not only did HRT show no benefit, but some studies such as the Heart and Estrogen/Progestin Replacement Study (HERS)13 showed evidence of 'early harm'; that is, increased cardiac events occurring in the first 1–2 years. While these trials were going on, in the USA, the WHI (sponsored by the NIH), was planned and began to enrol women. Although the WHI was comprised of several studies including diet, calcium and vitamin D supplementation, two hormone trials, considered to be primary prevention trials, were included. These trials involved 0.625 mg of CEE or placebo in women who had undergone a hysterectomy, and a fixed combination of 0.625 mg of CEE plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo in women with a uterus. Enrollees were aged 50–79 years, with only 20% of the women aged 50–60 years and 5% aged <54 years. The majority of women were, thus, older (>60 years) and, as atherosclerosis progresses with age, many of the women studied were considered to fall in the category of a secondary prevention trial, involving women with established disease.

In 2002, the initial results of the WHI for the fixed combination of CEE and MPA were published after a mean of 5.2 years of treatment[16], and the data were widely disseminated to the media. The bottom-line message was an increased risk of coronary disease and breast cancer, the latter finding being the major reason the CEE–MPA trial was terminated early. The message to the media was that HRT was associated with more harm than good, and that this correlation pertained to women of all ages and occurred with all types of HRT. More alarming for women, was the message the media heard and which was disseminated to the public; that is, a manifold increase in risk of harm was associated with HRT. For example, a borderline significant relative risk (RR) of breast cancer (1.24) was portrayed as a 24-fold increase in risk; absolute numbers of increased risk were never provided. Surprisingly, the principal investigators of these NIH-sponsored trials were not involved in the data analyses and did not see the data before it was presented to the media. The acting director of the NIH made the statement that the data were pertinent to all women and for all types of hormone therapy[17]. Following this announcement, almost all women abruptly stopped using HRT, which occurred before health-care providers had read the initial publication.

The oestrogen alone trial using 0.625 mg CEE in women who had undergone a hysterectomy continued and the initial data were published in 2004 after an average of 6.8 years of treatment[18]. Although no increased risk of breast cancer or coronary disease was noted, the trial was stopped early due to evidence of a risk of ischaemic stroke. With the pervading pessimism regarding HRT at the time, the overall message remained negative. However, the trials confirmed some of the benefits of HRT such as a reduction in osteoporotic fractures and colon cancer and, with CEE alone, a reduction in breast cancer[18]. These findings were, however, insufficient to offset the negative aspects associated with hormone use, including an increase in venous thromboembolism with oral oestrogen (discussed later).

A sub-study of the CEE–MPA trial did find a decline in cognition in the hormone group compared with the placebo group[19]; however, only women aged >65 years at initiation of therapy were studied. These observations on cognitive decline were not found in the CEE alone trial[20].

In subsequent publications from the WHI, the data were not as clear as those from the first publication. Indeed, many of the point estimates of risk changed several times (reviewed elsewhere[21]). For breast cancer risk with CEE plus MPA, the borderline statistically significant risk was not significant when adjustments were made for confounders[22]. Indeed, the risk over the 5.2 years of the trial only increased for previous users of HRT who had stopped therapy some time before entering the trial, and then restarted HRT during the trial. Women who had never used HRT in the past had no increase in risk over the duration of the trial[22]. In the CEE alone group, the incidence of breast cancer was significantly decreased, particularly among adherent women[23]. After 10 years of use, both total mortality and breast cancer mortality (in women who were diagnosed with breast cancer) were significantly lower in the CEE alone group than in the placebo group[24].

In 2006, the first study from the WHI that included age stratification for coronary disease outcomes with the use of CEE was published[25]. The findings showed that CEE had a protective effect in younger women (aged 50–59 years), but a significant trend of worsening outcomes was observed in older women (aged ≥60 years). A composite coronary score in women aged 50–59 years

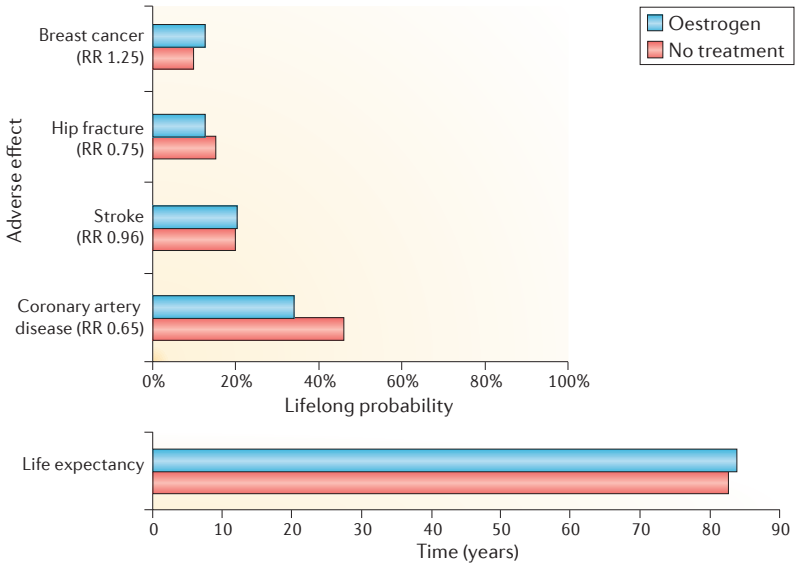

Figure 1 | **Adverse effects in women treated with HRT.** Data shown represent lifelong probability of adverse effects in 50-year-old white women; uterus status and progestogen addition have been omitted for simplicity. Effects of oestrogen (blue) versus no treatment (red). Relative risks (RR) and probabilities extracted taken from elsewhere[8]. HRT, hormone-replacement therapy.

showed a statistically significant benefit of using CEE alone[25]. In the following year, a subsequent paper from the WHI showed that in women aged 50–59 years or those <10 years from menopause onset, total mortality decreased significantly by 30%[26], when the CEE alone and CEE plus MPA groups were combined in the analysis. This figure is in line with reports from early observational data[9,10]. Although the findings were not robust, the two papers from the WHI[25,26] showed, for the first time, a modest interaction between coronary disease and age and time from menopause onset.

By this time, the media were again increasingly engaged in interpreting the findings of the WHI. In several reports, the media reported the shortcomings of the interpretation of the findings of the WHI. An example of this engagement was the report in 2007 in the Wall Street Journal, entitled "How NIH misread the Hormone Study in 2002"[27]. The article stated that "some aspects of what was reported were misleading or just wrong … women in their 50s had a 30% lower risk of dying…"[27].

In the 13 year follow up of the WHI, which included data from both the intervention (5.2 or 6.8 years on average for CEE plus MPA and CEE alone, respectively) and follow-up phases of the trial, for the original concern of coronary disease, no group showed a statistically significant risk (BOX 1)[28]. In this publication, the risk–benefit balance was clearly positive, favouring coronary benefit in the group aged 50–59 years, but the changes were less favourable with CEE plus MPA than with CEE alone. The beneficial changes in the group aged 50–59 years using CEE alone after 13 years of follow up are depicted in BOX 2. Even though participants in the CEE and CEE plus MPA trials were different populations of women and used different hormonal regimens that were not directly compared in the WHI, the data suggested an attenuating effect of the added progestogen. This finding was in keeping with the long acknowledged potential concern regarding the use of progestogens in HRT[11].

Cessation of HRT since the initial results of randomized trials. As noted earlier, prescriptions for HRT have decreased substantially since 2002 (REFS 29,30), with HRT now thought to be prescribed to 5% of the population of women in the USA over the age of 40 years[30]. A number of studies have reported on the effect of stopping HRT. Two studies have documented an increase in hip fractures in women who stopped taking HRT[31,32]. A mathematical model has also been used to suggest that women undergoing hysterectomy and bilateral salpingo-oophorectomy in the USA who did not receive oestrogen therapy would be expected, over a 10-year period, to have an excess of premature deaths (in the range of 19,000–92,000 women) due to coronary disease[33]. A 2015 report from Finland suggested that abrupt cessation of HRT leads to a significant increase in myocardial infarction and stroke, particularly in younger (aged <60 years) women[34]. While it is unclear how significant or relevant this finding is, as this increased risk was not observed in the WHI[28], this study provided additional indication of the benefits of HRT on the cardiovascular system, particularly in younger (aged <60 years) women[35].

An intriguing report has compared changes in male and female mortality in the mid 1990s with those in the years 2002–2006 in various states in the USA[36]. While the rate decreased in men, it increased in women[36]. Although we cannot point to the aftermath of the WHI as an explanation, it does make the important point that, at present, a major opportunity to improve the health care of women exists.

Early observational and secondary prevention trial data versus initial WHI findings. As publication of various secondary prevention trial data in the early 2000s[13–15], including that of the WHI[16], were at odds with the findings of observational data[9,10], the 'timing hypothesis' was put forth[37]. Simply stated, the timing hypothesis suggested that a different clinical effect occurs if hormones are initiated close to the onset of menopause compared with several years later. This hypothesis was developed on the basis of a series of basic and clinical studies that showed important vascular effects of oestrogen, which are mediated via the oestrogen receptor in both genomic and nongenomic ways (FIG. 2)[38]. Comparing the effects of HRT from observational data with that from randomized trials, agreement exists in many areas. This accord includes a decrease in osteoporosis, some increase in stroke, some increase in breast and endometrial cancer, a decrease in colon cancer and an increase in venous thrombosis with oral HRT. However, disagreement exists in the areas of CHD, cognitive decline and Alzheimer disease. Observational data showed that HRT was of benefit, yet the randomized trial data suggested no benefit and a suggestion of some harm. As the observational data pertained to women who initiated HRT at a younger age (usually at the onset of menopause for symptom relief) and the randomized trial data pertained to women who

Box 1 | **Relative risks for CEE and MPA**

Intervention phase (entire group)

- 1.18 (0.95–1.45)

Cumulative follow up:

- Entire group: 1.09 (0.96–1.24)
- 50–59 years: 1.27 (0.93–1.74)
- 60–69 years: 0.97 (0.79–1.18)
- 70–79 years: 1.17 (0.95–1.44)

Follow-up data from the conjugated equine oestrogens (CEE) plus medroxyprogesterone acetate (MPA) study of the Women's Health Initiative (WHI) showing coronary risk for the entire group during the intervention phase and the various age groups after 13 years. None of the findings were statistically significant[25].

were mainly asymptomatic and older (WHI, mean age 63 years; HERS, 67 years), the CHD and cognitive decline effects of HRT were hypothesized to be dependent on age and the time of HRT initiation. In the WHI, only women aged over >65 years were included in the sub-study for cognitive decline[19,20].

Testing of the timing hypothesis was first carried out in the cynomolgus monkey model[37]. After bilateral oophorectomy, monkeys treated immediately with CEE showed a 70% reduction in coronary atherosclerosis at necropsy compared with placebo-treated monkeys. However, monkeys who had the same treatment after a delay of 2 years showed no changes in coronary atherosclerosis[37,39]. This delay in the monkey model of 2 years was thought to correspond to ≥6 years in humans.

The women in the WHI aged 50–59 years had a beneficial (protective) effect for CHD compared with the older groups of women, which included women up to age 79 years. As discussed earlier, CEE alone had a beneficial composite coronary score in younger (aged <60 years) women[25] and, when both groups (CEE alone and CEE plus MPA) were combined, women aged 50–59 years in the WHI had a statistically significant reduction in mortality of 30%[26]. The coronary benefit reported in the WHI was predominantly with CEE alone rather than CEE plus MPA.

In a prospective trial, Early versus Late Intervention Trial with Estradiol (ELITE), that tested the timing hypothesis, carotid intima–media thickness as the primary end point, was shown to be significantly less over 5 years with oral oestradiol (1 mg daily) than with placebo, which is consistent with oestrogen causing an inhibition of atherosclerosis progression[40]. However, this effect only occurred in women within 6 years of the onset of menopause and was not present in another group of women who were >10 years from onset of menopause[40]. Another observational study evaluated incident CHD rates over an average of 13.4 years in women treated with HRT either when initiated <5 years or >5 years from onset of menopause. Early initiation, but not late initiation, of HRT had a protective effect[41].

The timing hypothesis could also relate to carbohydrate metabolism. In a prospective trial of two groups of postmenopausal women who were close to the onset of menopause in one group or at 10 years after onset in the other, short-term transdermal oestradiol increased the glucose disposal rate in women <6 years from menopause onset, but not in women >10 years from menopause onset[42]. This differential effect was thought to be due to loss of oestrogen receptor (ER; also known as ERα) function in older individuals.

The effects of cognitive decline and dementia are less clear cut at present owing to the lack of sufficiently long clinical trials in younger (aged <60 years) women. However, animal data clearly show an age and timing effect of neuroprotection, with oestrogen providing benefit only in younger animals, which relates to maintenance of ERα-related activity and levels of microRNAs that regulate genes important for cognitive activity[43,44]. Although the sub-study of the WHI in older (aged >65 years) women showed a worsening of cognition with CEE plus MPA[19], observational data including meta-analyses were consistent in showing a beneficial effect on cognition and Alzheimer disease[45]. One observational study found that the benefit was only associated with an earlier age (<60 years) of HRT initiation[46], which has also been shown in other cross-sectional data[47]; all these findings are consistent with a timing hypothesis for cognitive decline.

Taken together with basic and animal studies, the clinical studies supporting the timing hypothesis are convincing to many in the field, but detractors exist who point to a paucity of prospective randomized data.

Effects on various organ systems

Symptoms of menopause. Treatment of vasomotor symptoms remains the primary indication for HRT. All oestrogen products, with and without progestogen, have proven efficacy for the reduction of hot flushes (shown in many placebo-controlled studies and meta-analyses) and are superior to other non-hormonal therapies[48]. Symptoms of menopause extend beyond hot flushes alone; for example, musculoskeletal complaints are more prevalent than hot flushes in Asian women[49].

Other symptoms associated with onset of menopause include depressive mood, irritability and sleep disruption; HRT could also be beneficial for symptomatic relief and for improving quality of life[48–52]. Vulvovaginal complaints are more frequent later in menopause (usually after 10 years) and usually respond better to local than systemic therapy[53].

Osteoporosis. Observational and randomized trial data are all in agreement that HRT is beneficial for the prevention and treatment of osteoporosis. In the USA, owing to the concern for harm raised by the randomized trial data in older (aged >60 years) women discussed earlier, the 'treatment' indication has been dropped. A 2015 meta-analysis showed a highly significant reduction in fractures with HRT[54], and this effect seems to be greater in younger (aged <60 years) women than those treated later. Various types of oestrogen have been shown to be efficacious, but a dose-response effect exists, with higher doses usually being more effective, but with some women even responding well to very low doses[55]. The

addition of progestogen to oestrogen does not interfere with this benefit and might enhance the benefit by stimulating bone formation, particularly with certain more androgenic progestogens[56]. Women who do not complain of symptoms at the time of menopause but who are at increased risk of osteoporotic fractures are considered to be candidates for HRT[57].

Coronary heart disease. To be clear, randomized trial data show that young healthy women within 10 years of menopause onset do not have an increased coronary risk with HRT. Indeed, consistent data now exist that HRT prevents coronary disease in younger (aged <60 years) women at the onset of menopause, which ultimately translates to a reduction in mortality. In terms of available prospective randomized trial data, the strongest data are with the use of oestrogen alone. In older (aged >60 years) women, and particularly those who have established coronary disease and/or significant cardiovascular risk factors, concern exists that HRT might cause additional events within the first 1–2 years of use (called 'early harm'). When the coronary arteries are affected by atherosclerotic plaques, oral oestrogen induces levels of matrix metalloproteinases (MMPs) that dissolve away a portion of the plaque resulting in plaque instability, which can result in rupture and thrombosis[58,59]. In younger (aged <60 years) women with minimal coronary plaques, even if levels of MMPs increase with HRT, no substrate is present at the arterial wall for such action to occur. Early harm was observed in secondary prevention trials[13], when oral oestrogen in moderate doses was used. The follow-up cumulative data from use of CEE plus MPA, however, showed no increased coronary risk in any group[28] (BOX 1), whereas a trend was evident for risk in some years and particularly for the oldest group (>20 years from menopause onset). In a pooling of prospective trials of women <5 years from the onset of menopause who received CEE plus MPA for 1–2 years, no events were found[60].

In older women ≥10 years from the onset of menopause, HRT should be used with caution, and only in those who have significant symptoms, with a low dose non-oral regimen advocated. In older (aged >60 years) women with coronary plaques, not only could there be 'harm' as discussed earlier, but oestrogen action can be inhibited by several mechanisms: loss of receptors (ERα), methylation of ERα and interference by 27-hydroxycholesterol might inhibit oestrogen action[61,62]. Younger (aged <60 years) women with certain cardiovascular risk factors have been suggested to receive non-oral oestrogen. Transdermal oestrogen does not increase levels of MMPs and also does not carry a venous thrombosis risk.

The coronary benefit in younger (aged <60 years) women, mentioned earlier, fits in with the 'timing' or 'window' hypothesis. Prospective trial data suggest that treating women (primarily with oestrogen) within 6 years of menopause has a strong coronary benefit, whereas in the WHI, the data also pertained to women who were treated within 10 years of menopause[25,28,63,64]. A meta-analysis of randomized trials, including the WHI, showed that initiation of oestrogen <10 years from the onset of menopause resulted in a 32% reduction in coronary disease (RR 0.68, 95% CI 0.48–0.96.)[65].

In a prospective randomized trial comparing 0.05 mg transdermal oestradiol with 0.45 mg CEE and placebo in women within 3 years of menopause, carotid intima–media thickness was not different in the three groups over 4 years[66]. This trial did not test the 'timing hypothesis', as no group more distant than 3 years from menopause onset was treated. This study, the Kronos Early Estrogen Prevention Study (KEEPS), eliminated participants if they had measurable coronary levels of calcium, which also did not change over the 4 years. The lack of discrimination between the oestrogen and placebo groups was, therefore, thought to be related to the fact that these women were very healthy and the trial was not of a sufficient duration to see divergent effects. Micronized progesterone, 200 mg for 12 days each month, was used for endometrial protection. Both ELITE (described earlier) and KEEPS did not find significant changes in coronary levels of calcium, which suggests that longer time intervals might be required to see less calcium deposition with oestrogen, as was found in a sub-study of the WHI with CEE alone.

In sub-analysis of data from the WHI, the coronary and mortality effects were greater with CEE alone than with the fixed combination of CEE plus MPA[28]. However, randomized clinical trial data from Denmark[64] suggest that different hormonal regimens (17β-oestradiol with and without norethindrone acetate) are as effective in reducing coronary disease as CEE[28]. Similar findings using these hormonal preparations have also been reported in a series of observational studies conducted in Finland, which reported decreased mortality[67,68].

As the age-stratification data from the WHI was a secondary analysis, and there is only one other smaller randomized trial showing a coronary benefit with decreased mortality[64], some investigators are not convinced that a cardioprotective effect of oestrogen exists in younger (aged <60 years) women who initiate therapy soon after the onset of menopause. However, combined with newer observational data[67,68] and several meta-analyses[65,69,70], the data are extremely consistent in showing benefit, which is very similar to data from older observational studies[9,10].

Stroke risk. An increased risk of stroke with HRT has been reported in several studies, although the data are not consistent[71]. The putative risk is for ischaemic stroke, not haemorrhagic stroke, and a meta-analysis has suggested an overall risk in the range of 1.3 to 1.4[72]. In younger (aged <60 years) women, owing to the low

Box 2 | **Relative risks for CEE alone**

- Coronary heart disease: 0.65 (0.44–0.96)
- Myocardial infarction: 0.60 (0.39–0.91)
- Breast cancer: 0.76 (0.52–1.11)
- All cancers: 0.80 (0.64–0.99)
- Global index: 0.82 (0.82–0.98)
- Total mortality: 0.78 (0.59–1.03)

Cumulative data after 13 years in the conjugated equine oestrogens (CEE) alone trial of the Women's Health Initiative (WHI): findings presented for the 50–59-year-old group[25].

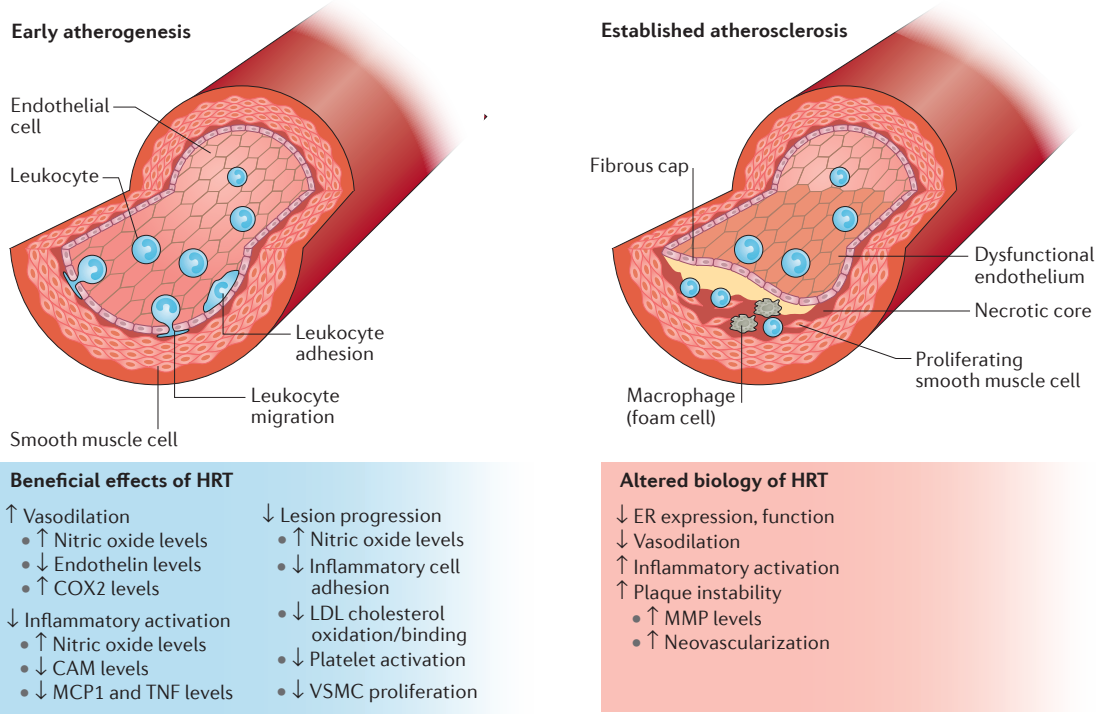

Figure 2 | **Coronary vessels in atherosclerosis.** Left panel depicts coronary vessels in a young woman with early atherosclerosis. Right panel depicts coronary vessels in an older (aged >65 years) woman with established atherosclerosis. Various effects of hormone-replacement therapy (HRT) on the vessels in the two stages of atherosclerosis are shown, with benefit in young arteries and altered biology in old arteries. CAMs, cell adhesion molecules; COX2, cyclooxygenase 2; ER, oestrogen receptor; MCP1, monocyte chemoattractant protein 1; MMP, matrix metalloproteinase; TNF, tumour necrosis factor; VSMC, vascular smooth muscle cell. Permission obtained from the American Association for the Advancement of Science © Mendelsohn, M. E. & Karas, R. H. *Science* **308**, 1583–1587 (2005).

prevalence of stroke, studies have varied as to whether a true statistically significant increase in risk exists, particularly when cofounders such as obesity and hypertension are controlled for[71]. A 2015 Cochrane analysis did not find an increased risk of stroke in younger (<60 years) women[70]. The studies suggesting some small risk of stroke, even in younger (aged 50–60 years) women, relate this risk to moderate to high doses of oral oestrogen[72]; an increased risk of stroke with non-oral oestrogen has not been found in observational studies[73]. Ischaemic stroke in younger (aged <60 years) women has, therefore, been proposed to be due to a thrombotic mechanism[74]. Indeed, young premenopausal women also have a thrombotic risk of stroke with oral contraceptives[75], and these events might be related to undiagnosed thrombophilia risk factors in the women affected. Although a genuine risk might not exist in younger (aged <60 years) women, if a statistical increase in the range of RR from 1.3 to 1.4 with moderate doses of oral oestrogen is assumed, the absolute risk is very small, increasing the event rate from 3.8 per 10,000 women per year in those aged 50–54 years by an additional 1.5 cases per 10,000 women per year.

Venous thrombosis risk. Oral oestrogen in HRT, as well as oral contraceptives, are well known to increase the risk of venous thromboembolism by about twofold[76–78], which is dose-related and increases with age. The risk is increased 5–10-fold if a known thrombophilia such as Factor V Leiden is present, although screening the general population for these risks is not considered cost effective at the present time. With HRT, progestogen increases the risk further[76,77], although the risk is not increased with transdermal oestrogen in observational studies[77,78]. Venous thromboembolism has not been found to be associated with an increase in mortality[70]. With moderate doses of oral oestrogen, the absolute risk of venous thromboembolism in women within 10 years of menopause increases from 6 to 11 cases per 1,000 women per year[28]. Women taking oral HRT who sustain a venous thromboembolism probably have some undiagnosed thrombophilia risk that was not triggered in the past if they were not been exposed to oral contraceptives. These events tend to occur early in treatment, in the first 2 years. Overall, the risk of venous thromboembolism decreases with time, as the susceptible population would have sustained events during earlier exposure to treatment.

Cancer. Although most women believe that the leading cause of death is due to breast cancer, the leading cause of death in women, by far, is actually cardiovascular disease[79]. The leading cause of cancer mortality is lung cancer[80]. Although some association between HRT and the risk of lung cancer has been suggested, in the 15-year follow-up to the WHI CEE–MPA trial, no statistically significant increase in lung cancer or change in mortality was found[81]. Concerns exist about a potential increased

risk of several other cancers with HRT, namely breast, endometrial and ovarian cancers. The data, however, are fairly consistent in suggesting a decrease in the risk of colon cancer[82].

Multiple observational studies and meta-analyses have shown a reduction in the risk of colon cancer in the range of 20%[82]. The WHI CEE–MPA trial showed a significant reduction, whereas the study with CEE alone did not, for reasons that are not clear[83]. The mechanism for this association might be manifold, but one strong possibility in that oestrogen working through ERβ might induce apoptosis in polypoid lesions[84]. However, HRT should not be used solely for the purpose of prevention of colon cancer.

The association between HRT and breast cancer has been studied for many years. The majority of studies have shown some increased risk with oestrogen combined with progestogen, related to dose and duration of use[85]. However, this increased risk is small and, therefore, is not statistically significant in some studies. Of interest, the level of risk seems to be greater in observational data than in data from randomized controlled trials, which is possibly related to confounders and duration of therapy. Oestrogen-alone therapy, at a standard dose of CEE (0.625 mg) has been shown not to increase the risk of breast cancer with up to 15 years of use[86], although some studies have suggested a small risk, both with CEE and oestradiol[87]. This finding has led to speculation that CEE has fewer promotional effects than oestradiol (as it contains a mixture of oestrogens, some which might have selective effects on the oestrogen receptor), although this speculation remains unproven. In the WHI, the CEE alone group showed a statistical decrease in breast cancer[23,24]. However, combined oestrogen plus progestogen therapy and, particularly the use of MPA, has been shown to increase the risk of breast cancer[16,88]. In the WHI, the borderline statistically significant increase with CEE plus MPA reported initially was not significant upon reanalysis when adjustment was made for confounding variables[22]. Furthermore, breast cancer risk was only increased in women who had used HRT in the past, which suggests that longer durations of use of oestrogen plus progestogen might increase the risk beyond the 5.6 years of the WHI trial. Other observational data using 'natural' progesterone have suggested no increased risk[87], raising the suggestion that the type of progestogen might influence the promotional effect.

Current thinking regarding the risk of breast cancer with HRT is that oestrogen might exert a promotional effect on occult tumours. As occult breast tumours are common and only become clinically detectable after ≥10 years, this slow doubling time is shortened by a promotional effect of oestrogen and/or oestrogen plus progestogen 'feeding' these usually ER$^+$ tumours[88]. This promotional effect is probably greater with oestrogen plus progestogen than with oestrogen alone, particularly with certain progestogens. With oestrogen alone, the promotional effect is low, or even negligible. The observation in the WHI of a decrease in breast cancer risk might be explained by an apoptotic effect in women who had not received oestrogen for some time after menopause. These occult dormant tumours, when deprived of oestrogen for several years after menopause, might then undergo increased apoptosis when exposed to oestrogen[89]. With oestrogen alone, both total mortality and breast cancer mortality have been shown to be decreased[24]. Other studies have also suggested that women who develop breast cancer while taking HRT also have decreased mortality.

To put the clinical risk of breast cancer with HRT in perspective, it is important to compare this putative risk (with oestrogen plus progestogen) with other endogenous and lifestyle risks (FIG. 3). The risk with CEE plus MPA (adjusted data)[22] or CEE alone[28] for 5 years is less than that of being overweight, having a late first birth, having been born with dense breasts (the single highest risk factor) or even occupational exposures such as being a flight attendant[90,91].

Uterine (endometrial) cancer has been associated with the use of oestrogen alone (without the addition of progestogen). Oestrogen in the absence of progestogen leads to hyperplasia of the endometrium and ultimately to well differentiated endometrioid cancer in some women[92]. Oestrogen alone therapy in the WHI was only used in women who had undergone a hysterectomy. In women with a uterus, the combined oestrogen plus progestogen regimen actually caused a statistical decrease in endometrial cancer (RR 0.65, 95% CI 0.48–0.89)[93] owing to the continuous progestogen exposure keeping the endometrium atrophic in comparison to that in women on placebo, who have some endogenous hormone production. Use of other progestogen regimens, such as sequential regimens, reduces the risk of oestrogen alone therapy but does not decrease endometrial cancer rates[94]. No association between HRT and poorly differentiated serous tumours, which are usually not ER$^+$, has been demonstrated.

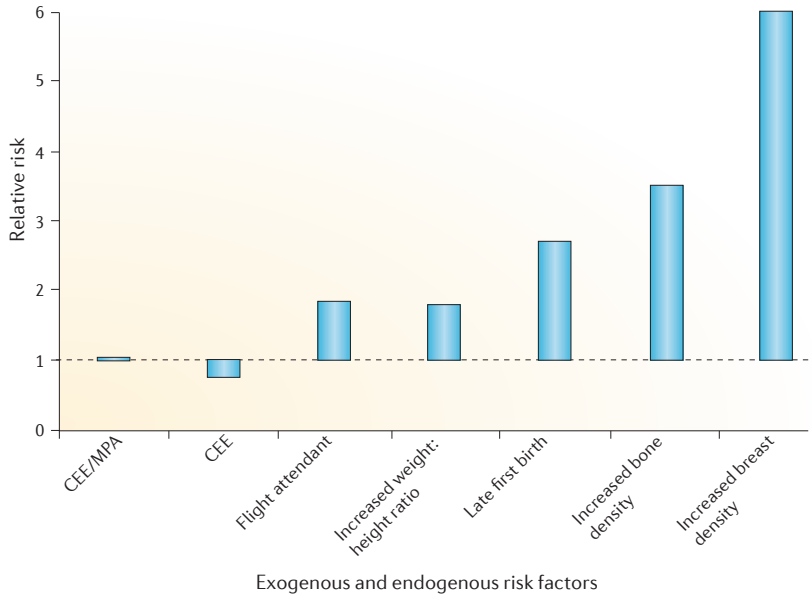

Figure 3 | **Breast cancer risk.** Relative risks of breast cancer associated with treatment with conjugated equine oestrogens (CEE) alone or with medroxyprogesterone acetate (MPA), occupational exposures and endogenous risks. Data obtained from elsewhere[19,25,81,82].

Box 3 | **Reduction in Mortality with HRT**

- Observational meta-analysis[86]: 0.78 (0.69–0.90)
- Randomized trials meta-analysis[86]: 0.73 (0.52–0.96)
- Bayesian meta-analysis calculation[86]: 0.72 (0.62–0.82)
- WHI combined groups[23]: 0.70 (0.62–0.82)
- WHI 13-year cumulative (CEE alone)[25]: 0.78 (0.59–1.03)
- WHI 13-year cumulative (CEE plus MPA)[25]: 0.88 (0.70–1.10)
- Cochrane meta-analysis[66] (randomized trials): 0.70 (0.52–0.95)
- DOPS oestradiol alone[61] (randomized trial): 0.66 (0.41–1.08)
- DOPS oestradiol/sequential NETA[61] (randomized trial): 0.57 (0.30–1.08)
- Finnish registry (pre-WHI)[87] (observational): 0.57 (0.48–0.66)
- Finnish registry (post-WHI)[87] (observational): 0.46 (0.32–0.64)
- Finnish data on oestradiol products[88] (observational): 0.63 (0.62–0.65)

Consistency of results for reduction in all-cause mortality with oestrogen or oestrogen plus progestogen for at least 5 years of hormone-replacement therapy (HRT) in women aged <60 years. CEE, conjugated equine oestrogens; DOPS, Danish Osteoporosis Prevention Study; MPA, medroxyprogesterone acetate; NETA, norethindrone acetate; WHI, Women's Health Initiative.

Controversy exists about whether HRT increases the risk of ovarian cancer, with some studies showing some small increase[95] and others showing no statistically significant increase[28,96]. Owing to the low prevalence of ovarian cancer, the absolute risk of ovarian cancer if there were to be a 20% increase would increase the rate from 5 per 10,000 women to 6 per 10,000 women per year. In women aged 50–59 years, in whom the overall prevalence of cancer is low, long-term follow up of oestrogen alone therapy showed that the total cancer risk was significantly decreased by 20% (RR 0.80, 95% CI 0.64–0.99)[28] (BOX 2).

Mortality changes. Observational data have been consistent in showing a 20–40% reduction in all-cause mortality with the use of oestrogen[9,10]. As discussed earlier, these cohorts were comprised of younger (aged <60 years) women within 10 years of menopause who were prescribed oestrogen primarily for symptoms of menopause. The current data from randomized clinical trials and meta-analyses are consistent with this finding (BOX 3). Data from the WHI in the combined groups of women aged 50–59 years showed a 30% reduction in mortality[28] and, in the follow-up study that collected data for up to 13 years, the CEE alone groups had a reduction in mortality of 22% (hazard ratio (HR) 0.78, 95% CI 0.59–1.03)[28]. A Bayesian meta-analysis, which analysed data from the observational and randomized clinical trials, showed a composite estimate of a 28% reduction in mortality (HR 0.72, 95% CI 0.62–0.82)[69]. A Cochrane analysis on mortality changes with HRT also showed a similar point estimate of 0.70 (0.52–0.95) for all-cause mortality in women <10 years from menopause onset, and a reduction in CHD mortality of 0.52 (0.29–0.96)[70]. As noted earlier, a randomized clinical study from Denmark and observational studies from Finland, using different HRT products, also produced consistent findings (BOX 3). These latter data suggest that oestradiol might be as beneficial as CEE, and certain progestogen preparations and regimens might not attenuate the benefits observed.

Although the consistent reduction in all-cause mortality is primarily thought to be explained by the reduction in cardiovascular mortality, it is important to note that in the WHI, breast cancer mortality with CEE alone was significantly decreased[24], as was the rate of all cancers[28].

Risks and benefits in perspective

Prescribing HRT to women might be associated with some adverse effects as well as the benefits described earlier. Many of the adverse effects are not life-threatening and can be dealt with by adjusting the dose and preparation of HRT. These effects include breast tenderness, abdominal bloating, mood changes, uterine bleeding and an idiosyncratic elevation in blood pressure that might occur with oral oestrogens.

More serious concerns such as venous thromboembolism and cancer risk have to be considered, but in young healthy women these risks are small or not significantly increased over placebo treatment. Understanding the balance of risk requires an examination of absolute risks (FIG. 4; long-term data taken from the WHI for consistency; however, this represents the results of one type of oestrogen and a fixed combination with MPA). Indeed, less specific information on event rates are available for other studies[64,67,68] using different oestrogens and progestogens; however, the available data suggest no increased risks or serious adverse effects of HRT. In the WHI analysis, the data (FIG. 4) clearly show a more beneficial effect in younger (aged <60 years) women than in women aged >60 years using oestrogen alone. The absolute rates of changes (difference in events minus placebo per 1,000 women for 5 years of therapy) are all beneficial with the exception of venous thromboembolism risk[28], which has an absolute excess rate of 2.5 additional cases per 1,000 women over 5 years (considered by the WHO to be in the 'rare' category). However, these beneficial rates averaging around five events per 1,000 women per 5 years are small in comparison with the reduction in symptomatic relief (hot flushes and vaginal atrophy), which are in the range of 800–900 women per 1,000 women per 5 years[97].

In studies before the WHI (2002), HRT was reported to be cost effective. A later publication in 2009 also showed an increase in quality-adjusted years, primarily in younger (aged <60 years) women, but also to some extent in older (aged >60 years) women who initiate HRT[98].

Recent guidelines

Several professional society guidelines have been published and updated recently[99,100] including one from the National Institute for Health and Care Excellence (NICE)[101]. As complete details of all these guidelines are beyond the scope of this Review, only the major points of distinction will be discussed. In general, all guidelines point to the efficacy and safety of prescribing oestrogen to women at or around the onset of menopause for relieving the symptoms of menopause[57,99-101]. In addition, several guidelines specifically state that HRT is efficacious for symptoms of menopause other than hot flushes[99,100]. The addition of progestogen in some form

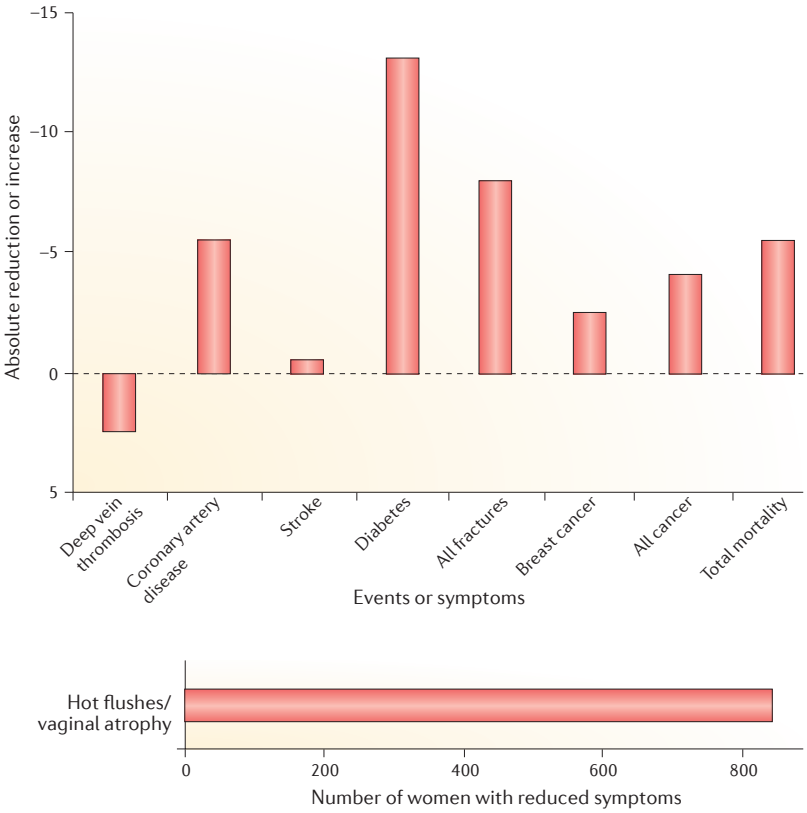

Figure 4 | **Events and symptoms associated with CEE.** Absolute changes in events or symptoms (minus placebo effect) per 1,000 women aged 50–59 years who were treated for 5 years with conjugated equine oestrogens (CEE). Data obtained from elsewhere[25,89].

is recommended for women with a uterus, but not for women who have undergone a hysterectomy. One statement specifically states that HRT is also appropriate even in asymptomatic young women who are at significant risk of osteoporotic fractures[57]. Statements from the Endocrine Society[100], the International Menopause Society[99] and NICE[101] do not give a pre-specified duration of treatment, but an earlier statement from the North American Menopause Society (NAMS)[57] suggested a reduced interval of use owing to concern about breast cancer risk. The 2016 International Menopause Society report also stated that a reduction in coronary disease as well as mortality occurs in younger (aged <60 years) women using oestrogen-based therapies[99].

The Endocrine Society statement[100] and an algorithm developed by NAMS[102] for treatment of moderate to severe hot flushes suggest screening women before the onset of menopause for cardiovascular disease and risk of breast cancer. Using the American College of Cardiology/American Heart Association risk calculator, women at moderate risk (that is, 5–10% cardiovascular disease risk over 10 years) should use transdermal therapy and women with a risk >10%, even at a young age, should avoid HRT[100,102]. The NICE guidelines[101] also suggest use of transdermal therapy in high-risk women, such as those who are obese. Regarding breast cancer, the NAMS algorithm[102] and that of the Endocrine Society[100] suggest that when using a breast cancer assessment tool such as that of the National Cancer Institute, women at intermediate risk of breast cancer (1.67–5.00% 5-year risk) should use HRT with caution and high-risk women (>5% 5-year risk) should avoid HRT[100,102].

It is important to note that the various instruments for cardiovascular disease 'risk' calculation remain somewhat controversial and have not been proven to be predictive. The breast cancer risk assessment models have also been extrapolated from chemoprevention trials rather than a treatment naive general population. Furthermore, women at high risk of breast cancer do not necessarily have an increased risk when prescribed oestrogen.

Finally, the NAMS algorithm[102] suggests that if there are no vasomotor symptoms and no vaginal complaints (where local oestrogen therapy would be indicated), HRT should be avoided. This later point is debatable.

A role in primary prevention?

The onset of menopause occurs at around the age of 50 years, whereas most diseases affecting older women begin to emerge 10 years later. These diseases include cardiovascular and metabolic diseases, osteoporosis, cancer and cognitive decline. Accordingly, the onset of menopause has been proposed to be an ideal time to institute preventative strategies that increase the quality and length of women's lives[103].

Most of the validated prevention strategies involve lifestyle management (that is, diet and exercise), screening for cancer and performing mentally stimulating activities[103]. Although these strategies are effective, the results are modest and difficult to maintain. For example, lifestyle interventions for the prevention of cardiovascular disease are expected to reduce the 10-year coronary risk by 12–14%[104].

Cardiovascular disease, and particularly CHD, is the leading cause of death in all women. Other primary interventions such as use of statins and aspirin, although effective in men, have not been shown to be effective in women in a primary prevention setting[105–108]. Such therapies do not change mortality when given to younger otherwise healthy postmenopausal women who have not sustained cardiovascular events[101,103–110]. While aspirin is not recommended by the American Heart Association for use in younger women (aged <65 years), statins have been recommended more rigorously. Nevertheless, for young healthy women at the onset of menopause, no data exists showing a primary prevention benefit. Therefore, apart from modest effects of lifestyle management, what other options are available? A consideration should be given to HRT, specifically oestrogen-based therapy. As discussed earlier, beyond symptomatic relief, improvements in quality of life and a reduction in osteoporosis, oestrogen-based therapy has been shown to be cost-effective and, specifically, to decrease CHD in younger (aged <60 years) women by up to 40% and to decrease mortality by 20–40%. HRT has also been shown to decrease the incidence of new-onset diabetes mellitus[28,111–112] (FIG. 4), whereas statins might be associated with an increased risk of the disease in women[113,114]. The effect on coronary risk and mortality is consistent between studies in younger (aged <60 years) women and shows an effect much larger than that of any other therapy.

The optimal duration of such therapy is unclear, but results from the WHI and other studies[64,67,68] suggest that 5–10 years of therapy from the onset of menopause has potentially valuable effects for many years and does not suggest the need for life-long therapy. As discussed earlier, the risks of such therapy, initiated in young fairly healthy women, have a very favourable risk–benefit balance.

Before the early reports from randomized trials, including the WHI, women were treated with oestrogen, largely for symptoms, but with the expectation that it also would be beneficial for osteoporosis, CHD and in reducing mortality. By the mid 2000s, almost no women, including those affected by severe hot flushes at the onset of menopause, were receiving HRT. In spite of a significantly affected quality of life, these women were denied HRT on the false perception that too many risks were associated with HRT. At that time the media depicted the risk of breast cancer to be 24-fold increased, rather than the 24% increase (RR 1.24) that was of borderline significance for treatment with CEE plus MPA. We now know that this risk is not even significant for first-time users of HRT over the length of the trial. Now, with our new knowledge, we need to consider whether we are coming full circle (to where we were before the randomized trials) and to consider again the role of HRT for prevention[103,115].

Consideration of HRT for prevention, in addition to its use as a specific therapy, is clouded by the risk side of the equation. Clearly, in young healthy women at the onset of menopause, the risk–benefit balance is very favourable (FIG. 4). However, some women might experience certain adverse effects, which could make women question why they are taking something that they might not need. In some women, the overall fear of potential problems is enough on its own to dissuade use, and we must respect that concern in the decision to use HRT. It has to be acknowledged that there is 'risk' in anything individuals do, including many everyday exposures of life. In real terms, however, the risks of HRT for young healthy women at the onset of menopause are less than that of everyday risk, such as being a flight attendant, which is associated with an increased risk of breast cancer (RR 1.87)[91] or taking calcium, which is associated with an increased risk of coronary disease (RR 2.0)[116].

Regimens

The type of HRT regimen is extremely important, yet we do not have precise information for guidance. While for symptom control we can titrate up to an effective dose, we do not know what dose of oestrogen is sufficient to prevent coronary disease or osteoporosis in a given woman. Although it seems that some doses, such as 0.625 mg CEE have both these features (based on observational and clinical trial data) and that some low doses and types of oestrogen probably have the same effects, at least in some women, we do not know this with certainty. Recent studies suggest that oestradiol, rather than CEE, might perform equally well in terms of coronary protection[64,67,68]. Transdermal oestrogen therapy has not been associated with venous thromboembolism or stroke risk based on observational data, and is considered safer in women with certain risk factors such as obesity.

In terms of the breast cancer promotional risk, the choice of progestogen and the regimen of administration are important. In addition, progestogens might attenuate some of the CHD benefit, hence the suggestion made for oestrogen-based therapy. Notably, some studies have not found attenuation of the benefit with norethindrone acetate or natural progesterone as the progestogen[64,67,68].

Oestrogen-based therapy simply means using only enough progestogen to protect the uterus while maintaining the benefits of oestrogen. Certain progestogens, such as MPA, have been suggested to increase breast cancer risk, whereas natural progesterone or dydrogesterone might be of less concern. Some progestogens also increase the risk of VTE with oral oestrogen[76,77,117]. Consideration could be given to using non-progestogen therapy, such as with the addition of bazedoxifene[118]; however, long-term data are lacking on its role in coronary benefit and prevention.

Alternative regimens exist that should be considered for minimizing systemic exposure to progestogen. These include the use of vaginal progesterone as in the ELITE trial[40], intermittent progestogen rather than monthly progestogen exposure if a lower dose of oestrogen is used, and intrauterine therapy. The current intrauterine system available uses levo-norgestrel, which, while an attractive option for some women, might deliver too much systemic progestogen (~180 pg/ml); no long-term data are available on this system. It is important to be flexible in prescribing. There is no ideal regimen for any particular woman and, unfortunately, changes along the way are important and necessary, both in terms of assuring efficacy and in improving quality of life by alleviating adverse effects, if present.

In the future, it is expected that personalized approaches will be available to enable prescribing based on a woman's genotype. Targeted therapies and pharmacogenomics would make for more effective and safer types and doses of HRT. For example, certain known polymorphisms in *ESR1* (encoding ERα) might influence all-cause, as well as cancer-related mortality[119]. Similarly, having the ERα C/C genotype is associated with an increase in HDL cholesterol levels with oral CEE that is twice that of levels in women with the ERα C/T or T/T genotype[120].

Compounded 'bioidentical' hormones are used widely in the USA, if not worldwide. This popularity has been driven by unsubstantiated claims of increased safety and efficacy. Indeed, these unapproved and unregulated formulations might be less safe and less efficacious than approved HRT products, and all major societies have discouraged their use over approved products[121].

The lost generation of trainees

Since the early 2000s, HRT has neither been prescribed nor taught to trainee physicians. Thus, for 10–15 years, in the USA, and possibly around the world, in primary care specialties such as internal medicine, general practice and family medicine, and even in obstetrics and gynaecology, more than a generation of trainee physicians have not received training in this area. Not only is there a need to understand the symptoms and consequences of menopause and possible treatments, but

also subtleties in 'flexible' prescribing to improve the quality of life of women. As elderly physicians retire, unless the current situation is remedied, women will continue to fail to obtain the health care and guidance they need and deserve.

Conclusion

The place of HRT in the health care of women has gone through many changes. The pendulum has swung widely and, at present, seems to be swinging back closer to where it was prior to various randomized trials in the late 1990s and early 2000s, in which the data were not properly interpreted or communicated. More recent data show that younger (aged <60 years) generally healthy women at the onset of menopause have a very favourable risk–benefit profile when using HRT. Indeed, the benefit for all-cause mortality, which is similar to that reported in observational trials many years ago, makes a strong argument to consider HRT for primary prevention in young women. Unfortunately, medicine has lost a generation of trainee physicians, who currently do not have adequate knowledge about HRT and how to prescribe it.

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Competing interests

R.A.L. declares that in the past 3 years he has consulted for Allergan, Pfizer and Teva, and has participated in clinical trials for TherapeuticsMD, with funds paid to Columbia University.