Editorial

New guidelines for hormone-replacement therapy: an update on risks and benefits for clinical practice



Haitham Hamoda*[1], Mike Savvas[1] & Nick Panay[1,2]

"...the risks associated with hormone-replacement therapy use are low overall, and these may be further lowered through individualized selection of the appropriate regimen and route of administration."

Over the last decade, and following the publication of the Women's Health Initiative Study (WHI) findings, there has been much confusion among clinical practitioners as well as the public regarding the adverse effects of hormone-replacement therapy (HRT) and the risks associated with its use. The WHI was a large randomized and observational study funded by the American NIH that addressed the major health issues affecting postmenopausal women including the risk of cardiovascular disease, cancer and osteoporosis. The study reported a higher incidence of stroke with the use of HRT, as well as a higher incidence of breast cancer and heart disease in women taking combined estrogen–progestogen replacement [1]. However, questions have been raised regarding the trial design and the population recruited as the study included an older age group of women with an average age of 63, who largely started HRT many years after the onset of the menopause (on average 10 years after the onset) and received a relatively high dose of conjugated equine estrogen (CEE) with a synthetic progestogen. Most international guidelines and consensus statements that followed were heavily based on the findings of the WHI and this unfortunately contributed to a significant change in clinical practice and decline in HRT prescribing [2,3].

Since the publication of the initial findings of the WHI in 2002, a number of reports, including further publications from the WHI group, have shown an age-related effect associated with these risks, with a lower-risk incidence noted in younger women starting HRT at the peri- or early menopause [4]. The British Menopause Society recently published guidelines recommending that all women should have access to advice on how they can optimize their menopausal transition and their life beyond the menopause, which include reference to lifestyle and dietary intake [5]. The guidelines also concluded

[1]King's College Hospital, Denmark Hill, London, SE5 9RS, UK
[2]Queen Charlotte's & Chelsea Hospital, Chelsea & Westminster Hospital & Imperial College, London, UK
*Author for correspondence: haitham.hamoda@nhs.net

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that women should also have the opportunity to discuss the advantages and disadvantages of complementary therapies in addition to those of HRT.

The main recommendations discussed in the guidelines included the following:

- Women should be able to make an informed choice on the use of HRT after being given sufficient information by their healthcare professional;
- The regimen, dose of HRT and the duration of treatment should be individualized, and the risks and benefits should be reviewed on an annual basis;
- The durations of HRT usage should be decided based on the menopausal symptoms experienced by the woman and should not be subject to arbitrary age limits;
- HRT prescribed before the age of 60 years has a favorable benefit–risk profile. When prescribing HRT beyond the age of 60 years, consideration should be made to using the transdermal route of administration (patch or gel), and to using the lowest effective dose for controlling symptoms;
- Women with premature ovarian insufficiency/premature menopause should be encouraged to use HRT at least until the natural age of the menopause;
- There is a pressing demand for further research to explore new preparations that will maximise benefits and reduce the risks and side effects associated with the use of HRT.

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Recent studies support a 'window-of-opportunity' for maximal reduction of cardiovascular disease and overall mortality and reduction of risks with HRT when treatment is initiated before the age of 60 years [6]. A recent multicenter large randomized study (KEEPS) reported on the cardiovascular effects of HRT taken in the early menopause. A total of 727 participants were randomized into three groups. One group received 0.45 mg/day of oral CEE; the second group received 50 µg/day of transdermal estradiol (t-E2), while the third group was given a placebo. Women prescribed active estrogens received 200 mg of micronized progesterone for 12 days each month, and women in the placebo arm were given identical placebo capsules during the same time period. The study showed a neutral impact on cardiovascular risk markers such as coronary calcium scores and intima–media thickness. There was no negative impact on blood pressure, lipid level and insulin resistance, suggesting that micronized progesterone given with t-E2 or with CEE did not negate the beneficial effects of estrogen in this cohort [6].

Furthermore, a recently published randomized trial from Denmark included over 1000 women aged 45–58 and demonstrated that HRT commenced within 10 years of the menopause reduced the incidence of coronary heart disease and overall mortality, supporting the 'window-of-opportunity' theory for primary prevention with no apparent increase in the risk of stroke, venous thrombosis or cancer, although the study was not sufficiently powered to adequately assess for the latter [7].

The different routes of administration follow different metabolic pathways and as a result may have different advantages and disadvantages. Oral estrogen administration follows a first-pass hepatic metabolism effect and this can result in adverse effects on the coagulation cascade and proinflammatory markers, including CRP, compared with transdermal administration. It has been demonstrated that women receiving oral estrogen resulted in increased thrombin generation compared with women not using HRT, while no such increases are noted in women receiving t-E2. Two large nested case–controlled studies reviewed the UK's General Practice Research Database and reported on the association between the risk of stroke and venous thromboembolism with transdermal estrogen replacement in women aged 50–79 years compared with oral administration and nonuse of HRT [8,9]. A total of 15,710 cases of stroke were matched to 59,958 controls. The risk of stroke was not increased with the use of low-dose (up to 50 µg of estradiol/day) transdermal estrogen (odds ratio[OR]: 0.81; 95% CI: 0.62–1.05) compared with women not using HRT. 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 nonuse of HRT. However, the risk was increased with high-dose (>50 µg/day) transdermal application (OR: 1.89; 95% CI: 1.15–3.11). Current users

of oral HRT were noted to have a higher rate of stroke than nonusers (OR: 1.28; 95% CI: 1.15–1.42) both with low-dose (up to 2 mg of estradiol or up to 0.625 mg of CEEs) and high-dose (>2 mg estradiol or >0.625 mg of CEEs) administration [8]. In the other series, a total of 23,505 cases with venous thrombosis were 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 nonuse of HRT. On the other hand, 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 [9].

Progestogens in HRT

The WHI study showed an increased risk of cardiovascular disease in women who received combined therapy with CEE (0.625 mg/day) and medroxyprogesterone acetate (2.5 mg/day), which was the most commonly used HRT regimen in the USA at the time that the WHI study was conducted, compared with those who received CEE alone [1].

However, more recent evidence suggests that micronized progesterone appears to have a better safety profile when compared with its synthetic counterparts and may result in a different risk profile compared with synthetic progestogens. Studies have suggested that androgenic progestogens appear to partly revert the beneficial arterial effects of estrogens, while the effect was noted to be lower with micronized progesterone. These reports have demonstrated a neutral effect on the vasculature and, therefore, a lower risk of venous thromboembolism, cardiovascular disease and breast cancer compared with synthetic progestogens [4,10–12].

In summary, recent evidence has clearly demonstrated that HRT should not be viewed as one intervention with set risks and side effects. The age of the woman at the time of starting HRT treatment, the route of administration of estradiol as well as the type of progesterone used may all have a significant impact on the risk profile that women may be exposed to, and this message should be put across to women to help them make an informed choice regarding the use of HRT and the preparation that may suit them best.

Further research is needed to assess the optimal regimen of HRT, with particular attention to the dose and route of estradiol administration. It is now widely believed that starting HRT in women in their early-to-mid 50s and using a transdermal preparation of estradiol in combination with micronized progesterone is likely to show a very different risk profile to that reported in the WHI, and this needs to be evaluated in future studies.

Women should be informed that the risks associated with HRT use are low overall, and these may be further lowered through individualized selection of the appropriate regimen and route of administration.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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