Hormone replacement therapy (HRT): cardiovascular outcomes after recent menopause

Data from long-term follow-up of an open-label randomised controlled trial suggest that HRT reduces cardiovascular endpoints in women if started early after menopause. However, limitations of the analysis make interpretation of the results difficult.

Overview: Hormone replacement therapy (HRT) provides low doses of oestrogen, with or without added progestogen, to replace what the body no longer produces after the menopause. In the UK, HRT products are licensed to help relieve the unpleasant symptoms that can accompany the menopause, including hot flushes, vaginal dryness and night sweats. Some HRT products may also be used for the longer-term prevention of osteoporosis in postmenopausal women who are unable to take any other osteoporosis prevention treatments or for whom other treatments have been unsuccessful.

Current advice: In 2007, the Medicines and Health Regulatory Agency (MHRA) updated its advice on the prescribing of HRT. It concluded that, before prescribing HRT, healthcare professionals should consider carefully the potential benefits and risks for every woman. HRT does effectively relieve vasomotor symptoms and it has a beneficial effect on bone while it is being taken. However, because of the risks associated with longer-term use, the lowest effective dose should be used for the shortest time to control menopausal symptoms, and HRT should be used for the prevention of osteoporosis only if other treatments are inappropriate.

In the large Women's Health Initiative RCT, involving over 27,000 women, HRT increased the risk of coronary heart disease and stroke. HRT has also been associated with increased risks of venous thromboembolism, endometrial cancer, breast cancer and ovarian cancer. The MHRA advises that these risks should be assessed in all women, but particularly in those older than 60 years who have an increased baseline risk of serious adverse events. Evidence for the risks of HRT in women who have premature menopause is limited. However, the baseline risk of adverse events in these younger women is low, and the balance of benefits and risks may be more favourable than in older women.

New evidence: Recently, data from a much smaller open-label RCT, the Danish Osteoporosis Prevention Study (n=1006) have been reanalysed to investigate the effect of HRT on cardiovascular outcomes in women if started early after menopause (Schierbeck et al. 2012). The study was originally designed to evaluate the effects of HRT in the primary prevention of fractures (Mosekilde et al. 2000). Healthy women who were recently postmenopausal or perimenopausal were randomised to HRT (n=502) or no treatment (n=504). Treatment consisted of triphasic estradiol and norethisterone acetate (or estradiol 2 mg a day in women who had undergone a hysterectomy). At inclusion the women were 50 years of age on average, and had been postmenopausal for about 7 months.

In the 2012 analysis, the primary endpoint was a composite of death, admission to hospital for heart failure, and myocardial infarction. This cardiovascular endpoint was a prespecified safety outcome, not an efficacy outcome, from the original study. After 10 years, there was a statistically significant reduction in the primary composite endpoint in the HRT group, compared with the control group that
did not take HRT (16 women versus 33 women in the control group, hazard ratio [HR] 0.48, 95% confidence interval [CI] 0.26 to 0.87, p=0.015). There was no statistically significant difference between the groups in the rates of death, heart failure, myocardial infarction, stroke, any cancer, breast cancer or deep vein thrombosis.

The authors suggested that the discrepancy between the results from this reanalysis of the Danish Osteoporosis Prevention Study, and those from the much larger WHI trial, may be explained by a difference in medication or that the women in this study were much younger, healthier and closer to menopause at randomisation. However, this analysis has numerous limitations, which are discussed by the authors and in several Rapid Responses. The Danish study was randomised, but it was open label with no placebo or blinding, which can introduce bias. The study was also originally designed with osteoporosis-related efficacy endpoints not cardiovascular ones, and the very low numbers of cardiovascular, cancer and thromboembolic events make interpretation of the results difficult. Although the composite cardiovascular outcome was a prespecified safety outcome from the original study, there were concerns that it was not standardised or monitored by the researchers but based on individual clinicians' inclusion of data in a national database.

Commentary: "The MHRA’s recommendation that HRT should be used at the lowest effective dose for the shortest time was issued primarily as a consequence of data derived from the initial results of the WHI study published more than a decade ago. The WHI population consisted of women with an average age of 63 years. Subsequent reanalysis of these data found that women who initiated HRT closer to menopause tended to have a reduced risk of coronary heart disease compared with women more distant from menopause, for whom an increased risk was observed. However, this trend was not statistically significant, and the risk of stroke was increased regardless of years since menopause. Although the recent trial data from Schierbeck et al. 2012 have limitations, they support this 'window of opportunity' for cardioprotective benefits in younger women without risks of cancer despite long-term use.

"The International Menopause Society updated their recommendations on HRT in 2011. In light of potentially more favourable data in younger women, and that many women have debilitating menopause symptoms persisting well beyond the menopause transition, their recommendations state the following: ‘There are no reasons to place mandatory limitations on the duration of HRT. Whether or not to continue therapy should be decided at the discretion of the well-informed woman and her health professional, dependent upon the specific goals and an objective estimation of ongoing benefits and risks.’

"It is timely that NICE has been commissioned to produce a guideline for the diagnosis and management of the menopause by 2015. This will enable identification of key quality indicators and allocation of quality and outcomes framework resources to support the primary and secondary care of women through the menopause transition and beyond”. – Nick Panay, Chair, British Menopause Society, Consultant Gynaecologist, Queen Charlotte’s and Chelsea & Chelsea and Westminster Hospitals

The author of a Cochrane review, ‘Long term hormone therapy for perimenopausal and postmenopausal women’ published in 2012, responded to say that the conclusions of their review remain unchanged despite the results from Schierbeck et al. 2012.

"HRT is not indicated for primary or secondary prevention of cardiovascular disease or dementia, nor for preventing deterioration of cognitive function in postmenopausal women. Although HRT is considered effective for the prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk, for whom non-oestrogen therapies are unsuitable. There are insufficient data to assess the risk of long term HRT use in perimenopausal women or postmenopausal women younger than 50 years of age." – Professor Cindy Farquhar, Department of Obstetrics and Gynaecology and National Women’s Health, University of Auckland
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