

HRT: updating the evidence

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It is now five years since the first findings were published from the Women's Health Initiative (WHI) trials that looked at whether long term use of hormone replacement therapy (HRT) could prevent health problems such as heart disease and hip fractures, and whether long term use was safe.

Current advice is that the risks of HRT use apply to all forms of HRT

This column, the first in a two-part series, looks at these original findings alongside recently published age subgroup data from WHI and results from the Women's International Study of Long Duration Oestrogen after Menopause (WISDOM). It also considers the evidence on the safety of HRT and indications for HRT in relation to recommendations published in 2004 by the New Zealand Guidelines Group (NZGG).

Risks identified

The WHI studies were the first large randomised placebo-controlled trials comparing the effects of combined continuous hormone replacement (0.625mg conjugated equine oestrogens plus 2.5mg medroxyprogesterone acetate) or oestrogen-only replacement (0.625mg conjugated equine oestrogens) with placebo in women aged 50–79 years. These studies had 16,608 women in the combined arm and 10,739 in the oestrogen-only arm. Both were stopped early as the expected benefit for coronary heart disease was not found.

The outcomes from the final analysis of both WHI studies are shown in the table.¹ There was a statistically significant increase in stroke, deep vein thrombosis, and gall bladder disease for both

combined and oestrogen-only therapy, with additional increases in breast cancer diagnosis and dementia (in women aged over 65 years) with combined therapy.

These negative outcomes outweighed potential benefits for colorectal cancer (with combined therapy) and decreases in fracture (both combined and oestrogen-only therapy).

Data published in 2007, from WISDOM, a randomised study evaluating similar hormone treatments, also showed a statistically significant increase in cardiovascular events and venous thromboembolism compared with placebo.²

Advice at present, from the FDA in the US, is to consider that the risks from the WHI studies also apply to other forms of HRT. Further evidence is required before we can give advice on a lower thrombotic risk for transdermal compared with oral oestrogen.

Timing hypothesis

Although the final results from the combined arm of the WHI did not show an increase in cardiovascular outcomes overall, there was an increased risk in the first year of use (hazard ratio 1.81; confidence interval 1.09–3.01).³ In addition, for women who were adherent to treatment (possibly providing a fuller picture with regard to safety), a 50 per cent increased risk of cardiovascular events over placebo was noted (hazard ratio 1.50; confidence interval 1.14–1.97).³

The last few years have seen publication of post-hoc age subgroup analyses from the WHI. These have looked at the risks for younger menopausal women, aged 50–59 years, who are the main users of hormones for menopausal symptoms. Combined results, from both the combined and oestrogen-only study, found women who started taking hormones closer to the onset of menopause tended to have a reduced risk of coronary events compared with

Useful resources

Women's Health Initiative study website: www.nhlbi.nih.gov/whi

- This site contains a video, information, and details of publications from the WHI study.

New Zealand Guidelines Group resources

- Hormone replacement therapy. Summary document 2004. www.nzgg.org.nz/guidelines/0078/HRT_summary_web.pdf
- Pamphlet for women re combined oestrogen and progestogen http://www.nzgg.org.nz/guidelines/0078/HRT_summary_web.pdf

Hormone replacement therapy: use

- HRT remains an appropriate treatment for women with moderate to severe menopausal symptoms.
- HRT should not be used for the prevention of chronic disease.
- Treatment should be at the lowest dose for the shortest time necessary to control symptoms.
- Women should be advised of the increased risk of stroke, deep vein thrombosis, and gallbladder disease with both combined and oestrogen-only therapy.
- Combined therapy is associated with increases in the risk of breast cancer and dementia (in women aged over 65).
- Low dose vaginal oestrogen is an effective treatment for vaginal dryness, dyspareunia and to prevent recurrent urinary tract infections and can be used as long as symptoms remain.

those beginning treatment at a later date. Although this combination led to increased numbers for evaluation in the 50–59 year subgroup, the trend did not reach the criterion for statistical significance. The risk of stroke was elevated regardless of how many years had elapsed since menopause.⁴

The most recent WHI publication, the Coronary Artery Calcium Study (WHI-CACS), is a surrogate outcome trial from the oestrogen-only arm of the WHI. This found a 42 per cent reduction (*versus* placebo) in coronary artery calcification for women aged 50–59 years randomised to oestrogen therapy, suggesting a potential cardioprotective effect in younger women.⁵

These findings, from the combined analysis and the WHI-CACS study, have led to a discussion about a "timing hypothesis" or "therapeutic window of opportunity", ie, oestrogen therapy may be cardioprotective if treatment is started early enough before vasculature is compromised. However, even the WHI investigators (who support this hypothesis) were clear the implication from CACS is not that recently menopausal women should be given HRT for coronary heart disease prevention, but rather that clinicians can be reassured about cardiac risks when considering short term use for vasomotor symptom relief.⁶

The enthusiasm for the "timing hypothesis" far exceeds the science.⁷ The recent statements from the director of the National Lung and Blood Institute of the National Institutes of Health clarify that results from CACS do not alter current recommendations and that hormone therapy should never be used to prevent heart disease.⁸

Indications for use

The indications for HRT use are not changed from the key messages outlined in the 2004 NZGG evidence-based best practice update on HRT^{9,10} (see panel). It should not be used for the prevention of chronic disease. However, HRT remains an appropriate treatment for those women with moderate to severe menopausal symptoms and is at present the most effective therapy for this indication (level of evidence A).¹ A Cochrane review showed a 75 per cent reduction in flushes (18 fewer per week) with therapy compared to a 50 per cent reduction with placebo.¹¹ Lower doses of oestrogen than those used in the WHI have also been shown to help flushes,¹² and recommendations are for the lowest dose for the shortest period of time.^{3,10} D

For references go to www.nzdoctor.co.nz under 'References'

The second article will discuss details of practical prescribing for low-dose HRT and what to do before starting therapy.

This column is coordinated by the New Zealand Guidelines Group. NZGG is an independent, not-for-profit organisation set up to promote effective delivery of health and disability services, based on evidence. NZGG works with a broad-based collaborative network of clinical leaders, opinion leaders and consumers, designing tools to promote an evidence-based culture within the New Zealand health and disability sector. www.nzgg.org.nz

Women's Health Institute studies		
Hazard ratios for various outcomes for women 50–79 years treated with combined or oestrogen-only therapy		
Outcome	Hazard ratio (95% CI) for combined oestrogen and progestogen	Hazard ratio (95% CI) for oestrogen only
Stroke (mainly ischaemic)	1.41 (1.07–1.85)	1.39 (1.10–1.77)
Breast cancer (final results)	1.24 (1.01–1.54)	0.77 (0.59–1.01)
Deep vein thrombosis	1.95 (1.43–2.67)	1.47 (1.06–2.06)
Coronary heart disease (final results)	1.24 (1.00–1.54)	0.95 (0.70–1.16)
Dementia (women >65 years)	2.05 (1.21–3.48)	1.49 (0.83–2.66)
Gall bladder disease and procedure	1.59 (1.20–1.97)	1.67 (1.35–2.06)
Hip fracture	0.66 (0.45–0.98)	0.61 (0.41–0.91)
Total fracture	0.76 (0.69–0.85)	0.70 (0.63–0.79)
Colorectal cancer	0.63(0.43–0.92)	1.08 (0.75–1.55)
Total mortality	0.98 (0.82–1.18)	1.04 (0.88–1.22)

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