

# Hormone replacement therapy: where to now?

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## SYNOPSIS

The Women's Health Initiative Study was stopped because of safety concerns about hormone replacement therapy with oestrogen and progestogen. There was an increase in breast cancer, however this was not greater than the increase reported in observational studies. Although there was an increase in vascular events, many of the women in the study had pre-existing risk factors for cardiovascular disease. No long-term trials of combined hormone replacement therapy are continuing, so the balance between benefit and harm will remain uncertain. Hormone replacement therapy can still be prescribed for menopausal symptoms and for osteoporosis prevention, but the need for continued use should be reviewed annually.

**Index words:** menopause, breast cancer, heart disease.

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## Introduction

The premature cessation of one arm of the ongoing US Women's Health Initiative study (WHI) undoubtedly caused more media alarm than scientific alarm.<sup>1</sup> This study is very important, as it was one of only two studies of long-term hormone replacement therapy (HRT). Although the combined oestrogen and progestogen arm was stopped the dietary and oestrogen-only arms continue. The combined HRT arm was stopped because the predetermined stopping point (a small but statistically significant increase in detected breast cancer) was reached. In addition, there was an increase in stroke and thromboembolism, and a trend to an increase in heart disease (Fig. 1).

Although breast cancer increased (by 8 cases per 10 000 women years) there was no overall difference in cancer rates or mortality between the placebo and combined HRT groups. This was because HRT was associated with a reduction in bowel and uterine cancers. The results observed in the WHI study were of similar magnitude as those seen in the systematic reanalysis of observational studies<sup>2</sup> of women taking combined oestrogen and progestogen (Table 1). The early cessation of this arm of the study at 5.2 years prevents the assessment of later benefits and risks.

## Cardiovascular disease

The reported results of WHI to date are little different from the published results of randomised trials looking at the secondary prevention of heart disease. Most women

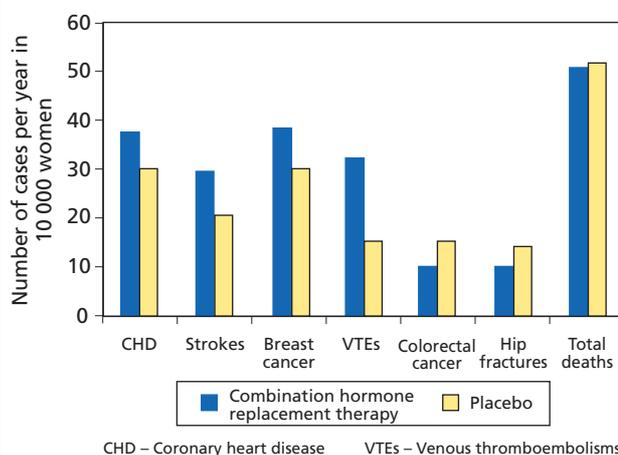
enrolled in the WHI study were overweight, 80% were between 60 and 79 years old, half had smoked and some had hypertension and increased concentrations of cholesterol. These cardiovascular risk factors suggest that many in the study could have had established atherosclerosis.

Recent studies suggest HRT may inhibit the process of atherosclerosis in healthy arteries soon after menopause<sup>3</sup>, and observational studies in younger women starting HRT suggest a potential cardiovascular benefit.<sup>4</sup> However, HRT may have a deleterious effect by destabilising plaques in the atherosclerotic arteries of older women. Secondary prevention studies such as HERS<sup>5</sup> confirm an early increase in adverse cardiovascular events when HRT is first prescribed after a cardiac event.

To improve the power of the study for cardiac events the WHI enrolled many older women, with cardiovascular risk factors, up to the age of 79 years. To what extent the effect of combined HRT seen in the WHI population applies to women commencing HRT at perimenopause remains debatable. The cardiovascular results of WHI are going to remain controversial until healthier and younger postmenopausal women are studied in a long-term trial. When counselling older women one could show the results of WHI (Fig. 1). A summary of the statistically significant results of major outcomes (Fig. 2) may help simplify counselling in younger women around the menopause.

Fig. 1

Event rates in the Women's Health Initiative Study



Adapted from US WHI Study, 2002<sup>1</sup>

### Unresolved issues

A long-term randomised trial can study only a few therapeutic regimens. Only conjugated equine oestrogens and medroxyprogesterone acetate were being tested in the long-term HRT trials, WHI and WISDOM (Women's International Study of long Duration Oestrogen after Menopause). No other HRT regimens are being tested. It is therefore impossible to know if HRT by non-oral routes,

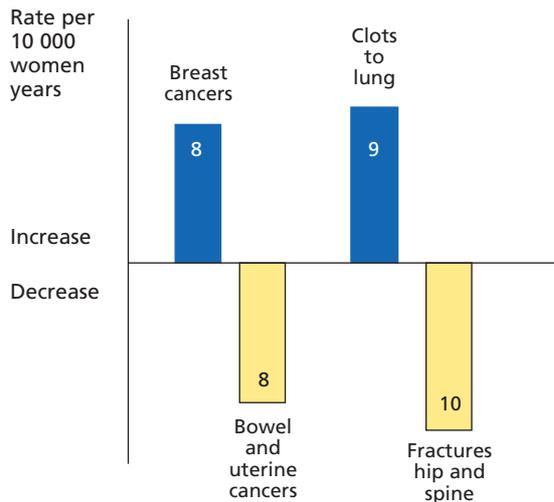
other oestrogens, other progestogens or other drugs such as tibolone have different effects. It would be wise to counsel that the outcomes for other combined HRT products may be similar to those reported by the WHI.

To date, oestrogen-only HRT does not have the same risk profile as combined oestrogen and progestogen and the oestrogen-only arm of the WHI study continues. Most importantly the WHI study does not give the overall harm:benefit ratio for long-term HRT as many outcomes were not measured. These include quality of life, menopausal symptom control, cognitive function, dementia, urogenital health, arthritis, other cancers and the effects of HRT on other body parts, e.g. eyes, teeth, skin. All these outcomes and a better understanding of the effects of HRT on the cardiovascular system are still greatly needed. WISDOM (the UK, Australian and New Zealand 15-year trial of HRT) was looking at these outcomes, but the study has been discontinued.<sup>6</sup> It is unlikely that we shall ever have good evidence to assess the risks, benefits and costs of long-term HRT.

It is important to emphasise that short-term trials of HRT show clear evidence of benefit for menopausal symptoms, especially vasomotor symptoms. These studies also show adverse effects which include start-up bleeding, breast tenderness and the uncommon but early risk of thromboembolism. The risk of breast cancer does not significantly increase until after five years of first use of combined HRT. The most pessimistic increase in breast cancer in all studies to date is one extra-detected breast cancer per 100 women after 10 years of use, but without an increase in breast cancer mortality. In women who have had a premature menopause and who require earlier HRT their risk at age 55 is approximately that of women commencing HRT at age 50. Long-term use in these women up to age 55 is appropriate.

Fig. 2

#### Summary of significant risks and benefits after 5 years of HRT\*



\* Although increased stroke and heart attacks were seen in the US WHI population, this population had many pre-existing risk factors for these problems. The effect of HRT on the blood vessels of younger, healthier women around menopause requires further study.

Adapted from US WHI Study, 2002<sup>1</sup>

Table 1

#### Comparison of outcomes from the Women's Health Initiative and observational studies \*

Outcome after 5 years of combined hormone replacement therapy	Relative risk ( $\pm$ CI) <sup>†</sup> in systematic reviews of observational studies	Hazard ratio ( $\pm$ adjusted CI) in WHI study at 5.2 years <sup>‡</sup>
<b>Cancer</b>		
Invasive breast <sup>2</sup>	1.35 (1.21–1.49) <sup>§</sup>	1.26 (0.83–1.92)
Endometrial <sup>7</sup>	0.80 (0.6–1.2)	0.83 (0.29–2.32)
Colorectal <sup>8</sup>	0.72 (0.53–0.96)	0.63 (0.32–1.24)
Total	–	1.03 (0.86–1.22)
<b>Fractures</b>		
Hip <sup>9</sup>	0.60 (0.4–0.91)	0.66 (0.33–1.33)
Vertebral <sup>10</sup>	0.67 (0.45–0.98)	0.66 (0.32–1.34)
Total	–	0.76 (0.63–0.92)
<b>Cardiovascular disease</b>		
Stroke <sup>11</sup>	1.45 (1.10–1.92)	1.41 (0.86–2.31)
Thromboembolism <sup>12</sup>	2.14 (1.64–2.81)	2.11 (1.26–3.55)
Coronary heart disease	–	1.29 (0.85–1.97)
Observational studies <sup>4</sup>	0.66 (0.53–0.84)	–
HERS <sup>#</sup> overall <sup>5</sup>	0.99 (0.8–1.22)	–
HERS <sup>#</sup> mortality	1.24 (0.87–1.75)	–
Total mortality	–	0.98 (0.70–1.37)

\* Observational studies and randomised controlled trials cannot be directly compared but it is reassuring to see the magnitude of effect is similar in this case.

<sup>†</sup> Confidence interval

<sup>‡</sup> Combined oestrogen and progestogen regimens

<sup>§</sup> All regimens of hormone replacement therapy

<sup>#</sup> The Heart and Estrogen/Progestin Replacement Study (HERS) was a randomised placebo-controlled trial.

## What to do now

It is not appropriate to prescribe HRT without an indication. The following points act as a guide to good practice.

- The main indication for HRT is for the control of menopausal symptoms and where quality of life is improved on HRT.
- Always counsel about the mixed risks and benefits of HRT and document this counselling. Supplementary written and video counselling is available from the Australasian Menopause Society web site ([www.menopause.org.au](http://www.menopause.org.au)).
- Oral HRT is still the route of choice. Women with a uterus require combined HRT, giving the progestogen cyclically over perimenopause and continuously after menopause. Women with a uterus should not receive oestrogen alone.
- In women who only have urogenital symptoms local vaginal oestrogens can be used.
- In women at risk of osteoporotic fractures, discuss and tailor the individual evidence-based therapies such as HRT, selective oestrogen receptor modulators or bisphosphonates, together with lifestyle advice.
- HRT is not advocated for the treatment or prevention of cardiovascular disease.
- Women on HRT should be reviewed yearly to determine optimal therapy and time for cessation of treatment.
- After 4–5 years of therapy it is appropriate to offer a trial off HRT. The dose can be reduced over 1–2 months before cessation.
- In women who have a return of disabling symptoms, HRT can be re-introduced for further treatment periods at the lowest effective dose and at any time of their lives.
- Women who are aware of the currently known mixed benefits and risks of long-term therapy and who have found that they have a better quality of life on HRT can be prescribed long-term HRT.

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*Professor MacLennan was a WISDOM investigator.*

## Self-test questions

*The following statements are either true or false (answers on page 23)*

3. The risk of breast cancer reported in the Women's Health Initiative study, of combined hormone replacement therapy, was significantly greater than the risk reported in previous observational studies.
4. Hormone replacement therapy should no longer be prescribed for the relief of menopausal symptoms.

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