

# Message about hormone therapy and cardiovascular risk becoming clearer

*New data on the risks and benefits of hormone replacement therapy and related treatments were presented last week at the American Heart Association scientific sessions in Chicago. Researchers say that trials are now showing that HRT carries cardiovascular risk, but many questions remain. Harriet Adcock reports*

THE recommendation that hormone replacement therapy (HRT) should not be used for the prevention of coronary heart disease gained further credence last week with the publication of the WAVE (Women's Angiographic Vitamin and Estrogen) trial.

Observational studies have consistently suggested that oestrogen therapy is associated with a reduced risk of coronary events and oestrogen is known to have beneficial effects on cholesterol and vascular function.

However, the only randomised, placebo-controlled trials of HRT in women with coronary disease have failed to show any benefit. Furthermore, a large primary prevention trial of HRT in postmenopausal women — the Women's Health Initiative (WHI) — was stopped prematurely earlier this year because of concerns over an increased risk of breast cancer and coronary disease among women who received active treatment (*Pf*, 13 July, p43). A similar trial — the Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) — was also terminated prematurely last month (*Pf*, 2 November, p633).

As a result of the conflicting results from the observational and prospective trials, advice on the use of HRT in postmenopausal women has not always been consistent.

Speaking at the American Heart Association scientific sessions held in Chicago last week, Dr Judith Hsia, of George Washington University, Washington DC and one of the WHI investigators drew attention to findings from the trial that combined oestrogen/progestogen use was associated with a small but real increase in the risk of breast cancer and cardiovascular disease. She said: "The [WHI] trial is not saying that women should not take combination therapy. But it provides the data for the first time so that women and their health care providers can make an informed decision about whether or not to take hormones."

Conclusions drawn from the terminated WHI trial only apply to combination HRT (specifically conjugated equine oestrogen plus medroxyprogesterone acetate [MPA]), which is generally prescribed for women with a uterus. A parallel trial — the oestrogen alone trial — is ongoing. "The same data safety board that stopped the oestrogen plus progestogen trial is carefully monitoring the data from the oestrogen alone trial and has so far voted to continue that trial," Dr Hsia said.

Because the WHI trial only tested one regimen it is possible that another regimen might provide different results. The burden

of proof, however, is on the manufacturers of other regimens to demonstrate both their efficacy and their long-term safety. "I do not think that it is appropriate to assume that any other combination regimen is safe and efficacious just because it is not conjugated oestrogens with MPA," she said.

The medical community had thought for decades that the oestrogen plus progestogen regimen was safe, indeed there was a lot of epidemiological evidence suggesting cardiovascular protection. "This trial underscores once again that safety and efficacy can only be determined with certainty in an appropriately designed randomised trial."

Dr Hsia believes that now is a good time for health care providers to evaluate the risk factor profile of postmenopausal women and to spread the message that they should not smoke and that they should maintain their ideal body weight. "They cannot expect that combination hormone therapy is going to provide cardiovascular protection," she said.

A series of papers is expected during 2003 once all data from the trial has been analysed. It is hoped that these will provide further answers about the risk-benefit ratios associated with HRT. "The quality of life and cognitive function aspects of HRT are the lifelines that the pro-hormone contingent are clinging to. The data are there on these two issues so hopefully we shall know quite quickly," Dr Hsia said.

Dr David Waters, of the University of California, San Francisco, presented data from the WAVE trial (see Panel 1) at the same meeting. He said: "These two treatments [HRT and antioxidant vitamins] that we had high hopes for seven or eight years ago when we began the study both turned

## Panel 1: WAVE of negative results for HRT

THE Women's Angiographic Vitamin and Estrogen (WAVE) trial was designed in the mid 1990s when observational data suggested that HRT was probably good for preventing heart disease in women. Unsurprisingly, data from the trial now show that postmenopausal women with coronary disease do not gain any cardiovascular benefit from HRT (*JAMA* 2002;288:2432). The trial also shows that antioxidant vitamin supplements do not provide cardiovascular protection. Instead, a potential for harm for each treatment was suggested.

The trial involved 423 women with coronary artery disease (measured by coronary angiography) who were randomised to HRT or placebo. HRT consisted of conjugated equine oestrogens (Premarin) 0.625mg daily for women who had had a hysterectomy plus medroxyprogesterone acetate 2.5mg daily for those who had not had a hysterectomy. Women were also cross randomised to antioxidant vitamins — vitamin E 400mg plus vitamin C 500mg twice daily — or corresponding placebos.

After a mean follow up of 2.8 years, coronary disease progression, as measured by changes in coronary artery narrowing, worsened in women taking HRT, although this was not statistically significant. If patients who died or suffered a myocardial infarction were allocated a "bad" angiographic outcome the risk for worsening of coronary narrowing became significant for women in the active HRT group ( $P=0.045$ ). However, this outcome was partially explained by differences in prevalence of diabetes — after adjusting for diabetes and diabetes-related variables the risk became non-significant again.

In terms of clinical events, 14 patients in the active HRT group died compared with eight in the HRT placebo group. There was also a bad outcome with respect to the antioxidant vitamins, with 16 deaths among women taking antioxidants compared with six in the placebo group. Angiographic changes also tended to worsen among patients taking antioxidants.

out to be not beneficial and potentially harmful." He added that the results with respect to HRT are no longer surprising.

The implication for women with existing coronary disease is that these treatments will not provide them with any protection. "We should turn back to the things that are known to work — diet, exercise, control of cholesterol, control of blood pressure and diabetes and use of medicines that prevent recurrent events in people with coronary disease," he said.

#### QUESTIONS REMAIN

Dr Richard Pasternak, Massachusetts General Hospital, Boston, does not believe that the HRT story is over. "I think there are some hard questions that remain. Why do women get heart disease about a decade later than men?" he asked.

"If the HRT story had been positive, I think we would have made a giant leap towards our understanding of this. The negativity of these trials tells us that we do not have the answer yet."

He added that when it was thought that HRT prevented heart disease a lot of time and energy was spent investigating what mechanism was responsible. "A tremendous amount of important research came out of that. We now need to be just as vigorous in investigating the mechanism of harm," he concluded.

Some clues about the mechanism of oestrogen's harm may come from studies investigating the use of raloxifene (Evista), a selective estrogen receptor modulator (SERM), in postmenopausal women.

A retrospective analysis of the Multiple Outcomes of Raloxifene Evaluation (MORE) study, also presented at the AHA scientific sessions (see Panel 2), suggests that this drug reduces the risk of stroke in women at high risk of coronary disease.

Dr Elizabeth Barrett-Connor, University of California, San Diego, who presented the results, explained that the MORE study was designed primarily to assess the efficacy of raloxifene in the treatment of postmenopausal women with osteoporosis. The trial was completed in 1999 and demonstrated that raloxifene reduced the risk of new spinal fractures in postmenopausal women by 55 per cent, and by 30 per cent in women with pre-existing fractures (*P*7, 18 September 1999, p411).

Although raloxifene is neither an oestrogen nor HRT, when data from some studies started to suggest HRT might cause harm, the MORE investigators decided to reanalyse the raloxifene data to see if the drug had any cardiovascular effects.

"We had a drug — a selective estrogen receptor modulator — which we were proposing to give to prevent fractures in women and we did not know whether it has a bad effect on the heart," Dr Barrett-Connor said.

She explained that because raloxifene has effects on oestrogen receptors it is possible that it could either be beneficial to the heart, harmful to the heart, or neutral, which is what the investigators expected. "We were looking at the data to reassure ourselves that there was not any early harm," she said.

The analysis revealed that raloxifene appeared to confer no cardiovascular benefit or harm in the average woman with osteoporosis taking part in the study. However, women treated with the drug who were at high risk of heart disease were found to have a 62 per cent reduction in the risk of all strokes. "These data are particularly interesting in light of recent findings from the Women's Health Initiative trial. While raloxifene and HRT are both prescribed for osteoporosis, the WHI data showed that combined oestrogen-progestogen HRT actually increased the risk of stroke," she said.

"This is an exciting time. Whether this will turn out to be a breakthrough or whether it will turn out to be some fortuitous findings we will have to wait and see. But I am optimistic."

Raloxifene has oestrogen-like effects in some tissues and anti-oestrogen effects in other tissues but it is thought to exert most of its effects on oestrogen receptors. So what could be causing this apparent protection from harm compared with what has been seen in the trials for HRT?

Dr Barrett-Connor said that a suggestion raised before the raloxifene results had been published was that the harmful effects of oestrogen were caused by its effects on clotting. "But raloxifene also increases the risk of deep vein thrombosis so clotting does not appear to be the mechanism for oestrogen's bad effect and it certainly would not explain raloxifene's apparently good effect," she said.

One possibility for raloxifene's cardio-

protection might be its effects on lipids. "We know from studies with lipid-lowering drugs that even though cholesterol is not terribly closely associated with stroke, when you give a cholesterol lowering drug the stroke risk goes down. So maybe it is the LDL reducing effect," suggested Dr Barrett-Connor.

Another possible explanation for the difference between oestrogen and raloxifene's effects on heart disease is inflammation. "Oestrogen increases inflammatory markers, including C-reactive protein. Raloxifene has no effect whatsoever, so it is possible that that is the mechanism."

#### UNCOMPLICATED MESSAGE

Dr Pasternak concluded that, as well as recommending that women do not start or continue combined HRT for the prevention of coronary heart disease, alternative cardioprotective regimens should be considered. "Unfortunately we are not doing a very good job implementing proven regimens," he said.

He added that the message for health care providers and patients was straightforward: "It is not necessarily as complicated as it sometimes seems. From a cardiac perspective the answer is simple. We can now say with a high degree of confidence that women should not take HRT to prevent cardiac disease or stroke. That is a simple, consistent message regardless of the patient."

He stressed that arguments suggesting that risk was only associated with particular agents did not hold up. "It is clear that replacing hormones that are similar to ones that women have until they reach menopause in order to prevent heart disease is not a strategy that is going to prevent heart disease."

HRT should be considered for the treatment of postmenopausal symptoms and for reducing the risk of osteoporosis. Whether a woman decides to take HRT for these reasons will depend on her individual assessment of the increased risk in breast cancer and coronary disease.

## Panel 2: MORE evidence for raloxifene

A POST-HOC analysis of the MORE (Multiple Outcomes of Raloxifene Evaluation) study has shown that raloxifene is associated with a reduced risk of stroke among postmenopausal women at increased cardiovascular risk.

Of the 7,705 women enrolled in MORE, 1,035 had established coronary disease or multiple cardiovascular risk factors. All women were assigned to daily raloxifene (60mg or 120mg) or placebo and the researchers found that overall there was no difference between raloxifene at either dose and placebo in terms of stroke or transient ischaemic attack. However, in women at high risk of coronary events, the rate of stroke or TIA was 3.5-fold higher than the total cohort. Raloxifene treatment was associated with a 62 per cent reduction for risk of any stroke (0.38, 95 per cent confidence interval 0.18–0.79). A risk reduction for non-fatal stroke was also observed (0.32, 0.14–0.76).