

Letter from the editor

Hormone replacement therapy and cardiovascular risk

Context: Although it is well established that hormone replacement therapy (HRT) relieves vasomotor symptoms and prevents osteoporotic fractures in postmenopausal women[1], the effects of HRT on cardiovascular disease remain contentious.

Observational studies have consistently found that postmenopausal HRT reduces the risks of coronary heart disease (CHD),[2] but the Women's Health Initiative (WHI) study, the first randomised trial of cardioprotection by HRT, found contradictory results.[3] [4] The WHI study consisted of two parallel RCTs, one assessing the cardiovascular effects of unopposed oestrogen in postmenopausal women after hysterectomy, and the second assessing the effects of oestrogen plus progestin in postmenopausal women with an intact uterus. Both RCTs were stopped prematurely because of adverse effects in those receiving the active intervention — the oestrogen plus progestin trial because of an increased risk of breast cancer, CHD, stroke, and pulmonary embolus,[3] and the unopposed oestrogen trial because of an increased risk of stroke, with no reduced risk of CHD.[4]

The premature closure of the WHI trials provoked vigorous debate among clinicians confused by the discrepancies between RCT and observational evidence. One potential reason for these discrepancies is the predisposition of observational studies to confounding: participants in observational studies choose to take an intervention, and tend to be healthier, more compliant, and more likely to adopt other protective types of behaviour than women randomised to an intervention, which can lead to spurious proof of benefit.[5]

Although randomisation aims to ensure that any confounding variables are equally distributed among the treatment and control groups, unsuitable population selection can still severely compromise the validity of an RCT's findings. In the WHI study, the mean age of participants was 63 years, with most women starting study hormones more than 10 years after reaching menopause. In practice, most women are prescribed HRT during the perimenopause period (in their late 40s to early 50s), and critics were concerned that results from this older WHI study group were not generalisable to a younger target population.[5]

A study recently published in *JAMA* revisits the controversy surrounding HRT and cardiovascular risk. Rossouw and colleagues performed a secondary analysis of the initial WHI trial data, specifically investigating whether the cardiovascular effects of HRT varied with age or with proximity to menopause.[6]

Summary: Because the number of cardiac events in the subgroups of the individual WHI RCTs was too small for useful analysis, Rossouw and colleagues pooled results from the two component trials, analysing data from a total of 27 347 postmenopausal women aged 50 to 79 years, followed up for a minimum of 5 years. They performed a subgroup analysis across three age groups (50-59 years, 60-69 years, and 70-79 years) and for initiation of HRT at different times after the onset of menopause (< 10 years, 10-19 years, and \geq 20 years).

Results: Consistent with the initial WHI study's findings, combined analysis of the oestrogen and oestrogen plus progestin trials found that HRT did not reduce the overall risk of CHD, and also significantly increased the overall risk of stroke (CHD events in the combined trials: overall hazard ratio [HR] 1.07, 95% CI 0.92 to 1.23; stroke: overall HR 1.32, 95% CI 1.12 to 1.56).

Pooled subgroup analysis found that there was no significant difference in the risk of CHD between HRT and placebo in women in their 50s, or in women starting hormone therapy less than 10 years after the onset of menopause (see tables 1 and 2). By contrast, women taking HRT in their 70s, and women starting hormone therapy more than 20 years after reaching menopause, had an increased risk of CHD compared with controls (see tables 1 and 2). Although, as expected, the number of cardiac events and strokes increased with increasing age in the intervention and the placebo groups, the increased risk of CHD in older women using HRT compared with non-users seemed to be more closely related to the time of initiation of HRT after the onset of menopause, rather than directly to increasing age.

There was no significantly increased risk of stroke in women aged 50 to 59 years on HRT, but women who started HRT less than 10 years after the onset of menopause had a 77% increased risk of stroke compared with controls.

Table 1: Outcomes according to age at start of treatment (HR [95% CI])

	50 to 59 yrs	60 to 69 yrs	70 to 79 yrs	P value for trend
CHD	0.93 (0.65 to 1.33)	0.98 (0.79 to 1.21)	1.26 (1.00 to 1.59)	0.16
Stroke	1.13 (0.73 to 1.76)	1.50 (1.17 to 1.92)	1.21 (0.93 to 1.58)	0.97

Table 2: Outcomes according to yrs since menopause at start of treatment (HR (95% CI))

	< 10 yrs	10 to 19 yrs	≥ 20 yrs	P value for trend
CHD	0.76 (0.50 to 1.16)	1.10 (0.84 to 1.45)	1.28 (1.03 to 1.58)	0.02
Stroke	1.77 (1.05 to 2.98)	1.23 (0.92 to 1.66)	1.26 (0.98 to 1.62)	0.36

Commentary: What are the implications of these data for younger postmenopausal women who are the main candidates for HRT in clinical practice? In response to the Rossouw study, the International Menopause Society issued a statement that the cardiovascular risks attributed to HRT now "seem irrelevant" at least for women less than 60 years old, and that "...healthy women in their early postmenopause period should not be concerned because of the 'alleged risks' of HT." [7] Rossouw and colleagues are more circumspect: they point out that their post-hoc analysis is exploratory [6], although they argue that it does provide some reassurance for younger women considering short term treatment with HRT for relief of menopausal symptoms.

A closer look at the results of the combined analysis suggests that, despite pooling results from the individual trials, dividing the data between several subgroups means that the number of cardiovascular events in each group is probably still too small to allow meaningful analysis. In other words, the subgroup analysis is underpowered to find a difference between HRT and placebo in cardiovascular morbidity if such a difference really exists. In the 50 to 59 year subgroup, there were only 59 cases of CHD in the 4476 women taking HRT, and only 61 cases of CHD in the 4356 women in the placebo group. The wide confidence limits for the HRs in the subgroup analysis are a reflection of the small subgroup sizes.

At the same time, by increasing the number of subgroups analysed, and thereby the number of comparisons, the likelihood of finding a false positive result increases. One way of correcting for the hazards of multiple comparisons is to 'raise the bar' by applying a stricter measure of statistical significance. For this analysis, the authors used a P value of 0.01 to signify statistical significance, instead of the conventional P = 0.05. This means that we accept that one in a hundred results will be statistically significant because of chance alone, rather than the one in twenty results represented by a P value of 0.05. Nevertheless, despite this adjustment, the inclusion of 137 comparisons in this analysis means that several statistically significant findings could have occurred by chance. [1]

Spurious 'chance' results in underpowered studies are often likely to be inconsistent clinically. Here, the three age groups are likely to overlap considerably with the three 'time since menopause' groups, so one would expect the findings for the 50 to 59 years age group to be close to the less than 10 years group. But, as shown in tables 1 and 2, there is a significantly increased risk of stroke in the less than 10 years group, but not in the 50 to 59 years age group. Similarly, although the risk of stroke is increased in women in their 60s, this is not the case in the 10 to 19 years group.

On the other hand, if we ignore the subgroup analysis and apply the overall risks from the well-powered combined data to younger women, the absolute risks (ARs) of adverse cardiovascular effects from HRT are small. [1] ARs are more useful than relative risks or HRs for conveying the clinical relevance of trial results as they take into account the baseline risk of illness in the population. So, for the total combined study population, an HR of 1.07 for CHD translates into 3 extra cases of CHD per 10000 women per year of hormone therapy. And the 32% total increased risk of stroke in hormone users compared with non-users translates into only 9 extra cases of stroke per 10000 women per year of hormone therapy. Many clinicians and patients believe that the benefits of symptom relief outweigh such risks. [1]

The Rossouw study attempts to provide some common ground in the polarising debate about HRT and cardiovascular risk, but, in our opinion, the 'jury is still out' on this controversial issue. Further high quality research, in the form of a large, long term RCT of HRT in women in early menopause, is needed to assess conclusively the cardiovascular risks and benefits of HRT.

Shannon Amoils

Clinical Editor, *BMJ Clinical Evidence*

s.amoils@bmjgroup.com

References

1. Grady D, Barrett-Connor E. Postmenopausal hormone therapy. *BMJ* 2007;344:860-861.
2. Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease and other considerations. *Annu Rev Public Health* 1998;19:55-72.
3. Manson JE, Hsia J, Johnson KC, et al. Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. *NEJM* 2003;349:523-534.
4. Hsia J, Langer RD, Manson JE, et al. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med* 2006;166:357-365.
5. Grodstein F, Clarkson TB, Manson JE. Understanding the divergent data on postmenopausal hormone therapy. *NEJM* 2003;348:645-650.
6. Rossouw J, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465-1477.
7. Pines A, Sturdee D, Birkhäuser M. Hormone therapy and cardiovascular disease in the early menopause: the WHI data revisited. Press Statement. Issued on behalf of the International Menopause Society April 3, 2007.