

## Commentary: Time to review all the evidence for hormone replacement therapy

Fay Crawford, Peter Langhorne

The meta-analysis by Bath and Gray provides evidence that hormone replacement therapy does not confer any protection against stroke in postmenopausal women but increases their risk of stroke.<sup>1</sup> These observations add to a rapidly expanding literature on the potential hazards and benefits of the therapy.<sup>2</sup>

The women's health initiative trial contributes well over half of the current trial data, and its findings dominate the meta-analysis. The women's health initiative trial sought to assess the risks and benefits of three separate interventions—a low fat diet, hormone replacement therapy, and calcium supplements—in 64 500 women over a 15 year period.<sup>3</sup> Two separate types of hormone replacement therapy were tested, monotherapy (oestrogen alone) and dual therapy (oestrogen plus progesterone), in two separate trial arms recruiting a total of 27 000 women.

In the dual therapy arm of the trial (n = 16 608) an increased risk of stroke became apparent by the second year, and the trial was ended three years early. Subgroup analysis indicated an increased risk of ischaemic strokes in women in all risk categories, not just those judged to be at high risk. The monotherapy arm (oestrogen alone, for women without a uterus) of the trial (n = 10 739) was also ended early because of an increase in non-fatal strokes. Full details from the subgroup analysis of this second arm are not yet available, and the evaluations of the low fat diet and calcium supplements are continuing.

What should women and their doctors now conclude about hormone replacement therapy? Although opinions may vary about whether the female menopause is a deficiency disease or a rite of passage, several facts seem clear: hormone replacement therapy can relieve some troublesome menopausal symptoms,<sup>4</sup> but it does have other important health effects, both bad and good.<sup>5</sup> The women's health initiative trial found that therapy did not meaningfully improve measures of physical and mental function or quality of life,<sup>5</sup> but some effects that women might value—namely perceptions on youthfulness, attractiveness, and skin tone—have not been adequately studied. Balancing these factors in individual treatment decisions can be difficult. There is a clear need for an overarching meta-analysis of all relevant individual patient data, which can include key baseline participant characteristics, hormone replacement therapy characteristics, and all relevant outcomes (including time to event analyses).

In the interim, all women who consult for hormone replacement therapy need to understand that it can carry an increased risk of ischaemic stroke, coronary events, venous thrombosis, and possibly breast cancer.<sup>2</sup> In order to minimise these hazards, doctors should recommend hormone replacement therapy only for severe menopausal symptoms and for the shortest possible time in women who are fully informed of these risks.

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- 1 Bath PWM, Gray LJ. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. *BMJ* 2005;330:342-4.
- 2 Grady D. Postmenopausal symptoms—therapy for symptoms only. *N Engl J Med* 2003;348:1835-7.
- 3 Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, Kooperberg C, Baird A, et al. Effect of estrogen plus progestin on stroke in postmenopausal women. The women's health initiative: a randomised trial. *JAMA* 2003;289:2673-84.
- 4 Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA for the HERS Research Group. Quality of life and depressive symptoms in postmenopausal women after receiving hormone replacement therapy. *JAMA* 2002;287:591-7.
- 5 Hays J, Ockene J, Brunner RL, Kotchen JM, Manson JE, Paterson RE, et al. Effects of estrogen plus progesterone on health related quality of life. *N Engl J Med* 2004;351:1839-54.

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### Corrections and clarifications

*Mother who drowned her five children is granted a retrial after witness gave false evidence*

In the full version (on bmj.com) of this News article by Fred Charatan we wrongly said that Andrea Yates had been granted a new trial because an expert medical witness for the prosecution had lied at her original trial (*BMJ* 2005;330:112, 15 Jan). We should have said that the expert witness gave "false testimony" at her original trial.

*Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies*

The authors of this paper, Mahyar Etminan and colleagues, alerted us shortly before publication to the fact that some of their results were incorrect, although the conclusions are unaffected (*BMJ* 2005;330:63-5, 8 Jan). We managed to correct the abridged version in the journal but not the full version on the web. To see the corrections relating to the web version, go to <http://bmj.bmjournals.com/cgi/content/full/bmj.383302.504063.8F/DC1>

*Effectiveness of helmets in skiers and snowboarders: case-control and case crossover study*

The wrong lowest recorded temperature mistakenly slipped through in the electronic version of this paper by Brent E Hagel and colleagues (*BMJ* 2005;330:281-3, 5 Feb). The value given in the text on data collection and in table 3 should have read  $< -10^{\circ}\text{C}$  [not  $\leq 10^{\circ}\text{C}$ ]. The version in the printed journal is correct.

*Agencies "failed miserably" over COX 2 inhibitor*

In this News article by Barbara Kermod-Scott, we inadvertently attributed the opening statement (about the failings of two of North America's regulatory agencies) to the Canadian Medical Association (*BMJ* 2005;330:113, 15 Jan). Later in the article we make it clear that the source of the statement is *CMAJ*. Although *CMAJ* is the journal of the Canadian Medical Association, it is at "arms length" from the association.