

Editorial

Time for new long-term trials of postmenopausal hormone therapies!

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The Women's Health Initiative (WHI) has shown the value of a well-conducted, medium-term, randomized, placebo-controlled trial. Specifically, it showed that there was no cardioprotective or neuroprotective benefit from combined hormone therapy (HT) when initiated in late menopause in the population studied¹. It also showed a small increase in breast cancer with this regimen after 5 years of therapy. Subanalyses of its results do not show an increase in cardiovascular events when therapy was initiated within 10 years of menopause (hazard ratio (HR) 0.89, 95% confidence interval (CI) 0.17–0.86), as opposed to therapy initiated more than 20 years after menopause (HR 1.75, 95% CI 1.18–2.40)². Blood vessels appear to lose their estrogen receptors in early postmenopause and the potential protective effect of estrogen on the vessel wall may be lost after several years³. The elegant monkey studies by Clarkson's group support the hypothesis of a cardioprotective effect when estrogen is initiated early after surgical menopause but not when initiated in later postmenopause⁴.

The challenge of WHI should be to help justify, design and fund a safer and more effective therapeutic regimen, to be tested long term in an appropriate population where there may be a primary protective effect. Most randomized trials of HT to date, including WHI, have unsuccessfully sought a secondary protective effect in women with established atherosclerosis or with risk factors for this disease. The hypothesis that estrogen may have a primary cardioprotective and neuroprotective effect when used from around menopause has not been tested in randomized trials, despite observational study evidence for both^{5,6}. As well as choosing more appropriate target populations, part of the challenge also will be to choose potentially safer regimens to be tested in such trials. There is an assumption that the estrogen-only arm of WHI continues because

this regimen has not yet been shown to be associated with a significant increased risk of breast cancer. If this proves to be true, then WHI has again pointed the way to the safer use of hormone therapy. In women with a uterus, it would be wise to use a progestogen or a regimen that did not affect the breast or the cardiovascular system. In this issue of *Climacteric*, Thomas and colleagues present interesting evidence that progestogens may also have an adverse effect on the arterial wall, further warranting a change to a safer delivery system, for example intrauterine progestogen⁷ or the addition of selective estrogen and progestogen receptor modulators⁸. Such regimens would also be much less likely to give long-term bleeding in placebo-controlled trials and resulting unblinding of the HT regimen. This was a problem in WHI and in the opinion of Shapiro, in an Invited Editorial in this issue, this turned WHI into an observational study because of the potential for detection bias after the unblinding⁹. Another potentially safer therapeutic option worthy of trial is to give estrogens by a non-oral route, as a recent study suggests transdermal estrogen may not be associated with the increased risk of thromboembolism seen with oral HT¹⁰.

There are few effective alternatives to estrogen for the management of menopausal symptoms, and none that are as effective, despite a burgeoning and inadequately controlled complementary medicine industry in most countries. Amato and Marcus, in this issue of *Climacteric*, review alternative therapies for menopausal symptoms and conclude that nearly all such complementary therapies have no greater effect than a placebo and their long-term side-effects are unknown¹¹. In another Invited Editorial in this edition, Breen strongly argues that the prescription or advocacy of such placebo therapies without informing the public of the therapy's lack of efficacy is unethical¹². Thus, it would follow that it is

unethical to advocate, prescribe or sell complementary therapies for menopausal problems, without a declaration of their effects being limited to their placebo effect.

Is it possible to find a cost-effective regimen that can be used by symptomatic women or women at risk of osteoporotic fractures that, first, does little or no harm and, second, can be tested for a potential added cardio- and neuroprotective effect in the long-term? The women to be recruited will have to be around menopause, and the trial must extend for at least 20 years for risk or benefit to be detected. Therapy could be for 10–15 years, with a less expensive follow-up period of 5–10 years. As in WHI and the Women's International Study of long Duration Oestrogen after Menopause (WISDOM), the numbers needed would be around 8000–12 000 for each regimen and placebo arm¹³.

WHI tried to enrol asymptomatic women and one question deserving study is whether estrogen will have a better effect on women with estrogen deficiency symptoms. However, if women with severe symptoms are enrolled, compliance in the placebo group will be reduced. The compromise is to enrol altruistic women, with mild to moderate menopausal symptoms, who can accept the chance of placebo therapy. Such women exist, as shown in the recruitment of 6.5% of the eligible age group for WISDOM¹³.

As always, the question will be, where can funding be obtained for such a long-term trial? The hysteria of the media and sometimes of members of the medical profession (often created by those not working directly with menopausal health) and their lack of perspective about the

WHI results have created a negative climate amongst funders. It is the role of those working in women's health to raise the awareness of the still unanswered questions and the need for more quality research. WHI should be a catalyst for more trials and not an inhibitor of further funding for research into hormonal and non-hormonal therapies to reduce the burden of disability after menopause. Ideally, such funding should not be from industry and should be jointly funded by governments around the world. Is this an initiative for the World Health Organization or are the diseases of the Third World its current priority? As recent articles in *Climacteric* have pointed out, the sequelae of the menopause are also becoming the problems of the Third World, as its populations experience increasing longevity.

Despite the partly negative results of WHI and the cessation of funding for the only other long-term trial of hormone therapy, WISDOM, there is justification for another long-term trial using potentially safer regimens in a population more typical of those who currently use HT and who might benefit from its use long-term from menopause. Without such data, we are left with the advice to use the lowest dose of HT for the shortest possible time. This advice may potentially under-treat some symptomatic women and may actively discourage studies to investigate whether there are simple and safe therapies to reduce the risk of osteoporosis, cardiovascular disease and dementia in postmenopausal women. It may seem a politically inopportune time to call for a new long-term trial of HT, but it is scientifically and clinically time!

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