

Hormone therapy in the WHI era

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Abstract

The announcement in July 2002 in the media of the results of the combined continuous hormone treatment arm of the Women's Health Initiative (WHI) had a profound effect on perceptions about hormone therapy among the lay public and the medical profession. Careful scrutiny of the announcement and the subsequent publications leads to the conclusion that the widespread fear of hormone therapy that was generated was not supported by the facts. WHI was not designed to be, nor can it be, interpreted as a randomised controlled trial of menopausal hormone therapy – rather, it was a trial of chronic disease prevention, particularly aimed at the possible cardiovascular benefits of a specific combination hormone therapy in postmenopausal women. The results, which were consistent with existing data, did not and do not warrant any major change in the previously established guidelines for the use of hormone therapy. Tibolone has emerged as an alternative treatment for menopausal symptoms, but its long-term benefits and risks have yet to be documented.

Key words: breast cancer, cardiovascular disease, hormone therapy, menopause, osteoporosis, venous thromboembolism.

Introduction

In July 2002, at a press conference in the USA, convened by the National Institutes of Health, the first announcement was made regarding the premature termination of the combined continuous treatment (CCT) arm of the Women's Health Initiative (WHI) randomised controlled trial (RCT),¹ a chronic disease prevention trial designed to evaluate the role, if any, of hormone therapy (HT) in reducing the risks of cardiovascular disease (CVD) in older women and at the same time to document the effects on the risks of breast cancer. The trialists had recruited postmenopausal 'healthy' US women, of average age 63 years, range 50–79, for randomisation to conjugated equine oestrogens 0.625 mg and medroxyprogesterone acetate 2.5 mg, both given daily continuously, or to placebo. The trial was to be of 7 years duration, but was terminated prematurely after 5.2 years, because the Data Safety Monitoring Board found that the rate of breast cancer in the active treatment arm exceeded that in the placebo arm by more than the pre-specified amount. The public announcement was potentially misleading in two major ways: it implied that there was an increase in breast cancer risk after 5.2 years of HT – in fact, for the 75% of subjects who had not used HT before entering the trial, there was no significant increase in risk; that increase was observed only in those women who had been prior hormone users for varying lengths of time. Second, the statement that there was a 26% increase in risk sounded ominous – but was uninterpretable in terms of actual risk increase without knowledge of

the baseline rate. It actually equated to one extra case of breast cancer for every 240 women (25% being long-term users, 75% users only for the duration of the trial) over 5.2 years – less than one in 1000 extra cases per year. There was actually no increase in the 'hormone naïve' subjects (hazard ratio, HR = 1.06, 95% CI 0.81–1.38).¹ One other factor should also be considered. In prior users of HT assigned to placebo, risks would fall to rates similar to those of untreated women by 5 years following discontinuation of their therapy.^{2,3} Thus, the risk in those who continued would be artificially raised in comparison with those who discontinued, a concept impossible to convey in the media (Fig. 1).

The announcement caused anxiety and panic – had the facts been presented objectively (and they confirmed what was known from observational data – see succeeding discussions),² it is the author's belief that no particular anxiety would have been engendered. It had been well established that long-term HT leads to a small increase in breast cancer risk, so it was difficult to understand why there was so much consternation among women and in the profession – one can only conclude that the way in which the results were

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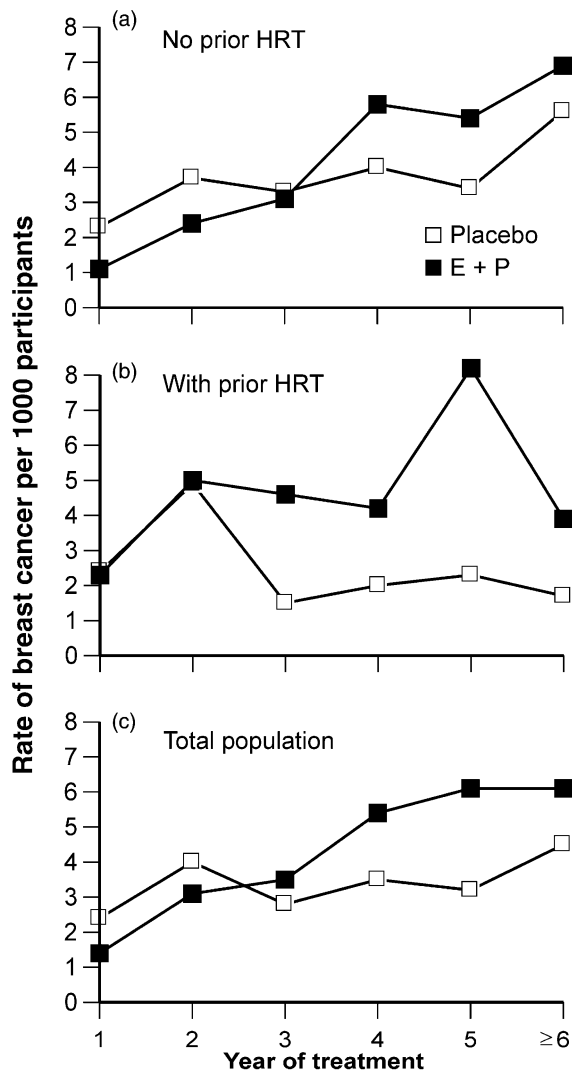


Figure 1 (a) Annual rates of breast cancer per 1000 women in WHI who had not received prior HRT (■ on CCT, □ placebo). (b) Annual rates in non-prior users (■ on CCT, □ placebo). Note the decline in rates in the placebo-treated prior users leading to an apparently increased rate in those in the active treatment arm. (c) Annual rates of breast cancer in the combined population (■ CCT, □ placebo). Data drawn from Chlebowski *et al.* (2003). E + P, combined oestrogen and progestin treatment.

announced was the major contributor. The considerations regarding cardiovascular risk will be detailed below.

Levels of evidence for benefits and risks of hormone therapy

The guiding principle regarding whether to use HT or not is that it is an individual choice made by the woman and her doctor, taking account of current knowledge regarding benefits and risks.^{4,5} A simplified summary of the levels of evidence from which benefit and risk can be assessed is shown in Table 1.

Table 1 Levels of evidence concerning hormone therapy

Randomised controlled clinical trials
Observational epidemiological studies:
Cohort, comparing hormone users and non-users for particular outcomes
Case-control, comparing outcomes for relative frequencies of hormone use

The strongest level of evidence is that from randomised controlled clinical trials. A prerequisite for such evidence is that the randomised trials shall have been conducted in a population relevant to the target population for a particular therapy. No randomised controlled clinical trials have been conducted to date in the population of women normally targeted for hormone therapy, namely symptomatic, peri- and early postmenopausal women. The WHI was not a relevant clinical trial – it was a chronic disease prevention trial conducted in a total of 16 607 mainly asymptomatic women on average 12–13 years postmenopausal, mean age 63 (± 7.11 , SD) and age range 50–79 years. There was a total of only 574 moderately to severely symptomatic women aged 50–54 in both groups combined.⁶ Thus, to weigh up benefits and risks of postmenopausal HT in the usual target population, we must still rely on observational epidemiological studies of which the most important are the large cohort studies such as the Nurses Health Study which have been done in the relevant target population.⁷ Cohort studies are subject to bias, in particular, the problem of adjusting for the factors that lead to individual women opting to use HT or not. Despite this limitation, it is noteworthy that the major conclusions of the WHI and Nurses Health Studies are very similar with the exception of the impact of HT on cardiovascular outcomes (see Fig. 2). These will be discussed in detail below with a rationale as to why these outcomes were different.⁸

The WHI randomised controlled clinical trials

WHI comprised two randomised controlled trials of HT in postmenopausal women. The first of these, the premature termination of which led to the concerns noted above, was a trial of combined continuous HT, using conjugated equine oestrogens, 0.625 mg per day, plus medroxyprogesterone acetate, 2.5 mg per day, in one tablet ($n = 8506$) or placebo ($n = 8102$).¹ The primary outcome was coronary heart disease (CHD), with invasive breast cancer as the primary adverse outcome. The mean age of participants at screening was just over 63 years, with approximately 33% aged 50–59, the majority of those 55–59, 45% 60–69 and 21% 70–79. 84% were of white race and 74% had never used hormones, whereas 26% were either past or current hormone users. Of the users, 30% had used hormones for 5 years or more. Mean body mass index was 28.5 with 30% of the participants having a normal body mass index < 25 and 34% having a body mass index > 30, that is, indicative of obesity.

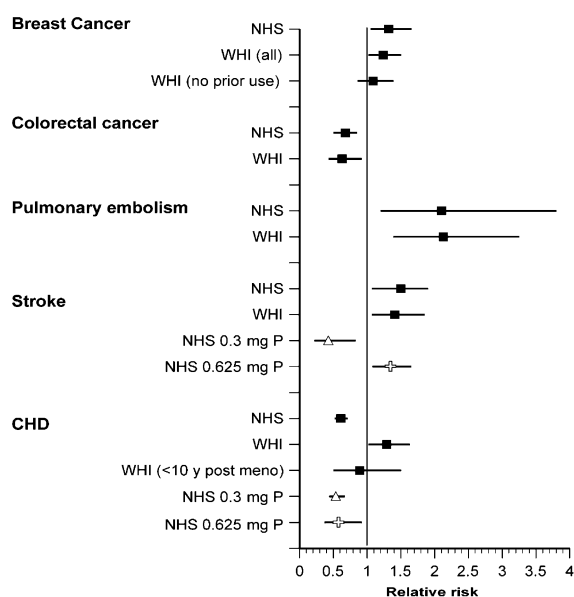


Figure 2 Comparison of relative risks (hazard ratios) for major outcomes in the WHI combined continuous treatment RCT and the Nurses Health Observational Study (NHS). Data for breast cancer in the WHI are shown for all participants and for the 74% who had not previously used HRT. For stroke and coronary heart disease (CHD) ratios for two different dose levels of conjugated equine oestrogen (P) in NHS are shown. For CHD, the ratio for participants in WHI who were less than 10 years postmenopausal is shown.

Note: The only overall difference is in CHD outcomes, potentially explicable in terms of the age of the participants – see text.

Fifty per cent of the participants were either past or current smokers. Thirty-six per cent were either being treated for hypertension or had blood pressure equal to or greater than 140/90 mm of mercury. The major cumulative hazards for selected clinical outcomes included those shown in Table 2, adapted from Writing Group for the Women's Health Initiative Investigators.¹

The second randomised trial was that of conjugated equine oestrogens 0.625 mg versus placebo, conducted in 10 739 hysterectomised women aged 50–79 years.⁹ Average follow-up was for 6.8 years and the age distribution was similar to that for the combined HT arm. In this population, 35% were past hormone users and 13% were current hormone

users. Forty-five per cent of the women had a body mass index (BMI) > 30 and 21% had a BMI in the normal range. The distribution of smokers was similar, whereas 48% were hypertensive.

In this trial, there was no significant difference in outcomes for CHD, venous thromboembolism, breast cancer, colorectal cancer or death, but there was a significant increase in stroke and a significant decrease in fractures. For women aged 50–59 years, the hazard ratio (HR) for CHD was 0.56 with 95% CI 0.30–1.02. In the two older age groups, the HRs were 0.92 and 1.04. For stroke there was no significant difference in the 50–59 group (HR 1.08, 95% CI 0.57–2.04), but the increased rate was significant in the 60–69 group (HR 1.65, 95% CI 1.16–2.36). Interestingly, the HR for invasive breast cancer was 0.77 with 95% CI 0.59–1.01, a 23% decrease in breast cancer rate in the treated arm, almost statistically significant.

One other RCT should be mentioned here, the Heart, Estrogen, Progestin Replacement Study (HERS), which was a secondary prevention trial of HT in older postmenopausal women with documented CHD.¹⁰

The following major conclusions can be drawn from these RCT's:

- They did not in general involve symptomatic peri- and early postmenopausal women.
- An increased risk of venous thromboembolism was clearly shown.
- An early increase in CHD events was seen in HERS and in the CCT arm of WHI.
- There was no net benefit for CHD prevention in HERS.
- Subgroup analysis in the WHI combined arm indicated no increased coronary heart risk (HR 0.89) in those women who were less than 10 years postmenopausal (36% of the total).
- Breast cancer risk was not significantly increased in the women in WHI who had not received prior HT.
- Breast cancer risk was not significantly increased in HERS.
- Overall, WHI showed a small increase in breast cancer risk after 67 months follow-up (HR 1.24, CI 1.02–1.50 for total breast cancer),¹¹ noteworthy including prior hormone users. It should be noted that this is in the same range as for other risk factors for breast cancer such as nulliparity, early menarche, obesity, etc. For those who had not used hormones previously, the HR

Table 2 Clinical outcomes by randomisation assignment

Outcome	HR (hazard ratio)	Nominal 95% CI	Adjusted 95% CI
Coronary heart disease	1.29	1.02–1.63	0.85–1.97
Stroke	1.41	1.07–1.85	0.86–2.31
Pulmonary embolism	2.13	1.39–3.25	0.99–4.56
Invasive breast cancer (overall)	1.26	1.00–1.59	0.83–1.92
Colorectal cancer	0.63	0.43–0.92	0.32–1.24
Hip fracture	0.66	0.45–0.98	0.33–1.33
Total fractures	0.76	0.69–0.85	0.63–0.92

was 1.09, 95% CI 0.86–1.39,¹¹ although the rate of breast cancer was higher in years 4 and 5, but lower in years 1 and 3 (not significant) (see Fig. 1).

Considering the CCT arm of WHI in particular, it is important to note the following points:

- WHI is the first RCT of standard oral HT for the prevention of chronic disease.
- WHI was not conducted in the population of women conventionally considered for HT initiation, in whom the absolute risks of major outcomes are clearly lower than in older women many years postmenopausal, who were the majority studied.
- Although the majority of participants did not have clinical CHD, two-thirds were overweight or obese, one-third were on treatment for hypertension and one-half were either past or current smokers. It is therefore likely that they had significant subclinical atherosclerotic vascular disease.
- WHI corroborated much existing data, particularly from the Nurses Health Study on benefit and risk (See Fig. 2).
- The findings should not and cannot be applied uncritically to women who have had long-term HT since menopause and who have not experienced adverse events such as CHD. If such women elect to continue to use hormone therapy, providing they are aware of their small increase in breast cancer risk, then WHI provides no grounds to cause them to alter that decision.
- The major benefits that can be reasonably extrapolated are fracture risk reduction and colorectal risk reduction, the latter seen only in the CCT arm.¹
- The increased risk of breast cancer with CCT does not appear for at least 5 years of therapy.

Management of symptomatic peri- and postmenopausal women

Many short-term randomised controlled clinical trials have attested to the benefits of standard menopausal HT in relieving menopausal symptoms much more effectively than do placebos.¹² Several studies indicate that doses of hormones lower than those conventionally used also provide equivalent symptomatic relief.^{13–15} The only significant risk of standard HT is a small increase in the risk of venous thromboembolism, estimated as an absolute increase in risk of < 1 per thousand women per annum in the age group conventionally treated with HT, i.e. women around age 50 years.¹⁶ Because lower than previously used standard hormone doses have been shown effective in providing symptom relief,^{13–15} prudence suggests that lower dose preparations are appropriately initiated in symptomatic women without specific contraindications to HT use.^{4,5} The range of such lower doses includes those shown in Table 3. It is noteworthy that in the NHS, low-dose therapy did not increase stroke risk (see Fig. 2).

Dose adjustments should be undertaken as necessary and annual reviews conducted of available data and perceptions

Table 3 Recommended starting doses of oestrogen for hormone therapy

0.5–1 mg 17- β -oestradiol (oral)
0.3–0.45 mg conjugated equine oestrogens (oral)
25–37.5 μ g transdermal (patch) oestradiol
0.5 mg oestradiol gel
150 μ g intranasal oestradiol

of benefit and risk with the individual woman. The question of duration of HT is a difficult and controversial one, but it may be appropriate to suggest to the individual woman after 2 to 4 years of therapy that she may wish to consider dose reduction or cessation. However, it is noteworthy that 20–25% of women will remain symptomatic for more than 5 years¹⁷ and that efforts should be made to tailor the dose to the lowest effective one.

The need for HT continuation can be determined by temporarily lowering or discontinuing therapy.

Where the individual symptoms are primarily those of urogenital atrophy, with vaginal dryness, dyspareunia or urinary frequency, topical vaginal therapy is the most appropriate.^{4,5} This may need to be used long-term. There are no long-term trials available of the safety of such topical therapy, but shorter term data certainly indicate safety, and in principle there is no reason to believe that topical therapy would have adverse long-term consequences.

Thus, for women conventionally considered for HT, reappraisal of the results from WHI would suggest that previously well-established guidelines for HT are still appropriate and that the results of WHI provide no plausible reasons to alter such guidelines. It is, however, recommended that lower doses than formerly used should be considered. No evidence currently exists that long-term effects on breast cancer would be less, nor that the benefits for fracture prevention would be the same as those of conventional doses.

Alternatives to hormone therapy – tibolone

In any consideration of menopausal HT, it is important to review the place of tibolone, a synthetic steroid-precursor molecule, metabolised in a tissue-selective fashion and sometimes referred to as a STEAR (selective tissue oestrogen activity regulator).¹⁸ Tibolone has oestrogenic effects on bone, on the vagina and on menopausal symptoms, but not on the breast. It has progestogenic effects on the endometrium and it has androgenic effects on well-being and libido.

Tibolone is as effective as conventional HT on symptom relief and reverses vaginal atrophy with improvement in vaginal dryness, dyspareunia and urinary symptoms. It affects sexual well-being positively, although there are no RCTs to support this at present. It may positively affect mood and quality of life and has been shown to prevent bone loss, though fracture prevention data are currently awaited.

Tibolone causes less breast tenderness and mastalgia than standard HT and does not increase mammographic density.

Its effect on breast cancer is the subject of current RCTs. Endometrial safety is the subject of current randomised trials, and cardiovascular effects are unclear.

Tibolone may have added value in symptomatic postmenopausal women with low sex drive, mood disorders, on psycho-active treatments, women who are at risk of accelerated bone loss, those who have a history of premenopausal mastalgia, those who have high breast density, those who have fibroids and those who have urogenital complaints. Several major randomised trials of tibolone are currently in progress.

Management of women at significantly increased risk of osteoporotic fracture

One of the significant consequences of the announcement of the WHI combined continuous treatment results has been a change in the attitudes of many national regulatory authorities to the use of HT for osteoporotic fracture risk reduction in asymptomatic peri- and early postmenopausal women. It has been generally concluded that HT should be used for this purpose only when other treatments are contraindicated or ineffective. The conclusion has been based on the perception that the risks of HT exceed the benefits in women who are not symptomatic, despite the fact that the two WHI trials are the first to show unequivocally a significant reduction in the risks of osteoporotic fracture in a population not selected to be at significantly increased risk.^{1,9}

The decision as to when to initiate prophylactic treatment to reduce osteoporotic fracture risk is a controversial issue that troubles many clinicians.¹⁹ The most important factor to be considered is the individual's absolute fracture risk.²⁰ In Australia, HT is the only reimbursed therapeutic option in women with osteoporosis who have not yet suffered a fragility fracture. It can be noted that low-dose HT has positive effects on bone mineral density, although no RCT data are available as to its efficacy in reducing fracture risk.^{21,22} If it is appreciated that an increased risk of breast cancer emerges slowly only after at least 5 years of standard-dose CCT, it seems reasonable to propose HT, particularly low-dose HT, as an appropriate initial strategy for at risk postmenopausal women whether symptomatic or not. There are few data regarding fracture risk reduction efficacy for other forms of therapy in women at this age. For an average Australian woman aged 50, a bone mineral density (BMD) T score

< -2.5 to -3, or a score of -2 to -2.5 in the presence of other substantial risk factors such as a strong family history, would provide reasonable guidelines for such therapy initiation. Thus in Australia, HT appears an appropriate first-line therapy in what needs to be a lifelong program of risk reduction. Hormone therapy could be used for 5 years or somewhat longer depending on individual benefit/risk discussion, with change to a SERM for a further 5 to 10 years and ultimately use of a bisphosphonate, given the current range of therapeutic options. Whether strontium ranelate should have a place in such a therapeutic program is yet to be established.²³ It must be emphasised that the proposal for HT use is as an initial step in a lifelong program and not that HT alone should generally be used for 10, 15 or 20 years for risk reduction. Use of oestrogen alone for this purpose may, however, be appropriate, given the results of the second WHI trial.⁹

Risk reduction for cardiovascular disease

The major reason for the conduct of the WHI RCT was to determine whether the administration of standard-dose HT was cardioprotective, as had become common practice in the USA in the early 1990s. The trials were conducted in older postmenopausal women in whom event rates for CHD would be sufficient to be able to demonstrate an effect. It should be noted that the cardioprotective effect of HT had been demonstrated in women who initiated HT around the time of menopause, primarily for the treatment of symptoms and who then continued on their therapy longer term (see Table 4).^{7,24}

The HERS had shown that standard-dose HT given orally was not cardioprotective as a secondary prevention agent in women who had previously had clinically significant CHD.¹⁰ The WHI trials were conducted in older postmenopausal women, in whom the presence of subclinical atherosclerotic vascular disease was highly likely, given their age, BMI, treatment for hypertension and smoking history. Evidence from experimental studies of CHD in the cynomolgus primate model had shown that HT initiated at the same time as ablation of ovarian function was highly significantly protective against the development of atherosclerotic lesions, whereas a delay of 2 years before the initiation of therapy in monkeys given an atherogenic diet failed to prevent atheroma formation.²⁵ It was calculated that the 2-year interval in monkeys

Table 4 Baseline characteristics – Nurses Health Study versus Women's Health Initiative

Characteristic	Nurses Health Study	WHI
Age range at enrolment (years)	30–55	50–79
Smokers (past and current) %	6.9	49.9
BMI (mean, kg/m ²)	25.11	28.5
Aspirin users percentage	43.9	19.1
HRT regimen	Unopposed, sequential	Continuous combined
Menopausal symptoms	Predominant	Largely excluded

The rates of hypertension and diabetes were similar between the two study groups.

was equivalent to an approximately 7-year interval in women, that is, if HT were initiated more than 7 years after the occurrence of menopause, it was likely that it would not be cardioprotective. This was indeed exactly borne out in the WHI trial. Thus, in the CCT arm, the hazard ratio for the occurrence of CHD in women less than 10 years postmenopausal was 0.89, for those 10–19 years postmenopausal 1.22 and for those more than 20 years postmenopausal 1.71 and highly statistically significant.²⁶ The WHI was not adequately powered to enable effects on women less than 5 years postmenopausal to be calculated reliably.²⁷ Thus, the apparent difference between the results of the WHI trials and the observational data from studies such as the Nurses Health Study is explicable in terms of time from the loss of ovarian function (Table 4).²⁸ It seems that HT initiated within 7 years of menopause might well be cardioprotective, whereas therapy initiated more than 7 to 10 years postmenopausally would not be cardioprotective and might in fact cause adverse effects as demonstrated in HERS and in the first year of the CCT arm of WHI. Explanations for such adverse effects include the effects of estradiol plus progesterone on the stability of atherosclerotic plaques.²⁸ There is no evidence that low-dose HT initiated perimenopausally leads to adverse cardiovascular outcomes.²⁹

From the above considerations, the place of HT for cardiovascular protection remains unclear. Clearly HT should not be used for CHD risk reduction in women with evidence of atherosclerotic vascular disease and in women who are more than 7 to 10 years postmenopausal. For women without known disease, however, particularly those who are less than about 7 years postmenopausal, the place of preventative therapy is less clear. It is inappropriate to extrapolate the results of WHI to such women. Clearly known risk factors such as obesity, sedentary lifestyle, smoking, diabetes, hypertension and hyperlipidaemia should be dealt with by known and proven approaches. Although there is a widespread opinion that HT is indicated, neither for primary nor for secondary cardiovascular prevention, the situation regarding primary prevention in particular is controversial and could be defended particularly in women with a strong family history of premature cardiovascular mortality.

Risk reduction for cognitive decline and Alzheimer's dementia

A further area of controversy introduced by the results of the WHI RCTs is the place of HT in reducing the risk of cognitive decline and in particular Alzheimer's dementia. In the WHI trials, a substudy, WHIMS (Women's Health Initiative Memory Study) was conducted in women aged more than 65 years at recruitment, average age 72.³⁰ In them, standard-dose HT was shown to slightly increase rather than decrease the risk of developing Alzheimer's disease. On the other hand, a body of observational data on women treated long-term from the time of menopause strongly suggests risk reduction for Alzheimer's disease, although there is no RCT evidence in such a population.³¹ Similar to the position with

CHD, it seems likely that early initiation of HT and its use long-term may be protective against the risk of Alzheimer's dementia, whereas late initiation many years after menopause is not beneficial and could even be harmful. In the absence of more comprehensive data, no firm recommendation can be made regarding HT for Alzheimer's risk reduction, although it may be reasonable to suggest that women with a family history of Alzheimer's and a substantial fear of developing it themselves might consider long-term HT, providing again that they were fully familiar with the other benefits and risks.

Risk reduction for colorectal cancer

An important observation in the CCT arm of the WHI was a significant reduction in colorectal cancer risk, not seen in the oestrogen alone arm of the study.^{1,9,32} The magnitude of the colorectal risk reduction was approximately the same as the increase in breast cancer.¹ Because colorectal cancer is a common cause of morbidity and mortality in older women, consideration can be given to the use of CCT for risk reduction. Although this has not been an important aspect of counselling women regarding HT use, it seems logical to suggest that it should become a significant part of such discussion. No data are available as to whether women at particularly increased risk of colorectal cancer will experience such protective effects.

Hormone therapy in type II diabetes

The results of WHI do not have a particular impact on decision-making regarding the use of HT in women with diabetes, although such women would be considered as being at increased cardiovascular risk and hence perhaps not suited for use of hormone therapy. Studies of HT in women with diabetes do not suggest that this is a contraindication to treatment with HT.^{33,34} Both HERS and the WHI^{35,36} demonstrated a reduction in risk of developing type II diabetes. It is recommended that in diabetic postmenopausal women, oestrogen administration should be by a non-oral route.

Overall conclusions

Regulatory authorities expressed major concerns about HT use in the wake of results from WHI. Such concerns appear to be based largely on the extrapolation of the entire range of outcomes in WHI to symptomatic peri- and early postmenopausal women, an extrapolation that seems entirely inappropriate. Limited data indicate that no increase in CHD or stroke events occurs in the population of women normally targeted for HT when HT is administered, particularly in the now recommended lower dose ranges.

Thus, the results of the WHI should not have altered current guidelines regarding optimal use of HT for 3 to 5 years in symptomatic women and in women at substantially increased osteoporotic fracture risk.

It is suggested that lower doses of HT should now become standard practice and that tibolone can be considered as an alternative, particularly for certain groups of symptomatic women.

The author's conclusions are strongly supported by the position taken by the International Menopause Society³⁷ in its response to the WHI reports and to the conclusions of groups of experts convened to discuss these issues.^{4,5}

Note added in proof

Three relevant articles (a, b, d) and an editorial (c) were published while this article was in proof. The authors include Manson, the principal cardiovascular investigator for WHI, and Grodstein and Stampfer, major investigators of the Nurses Health Study. The articles emphasise the importance of the timing of hormone therapy in terms of favourable or unfavourable cardiovascular outcomes. A cardioprotective effect was confirmed in the oestrogen-only arm of WHI for women aged 50–59 (b).

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Acknowledgements

The author is a past president of the International Menopause Society and the Australasian Menopause Society. He has been an advisory board member, consultant, symposium speaker or dinner speaker for the majority of companies that market HT products, including Wyeth, Servier, Solvay, Novo Nordisk, Novartis, Organon, Eli Lilly, Aventis and Procter and Gamble. He was a member (and the Rapporteur) of the first Scientific Group on the Menopause convened by WHO (in 1980) and was chairman of the Second Group (in 1994). He has been an adviser to NHMRC regarding menopausal HT. He served on a Working Party on HT convened in 2004 by the RCOG. He represented the Endocrine Society of Australia on the Consensus Group to propose guidelines on HT use in 2004. He serves on the Editorial Boards of Menopause, The Journal of the North American Menopause Society, and Climacteric, the Journal of the IMS, and in the past has served on the Board of Maturitas, the Journal of the European Menopause Society. The first menopause clinic in Australia was founded by the late Dr Jean Hailes under his direction in 1971. He has been an invited speaker at numer-

ous meetings related to HT including the Lancet International Meeting on HRT, The Royal Society of Medicine, RANZCOG, The Lorenzini Foundation and the American Society for Reproductive Medicine.

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