



CLIMACTERIC

The Journal of Adult Women's Health & Medicine

Volume 15 Number 3
Published bimonthly

June 2012
ISSN 1369-7137

Contents

The Women's Health Initiative – a decade of progress

EDITORIAL

- The Women's Health Initiative – a decade of progress 205
Anna Fenton and Nick Panay

REVIEWS

- Have we come full circle – or moved forward? The Women's Health Initiative 10 years on 206
R. D. Langer, J. E. Manson and M. A. Allison
- Quality of life and the role of menopausal hormone therapy 213
A. Pines, D. W. Sturdee and A. H. MacLennan
- The timing hypothesis for coronary heart disease prevention with hormone therapy: past, present and future in perspective 217
H. N. Hodis, P. Collins, W. J. Mack and L. Lind Schierbeck
- Hormone therapy and the risk of stroke: perspectives 10 years after the Women's Health Initiative trials 229
V. W. Henderson and R. A. Lobo
- Estrogen and progestogen effect on venous thromboembolism in menopausal women 235
D. F. Archer and E. Oger
- Hormone therapy and breast cancer risk, 10 years after the WHI 241
A. Gompel and R. J. Santen
- Colorectal cancer in women: hormone replacement therapy and chemoprevention 250
E. L. Barnes and M. D. Long
- Hormone therapy, dementia, and cognition: the Women's Health Initiative 10 years on 256
P. M. Maki and V. W. Henderson
- The WHI: the effect of hormone replacement therapy on fracture prevention 263
T. J. de Villiers and J. C. Stevenson
- The use of hormone therapy for the maintenance of urogynecological and sexual health post WHI 267
R. E. Nappi and S. R. Davis
- Shock, terror and controversy: how the media reacted to the Women's Health Initiative 275
S. Brown

Evidence-based assessment of the impact of the WHI on women's health <i>H. G. Burger, A. H. MacLennan, K-E. Huang and C. Castelo-Branco</i>	281
Future long-term trials of postmenopausal hormone replacement therapy – what is possible and what is the optimal protocol and regimen? <i>B. Purbrick, K. Stranks, C. Sum and A. H. MacLennan</i>	288

Editorial

The Women's Health Initiative – a decade of progress

Anna Fenton and Nick Panay

EDITORS-IN-CHIEF

July 2002 marks an important milestone in our understanding of the risks and benefits of using hormone therapy to manage symptoms of menopause. Prior to that date, hormone replacement therapy (HRT) had been widely prescribed for women on the understanding that it improved quality of life and reduced the incidence of fractures. Research also supported reductions in the risks of coronary artery disease, bowel cancer and dementia¹. These benefits appeared to be counterbalanced by increased risks of breast cancer and venous thromboembolic events (VTE).

The Women's Health Initiative (WHI) set out to examine the effects of HRT in a much older, largely asymptomatic population of women. The premature cessation of the WHI in mid-2002 was accompanied by reports that HRT not only worsened quality of life but led to increases in the incidence of coronary heart disease, stroke, dementia, breast cancer and VTE². Benefits related to bowel cancer, fracture incidence and overall mortality, as well as risk stratification based on age, received substantially less attention.

Over the past decade, there has been much critical appraisal of this study, not least from the International Menopause Society (IMS)^{3–5}. Problems with study design, drop-out and cross-over rates within the study groups, the nature of the statistical analysis, the use of a non-validated outcome index, and the premature release of preliminary data to the media in advance of manuscript publication have all been discussed at length. The authors and the media have pursued a persistently negative spin on the data that has led to mass fear being generated

among women and their doctors. A largely non-evidence-based proclamation of 'lowest dose for the shortest period of time' became accepted practice if HRT was prescribed. The reality, however, is that an entire generation of younger doctors has never prescribed HRT. We might also speculate that the mishandling of the WHI results helped spawn the rise of so-called bioidentical hormone therapy.

We have now, a decade later, started to see some more positive results emerging from the WHI and we have the two major international menopause societies 'singing from the same songbook'. The guidelines from both the IMS and the North American Menopause Society state, respectively that '*new data and re-analyses of older studies by women's age show that, for most women, the potential benefits of HRT given for a clear indication are many and the risks are few when initiated within a few years of menopause*' and '*the absolute risks known to date for use of HT in healthy women ages 50 to 59 years are low*'^{6,7}.

This issue of *Climacteric* is dedicated to providing a state-of-the-art review of the literature, a decade on from the release of the preliminary data from the WHI. In addition to reviews by leading researchers in our area, it includes the unique perspective of a journalist. Although it is very easy to focus on the harm done to women's health by the WHI, this special edition highlights the facts and demonstrates just how far we have come in better understanding the benefits and risks of HRT. It is now time for regulatory bodies to reassess their warnings and re-issue updated recommendations about HRT use.

References

1. Calaf I, Alsina J. Benefits of hormone replacement therapy – overview and update. *Int J Fertil Womens Med* 1997;42(Suppl 2): 329–46
2. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 2002;288:321–33
3. Schneider H. The view of The International Menopause Society on the Women's Health Initiative. *Climacteric* 2002;5:211–16
4. Stevenson JC, Hodis HN, Pickar JH, Lobo RA. Coronary heart disease and menopause management: the swinging pendulum of HRT. *Atherosclerosis* 2009;207:336–40
5. Panay N, Fenton A. Has the time for the definitive, randomized, placebo-controlled HRT trial arrived? *Climacteric* 2011;14: 195–6
6. International Menopause Society Writing Group. Updated IMS recommendations on postmenopausal hormone therapy and preventive strategies for midlife health. *Climacteric* 2011;14: 302–20
7. The North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2012 Position Statement of The North American Menopause Society. *Menopause* 2012; 19:257–71

Have we come full circle – or moved forward? The Women’s Health Initiative 10 years on

R. D. Langer, J. E. Manson* and M. A. Allison†

Jackson Hole Center for Preventive Medicine, Jackson, Wyoming; *Brigham and Women’s Hospital and Harvard Medical School; Boston, Massachusetts; †University of California, San Diego, School of Medicine, La Jolla, California, USA

Key words: POSTMENOPAUSAL, CORONARY, CARDIOVASCULAR, BREAST, CANCER, FRACTURE, QUALITY OF LIFE, WHI

ABSTRACT

In mid-summer 2002, the announcement that the Women’s Health Initiative (WHI) trial of combination hormone therapy (HRT) had stopped jolted the field of women’s health. It set off a cascade that first stunned, then meaningfully changed the future for millions of women, their partners, and tens of thousands of clinicians and scientists. With 10 years’ hindsight, we can begin to put the lessons learned from the WHI HRT trials into perspective. These trials were primarily designed to test whether women considerably past menopause, and mostly asymptomatic, experienced treatment benefits from HRT expected from studies of generally symptomatic women who started near menopause. The definitive answer was ‘no’. Unfortunately, the findings were generalized to all postmenopausal women regardless of age. Data accumulated from the WHI and other studies over the past decade have shown that, in women with symptoms or other indications, initiating HRT near menopause – the classic pattern of use – will probably provide a favorable benefit : risk ratio. Spurred by the WHI, many hypotheses and some insights about potential mechanisms for HRT effects on diverse organ systems have emerged, along with new perspectives on regimens, compounds, and routes of administration. This overview provides an historical perspective on the WHI design and the evolution of its message; summarizes current perspectives and insights contributed by eminent colleagues; reviews the state of the art; and looks to the future. We have come full circle in some ways, with mounting evidence supporting benefit for HRT started near menopause and with hard lessons learned about pathophysiology, publicity and interpreting data. Now we move on.

INTRODUCTION

The unexpected announcement of the early termination of the Women’s Health Initiative (WHI) clinical trial of conjugated equine estrogens plus medroxyprogesterone acetate (estrogen + progestin) set off a cascade that changed the landscape of menopause management world-wide. How did this groundswell happen? Were these changes supported by the data as they evolved? With the benefit of hindsight and perspective, what can we say about the WHI’s legacy? Are new surprises around the corner?

The WHI deserves credit for evaluating, and ultimately halting, what had become an increasingly common clinical practice of prescribing menopausal hormone replacement therapy

(HRT) for women well past menopause or at high risk of coronary heart disease, with the expectation of providing cardioprotection. However, the ‘overgeneralization’ of the WHI findings to newly menopausal women may have been detrimental, leading to needless suffering and lost opportunities for some women.

With 10 years now past, what does a fresh re-evaluation of the best available data from the WHI and other sources suggest for contemporary evidence-based practice? This special issue of *Climacteric* offers the opportunity to take stock and re-frame the evidence on HRT that has evolved through this decade since the first report from the WHI, and to move forward in the best interests of our patients. The authors contributing to this issue include some of world’s leading

Correspondence: Professor R. D. Langer, Jackson Hole Center for Preventive Medicine, PO Box 7416, Jackson, Wyoming 83002, USA

authorities in the relevant disciplines, and the topics span the breadth of postmenopausal health.

THE ‘SHOT HEARD ROUND THE WORLD’

On July 8th, 2002, the first reports of the early termination of the WHI clinical trial of estrogen + progestin appeared in the popular press. The headline on the news release¹ distributed by the National Heart Lung and Blood Institute (NHLBI) was ‘NHLBI Stops Trial of Estrogen Plus Progestin Due to Increased Breast Cancer Risk, Lack of Overall Benefit.’ The *New York Times* headline² read ‘Study Is Halted Over Rise Seen in Cancer Risk.’ A quote¹ from the NHLBI Director said, ‘The cardiovascular and cancer risks of estrogen plus progestin outweigh any benefits – and a 26% increase in breast cancer risk is too high a price to pay, even if there were a heart benefit. Similarly, the risks outweigh the benefits of fewer hip fractures.’

The NIH news release said ‘the WHI involved 16608 women ages 50–79 years’ but did not highlight that it was a study focused on older postmenopausal women, leaving the impression that it reflected typical clinical use in newly menopausal women, although it did not. This impression was reinforced by a quote from the acting study director¹ who said, ‘the adverse effects of estrogen plus progestin applied to all women, irrespective of age, ethnicity, or prior disease status.’ In hindsight, although the WHI estrogen + progestin trial did not show clear differences by age group, the estrogen-alone trial (which was reported later) did³. So did the pooled results of the two trials⁴.

The press release indicated that the study was stopped because ‘the number of cases of invasive breast cancer in the estrogen plus progestin group had crossed the boundary established as a signal of risk.’ It continued, ‘Since breast cancer is so serious an event, we set the bar lower to monitor for it,’ and noted ‘evidence of overall health risks exceeding any benefits’¹.

Although the news release described relative risks on the first page, further down it listed absolute numbers of events per 10 000 women per year. The press focused on the relative risks, e.g. a 26% increase in breast cancer. Much has been written since about the difficulty most people have in properly interpreting relative risks (which depend on the background rate in the population), and the fear they can trigger.

Another quote from the acting study director¹ said that women ‘who are currently taking estrogen plus progestin should have a serious talk with their doctor to see if they should continue it. Long-term use or use for disease prevention must be re-evaluated given the multiple adverse effects noted in WHI.’

This played out in the press on July 8–10, a full week prior to the distribution of the paper to subscribers in the print issue of July 17. A strong impression of harm was established in the press before the vast majority of clinicians and peers in science had the opportunity to read the paper, digest it, and put its findings into context. Consistent with the headline of

the news release, press reports focused on breast cancer – the disease women fear most – so a dramatic response was predictable. A quote in the *Atlanta Journal-Constitution* from a 15-year user⁵ was typical, ‘It’s terrifying for those who’ve been told we’ll be on HRT for life ... it’s devastating to feel that what you have been doing for yourself all this time has been harmful when you believed it was beneficial.’

First impressions are nearly impossible to reverse. Although the news release mentioned that the estrogen-alone study was continuing because there was no indication of increased risk, the impression of harm carried over, so that use of estrogen declined rapidly along with estrogen + progestin therapy. More importantly, when reported 2 years later, the contrasting results of the estrogen-alone trial – no increase in breast cancer, a lower rate of coronary events including revascularization in women aged 50–59 years – were largely ignored because of the negative perspective surrounding HRT by that time.

THE WHI DESIGN

Although the WHI design has been criticized and its external validity questioned, objective assessment shows that the trials were sound and that the results are valid for the questions the study was planned to answer. The WHI was a multi-outcome study with multiple interventions tested in four overlapping trials⁶. From largest to smallest, they were: low-fat diet, calcium–vitamin D supplementation, estrogen + progestin therapy, and estrogen-alone therapy. When the WHI was designed in the early 1990s, it was not anticipated that intervention effects would vary by age group. Since the rates of the primary outcomes (respectively: breast cancer, fracture, coronary heart disease (CHD)) increase with age, and no age-related differences were expected for any of the interventions, recruitment was restricted within age groups to enroll a cohort that was, on average, well beyond menopause. Enrolling an older cohort, with higher background rates of disease and a greater burden of risk factors, afforded the opportunity to get more timely and cost-effective answers to the questions posed. And, with HRT increasingly being prescribed for older women at that time, it was important to assess the benefits and risks in that population.

Fully 70% of participants were to be aged 60 and older, with just 10% aged 50–54 years⁶. Actual enrollment came quite close to those targets so that the average age at entry was 63 years, and the average time since menopause was at least 12 years⁷. For HRT as a potential preventive strategy for CHD, the WHI protocol referenced the existing observational literature that reflected clinical use, the vast majority of which reflected initiation near menopause, and the single inconclusive, but promising, clinical trial then available by Nachtigall and colleagues⁸. Appropriately, it noted that most of the available literature reflected use of estrogen-alone, that progestins could counteract some of the potential benefits of estrogens, and that data on combination therapy were limited. It also cited the positive findings for likely pathways from the then recently completed Postmenopausal

Estrogens–Progestins Interventions (PEPI) trial, conducted in women aged 45–64 years⁶.

Based on the enrollment of women who were on average more than a decade past menopause, age-specific US event rates, and likely pathways, the WHI design anticipated the need for about 6 years of follow-up to detect a difference in coronary events, and as much as 12 years to detect a difference in breast cancer rates. The emergence of trends that could halt the study much earlier in follow-up was wholly unanticipated. In retrospect, it is likely that the trends observed were partially attributable to age-related differences in pathophysiology and metabolism that were unrecognized prior to the WHI. Indeed, this is one of the program's important contributions.

The WHI findings have been criticized as inaccurate because of the drop-out rates of 42 and 38%, and drop-in rates of 6 and 11%, in the active and placebo groups, respectively. While the drop-out rates were modestly greater than anticipated in the study design, they compare favorably with real-world experience⁷. Also, non-compliance in randomized trials usually biases results toward the null, so would not be expected to produce spurious adverse associations.

EVOLUTION OF THE WHI MESSAGE

The initial paper in *JAMA* on July 17, 2002, provided an overview of the preliminary and not fully adjudicated findings for the major outcomes⁷. Subsequent papers focused on specific outcomes using centrally adjudicated data through the end of the trial. There were no meaningful differences between the preliminary and final results, with the final hazard ratios (HRs) (95% confidence intervals, CI) for CHD⁹ and breast cancer¹⁰ being, respectively, 1.24 (1.00–1.54) and 1.24 (1.01–1.54). Nominal (unadjusted) confidence intervals were used to interpret these primary study outcomes. However, reflecting the marginal nature of these results, adjusted 95% CIs were not significant, being 0.97–1.60 and 0.97–1.59, respectively. Absolute risks per 10 000 women per year were also reported. There were seven more CHD events, eight more strokes, eight more pulmonary emboli, and eight more invasive breast cancers, along with six fewer colorectal cancers and five fewer hip fractures⁷. These absolute rates of excess events, which are easier to understand for most patients (and at <1 : 1200 are rare by generally accepted criteria), were lost in the media uproar over the relative risks that are more difficult for most people to interpret properly.

As questions emerged regarding potential interactions between pathophysiology, biological age, and treatment, disease-specific papers began to investigate associations by constructs such as years since menopause, age decade, and the presence or absence of vasomotor symptoms. Given the relatively small numbers of women still close to menopause, the statistical power to test differences between typical HRT users in clinical practice, and women well beyond those ages, was limited. Nonetheless, potential differences were suggested by contrasting findings for coronary disease for women

<10, 10–19, and \geq 20 years from menopause and for women with vasomotor symptoms compared to those without⁹. Importantly, the elevated CHD risk emerged in the first year (in contrast to the design assumption that CHD differences would emerge in about 6 years). There was also a significant trend towards lower rates over time. The publication that focused on breast cancer outcomes found no suggestion of interaction by age, years since menopause, or family history. It showed an apparent increase in breast cancer beginning after about 3–4 years on treatment, also much earlier than anticipated in the study design⁹. A paper on quality of life after 1 year of estrogen + progestin therapy found no benefit in the cohort overall¹¹. Benefits found for vasomotor symptoms and sleep in symptomatic women aged 50–54 years at baseline were largely ignored in summaries published in the professional media and popular press.

With a skeptical climate for HRT established, the estrogen-alone trial was also stopped early. The decision was driven by an increase in stroke rates (HR 1.39, 95% CI 1.10–1.77). However, there was an odd juxtaposition of findings – a lower rate of breast cancer was at the cusp of significance (HR 0.77, 95% CI 0.59–1.01), and there was a non-significant reduction in CHD (HR 0.91, 95% CI 0.75–1.12)¹². A subsequent paper on breast cancer found no effect of estrogen-alone in intention-to-treat analyses, but a significant reduction in breast cancer among women with \geq 80% adherence to treatment¹³. A paper focused on CHD found significant age-related effects with a reduced incidence of CHD including coronary revascularization and confirmed angina among women aged 50–59 years (HR 0.66, 95% CI 0.45–0.96), and increased risk in women 60 years and older³. A paper using the surrogate end-point of coronary artery calcium score in women aged 50–59 years also found a significant benefit from estrogen-alone therapy¹⁴.

The larger observational study cohort of over 93 000 women was established in part to serve as an external comparison for the clinical trials⁶. A series of papers was published incorporating data from both the observational study and the clinical trials. These were initially focused on exploring differences in outcomes resulting from the two study designs, including the extent of residual confounding inherent in observational studies¹⁵. As the series progressed, this goal was largely supplanted by the use of the larger numbers in the combined cohorts to further explore outcomes^{16–19}, although different adjustment strategies were applied to the observational study and clinical trials in these analyses²⁰. A construct of 'gap time', defined as time from menopause to the first use of HRT, was explored in later papers in this series^{17–19}. This construct places women with early, brief use in the same category as women with early initiation and sustained use. It is not the same as cumulative time after menopause without HRT, which may be more reflective of concerns in clinical practice²⁰.

Was the WHI a failure? Unequivocally not. It was designed to test whether preventive interventions that showed promise in studies available in the early 1990s would be effective in women well past the menopause. For HRT, the WHI results

showed that treating women with an average age of 63 years, and 12 years postmenopause, did not provide the cardiovascular benefit predicted from studies in which the majority of women started HRT near the time of menopause. In demonstrating this, the WHI, along with the Heart and Estrogen/progestin Replacement Study (HERS), forced us to re-consider some of our assumptions about hormonal aging and the mechanisms underlying hormone actions. The unfortunate effects of the WHI came not from problems with the design or the findings; rather, they were the result of generalizing findings from a well-conducted study to a subgroup that was not adequately represented.

In essence, the negative perspective established by the initial reports of each trial, both published in the heightened context of early stopping, influenced reporting in the press. This was further reinforced by the dominant influence of older ages (associated with genuinely poorer results for most outcomes) in reports on the cohort overall, and through a policy of the study leadership to maintain consistency in the interpretation of results and avoid contradictory publications.

THE CURRENT STATE OF THE ART AS REFLECTED IN THIS SPECIAL ISSUE

Unlike virtually any other pharmacologic intervention, HRT has myriad effects that influence nearly all aspects of a woman's health. As noted by Sturdee and colleagues in their contribution²¹, the construct of quality of life is dependent upon the instruments used to assess it. They argue that the WHI's conclusion that estrogen + progestin therapy had no clinically meaningful effect on any aspect of health-related quality of life 'should have had many caveats including that WHI assessed the effect of HRT in mostly asymptomatic elderly women using a generic quality-of-life instrument and asking only one question on sexuality.' They review findings of declines in quality of life following cessation of HRT, an important negative consequence of the abandonment of HRT that resulted from the WHI reports. They also note that the WISDOM Study, using a different instrument, found significant improvements in vasomotor symptoms, sexual function, sleep, musculoskeletal symptoms, and vaginal dryness.

In contrast, systemic HRT has been associated with increased urinary incontinence in most studies, including the WHI. Nappi and Davis point out that local therapy is generally more effective for urogenital symptoms, including dyspareunia, which can be a critical determinant of a woman's interest in sex. They note that the WHI collected limited data on sexual function, so that better information is available from other sources²².

Evidence that the timing of HRT initiation is critical to the benefit : risk ratio for HRT has steadily accumulated over these 10 years. Hodis and Collins argue that initiation near menopause is associated with benefits, including a substantial increase in quality-adjusted life years, while initiation after age 60 years is associated with harm. They note that randomized, controlled trials (RCTs) have not shown lipid-lowering

and aspirin therapy to be effective for primary prevention of coronary disease in women, while RCT evidence supports the use of HRT started near menopause for this purpose²³. In contrast, Henderson and Lobo review the findings for stroke from multiple sources. They conclude that there is consistent evidence for a modest increase in stroke risk with standard doses of HRT, regardless of regimen, compound, timing of use, or age at initiation – although the absolute risk is low early in menopause (<2 per 10 000 woman-years for women <60 years old). They cite limited evidence that low doses of transdermal estradiol ($\leq 50 \mu\text{g/day}$), and oral conjugated estrogens (0.3 mg/day) are not associated with elevated stroke risk²⁴.

Similarly, oral HRT has been associated with an increase in venous thromboembolic events in reports from RCTs including HERS and WHI, as well as observational studies since the late 1990s. As reviewed by Archer and Oger²⁵, limited evidence suggests that transdermal estrogen may be safer in this regard, since oral estrogens have clear effects on coagulation factors. The form of progestin may also be important, while age and obesity also increase thromboembolic risk.

Concerns about breast cancer risk have been paramount in the reaction to the WHI. Gompel and Santen write that the impact of HRT on breast cancer risk is relatively low and that the use of relative risks tends to exaggerate the perception of excess risks. They conclude that women with a low underlying risk of breast cancer and substantial menopausal symptoms will experience benefits that outweigh possible harm²⁶.

The question of a chemoprotective effect of HRT on colorectal cancer is addressed by Barnes and Long who acknowledge the inconsistency in the results for the WHI estrogen + progestin (protective, but mainly for local disease) and estrogen-alone (null) trials. Their review of observational studies published since the WHI suggests protection with both combination and estrogen-alone therapy that is strongest in current users, with incidence reduced by approximately 40%²⁷.

The findings of increased risk of dementia for both estrogen + progestin therapy and estrogen-alone therapy in the WHI Memory Study (WHIMS) were among the most disturbing results from the WHI trials. Maki and Henderson note that, shortly after the end of the WHI, the Multi-Institutional Research in Alzheimer Genetic Epidemiology case-control study reported an age interaction between the time of initiation of HRT and subsequent dementia. They argue that, together with studies showing greater protection for past than current use, these findings suggest that timing may be important for dementia outcomes, as for CHD, with benefit realized only with initiation near menopause²⁸.

The benefits for fracture prevention seen in the WHI were discounted because of the competing adverse effects. de Villiers and Stevenson suggest that reliance on the Global Index, and lack of information on non-clinical vertebral fractures, and non-vertebral fractures, that are routinely collected in bone-focused trials, inappropriately downgraded the strength of evidence for fracture prevention that should have come from the WHI. They note that the WHI proved that HRT is effective for fracture prevention in osteopenic

women, while there is no similar evidence for bisphosphonates, and that the WHO FRAX tool identifies a significant number of women in this situation. They conclude that restrictions on HRT for bone-specific benefits are not supported by the data²⁹.

Given the influence of HRT on most female organ systems, the steep decline in usage following the initial WHI report in summer 2002 could be expected to cause shifts in disease rates. As discussed by Burger and colleagues, the reality is more complicated³⁰. One reason is that the level of data on use is highly variable by country. In countries where data are available, the picture is still clouded because most major diseases influenced by HRT have long lag times, especially in young menopausal women for whom HRT may still be indicated, so that HRT-related differences will take substantial time to emerge. The primary exception is fracture, the risk of which was shown in one large study to rise beginning 2 years after stopping HRT, and to increase by 55% after 6.5 years. They note that a small, transient decline in breast cancer that would be consistent with an effect on existing tumors was seen in some, but not all, countries that had large declines in HRT use. They voice concerns that a potential increase in cardiovascular disease may not become apparent for still another decade, and that negative attitudes towards HRT have fueled the rise of potentially dangerous complementary-alternative therapies of dubious efficacy.

Since the greatest impact of the WHI came by way of its coverage in the popular press, it is both informative and refreshing to have a medical writer recount the history of the WHI in the media as it evolved from the first leaks and press reports to the present. Beginning with ‘shock and terror’ and continuing through reaction, controversies, reversals, and re-considerations, Simon Brown weaves a fascinating tale of science in the information age³¹.

THE CRYSTAL BALL – WHAT MIGHT WE EXPECT IN THE NEXT DECADE?

As the surprises of the WHI illustrate, predicting future trends in medicine is a perilous pursuit. Results of the KEEPS and ELITE trials (described below) should contribute to our understanding of differences between oral and transdermal regimens, the safety of micronized progesterone, and age-related effects. In this issue, Purbrick and colleagues acknowledge and build upon those designs, suggesting a potential trial that would use an oral and/or transdermal selective estrogen receptor modulator in place of a progestin³².

Fortunately, we begin this decade with heightened awareness of the diverse and complex issues involved in HRT, and with the well-informed guidance of evolved consensus statements from the International Menopause Society (IMS) and the North American Menopause Society (NAMS). This is certainly a far better situation than the complacency that marked our field when the early termination of the WHI estrogen + progestin trial seemed to turn the world upside-down a decade ago.

The IMS emphasizes the importance of individualized treatment, and that safety largely depends on age, with a balance towards benefits for most women who initiate with a clear indication within a few years of menopause³³. The NAMS position statement is similar, concluding that data support the use of HRT to treat menopausal symptoms near the time of menopause, and/or to address specific disorders such as osteoporosis, and that benefit–risk is favorable near menopause but decreases with age thereafter³⁴. The IMS notes mounting evidence for the timing hypothesis for cardiovascular protection, emerging evidence suggesting reduced thromboembolic risk with non-oral estrogen, recommends minimizing progestin exposure to that necessary for endometrial safety, and cautions that there are no medical or scientific reasons to recommend unregistered bio-identical hormones; NAMS offers similar opinions. Both organizations emphasize that treatment should be titrated to the lowest effective dose.

With regard to breast cancer, both organizations endeavor to put the risk into perspective, citing the best available data of a rate of <1 per 1000 per year based on the WHI, and note that in the WHI the risk was further limited to women with prior use before the enrollment, and not observed in women whose first exposure was in the RCT. NAMS makes the further point that the risk is associated with current use – returning to the population baseline in 3–5 years after treatment ceases. Both acknowledge the suggestion of reduced risk with estrogen-alone in the WHI and the Nurses’ Health Study, although the IMS cautions that European data suggest potential increased risk with estrogen alone after 5 years, but does not speculate whether this difference could be related to the prominence of estradiol in Europe and conjugated equine estrogens (CEE) in the US.

While the IMS makes no distinction between combination therapy and estrogen-alone therapy with regard to emerging evidence for cardiovascular protection at younger menopausal ages, NAMS restricts this opinion to estrogen-alone therapy. Currently, ambiguity surrounds potential differences between outcomes associated with continuous versus sequential regimens, oral versus transdermal estrogens, and the choice of progestin. At present, there are no clinical trial data to address these questions for disease outcomes, and the available observational data are not definitive. The most consistent data pertain to venous thromboembolic events, where non-oral estrogens have generally been associated with lower risk^{35,36}.

Differences in outcomes by progestin remain controversial. The PEPI trial found modest differences between micronized progesterone and medroxyprogesterone acetate (MPA) in lipid benefits, although both were better than placebo³⁷. However, there are no clinical trial data supporting a difference in CHD rates. The Kronos Early Estrogen Prevention Study (KEEPS)³⁸ and the Early versus Late Intervention Trial with Estradiol (ELITE)³⁹ trials will shed some light on this in the near future. Both are primary prevention RCTs testing the surrogate cardiovascular outcomes of carotid intima medial thickness and coronary artery calcium, and both are expected to report their results within the next year. KEEPS enrolled

729 early menopausal women and is testing mid-dose oral CEE (0.45 mg), low-dose transdermal estradiol (50 µg/day), or placebo, with cyclical oral micronized progesterone 200 mg for 12 days/month for women on active estrogen. ELITE is testing conventional-dose oral estradiol (1 mg/day) or placebo with vaginal progesterone gel or placebo for 10 days each month in 643 women either <6 years, or >10 years, since menopause.

Early results from the E3N observational study suggested that regimens with transdermal estradiol and oral micronized progesterone were associated with lower rates of breast cancer⁴⁰. However, that difference was not sustained in the most recent report from this cohort⁴¹. The PEPI trial found equivalent endometrial protection for both continuous and sequential combined regimens with MPA, and as well as a 12-day/month sequential regimen with micronized progesterone, all evaluated for 3 years⁴². Some observational data suggest a lower rate of breast cancer with sequential regimens, but this remains speculative³⁴. Although some have advocated long-cycle progestin to minimize exposure, data on endometrial safety remain inadequate at present; this is an area ripe for potential investigation in the near term.

Signaling the evolution of thought over the past decade, the IMS statement³³ concludes that: ‘The excessive conservatism engendered by the presentation to the media of the first results of the WHI in 2002 has disadvantaged nearly a decade of women who may have unnecessarily suffered severe menopausal symptoms and who may have missed the potential therapeutic window to reduce their future cardiovascular, fracture and dementia risk.’

Most, if not all, of the contributors to this special issue would agree. Nonetheless, the WHI deserves credit for demonstrating that the practice of starting HRT in older and high-risk women to prevent CVD and dementia is not supported by scientific evidence.

The WHI was inspired by findings from observational studies reflecting initiation primarily in newly menopausal women

with long-term exposure suggesting that HRT could prevent major age-related diseases. Historically, in cardiovascular trials, patients with the greatest burden of risk often obtained the strongest benefit from a treatment. Against that background, the WHI tested benefit in older women in whom risk factor-loading was considerably greater than those represented in observational studies. Benefit was not found.

The WHI was not intended to test benefits in recently menopausal women. However, data from it and other studies published since suggest a ‘window of opportunity’, consistent with the literature that led to the WHI. We have come nearly full circle, but with a hard-won understanding of factors that modulate the balance between benefit and risk for this key intervention in women’s health.

Moving forward, evidence supports the return to rational use of HRT, generally with initiation near menopause, the classic clinical approach. While HRT is certainly not appropriate for every woman, it may be for those with symptoms or other indications. In that setting, with initiation near menopause, the weight of evidence supports benefits over risks, with the potential to prevent or ameliorate downstream morbidity.

ACKNOWLEDGEMENT

The authors wish to thank Dr Sima Sconyers for assistance in reviewing the manuscript.

Conflict of interest The opinions expressed are those of the authors; they do not necessarily reflect the opinions of the Women’s Health Initiative Program or other WHI investigators. Dr Langer has served as an expert witness for Wyeth Pharmaceuticals, and as an expert in intellectual property matters for Breckenridge Pharmaceuticals. Dr Manson and Dr Allison report no conflicts.

Source of funding Nil.

References

1. NHLBI Communications Office. NHLBI Stops Trial of Estrogen Plus Progestin Due to Increased Breast Cancer Risk, Lack of Overall Benefit. Embargoed for release Tuesday, July 9, 2002, 9:30 a.m. Eastern Time. July 8, 2002. <http://www.nhlbi.nih.gov/new/press/02-07-09.htm>
2. Kolata G. Study Is Halted Over Rise Seen in Cancer Risk. *New York Times*, July 9, 2002. <http://www.nytimes.com/2002/07/09/us/study-is-halted-over-rise-seen-in-cancer-risk.html?pagewanted=all>
3. Hsia J, Langer RD, Manson JE, *et al.* Conjugated equine estrogens and coronary disease. *Arch Intern Med* 2006;166:357–65
4. Rossouw JE, Prentice RL, Manson JE, *et al.* Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465–77
5. Guthrie P. Women React to Finding on Hormone Replacement Therapy. *Atlanta Journal-Constitution*, 7/10/02. <http://www.highbeam.com/doc/1G1-88731840.html>
6. Women’s Health Initiative Investigators. Protocol for clinical trial and observational study components. WHI manuals: Volume 1 - Study protocol and policies 01/07/03. http://www.whiscience.org/about/manual/manual_1_1.pdf
7. Writing Group for the Women’s Health Initiative. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women’s Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33
8. Nachtigall LE, Nachtigall RH, Nachtigall RD, Beckman EM. Estrogen replacement therapy. II. A prospective study in the relationship to carcinoma and cardiovascular and metabolic problems. *Obstet Gynecol* 1979;54:74–9
9. Manson JE, Hsia J, Johnson KC, *et al.*; Women’s Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523–34
10. Chlebowski RT, Hendrix SL, Langer RD, *et al.*; WHI Investigators. Influence of estrogen plus progestin on breast cancer and

- mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA* 2003;289:3243–53
11. Hays J, Ockene JK, Brunner RL, *et al.*; Women's Health Initiative Investigators. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med* 2003;348:1839–54
 12. Anderson GL, Limacher M, Assaf AR, *et al.*; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701–12
 13. Stefanick ML, Anderson GL, Margolis KL, *et al.*; Women's Health Initiative Investigators. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA* 2006;295:1647–57
 14. Manson JE, Allison MA, Rossouw JE, *et al.*; WHI and WHI-CACS Investigators. Estrogen therapy and coronary-artery calcification. *N Engl J Med* 2007;356:2591–602
 15. Prentice RL, Langer R, Stefanick ML, *et al.*; Women's Health Initiative Investigators. Combined postmenopausal hormone therapy and cardiovascular disease: toward resolving the discrepancy between observational studies and the Women's Health Initiative clinical trial. *Am J Epidemiol* 2005;162:404–14
 16. Prentice RL, Langer RD, Stefanick ML, *et al.*; Women's Health Initiative Investigators. *Am J Epidemiol* 2006;163:589–99
 17. Prentice RL, Chlebowski RT, Stefanick ML, *et al.* Estrogen plus progestin therapy and breast cancer in recently postmenopausal women. *Am J Epidemiol* 2008;167:1207–16
 18. Prentice RL, Chlebowski RT, Stefanick ML, *et al.* Conjugated equine estrogens and breast cancer risk in the Women's Health Initiative clinical trial and observational study. *Am J Epidemiol* 2008;167:1407–15
 19. Prentice RL, Manson JE, Langer RD, *et al.* Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause. *Am J Epidemiol* 2009;170:12–23
 20. Langer RD. Re: Estrogen plus progestin therapy and breast cancer in recently postmenopausal women. *Am J Epidemiol* 2009;169:784–5
 21. Pines A, Sturdee DW, MacLennan AH. Quality of life and the role of menopausal hormone therapy. *Climacteric* 2012;15:213–16
 22. Nappi RE, Davis SR. The use of hormone therapy for the maintenance of urogynecological and sexual health post WHI. *Climacteric* 2012;15:267–74
 23. Hodis HN, P. Collins P, Mack WJ, Lind Schierbeck L. The timing hypothesis for coronary heart disease prevention with hormone therapy: past, present and future in perspective. *Climacteric* 2012;15:217–28
 24. Henderson VW, Lobo RA. Hormone therapy and the risk of stroke: perspectives 10 years after the Women's Health Initiative trials. *Climacteric* 2012;15:229–34
 25. Archer DF, Oger E. Estrogen and progestogen effect on venous thromboembolism in menopausal women. *Climacteric* 2012;15:235–40
 26. Gompel A, Santen RJ. Hormone therapy and breast cancer risk 10 years after the WHI. *Climacteric* 2012;15:241–9
 27. Barnes EL, Long MD. Colorectal cancer in women: hormone replacement therapy and chemoprevention. *Climacteric* 2012;15:250–5
 28. Maki PM, Henderson VW. Hormone therapy, dementia, and cognition: the Women's Health Initiative 10 years on. *Climacteric* 2012;15:256–62
 29. de Villiers TJ, Stevenson JC. The WHI: the effect of hormone replacement therapy on fracture prevention. *Climacteric* 2012;15:263–6
 30. Burger HG, MacLennan AH, Huang K-E, *et al.* Evidence-based assessment of the impact of the WHI on women's health. *Climacteric* 2012;15:281–7
 31. Brown S. Shock, terror and controversy: how the media reacted to the Women's Health Initiative. *Climacteric* 2012;15:275–80
 32. Purbrick B, Stranks K, Sum C, *et al.* Future long-term trials of postmenopausal hormone replacement therapy – what is possible and what is the optimal protocol and regimen? *Climacteric* 2012;15:288–93
 33. Sturdee DW, Pines A, on behalf of the International Menopause Society Writing Group. Updated IMS recommendations on postmenopausal hormone therapy and preventive strategies for midlife health. *Climacteric* 2011;14:302–20
 34. Writing Group for the North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause* 2010;17:242–55
 35. Canonico M, Fournier A, Carcaillon L, *et al.* Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. *Arterioscler Thromb Vasc Biol* 2010;30:340–5
 36. Renoux C, Dell'Aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. *J Thromb Haemost* 2010;8:979–86
 37. The Writing Group for the PEPI Trial. Effects of estrogen on estrogen/progestin regimens on heart disease risk factors in postmenopausal women: The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995;273:199–208
 38. Harman SM, Brinton EA, Cedars M, *et al.* KEEPS: The Kronos Early Estrogen Prevention Study. *Climacteric* 2005;8:3–12
 39. ELITE: Early Versus Late Intervention Trial With Estradiol. <http://clinicaltrials.gov/ct2/show/NCT00114517>
 40. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat* 2008;107:103–11
 41. Fournier A, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F. Estrogen–progestagen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment initiation influence risks? *J Clin Oncol* 2009;27:5138–43
 42. The Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1996;275:370–5

Quality of life and the role of menopausal hormone therapy

A. Pines, D. W. Sturdee* and A. H. MacLennan†

Ichilov Hospital, Tel Aviv, Israel; *Solihull Hospital, UK; †The Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia

Key words: QUALITY OF LIFE, WOMEN'S HEALTH INITIATIVE, STOPPING HRT

ABSTRACT

The quality of life of countless menopausal women world-wide has been significantly diminished following the sensationalist reporting of the Women's Health Initiative (WHI) and the resulting 50% or more decline in the use of hormone replacement therapy (HRT) over the subsequent 10 years. Quality of life is difficult to measure as there are so many contributing factors and a large number of different instruments, some of which assess general health and only a few which specifically include symptoms related to menopause. HRT improves quality of life of symptomatic menopausal women and some studies of the effects of HRT provide reliable evidence on quality of life other than reduction in vasomotor symptoms. Until there is a better understanding of the minimal risks of HRT for the majority of women, too many will continue to suffer a reduced quality of life unnecessarily.

INTRODUCTION

Good quality of life is a fundamental right and legitimate aspiration for everyone. During a lifetime there will be many fluctuations in quality of life resulting from relationship, domestic, financial, work and health issues in particular. It is also well recognized that normal physiological changes can impact on quality of life and in women this is especially evident during the menstrual cycle, pregnancy and the climacteric. The normal hormonal changes associated with the climacteric and causing menopausal symptoms are a major cause of reduced quality of life; this has been confirmed by many studies, with highly significant reduction in the most important menopausal symptoms of hot flushes and sweats with hormone replacement therapy (HRT)¹. The definite improvement also in quality of life has been documented in scientific controlled trials^{2,3} and recognized in Professional Society recommendations^{4–6}. However, the Women's Health Initiative (WHI) study and the reason for this special issue, concluded that...*'Estrogen plus progestin did not have a clinically meaningful effect on any aspect of health-related quality of life assessed in the WHI trial of estrogen plus progestin'*⁷. This conclusion should have had many caveats, including that the WHI assessed the effect of HRT in mostly asymptomatic elderly women using a generic quality-of-life instrument and asking only one question on sexuality.

The other large, randomized, controlled trial, the Heart and Estrogen/progestin Replacement Study (HERS), which reported just before the WHI, concluded that...*'hormone therapy has mixed effects on quality of life among older women'* and ...*'depend on the presence of menopausal symptoms'*⁸. Neither of these large, randomized, controlled trials (RCT) were designed to assess the effects of HRT as a primary outcome measure, since they recruited women with a mean age of 63 and 69 years, respectively, of whom no more than 12% were symptomatic, and over 60% were 10 or more years post menopause. Furthermore, the validity of the WHI as a RCT has also been questioned as 45% of the estrogen plus progestin group were unblinded so that they were aware of their treatment and several warnings were sent to the participants about the detection of increased risks of myocardial infarction, stroke and pulmonary embolism during the study. These issues compromise the reliability and make the WHI study no better than any observational study with all of their limitations^{9,10}. Nevertheless, as a result of the adverse media publicity following the various WHI reports, there has been a dramatic reduction in the prescribing to and requests for HRT by symptomatic menopausal women all around the world, which is probably still continuing even at 10 years later.

The Women's International Study of long Duration of Oestrogen after the Menopause (WISDOM) has been the only

Correspondence: Dr D. W. Sturdee, Solihull Hospital, Solihull, West Midlands, UK

other large, randomized, placebo-controlled trial of HRT³. It showed that combined HRT started many years after menopause is associated with significant improvements in vasomotor symptoms, sexual function, sleep disturbance, aching joints and muscles, insomnia and vaginal dryness, although more women in the HRT group experienced breast tenderness and vaginal discharge. Aching joints and muscles, insomnia, and vaginal dryness improved independently of whether participants experienced vasomotor symptoms at baseline. Combined HRT improves condition-specific but not overall generic measures of health-related quality of life at 1 year. Thus, the choice of the quality-of-life instrument is important when assessing the effect of menopausal symptoms.

MEASUREMENT OF QUALITY OF LIFE

Health-related quality of life refers to the effects of an individual's physical and emotional state on their overall quality of life, and an improvement in health-related quality of life is a primary purpose of health promotion and health care¹¹ and of those involved in running a menopause clinic. However, measurement of this is very subjective and complex, with a multitude of different aspects that contribute to the overall picture, so not surprisingly a large number of instruments have been developed. There are two major categories of measures – generic and condition-specific. Among the most commonly used generic measures is the Short Form (SF)-36 Health Survey, which evaluates domains under the headings of physical functioning, role-physical, bodily pain and general health with vitality, social functioning, role-emotional and mental health under the mental health section¹². Good examples of condition-specific instruments are the Women's Health Questionnaire (WHQ), which was designed specifically to study changes in perception of health and well-being during the menopausal transition¹³, and the Menopause Rating Scale (MRS), developed to provide the physician with a tool to document specific climacteric symptoms and their changes during treatment¹⁴. The WHQ has nine domains, each providing a score for: depressed mood, somatic symptoms, memory/concentration, vasomotor symptoms, anxiety/fear, sexual behavior, sleep problems, menstrual symptoms and attractiveness. The MRS evaluates 11 symptoms under the categories of psychological, somatovegetative and urogenital.

The WHI study did not measure the impact of HRT on quality of life using validated instruments¹⁵, but used a mixture of a generic measure, the RAND 36-item Health Survey¹⁶, which has the same items as the SF-36 and an additional checklist of symptoms that was used in the HERS study to assess symptoms associated with the menopause. It was not clear how moderate and severe flushes were defined and vaginal symptoms were not evaluated at all. In addition, the symptom scores were high at baseline, which limited the potential for HRT to cause a further increase.

It is important to choose validated and appropriate instruments for assessing health-related quality of life, which will depend on many factors including the population and

treatment being evaluated. These issues have been reviewed and all the current instruments listed and analyzed by Schneider and colleagues¹¹.

QUALITY OF LIFE AFTER STOPPING HRT

Since vasomotor symptoms are perceived as the hallmark of quality of life in the early postmenopause period, ample data related to discontinuation of HRT are available in this respect from various parts of the globe^{17–19}. A recent survey on a menopause website of 1100 women who stopped using HRT following the WHI reports in the media in 2002 found that most did so without seeking medical advice²⁰. This was significantly more likely in those aged under 50 years at 73% compared to older women, where each of the 49% of those who had stopped taking HRT had made this decision herself ($p < 0.001$). Of the women who had previously taken HRT for menopausal symptoms, 89% had a return of symptoms and 74% said that their symptoms were worse. Due to the return of symptoms, HRT was restarted in 41%. A further response of relevance is that, overall, 47% of women would not have stopped HRT given the current understanding of risk. Other studies have looked into potential changes in the incidence of fractures, breast cancer and coronary events in the post-WHI era, when less and less women have been using HRT, but fewer studies have focused on the consequences for quality of life of stopping HRT. Since quality of life is a complex, multifactorial entity, especially in the menopause transition and during the first years in menopause, it is not easy to document all the aspects of quality of life in women who stopped HRT. Utian referred to this issue of measuring quality of life in menopausal women, urging investigators to add quality-of-life questionnaires to the protocol of all studies which examine the effects of drug therapies in menopausal women²¹.

A group from Finland followed quality of life of women during long-term use of HRT and 1 year after stopping therapy²². While quality-of-life ratings improved with HRT, irrespective of dosage, including depressed mood, anxiety,

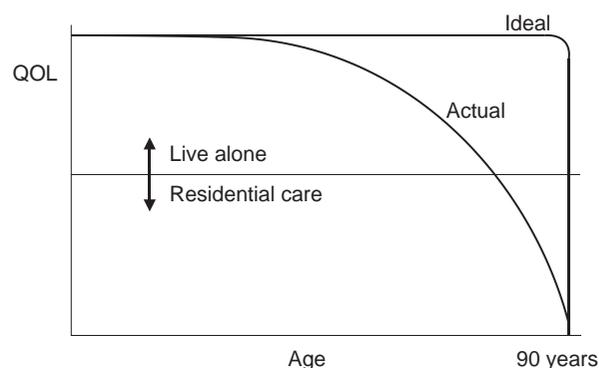


Figure 1 Schematic representation of the change in quality of life (QoL) with age, comparing the most common (actual) scenario and the ideal to which most will aspire. (Reproduced with permission from Professor Janice Rymer)

health perception, sexual interest, daily functioning and enjoyment, they deteriorated during follow-up in women not continuing HRT. Some additional information, however, can be obtained from studies which evaluated health-related quality of life parameters comparing abrupt to a more prolonged mode of discontinuation of HRT¹⁸. Although not being the primary aim of the studies, their data clearly demonstrated a decline in quality-of-life scores versus baseline values in women who stopped HRT. Another well-designed study looked at quality of life following cessation of HRT in women older than 65 years²³. The study took place immediately after the release of data from the estrogen + progestin arm of the WHI in 2002–2003, as a result of which 43% of women in the cohort stopped HRT. Quality-of-life questionnaires completed by those women indicated a decline in physical and mental health outcomes in those aged 65 and even up to the age of 84 years, but, above this age, cessation of HRT was associated with an improvement in quality-of-life measures. When and how to stop HRT is a common dilemma and clearly many women continue for longer than needed, but it is only on cessation that this can be determined. Ironically, despite the immense impact of the WHI studies on prescription habits and the use of postmenopausal hormones, the WHI study investigators, who addressed quality-of-life issues as part of their initial reports on the estrogen + progestin arm⁷ and the estrogen-only arm²⁴, did not attempt

to follow these aspects in what they called the post-intervention phase of the study.

CONCLUSIONS

Maintaining quality of life is a fundamental aspect of good health care. The menopausal transition and subsequent years can be associated with a significant decline in quality of life due to the effects of the decrease of circulating estrogen; these effects will contribute to the overall diminishing quality of life with age (Figure 1). HRT will reduce this decline in symptomatic women, although it is not a panacea for all the effects of aging and will not produce the ideal scenario as in Figure 1. The impact of the massive withdrawal of HRT usage on quality of life following the WHI reports is impossible to quantify but is clearly considerable. Symptomatic menopausal women and their medical advisers need to be reassured that HRT can safely ameliorate most menopausal symptoms⁵ and, until this is realized, far too many women around menopause will continue to experience a reduced quality of life unnecessarily.

Conflict of interest The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

Source of funding Nil.

References

1. MacLennan AH, Lester S, Moore V. Oral oestrogen replacement therapy versus placebo for hot flushes. *Cochrane Database Syst Rev* 2000;CD002978
2. Daly E, Gray A, Barlow D, *et al.* Measuring the impact of menopausal symptoms on quality of life. *BMJ* 1993;307:836–40
3. Welton AJ, Vickers MR, Kim J, *et al.* Health related quality of life after combined hormone replacement therapy: randomised controlled trial. *BMJ* 2008;337:a1190
4. Santen RJ, Allred DC, Ardoin SP, *et al.* Postmenopausal hormone therapy: an Endocrine Society scientific statement. *J Clin Endocrinol Metab* 2010;9(Suppl 1):S1–66
5. Sturdee DW, Pines A, on behalf of the IMS Writing Group. Updated IMS recommendations on postmenopausal hormone therapy and preventive strategies for midlife health. *Climacteric* 2011;14:302–20
6. North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2010 position statement of the North American Menopause Society. *Menopause* 2010;17:242–55
7. Hays J, Ockene J, Brunner R, *et al.* Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med* 2003;348:1839–54
8. Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley M. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/progestin Replacement Therapy Study (HERS) Trial. *JAMA* 2002;287:591–7
9. Clark JH. A critique of Women's Health Initiative studies (2002–2006). *Nuclear Receptor Signalling* 2006;4:e023
10. Shapiro S. Risks of estrogen plus progestin therapy: a sensitivity analysis of findings in the Women's Health Initiative randomized controlled trial. *Climacteric* 2003;6:302–10
11. Schneider HPG, MacLennan AH, Feeny D. Assessment of health-related quality of life in menopause and aging. *Climacteric* 2008;11:93–107
12. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). *Med Care* 1992;30:473–83
13. Hunter M. The Women's Health Questionnaire (WHQ): a measure of mid-aged women's perceptions of their emotional and physical health. *Psychol Health* 1992;7:45–54
14. Schneider HPG, Heinemann LAJ, Rosemeier HP, Potthoff P, Behre HM. The Menopause Rating Scale (MRS): reliability of scores of menopausal complaints. *Climacteric* 2000;3:59–64
15. Lopes AA, Latado A, Lopes GB. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med* 2004;350:622
16. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-item Health Survey 1.0. *Health Econ* 1993;2:217–27
17. Grady D, Sawaya GF. Discontinuation of postmenopausal hormone therapy. *Am J Med* 2005;118(Suppl 12B):163–5
18. Lindh-Astrand L, Bixo M, Hirschberg AL, *et al.* A randomized controlled study of taper-down or abrupt discontinuation of hormone therapy in women treated for vasomotor symptoms. *Menopause* 2010;17:72–9
19. Blumel JE, Chedraui P, Baron G, *et al.* A large multinational study of vasomotor symptom prevalence, duration, and impact on quality of life in middle-aged women. *Menopause* 2011;18:778–85

20. Cumming GP, Currie HD, Panay N, Lee AJ. Stopping hormone replacement therapy: were women ill advised? *Menopause Int* 2011;17:82-7
21. Utian W. Quality of life (QOL) in menopause. *Maturitas* 2007; 57:100-2
22. Heikkinen J, Vaheeri R, Timonen U. A 10-year follow-up of postmenopausal women on long-term continuous combined hormone replacement therapy: Update of safety and quality-of-life findings. *J Br Menopause Soc* 2006;12:115-25
23. Heller DA, Gold CH, Ahern FM, *et al.* Changes in elderly women's health-related quality of life following discontinuation of hormone replacement therapy. *BMC Womens Health* 2005; 5:7
24. Brunner RL, Gass M, Aragaki A, *et al.* Effects of conjugated equine estrogen on health-related quality of life in postmenopausal women with hysterectomy: results from the Women's Health Initiative randomized clinical trial. *Arch Intern Med* 2005;165: 1976-86

The timing hypothesis for coronary heart disease prevention with hormone therapy: past, present and future in perspective

H. N. Hodis, P. Collins*, W. J. Mack† and L. Lind Schierbeck‡

Atherosclerosis Research Unit, Departments of Medicine and Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, USA; *National Heart and Lung Institute, Imperial College London and Royal Brompton Hospital, London, UK; †Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; ‡Department of Endocrinology, Hvidovre Hospital and University of Copenhagen, Copenhagen, Denmark

Key words: TIMING HYPOTHESIS, HORMONE THERAPY, ESTROGEN, MENOPAUSE, WOMEN, CORONARY HEART DISEASE, RANDOMIZED CONTROLLED TRIALS, MORTALITY, META-ANALYSIS

ABSTRACT

Over the past decade, two informative events in primary prevention of coronary heart disease (CHD) have occurred for women's health. The first concerns hormone replacement therapy (HRT) where data have come full circle from presumed harm to consistency with observational data that HRT initiation in close proximity to menopause significantly reduces CHD and overall mortality. The other concerns sex-specific efficacy of CHD primary prevention therapies where lipid-lowering and aspirin therapy have not been conclusively shown to significantly reduce CHD and, more importantly, where there is lack of evidence that either therapy reduces overall mortality in women. Cumulated data support a 'window-of-opportunity' for maximal reduction of CHD and overall mortality and minimization of risks with HRT initiation before 60 years of age and/or within 10 years of menopause and continued for 6 years or more. There is a substantial increase in quality-adjusted life-years over a 5–30-year period in women who initiate HRT in close proximity to menopause, supporting HRT as a highly cost-effective strategy for improving quality-adjusted life. Although primary prevention therapies and HRT contrast in their efficacy to significantly reduce CHD and especially overall mortality in postmenopausal women, the magnitude and types of risks associated with HRT are similar to those associated with other medications commonly used in women's health. The cumulated data highlight the importance of studying the HRT cardioprotective hypothesis in women representative of those from whom the hypothesis was generated.

INTRODUCTION

In the public health arena, there are very few potential therapies with such consistent data for reducing coronary heart disease (CHD) and overall mortality as postmenopausal hormone replacement therapy (HRT). The Women's Health Initiative (WHI) data over the past 10 years have spanned from presumed harm to consistency with observational data that postmenopausal HRT reduces CHD and, more importantly, overall mortality in recently menopausal women. Simultaneously, randomized controlled trials (RCTs) have failed to

conclusively prove that lipid-lowering and aspirin therapy statistically significantly reduce CHD and overall mortality in women under primary prevention conditions. On the other hand, RCTs, observational studies and meta-analyses consistently support primary prevention of CHD and reduction of overall mortality in women who initiate HRT in close proximity to menopause. The totality of data indicates that the 'window-of-opportunity' for reducing CHD and overall mortality is initiation of HRT before 60 years of age and/or within 10 years of menopause. HRT use for 5–30 years in postmenopausal women who initiate HRT in their fifties substantially

Correspondence: Professor H. N. Hodis, Keck School of Medicine, University of Southern California, 2250 Alcazar Street, CSC 132, Los Angeles, CA 90033, USA

increases quality-adjusted life-years (QALYs) by 1.5 QALYs and is highly cost-effective at \$2438 per QALY gained. Cumulated RCT results show a consistency with observational data that young postmenopausal women who use HRT for long periods of time have lower rates of CHD and overall mortality than comparable postmenopausal women who do not use HRT. The WHI has contributed to this knowledge base. Herein, we provide a historical perspective of the reporting of WHI results along with other studies and show the consistency of these data with observational data that show that CHD and overall mortality are reduced in young women who initiate HRT in close proximity to menopause.

PRE-WOMEN'S HEALTH INITIATIVE

Over the past five decades, approximately 40 observational studies (including the WHI observational study) consistently show that HRT is associated with a 30–50% reduction in CHD and overall mortality in postmenopausal women^{1–10}. Results of the Heart and Estrogen/progestin Replacement Study (HERS), the first large RCT of HRT and CHD (conducted in women with pre-existing CHD) were null for conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) taken daily versus placebo (hazard ratio (HR) 0.99; 95% confidence interval (CI) 0.80–1.22)¹¹. Consistent with HERS were the Estrogen Replacement and Atherosclerosis (ERA) trial results that showed neither unopposed CEE nor CEE + MPA reduced coronary artery atherosclerosis progression¹². On the other hand, the Estrogen in the Prevention of Atherosclerosis Trial (EPAT) showed a reduction in sub-clinical atherosclerosis progression in healthy postmenopausal women who were randomized to unopposed oral estradiol versus placebo¹³. Since women randomized to EPAT were younger than those randomized to HERS and ERA, and the time from menopause to randomization was 10 years earlier in EPAT, the divergence in outcomes between EPAT and observational studies versus HERS and ERA was hypothesized to be dependent upon timing of HRT initiation, particularly when initiated early in the intervention of atherosclerosis progression at the start of menopause as the key to preventing CHD with HRT¹³. This hypothesis, further supported by EPAT's sister study, the Women's Estrogen-progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART) and animal studies, later became known as the 'timing hypothesis' or the 'window-of-opportunity' for the reduction of CHD with HRT in postmenopausal women¹⁴. Over the past 10 years, a large accumulation of data strongly support the timing hypothesis, including the WHI data¹⁵.

DATA FROM THE WOMEN'S HEALTH INITIATIVE

WHI data on CHD (including its interpretation) have changed no less than three times over the course of the past 10 years¹⁶. In July 2002, WHI investigators claimed¹⁷ 'the adverse effects

of estrogen plus progestin applied to all women irrespective of age, ethnicity, or prior disease state.' In 2007, WHI investigators reported¹⁸ 'women who initiated therapy closer to menopause tended to have reduced CHD risk compared with the increase in CHD risk among women more distant from menopause.' In the first WHI publication (July 2002), a significantly increased CHD risk was reported for CEE + MPA with the nominal statistic (HR 1.29; 95% CI 1.02–1.63) but not with the adjusted statistic (HR 1.29; 95% CI 0.85–1.97) that accounted for the multiple testing across time and across outcome categories that were conducted in this trial¹⁹. The authors reported 'no noteworthy interaction with age for the effect of CEE + MPA on CHD.' These initial results were published before all outcome data were collected and before final adjudication of the CHD outcome. In August 2003, the 'final [adjudicated] results' of the WHI CEE + MPA trial were published; the HR decreased and the nominal CI now included 1.0 (HR 1.24; 95% CI 1.00–1.54) and, after a significant increase in CHD events in the overall cohort within the first year of randomization (unknown whether this was related to age or pre-existing CVD), a trend for decreasing CHD risk with HRT duration was statistically significant²⁰. Although the data showed an 11% reduction in CHD risk among women randomized within 10 years of menopause and a trend toward increasing risk with greater time from menopause when randomized, the categorical interaction between treatment and years since menopause on CHD was not statistically significant²⁰. However, in a re-analysis of the data using a *p*-for-trend analysis, a statistically significant trend of an HRT effect on CHD according to time since menopause was subsequently reported²¹. In April 2004, WHI CEE trial results showed a non-significant CHD reduction among women who received CEE relative to placebo (HR 0.91; 95% CI 0.75–1.12) and a 44% CHD reduction (HR 0.56; 95% CI 0.30–1.03) in women who were 50–59 years of age when randomized²². These results were published before collection of all outcome data and before final adjudication of the CHD outcome; the 'final [adjudicated] results' of the WHI CEE trial were published in February 2006²³. Among women aged 50–59 years when randomized, several categories of CHD composite outcomes of non-fatal myocardial infarction (MI), coronary death, confirmed angina and coronary artery revascularization were significantly reduced by 34–45% in the CEE-treated group relative to placebo²³.

Addressing accumulating data supportive of the timing hypothesis from both within the WHI as well as from independent research (see below), WHI data supportive of the timing hypothesis were published in April 2007¹⁸. The HRs and CIs for CHD in this publication were different from the 'final' results reported previously for CEE (HR 0.95; 95% CI 0.78–1.16) and for CEE + MPA (HR 1.23; 95% CI 0.99–1.53), especially for the latter in which the CEE + MPA effect on CHD over all ages was clearly non-significant. Significant trends of an HRT effect on CHD according to years since menopause were reported; women randomized to HRT within 10 years of menopause showed a non-significant decreased risk relative to placebo (Table 1).

Similar to CHD trends, overall mortality was reduced by 30% with both CEE + MPA and CEE relative to placebo among women who were aged 50–59 years when randomized¹⁸ (Table 2). With both WHI trials combined (effectively increasing the total sample size), overall mortality was statistically significantly reduced by 30% in those women aged 50–59 years when randomized to HRT relative to placebo (Table 2).

The 11-year WHI CEE trial follow-up (7 years of randomized treatment and 4 years of post-intervention follow-up) showed that women aged 50–59 years when randomized to CEE versus placebo had statistically significant reductions in CHD (HR 0.59; 95% CI 0.38–0.90), total MI (HR 0.54; 95% CI 0.34–0.86) and overall mortality (HR 0.73; 95% CI 0.53–1.00); compared with women aged 60–69 and 70–79 years, the *p*-for-interaction was statistically significant for each outcome, *p* = 0.05, *p* = 0.007 and *p* = 0.04, respectively²⁴. Importantly, invasive breast cancer was statistically significantly reduced by 23% (HR 0.77; 95% CI 0.62–0.95) in women who received CEE relative to placebo regardless of age at randomization²⁴.

Although only one-third of the women randomized to the WHI trials were younger than 60 years of age and less than 5% were within a few years of menopause, the subgroup of women randomized to these trials who are more representative of women using HRT in observational studies had reduced CHD and overall mortality with HRT. On the

other hand, women older than 60 years of age who were randomized to HRT many years beyond menopause (>10 years) who are not representative of women in HRT observational studies showed no reduction in CHD or overall mortality with HRT¹⁵.

STUDIES SUPPORTING THE TIMING HYPOTHESIS

Although the HRT effect on CHD over all ages is null in RCTs, these trials indicate that there are distinct populations of women who are HRT-responsive. Specifically, beneficial HRT effects on CHD and overall mortality occur when HRT is initiated in younger women in close proximity to menopause and a null effect and possible adverse effect (in women >20 years since menopause) when initiated in older women remote from menopause¹⁵. The beneficial HRT effect on CHD according to timing of HRT initiation has been shown in a large meta-analysis of 23 RCTs (191 340 patient-years of follow-up)²⁵. Over all ages, the HRT effect on CHD was null, whereas a statistically significant 32% reduction in CHD was found for women younger than 60 years of age or within 10 years since menopause when randomized to HRT relative to placebo (Table 1). The magnitude of CHD reduction for women younger than 60 years of age or within 10 years since

Table 1 Number of participants and relative risks of coronary heart disease for hormone replacement therapy (HRT) and raloxifene compared to placebo by age and years since menopause (YSM) at randomization

Study	Relative risk	Number of participants	<i>p</i> Value for trend
HRT meta-analysis²⁵	OR (95% CI)		
All ages	0.99 (0.88–1.11)	39 049	
<60 years old or <10 YSM	0.68 (0.48–0.96)	not given	
≥60 years old or ≥10 YSM	1.03 (0.91–1.16)	not given	
WHI¹⁸	HR (95% CI)		
CEE + MPA trial			0.05
<10 YSM	0.88 (0.54–1.43)	5494	
10–19 YSM	1.23 (0.85–1.77)	6041	
≥20 YSM	1.66 (1.14–2.41)	3653	
CEE trial			0.15
<10 YSM	0.48 (0.20–1.17)	1643	
10–19 YSM	0.96 (0.64–1.44)	2936	
≥20 YSM	1.12 (0.86–1.46)	4550	
Combined CEE + MPA and CEE trials			0.02
<10 YSM	0.76 (0.50–1.16)	7137	
10–19 YSM	1.10 (0.84–1.45)	8977	
≥20 YSM	1.28 (1.03–1.58)	8203	
RUTH²⁸			0.01
<60 years old	0.59 (0.41–0.83)	1670	
60–69 years old	1.06 (0.88–1.28)	4534	
≥70 years old	0.98 (0.82–1.17)	3897	

OR (95% CI), odds ratio (95% confidence interval); HR (95% CI), hazard ratio (95% confidence interval); WHI, Women's Health Initiative; CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate; RUTH, Raloxifene Use for the Heart

Table 2 Number of participants and relative risks of overall mortality for hormone replacement therapy (HRT) compared to placebo by age at randomization

Study	Relative risk	Number of participants	<i>p</i> Value for trend
HRT meta-analysis²⁷	OR (95% CI)		
All ages	0.98 (0.87–1.18)	26 708	
< 60 years old	0.61 (0.39–0.95)	not given	
≥ 60 years old	1.03 (0.90–1.18)	not given	
WHI¹⁸	HR (95% CI)		
CEE + MPA trial			0.19
50–59 years old	0.69 (0.44–1.07)	5494	
60–69 years old	1.09 (0.83–1.44)	6041	
70–79 years old	1.06 (0.80–1.41)	3653	
CEE trial			0.18
50–59 years old	0.71 (0.46–1.11)	1643	
60–69 years old	1.02 (0.80–1.30)	2936	
70–79 years old	1.20 (0.93–1.55)	4550	
Combined CEE + MPA and CEE trials			0.06
50–59 years old	0.70 (0.51–0.96)	7137	
60–69 years old	1.05 (0.87–1.26)	8977	
70–79 years old	1.14 (0.94–1.37)	8203	

OR (95% CI), odds ratio (95% confidence interval); HR (95% CI), hazard ratio (95% confidence interval); WHI, Women's Health Initiative; CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate

menopause when randomized to HRT was similar to observational studies^{1–10}. This large meta-analysis of cumulated RCTs of HRT clearly demonstrates two distinct populations of women who respond differently to HRT according to timing of HRT initiation relative to age and/or time since menopause. Another line of evidence that HRT initiation in young postmenopausal women in close proximity to menopause may reduce CHD derives from 1064 women who participated in the WHI Coronary Artery Calcium Study in which 50–59-year-old women who were randomized to CEE had significantly less coronary artery calcium at year 7 of the trial compared with those women randomized to placebo²⁶.

Most recently, the cardiovascular outcome from the Danish Osteoporosis Prevention Study (DOPS) was presented (by L.L.S.) at the American Heart Association Scientific Meeting in 2011. These results included more than 1000 postmenopausal women who were on average 50 years old and on average 7 months postmenopausal when randomized for 11 years to oral 17 β -estradiol daily plus sequential norethisterone acetate 10 days each month or to control in an open-label, parallel design. Hysterectomized women received oral 17 β -estradiol daily. The overall cardiovascular results of this study are remarkably similar to the 11-year WHI CEE trial follow-up data of the women who were 50–59 years of age when randomized to WHI CEE²⁴ and to the HRT meta-analyses of RCTs and CHD²⁵ and mortality²⁷ outcomes in women < 60 years old or < 10 years since menopause when randomized. No significant difference in breast cancer, stroke or venous thromboembolism (VTE) was found between treatment groups.

OTHER ESTROGEN RECEPTOR-BINDING AGENTS THAT SUPPORT THE TIMING HYPOTHESIS

Broadening support for the timing hypothesis are accumulating data that show products other than mammalian hormones that bind to the estrogen receptor (ER) exert similar CHD beneficial effects as HRT in young postmenopausal women. In the Raloxifene Use for the Heart (RUTH) trial (10 101 postmenopausal women), raloxifene, a selective estrogen receptor modulator, had no effect on CHD incidence over all ages after a median treatment of 5.6 years. However, among women younger than 60 years of age when randomized to raloxifene, CHD was statistically significantly reduced by 41% relative to placebo²⁸ (Table 1), a finding similar to the WHI in which CHD was reduced by 52% in women who were < 10 years since menopause when randomized to CEE relative to placebo¹⁸ (Table 1).

Although an age or time since menopause analysis is not presented, randomized treatment for 5 years of lasofoxifene 0.5 mg daily versus placebo in a cohort of 8556 women between the ages of 59 and 80 years statistically significantly reduced: CHD by 32% (HR 0.68; 95% CI 0.50–0.93), stroke by 36% (HR 0.64; 95% CI 0.41–0.99); vertebral fractures by 42% (HR 0.58; 95% CI 0.47–0.70), non-vertebral fractures by 24% (HR 0.76; 95% CI 0.64–0.91), ER-positive breast cancer by 81% (HR 0.19; 95% CI 0.07–0.56) and invasive breast cancer by 85% (HR 0.15; 95% CI 0.04–0.50); VTE was statistically significantly increased two-fold (HR 2.06; 95% CI 1.17–3.61), indicating 15 additional VTE events per 10 000 women per year of lasofoxifene therapy²⁹.

In the Women's Isoflavone Soy Health (WISH) study, a RCT examining the effects of high-dose isoflavone soy protein supplementation on the progression of subclinical atherosclerosis, women who were randomized within 5 years of menopause to isoflavone soy protein supplementation had a significant reduction in progression of subclinical atherosclerosis relative to placebo, whereas women more than 5 years beyond menopause when randomized had no significant effect³⁰. Isoflavones are plant estrogens that preferentially bind to ER β .

OVERALL MORTALITY AND BENEFIT-RISK OF HRT

The beneficial HRT effect on overall mortality according to age has also been demonstrated in a large meta-analysis of 30 RCTs (119 118 patient-years)²⁷. Over all ages, the HRT effect on overall mortality was null whereas a statistically significant 39% reduction in overall mortality was found for subjects younger than 60 years of age (mean age 54 years) when randomized to HRT relative to placebo (Table 2), a reduction similar to observational studies¹⁻¹⁰. Ages at HRT initiation among women in observational studies and age of younger women randomized to RCTs examined in the meta-analysis are similar. On the other hand, in this meta-analysis, the HRT effect on overall mortality in women who were older than 60 years of age (mean age 66 years) when randomized was null as reported over all ages in RCTs.

To address benefit-risk of HRT, a Bayesian meta-analysis was conducted using RCTs and observational studies to evaluate the HRT effect on overall mortality in young postmenopausal women who initiated HRT in close proximity to menopause³¹. Results from this meta-analysis using 19 RCTs with 16 283 women (mean age 54.5 years) followed for 83 043 patient-years over 5.1 years (range 1-6.8 years) showed an overall mortality reduction of 27% (relative risk (RR) 0.73; 95% credible interval (CrI) 0.52-0.96) among women randomized to HRT relative to placebo. The 95% CrI used in the Bayesian analysis is comparable to the 95% CI used in traditional meta-analyses. Using pooled data from eight prospective, observational studies in which a total of 212 717 women were followed for 2 935 495 patient-years over a mean of 13.8 years (range 6-22 years), overall mortality was reduced by 22% (RR 0.78; 95% CrI 0.69-0.90) in HRT users relative to non-users. Overall mortality was reduced by 28% (RR 0.72; 95% CrI 0.62-0.82) with the RCT and prospective observational data combined. Results from this study indicate a convergence of evidence from several sources that support a beneficial HRT effect on overall mortality in women who initiate HRT in close proximity to menopause. Further, results from this meta-analysis indicate that RCTs and observational studies are similar, each with an overall mortality reduction of approximately 25%, results similar to the 30% reduction in overall mortality shown in postmenopausal women who were younger than 60 years of age when randomized to HRT in the WHI trials (Table 2).

HRT COST EFFECTIVELY EXTENDS LIFE WHEN INITIATED AT YOUNGER AGE

A cost-effectiveness analysis indicates that, compared with no therapy, HRT given to postmenopausal women in their fifties for 5-30 years results in a substantial increase of 1.5 QALYs at a cost of \$2438 per QALY gained³². Net gains gradually increase with treatment durations of 5-30 years and results for younger women are robust to all sensitivity analyses with HRT remaining highly cost-effective (defined as <\$10 000 per QALY gained). At \$2438 per QALY gained, these data indicate that HRT is a highly cost-effective strategy for improving quality-adjusted life. The substantial increase in QALYs in younger women is due to a net benefit in quality of life and reduced overall mortality compared with no therapy. On the other hand, for 65-year-old postmenopausal women initiating HRT, there is a smaller net gain of 0.11 QALYs at a cost of \$27 953 per QALY gained³².

In sum, the totality of RCT data indicates that young postmenopausal women who initiate HRT in close proximity to menopause have a reduced incidence of CHD and overall mortality¹⁵. These results parallel the consistent reduction in CHD and overall mortality in observational studies, where the majority of women initiated HRT within 6 years of menopause¹⁻¹⁰. Focused on young healthy postmenopausal women (average age 50 years) randomized early after menopause (average of 7 months), DOPS provides strong evidence for the long-term efficacy and safety of HRT for reducing CHD and overall mortality when initiated in young postmenopausal women in close proximity to menopause. Additionally, the timing hypothesis appears to extend to other agents that bind to the estrogen receptor.

CLINICAL PERSPECTIVE OF HRT RELATIVE TO OTHER PRIMARY PREVENTIVE THERAPIES

A detailed discussion of current primary prevention therapies for women is beyond the scope of this review. However, it is important to appreciate that meta-analyses of cumulated RCT data show a sex-specific efficacy for the major therapies used for CHD primary prevention. Relative to placebo, lipid-lowering³³⁻³⁵ and aspirin^{36,37} therapy have a null effect on CHD primary prevention in women, including aspirin use in women with diabetes mellitus³⁸. There is no evidence that either therapy reduces overall mortality in women³³⁻³⁷.

Although the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) is the only primary prevention trial to show a possible reduction in CHD in women, this result deserves special attention since it is unclear whether this finding resulted from the unique characteristics of the cohort (women \geq 60 years of age with low density lipoprotein cholesterol levels < 130 mg/dl and high-sensitivity C-reactive protein (hsCRP) \geq 2 mg/dl)³⁹, the controversial aspects of trial conduct^{40,41} or from the subjective nature of certain components of the primary

end-point³⁹. The primary cardiovascular end-point of JUPITER was a composite end-point comprised of 'hard end-points' (non-fatal MI; any MI; non-fatal stroke; any stroke; MI, stroke, or confirmed death resulting from cardiovascular causes) and 'soft end-points' whose occurrence relies on medical decisions (arterial revascularization; arterial revascularization or hospitalization for unstable angina). In men, all of the 'hard' and 'soft' components of the composite primary end-point were statistically significantly reduced in the rosuvastatin arm versus placebo arm³⁹. In women, only the 'soft' end-points were statistically significantly reduced in the rosuvastatin arm versus placebo arm. These 'soft' composite end-points (revascularizations and hospitalizations) clearly drove the primary end-point to statistical significance in the women since all of the 'hard' end-points in the women were firmly non-significantly different ($p > 0.1$) between the rosuvastatin arm and placebo arm³⁹. Overall mortality was not statistically different between the rosuvastatin arm versus the placebo arm in women ($p = 0.12$) or in men ($p = 0.08$)³⁹. Including JUPITER in a meta-analysis with other primary prevention trials does not alter the conclusion that statin therapy has a null effect on CHD and overall mortality in primary prevention in women³⁵.

Aspirin therapy is interesting in that, in men, aspirin statistically significantly reduces MI by 32%, with a null effect on stroke, whereas, in women, aspirin has a null effect on MI but statistically significantly reduces ischemic stroke by 17%³⁷. With aspirin therapy, there is a non-significant increase in odds of hemorrhagic stroke in women (odds ratio (OR) 1.07; 95% CI 0.42–2.69) and a significant 69% increase in the odds of hemorrhagic stroke in men (OR 1.69; 95% CI 1.04–2.73)³⁷. Although the Women's Health Study showed a null effect of aspirin therapy versus placebo with the a-priori defined statistical analysis of the primary cardiovascular end-point amongst all women (≥ 45 years of age) randomized to this trial, a statistically significant reduction in the subgroup of women ≥ 65 years of age was found amongst multiple subgroup comparisons that requires cautious interpretation³⁶.

Recommendations for lipid-lowering and aspirin therapy for CHD primary prevention in women are extrapolated from data derived from men and secondary prevention trials in women^{42,43}. In contrast to the lack of demonstrated efficacy of lipid-lowering and aspirin therapy on CHD and mortality in primary prevention for women, cumulated data across more than 24 RCTs (including the recently completed DOPS) demonstrate a significant reduction in CHD and overall mortality in women who initiate HRT before 60 years of age and/or within 10 years of menopause^{25,27,31,32} (Tables 1 and 2).

WEIGHING THE RISKS OF HRT RELATIVE TO OTHER MEDICATIONS

Although the benefits and risks of postmenopausal HRT are known, over the past decade their magnitude and perspective to other therapies have become more fully defined. Review of RCTs indicates that the risks of postmenopausal HRT,

including breast cancer, stroke and VTE, are similar to other agents commonly used in women's health. The majority of these risks are rare (< 1 event per 1000 treated women) and even rarer when HRT is initiated in women less than 60 years of age and/or within 10 years of menopause. These data have been extensively reviewed previously^{15,16,44–47} and are only summarized here.

Breast cancer

In the WHI CEE + MPA trial, breast cancer risk was originally reported to 'almost reach nominal statistical significance' in the CEE + MPA arm versus the placebo arm (HR 1.26; 95% CI 1.00–1.59) and was clearly non-significant with adjustment for multiple testing across time and across outcome categories (HR 1.26; 95% CI 0.83–1.92)¹⁹. This 26% increased risk accounted for eight additional breast cancer cases per 10 000 women treated with CEE + MPA per year, a rare event (< 1 event per 1000 treated women). A subsequent analysis in the same cohort of subjects that adjusted for baseline risk factors for breast cancer (i.e. age, body mass index, alcohol intake, physical activity, parity, family history, etc.) resulted in a slightly reduced relative risk with a nominal non-significant statistical difference in breast cancer risk in the CEE + MPA arm relative to the placebo arm (HR 1.20; 95% CI 0.94–1.53)⁴⁸. Additionally, there was clearly no increased risk of breast cancer over an average 5.6 years amongst those women who were randomized to CEE + MPA therapy and previously never used HRT, that is, for those women who were HRT naive (HR 1.02; 95% CI 0.77–1.36)⁴⁸. In the 3-year open-label follow-up in which women were no longer on their randomized regimens (CEE + MPA versus placebo), the HR over time from the randomized phase to the open-label phase was unchanged⁴⁹.

In contrast, the initial results for the WHI CEE trial showed a non-significant trend toward a reduction in breast cancer (HR 0.77; 95% CI 0.59–1.01) in the CEE arm relative to the placebo arm, indicating eight fewer breast cancer cases per 10 000 women treated with CEE per year²². Ductal carcinoma was statistically significantly reduced by 29% in the CEE arm versus placebo arm (HR 0.71; 95% CI 0.52–0.99) in the WHI CEE trial⁵⁰. Regardless of age at randomization, women in the WHI CEE trial had a reduction in breast cancer with CEE therapy, including those in the highest age group (70–79 years old) with the greatest expected risk of breast cancer⁵⁰. In a compliance analysis among women who were actually adherent to their study regimen, consuming $\geq 80\%$ of their study medication, there was a statistically significant 33% reduction in breast cancer with CEE therapy relative to placebo (HR 0.67; 95% CI 0.47–0.97) after a mean randomized follow-up of 7.1 years⁵⁰. The decreasing trend in breast cancer was confirmed in the WHI CEE follow-up study of 11 years; over the entire follow-up period, the lower incidence of breast cancer amongst the CEE-treated group persisted and was statistically significantly 23% lower relative to the placebo group (HR 0.77; 95% CI 0.62–0.95)²⁴. Although the CI is wide,

data from the Women's Estrogen for Stroke Trial (WEST) showed that 17 β -estradiol had a null effect on breast cancer risk relative to placebo (HR 1.00; 95% CI 0.30–3.50)⁵¹. DOPS confirms these results as HRT did not increase the risk of breast cancer after 11 years of randomized follow-up.

Stroke

Although WEST has been the only randomized controlled trial of HRT designed with stroke as the primary trial outcome⁵¹, HERS and WHI have also provided information concerning HRT and stroke as an additional secondary trial outcome. In WEST, including 664 postmenopausal women who were on average 71 years old and approximately 20 years postmenopausal at randomization, 17 β -estradiol 1 mg daily had a null effect on the combined outcome of non-fatal stroke or all-cause mortality (RR 1.1; 95% CI 0.8–1.4) relative to placebo⁵¹. Although the women had a documented non-disabling stroke or transient ischemic attack within 90 days of randomization into the trial, the effect of HRT on non-fatal and fatal stroke and both strokes combined was non-significant in this trial of secondary prevention of stroke in women at high risk for recurrent stroke. HERS showed that continuous combined CEE + MPA had a null effect on the primary prevention of non-fatal and fatal stroke in postmenopausal women with established CHD⁵². In the WHI CEE + MPA trial, there was nominal statistical significance of eight additional strokes per 10 000 women treated with CEE + MPA per year in the CEE + MPA arm versus the placebo arm (HR 1.31; 95% CI 1.03–1.68)¹⁸, but this difference was non-significant in the a-priori defined outcome adjusting for multiple testing across time and across outcome categories (HR 1.31; 95% CI 0.93–1.84)⁵³. In the WHI CEE trial, there was nominal statistical significance of 11 additional strokes per 10 000 women treated with CEE per year in the CEE arm versus the placebo arm (HR 1.33; 95% CI 1.05–1.68)¹⁸, but this difference was non-significant in the a-priori defined outcome adjusting for multiple testing across time and across outcome categories (HR 1.39; 95% CI 0.97–1.99)²². Importantly, the risk of stroke is statistically non-significant and rare in women who initiate HRT when <60 years of age. The WHI showed that there are five additional strokes per 10 000 women per year of CEE + MPA therapy when initiated in women <60 years of age and even lower for CEE therapy, two fewer strokes per 10 000 women per year of CEE therapy¹⁸. DOPS results are consistent with these findings as HRT did not increase the risk of stroke after 11 years of randomized follow-up.

Venous thromboembolism

Although CEE + MPA therapy was associated with a doubling of VTE risk compared with placebo in the WHI CEE + MPA trial, the increase in absolute risk was small, 18 additional VTE events per 10 000 women treated with CEE + MPA per year¹⁹. This risk of VTE was statistically significant with both

the nominal statistic and with adjustment for multiple testing across time and across outcome categories^{19,54}. The absolute risk of VTE was lowest for women <60 years old when randomized. The additional absolute risk for VTE events per 10 000 women treated with CEE + MPA per year was 11 events for women 50–59 years old at randomization, 16 events for women 60–69 years old at randomization, and 35 events for women 70–79 years old at randomization⁵⁴. Although there were seven additional VTE events per 10 000 women treated with CEE per year in the WHI CEE trial, the risk of VTE was not statistically significant with either the nominal statistic (HR 1.33; 95% CI 0.99–1.79) or with adjustment for multiple testing across time and across outcome categories (HR 1.33; 95% CI 0.86–2.08)^{22,55}. The additional absolute risk for VTE events per 10 000 women treated with CEE per year was five events for women 50–59 years old at randomization, six events for women 60–69 years old at randomization, and 12 events for women 70–79 years old at randomization⁵⁵. In WEST, there was a 20% non-significant decrease in VTE events (HR 0.80; 95% CI 0.20–3.40) accounting for 12 fewer VTE events per 10 000 women treated with 17 β -estradiol per year⁵¹. Over 11 years of randomized follow-up, VTE events were not different between treatment groups in DOPS.

Comparing HRT risks with risks of other medications

Although recommended primary prevention therapies and HRT contrast in their efficacy to reduce CHD and overall mortality in women, the magnitude and types of risk associated with HRT are similar to those associated with other common therapies used in women's health such as lipid-lowering drugs including statins and fibrates, aspirin, oral anti-diabetic medications, bisphosphonates, calcium supplements and vitamin supplements (Table 3).

In RCTs of statins published to date, the risk of breast cancer in the women randomized to a statin relative to placebo ranges from a reduction of 25% to a 12-fold increase, indicating an absolute risk of ten fewer to 77 additional breast cancer cases per 10 000 women per year of statin therapy^{44–47}. In three meta-analyses of statins and cancer risk^{56–58}, statin therapy was associated with a non-significant increase in breast cancer risk relative to placebo (HRs ranging from 1.04 to 1.33), accounting for two to seven additional breast cancer cases per 10 000 women per year of statin therapy. These data suggest similar magnitudes of risk for breast cancer diagnosis for continuous combined CEE + MPA and statin therapy^{44–47}. On the other hand, the 23–33% reduced breast cancer risk indicating eight fewer breast cancer cases per 10 000 women treated with CEE per year contrasts with the 4–33% increased risk of two to seven additional breast cancer cases per 10 000 women per year of statin therapy^{44–47}.

Other medications used in women's health are associated with the same magnitude of risk for stroke and VTE and also exhibit other types of risk equal to or exceeding those of

Table 3 Relative and absolute risks of commonly used agents

Therapy	Event	Risk ratio (95% CI)	Additional cases per 10 000 persons/year
Atorvastatin ⁶⁷	hemorrhagic stroke	1.66 (1.08–2.55)	19
Simvastatin ⁶⁸	hemorrhagic stroke	1.86 (not reported)	2
Pravastatin ⁶⁹	new cancer diagnosis	1.25 (1.04–1.51)	52
Rosuvastatin ³⁹	new-onset diabetes mellitus	1.49 (1.11–2.01)	50
Fenofibrate ⁷⁰	deep vein thrombosis	not reported	7
Fenofibrate ⁷⁰	pulmonary embolus	not reported	9
Aspirin ³⁶	GI bleeding requiring blood transfusion	1.40 (1.07–1.83)	2
Aspirin ³⁶	GI bleeding	1.22 (1.10–1.34)	8
Rosiglitazone ⁷¹	myocardial infarction	1.66 (0.73–3.80)	8
Rosiglitazone ⁷²	bone fracture	1.82 (1.37–2.41)	94
Pioglitazone ^{73,74}	bone fracture	2.04 (1.22–3.41)	88
Alendronate ⁷⁵	atrial fibrillation	1.86 (1.09–3.15)	not reported
Zoledronate ⁷⁶	serious atrial fibrillation	~2.5 ($p < 0.001$)	26
Bisphosphonates ⁷⁷	atypical spiral fracture of the femoral shaft	47.3 (25.6–87.3)	5
Calcium supplements ⁷⁸	CHD (MI, stroke, sudden death)	1.43 (1.01–2.04)	70
Calcium supplements ⁷⁸	stroke	1.45 (0.88–2.49)	36
Calcium supplements ⁷⁸	myocardial infarction	1.67 (0.98–2.87)	45
Beta-carotene ⁷⁹	lung cancer	1.28 (1.04–1.57)	13
<i>Relative and absolute risks of mortality with commonly used agents</i>			
Fenofibrate ⁷⁰	total mortality	1.11 (0.95–1.29)	13
Aspirin ⁸⁰	sudden death	1.96 (0.91–4.23)	5
Rosiglitazone ⁸¹	total mortality	1.14 (1.05–1.24)	45
Calcium supplements ⁸²	total mortality	1.09 (0.96–1.23)	8
Beta-carotene ⁷⁹	total mortality	1.17 (1.03–1.33)	25

CHD, coronary heart disease; MI, myocardial infarction; GI, gastrointestinal; CI, confidence interval

HRT seen over all ages (Table 3). One risk of particular importance is mortality, which is decreased with HRT while it is increased with certain medications commonly used in women's health (Table 3). Certain risks appear to be greater in women than men, such as the association of bone fracture risk with thiazolidinedione use and new-onset diabetes mellitus with statin use (Table 3). Although aspirin significantly reduces ischemic stroke by 24% in women without pre-existing CVD, the risk of hemorrhagic stroke is non-significantly increased by 24% with aspirin versus placebo³⁶. In addition, bleeding diatheses are significantly increased with aspirin use. Any gastrointestinal bleeding is statistically significantly increased by 22% with aspirin versus placebo, and gastrointestinal bleeding requiring blood transfusion is statistically significantly increased by 40% with aspirin versus placebo (Table 3). RCTs have also shown increased hemorrhagic stroke with statins versus placebo in secondary prevention (Table 3).

Another important consideration for the use of primary prevention therapy for CHD is the risk of new-onset diabetes mellitus. Analysis of both the WHI and HERS indicates that CEE + MPA therapy significantly reduces the incidence of diabetes mellitus. In the WHI, CEE + MPA statistically significantly reduced new-onset diabetes mellitus by 21% (HR 0.79; 95% CI 0.67–0.93) relative to placebo, accounting for 15 fewer cases of new-onset diabetes mellitus per 10 000 women

treated with CEE + MPA per year⁵⁹. In HERS, CEE + MPA statistically significantly reduced new-onset diabetes mellitus by 35% (HR 0.65; 95% CI 0.48–0.89) relative to placebo, accounting for 81 fewer cases of new-onset diabetes mellitus per 10 000 women treated with CEE + MPA per year⁶⁰. In the WHI, CEE alone reduced new-onset diabetes mellitus by 12% (HR 0.88; 95% CI 0.77–1.01) relative to placebo, accounting for 14 fewer cases of new-onset diabetes mellitus per 10 000 women treated with CEE per year⁶¹.

In contrast, statin therapy is associated with an increased risk of new-onset diabetes mellitus^{39,62,63}. In a meta-analysis of 13 RCTs with 91 140 participants, statin therapy was associated with a statistically significant 9% increased risk of incident diabetes mellitus (HR 1.09; 95% CI 1.02–1.17), accounting for ten additional cases of new-onset diabetes mellitus per 10 000 individuals treated with statin therapy per year⁶².

Higher versus lower dosages of statin therapy are also associated with increased risk for new-onset diabetes mellitus. In a meta-analysis of five RCTs with 32 752 participants, intensive-dose statin therapy versus moderate-dose statin therapy was associated with a statistically significant 12% increased risk of incident diabetes mellitus (HR 1.12; 95% CI 1.04–1.22), accounting for 20 additional cases of new-onset diabetes mellitus per 10 000 individuals treated with intensive-dose statin therapy per year⁶⁴.

Female sex is particularly associated with an increased risk of statin-induced new-onset diabetes mellitus⁶³ and, in JUPITER, new-onset diabetes mellitus was statistically significantly increased by 49% in women in the rosuvastatin arm versus the placebo arm (HR 1.49; 95% CI 1.11–2.01) while non-significantly increased by 14% in men (HR 1.14; 95% CI 0.91–1.43)³⁹. In women, the JUPITER results indicate 50 additional incident diabetes mellitus cases per 10 000 women treated with rosuvastatin per year while in men it indicates 16 additional incident diabetes mellitus cases per 10 000 men treated with rosuvastatin per year³⁹. In the largest study to date with 1 004 446 person-years of follow-up, the WHI verifies the increased risk of new-onset diabetes mellitus in postmenopausal women who use statins. The WHI showed, in a cohort of 153 840 postmenopausal women without diabetes mellitus at baseline, a 48% (HR 1.48; 95% CI 1.38–1.59) increased risk of incident diabetes mellitus accounting for 51 additional cases of new-onset diabetes mellitus per 10 000 women per year of statin therapy versus those women who did not use statins⁶⁵. These results are important in that, in the same cohort of women, the WHI shows that randomization to HRT reduces new-onset diabetes mellitus whereas statin therapy is associated with an increased risk of incident diabetes mellitus. Although statin therapy was not randomized in the WHI, the HR (1.48) and absolute risk (51 additional incident diabetes mellitus cases per 10 000 women per year of statin therapy) for increased diabetes mellitus in the WHI are highly consistent with the HR (1.49) and absolute risk (50 additional incident diabetes mellitus cases per 10 000 women per year of statin therapy) reported in women from JUPITER, a randomized, controlled trial of statin therapy³⁹. These findings are especially important in the absence of convincing evidence that statins significantly reduce CHD or overall mortality when used for primary prevention in women.

In summary, all medications present benefits and risks that can only be placed into perspective when viewed in relation to other commonly used medications. HRT benefits and risks vary by dosage, regimen and timing of initiation. As such, broad-sweeping conclusions concerning HRT risks are not possible and attempts to generalize risk as comparable to continuous combined CEE + MPA result in misleading and inaccurate information concerning HRT. Regardless, a few overall consistencies concerning HRT risks are apparent, even when considering continuous combined CEE + MPA as the 'worse-case scenario' for risk:

- (1) HRT risks are predominantly rare and even rarer when initiated in women before 60 years of age and/or within 10 years of menopause (<one event per 1000 treated women);
- (2) Overall benefit–risk of HRT favors reduced overall mortality; and
- (3) HRT risks are of similar type and magnitude as those of other medications commonly used in women's health and for the primary prevention of CHD in women. Placing medications into clinical perspective is perhaps the most common approach to understanding overall utility and reasonable acceptance of benefits and risks.

TEST OF THE ESTROGEN CARDIOPROTECTIVE TIMING HYPOTHESIS

In the wake of early trial results showing discordance between RCTs and observational studies, the Early versus Late Intervention Trial with Estradiol (ELITE; clinicaltrials.gov NCT00114517) was funded by the National Institutes of Health (NIH); enrollment was initiated in 2004. Designed to specifically test the timing hypothesis, 643 postmenopausal women have been randomized to a 2 × 2, double-blind, placebo-controlled, single-center trial according to time since menopause. Women without pre-existing clinical cardiovascular disease <6 years and >10 years since menopause were randomized to oral estradiol (1 mg/day) or placebo (with vaginal progesterone gel or placebo for 10 days each month) in each stratum. The primary trial end-point is carotid artery intima-media thickness (CIMT) progression measured every 6 months. The secondary trial end-point is rate of cognitive decline. Based on the wealth of evidence that has accumulated since 2003 in support of the initial ELITE proposal to the NIH of the timing hypothesis^{13–15,44–47}, a 3-year extension of the trial was awarded. The three specific aims of the ELITE extension include: (1) increased randomized treatment for an average of 5 years; (2) addition of a secondary vascular end-point using non-contrast and contrast cardiac computed tomography to non-invasively measure coronary artery calcium and coronary artery lesions; and (3) addition of a third cognitive assessment to extend measurement of cognitive decline over an average of 5 years. Primary trial results from ELITE are expected in 2013. In the Kronos Early Estrogen Prevention Study (KEEPS; clinicaltrials.gov NCT00154180), 720 women within 6–36 months of menopause were randomized across nine sites to oral CEE 0.45 mg/day, transdermal estradiol 50 µg/day or to placebo with oral micronized progesterone 200 mg/day or placebo for 12 days each month. The primary trial end-point is progression of CIMT measured every year by the same methodology and technology as used in ELITE. Although women were screened for coronary artery calcium at baseline and excluded if their Agatston score was >50 U, repeat coronary artery calcium measurements will be determined at the end of study and progression and incident coronary artery calcium determined as a secondary end-point. Cognition will also be assessed in KEEPS. Primary trial results from KEEPS are expected in 2012.

CONCLUSION

Ten years after the WHI, the data have come full circle and we are left with the task of more appropriately studying the estrogen cardioprotective hypothesis in a cohort of women from whom the hypothesis was derived, namely, young postmenopausal women in close proximity to menopause. The totality of data shows that the postmenopausal HRT effect on CHD and overall mortality is modified by duration of therapy and by age and/or time since menopause when

initiated. HRT appears to exert its greatest benefit when initiated in women before 60 years of age and/or within 10 years of menopause. It is this latter group of women who are in most need of symptomatic relief from menopausal symptoms such as flushing, for which estrogen remains the most effective therapy⁶⁶. RCTs are supported by approximately 40 observational studies that also indicate that HRT initiation early in the postmenopausal period and continued for a prolonged period of time results in a significant reduction of CHD and overall mortality. Initiation of HRT before tissue damage due to aging becomes too extensive appears to be key for successful amelioration of further damage. Comparison of RCT and observational data indicates that selection bias does not explain the consistent evidence that HRT is associated with a duration- and time-dependent lowering of CHD and overall mortality; DOPS results directly confirm this evidence. Analyses of the subgroups of women within RCTs that resemble women from observational studies indicate a consistency between the two study designs with similar HRT benefit on the reduction of CHD and overall mortality. The 'window-of-opportunity' for maximal expression of HRT beneficial effects on CHD and overall mortality, while minimizing the risks, appears to occur with HRT initiation before 60 years of age and/or within 10 years of menopause and continued for 6 years or more¹⁵. HRT risks, especially in this subgroup of women, appear comparable to medications commonly used in women's health. Due to reduced overall mortality, there is a substantial increase in QALYs in younger postmenopausal women who initiate

HRT in close proximity to menopause, supporting HRT as a highly cost-effective strategy for improving quality-adjusted life^{31,32}.

In the final analysis, discordance in the association of HRT with CHD and overall mortality between RCTs and observational studies is a function of differences in study design and characteristics of the populations studied. As such, the cardioprotective hypothesis is only beginning to be appropriately tested with RCTs like DOPS in a cohort of women with characteristics like those women from whom the hypothesis was generated. ELITE is a 2 × 2 factorial RCT designed specifically to study the estrogen-cardioprotective hypothesis through the timing hypothesis. KEEPS will extend the findings from EPAT¹³ to women < 3 years since menopause and will provide a comparison between low-dose oral and transdermal HRT. As data from RCTs accumulate, it has become clearly evident that there is concordance with observational studies that indicate that young postmenopausal women who use HRT for long periods of time have lower rates of CHD and overall mortality than comparable postmenopausal women who do not use HRT.

Conflict of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Source of funding Funded in part by the National Institutes of Health, National Institute on Aging, R01AG-024154.

References

- Grodstein F, Stampfer M. The epidemiology of coronary heart disease and estrogen replacement in postmenopausal women. *Prog Cardiol Dis* 1995;38:199–210
- Grodstein F, Stampfer M. Estrogen for women at varying risk of coronary disease. *Maturitas* 1998;30:19–26
- Thompson SG, Meade TW, Greenberg G. The use of hormonal replacement therapy and the risk of stroke and myocardial infarction in women. *J Epidemiol Commun Health* 1989;43:173–8
- Falkeborn M, Persson I, Adami HO. The risk of acute myocardial infarction after oestrogen and oestrogen-progestogen replacement. *Br J Obstet Gynaecol* 1992;99:821–8
- Psaty BM, Heckbert SR, Atkins D, et al. The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. *Arch Intern Med* 1994; 154:1333–9
- Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996;335:453–61
- Prentice RL, Langer R, Stefanick ML, et al. Combined postmenopausal hormone therapy and cardiovascular disease: toward resolving the discrepancy between observational studies and the Women's Health Initiative clinical trial. *Am J Epidemiol* 2005;162:404–14
- Prentice RL, Langer R, Stefanick ML, et al. Combined analysis of Women's Health Initiative observational and clinical trial data on postmenopausal hormone therapy and cardiovascular disease. *Am J Epidemiol* 2006;163:589–99
- Henderson BD, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. *Arch Intern Med* 1991; 151:75–8
- Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000;133:933–41
- Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;280:605–13
- Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary artery atherosclerosis. *N Engl J Med* 2000;343:522–9
- Hodis HN, Mack WJ, Lobo RA, et al. Estrogen in the prevention of atherosclerosis: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001;135:939–53
- Hodis HN, Mack WJ, Azen SP, et al. Hormone therapy and the progression of coronary artery atherosclerosis in postmenopausal women. *N Engl J Med* 2003;349:535–45
- Hodis HN, Mack WJ. A window of opportunity: the reduction of coronary heart disease and total mortality with menopausal therapies is age and time dependent. *Brain Res* 2011;1379: 244–52
- Stevenson JC, Hodis HN, Pickar JH, Lobo RA. Coronary heart disease and menopause management: the swinging pendulum of HRT. *Atherosclerosis* 2009;207:336–40

17. NHLBI stops trial of estrogen plus progestin due to increased breast cancer risk, lack of overall benefit. National Institutes of Health, NIH News Release; 9 July 2002. <http://www.nhlbi.nih.gov/new/press/02-07-09.htm>
18. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465-77
19. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy menopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33
20. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523-34
21. Grodstein F, Manson JE, Stampfer MJ. Hormone therapy and coronary heart disease: the role of time since menopause and age at hormone initiation. *J Women's Health* 2006;15:35-44
22. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701-12
23. Hsia J, Langer RD, Manson JE, et al. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med* 2006;166:357-65
24. LaCroix AZ, Chlebowski RT, Manson JE, et al., for the WHI Investigators. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with hysterectomy: a randomized controlled trial. *JAMA* 2011;305:1305-14
25. Salpeter SR, Walsh JME, Greyber E, Salpeter EE. Coronary heart disease events associated with hormone therapy in younger and older women: a meta-analysis. *J Gen Intern Med* 2006;21:363-6
26. Manson JE, Allison MA, Rossouw JE, et al., for the WHI and WHI-CACS Investigators. Estrogen therapy and coronary-artery calcification. *N Engl J Med* 2007;356:2591-602
27. Salpeter SR, Walsh JME, Greybe E, Ormiston TM, Salpeter EE. Mortality associated with hormone replacement therapy in younger and older women: a meta-analysis. *J Gen Intern Med* 2004;19:791-804
28. Collins P, Mosca L, Geiger MJ, et al. Effects of the selective estrogen receptor modulator raloxifene on coronary outcomes in the raloxifene use for the heart trial: results of subgroup analyses by age and other factors. *Circulation* 2009;119:922-30
29. Cummings SR, Ensrud K, Delmas PD, et al., for the PEARL Study Investigators. Lasofoxifene in postmenopausal women with osteoporosis. *N Engl J Med* 2010;362:686-96
30. Hodis HN, Mack WJ, Kono N, et al., for the WISH Research Group. Isoflavone soy protein supplementation and progression of subclinical atherosclerosis in healthy postmenopausal women: a randomized controlled trial. *Stroke* 2011;42:3168-75
31. Salpeter SR, Cheng J, Thabane L, Buckley NS, Salpeter EE. Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women. *Am J Med* 2009;122:1016-22
32. Salpeter SR, Buckley NS, Liu H, Salpeter EE. The cost-effectiveness of hormone therapy in younger and older postmenopausal women. *Am J Med* 2009;122:42-52
33. Walsh JME, Pignone M. Drug treatment of hyperlipidemia in women. *JAMA* 2004;291:2243-52
34. Petretta M, Costanzo P, Perrone-Filardi P, Chiariello M. Impact of gender in primary prevention of coronary heart disease with statin therapy: a meta-analysis. *Int J Cardiol* 2010;138:25-31
35. Brugts JJ, Yetgin T, Hoeks SE, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. *BMJ* 2009;338:b2376
36. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;352:1293-304
37. Berger JS, Roncaglioni MC, et al. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA* 2006;295:306-13
38. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008; 300:2134-41
39. Mora S, Glynn RJ, Hsia J, MacFadyen JG, Genest J, Ridker PM. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. *Circulation* 2010;121:1069-77
40. de Lorgeril M, Salen P, Abramson J, et al. Cholesterol lowering, cardiovascular diseases, and rosuvastatin - JUPITER controversy. *Arch Intern Med* 2010;170:1032-6
41. Kaul S, Morrissey RP, Diamond GA. By jove! What is a clinician to make of JUPITER? *Arch Intern Med* 2010;170:1073-7
42. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97
43. Mosca L, Appel LJ, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation* 2004;109:672-93
44. Hodis HN, Mack WJ. Postmenopausal hormone therapy and cardiovascular disease in perspective. *Clin Obstet Gynecol* 2008; 51:564-80
45. Hodis HN, Mack WJ. Postmenopausal hormone therapy in clinical perspective. *Menopause* 2007;14:944-57
46. Hodis HN. Assessing benefits and risks of hormone therapy in 2008: new evidence, especially with regard to the heart. *Cleveland Clin J Med* 2008;75(Suppl 4):S3-12
47. Stevenson JC, Hodis HN, Pickar JH, Lobo RA. HRT and breast cancer risk: a realistic perspective. *Climacteric* 2011;14:33-6
48. Anderson GL, Chlebowski RT, Rossouw JE, et al. Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. *Maturitas* 2006;55:103-15
49. Heiss G, Wallace R, Anderson GL, et al., for the WHI Investigators. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008; 299:1036-45
50. Stefanick ML, Anderson GL, Margolis KL, et al., for the WHI Investigators. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA* 2006;295:1647-57
51. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen replacement therapy after ischemic stroke. *N Engl J Med* 2001;345:1243-9
52. Simon JA, Hsia J, Cauley JA, et al., for the HERS Research Group. Postmenopausal hormone therapy and risk of stroke: the Heart and Estrogen-progestin Replacement Study (HERS). *Circulation* 2001;103:638-42
53. Wassertheil-Smoller S, Hendrix SL, et al., for the WHI Investigators. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA* 2003;289:2673-84
54. Cushman M, Kuller LH, Prentice R, et al., for the Women's Health Initiative Investigators. Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004;292:1573-80

55. Curb JD, Prentice RL, Bray PF, *et al.* Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med* 2006;166:772–80
56. Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. *JAMA* 2006;295:74–80
57. Bonovas S, Filioussi K, Tsavaris N, Sitaras NM. Use of statins and breast cancer: a meta-analysis of seven randomized clinical trials and nine observational studies. *J Clin Oncol* 2005;23:8606–12
58. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267–78
59. Margolis KL, Bonds DE, Rodabough RJ, *et al.*, for the Women's Health Initiative Investigators. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative hormone trial. *Diabetologia* 2004;47:1175–87
60. Kanaya AM, Herrington D, Vettinghoff E, *et al.* Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2003; 138:1–9
61. Bonds DE, Lasser N, Qi L, *et al.* The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative randomized trial. *Diabetologia* 2006;49:459–68
62. Sattar N, Preiss D, Murray HM, *et al.* Statins and risk of incident diabetes: a collaborative meta-analysis of randomized statin trials. *Lancet* 2010;375:735–42
63. Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. *Diabetes Care* 2009;32:1924–9
64. Preiss D, Seshasai SRK, Welsh P, *et al.* Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* 2011;305:2556–64
65. Culver AL, Ockene IS, Balasubramanian R, *et al.* Statin use and risk of diabetes mellitus in postmenopausal woman in the Women's Health Initiative. *Arch Intern Med* 2012, Jan 9. Epub ahead of print
66. Nelson HD, Vesco KK, Haney E, *et al.* Nonhumoral therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA* 2006;295:2057–71
67. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;355:549–59
68. Collins R, Armitage J, Parish S, Sleight P, Peto R, for the Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet* 2004;363:757–67
69. Shepherd J, Blauw GJ, Murphy MB, *et al.*, on behalf of the PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. *Lancet* 2002;360:1623–30
70. The FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005;366:1849–61
71. DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: randomised controlled trial. *Lancet* 2006;368:1096–105
72. Home PD, Pocock SJ, Beck-Nielsen H, *et al.*, for the RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomized, open-label trial. *Lancet* 2009;373: 2125–35
73. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* 2009;180:32–9
74. Dormandy J, Bhattacharya M, de Bruyn ART, on behalf of the PROactive investigators. Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: an overview of data from PROactive. *Drug Safety* 2009;32: 187–202
75. Heckbert SR, Li G, Cummings SR, Smith NL, Psaty BM. Use of alendronate and risk of incident atrial fibrillation in women. *Arch Intern Med* 2008;168:826–31
76. Black DM, Delmas PD, Eastell R, *et al.*, for the HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809–22
77. Schilcher J, Michaelsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. *N Engl J Med* 2011; 364:1728–37
78. Bolland MJ, Barber PA, Doughty RN, *et al.* Vascular events in healthy older women receiving calcium supplementation: randomized controlled trial. *BMJ* 2008;336:262–6
79. Omenn GS, Goodman GE, Thornquist MD, *et al.* Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 1996;334:1150–5
80. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 1989;321:129–35
81. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, *et al.* Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA* 2010;304:411–18
82. Bolland MJ, Avenell A, Baron JA, *et al.* Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010;341:c3691

Hormone therapy and the risk of stroke: perspectives 10 years after the Women's Health Initiative trials

V. W. Henderson and R. A. Lobo*

Departments of Health Research & Policy (Epidemiology) and of Neurology & Neurological Sciences, Stanford University, Stanford, California, USA; *Department of Obstetrics & Gynecology, Columbia University, New York, New York, USA

Key words: ESTROGEN, HORMONE THERAPY, PROGESTOGEN, RALOXIFENE, REVIEW, STROKE, TAMOXIFEN, TIBOLONE, WOMEN'S HEALTH INITIATIVE

ABSTRACT

Principal findings on stroke from the Women's Health Initiative (WHI) clinical trials of hormone therapy indicate that estrogen, alone or with a progestogen, increases a woman's risk of stroke. These results were not unexpected, and research during the past decade has tended to support these findings. Consistent evidence from clinical trials and observational research indicates that standard-dose hormone therapy increases stroke risk for postmenopausal women by about one-third; increased risk may be limited to ischemic stroke. Risk is not modified by age of hormone initiation or use, or by temporal proximity to menopause, and risk is similar for estrogen plus progestogen and for unopposed estrogen. Limited evidence implies that lower doses of transdermal estradiol (≤ 50 $\mu\text{g/day}$) may not alter stroke risk. For women less than 60 years of age, the absolute risk of stroke from standard-dose hormone therapy is rare, about two additional strokes per 10 000 person-years of use; the absolute risk is considerably greater for older women. Other hormonally active compounds – including raloxifene, tamoxifen, and tibolone – can also affect stroke risk.

INTRODUCTION

Stroke can be defined as a persistent neurological deficit caused by vascular disease affecting the brain. The age-adjusted incidence is estimated at 94 per 100 000 person-years in high-income countries, and 117 per 100 000 person-years in other countries¹. Although stroke incidence has declined steadily in recent decades in high-income countries¹, stroke remains the leading cause of prolonged adult disability and the third leading cause of death among women². In many developing countries, stroke mortality and disability exceed those of ischemic heart disease³. Risk factors for stroke include hypertension, current smoking, increased waist-to-hip ratio, unhealthy diet, less regular physical activity, diabetes mellitus, high alcohol intake, psychosocial stress or depression, atrial fibrillation and other forms of cardiac disease, and elevated ratio of apolipoprotein B to apolipoprotein A1⁴.

The incidence of stroke increases steadily with age⁵. At least until late-old age, the age-specific incidence remains lower for women than for men⁶. However, because of longer life expectancy, estimates from the Framingham Study indicate that

women's life-time risk of stroke at age 45 years (about one in five) exceeds that of men (about one in six).

Early natural menopause is associated with elevated risk of ischemic stroke later in life⁷, as might be early surgical menopause⁸. The mean age of first stroke occurs 4 years later for women compared to men (75 versus 71 years)⁶. It has long been suspected that sex differences in stroke incidence might be hormonally mediated, with ovarian estrogens produced cyclically during a woman's reproductive years acting to reduce stroke risk. Estrogen actions affect neurons and glia, vascular endothelium and smooth muscle, formed elements of the blood, plasma lipids and proteins, and inflammatory pathways. These complex actions have the potential to modify stroke risk and outcomes. The magnitude and direction of potential risk modification are not necessarily obvious.

BEFORE THE WOMEN'S HEALTH INITIATIVE

Stroke is a highly heterogeneous disorder. The primary clinical distinction is between ischemia and hemorrhage. Major subtypes

Correspondence: Professor V. W. Henderson, Stanford University, 259 Campus Drive (mc 5405) Stanford, CA 94305-5405, USA

of ischemic stroke include atherothrombotic (often related to atherosclerosis in the carotid artery or other large extracranial artery), cardioembolic (often related to atrial fibrillation or valvular heart disease), and lacunar (often related to occlusion of small perforating arteries within the brain)⁹. Major subtypes of hemorrhagic stroke include intracerebral hemorrhage due to rupture of a small artery and subarachnoid hemorrhage due to rupture of an aneurysm or vascular malformation⁹. Other classifications have been proposed¹⁰. Given this striking etiological heterogeneity, it is not surprising that risk factors for stroke, even ischemic stroke, differ in important ways from risk factors for ischemic heart disease¹¹.

Even prior to the Women's Health Initiative (WHI), the relation between hormone therapy and stroke risk had been widely studied. In 2002, Paganini-Hill reviewed 29 observational studies, finding no clear evidence that hormone use benefited stroke risk in postmenopausal women¹². This conclusion contrasted with other observational evidence that implied that hormone therapy could benefit postmenopausal women at risk for coronary heart disease¹³. Before the WHI, stroke outcomes had been investigated in two large clinical trials, both focused on women with established vascular disease. The Heart and Estrogen/progestin Replacement Study enrolled postmenopausal women with established coronary disease¹⁴. Women, who were randomly assigned to daily

estrogen combined with a progestogen or to placebo, were followed for a mean of 4.1 years. There was no significant effect on risk of stroke (Table 1¹⁵), a secondary outcome in this trial. In the Women's Estrogen for Stroke Trial, eligible women were postmenopausal, and they had a mild ischemic stroke or transient ischemic attack within the preceding 90 days¹⁶. After a mean follow-up period of 2.8 years, stroke events were similar for women allocated to an estrogen or to placebo (Table 1). Among women with non-fatal stroke, neurological and functional outcomes did not differ significantly between women in the two treatment arms¹⁶.

STROKE OUTCOMES IN THE WOMEN'S HEALTH INITIATIVE

Findings from the WHI hormone therapy trials were reported soon after those from the Heart and Estrogen/progestin Replacement Study and the Women's Estrogen for Stroke Trial. The multicenter WHI included a large observational cohort and two parallel clinical trials stratified by hysterectomy status¹⁷. The dual clinical trial used a partial factorial design, with three randomized interventions: low-fat diet, hormone therapy (conjugated estrogens with or without medroxyprogesterone acetate, depending on hysterectomy status), and

Table 1 Stroke risk in large randomized, placebo-controlled trials of hormone therapy or raloxifene in postmenopausal women*

Trial, year	Clinical population (hysterectomy status)	Number contributing to analysis	Active intervention	Type of stroke	Number of events		Hazard ratio (95% confidence interval)
					Active group	Placebo group	
<i>Hormone therapy</i>							
HERS, 2001 ¹⁴	coronary heart disease (uterus)	2 763	CE + MPA	any	82	67	1.2 (0.9–1.7)
				ischemic	69	59	1.2 (0.8–1.7)
				fatal	16	10	1.6 (0.7–3.6)
WEST, 2001 ¹⁶	recent stroke or transient ischemic attack (uterus or no uterus)	664	estradiol [†]	any	63	56	1.1 (0.8–1.6)
				ischemic	56	51	1.1 (0.8–1.5) [‡]
				fatal	12	4	2.9 (0.9–9.0)
WHI, 2003 ²⁰	generally healthy (uterus)	16 608	CE + MPA	any	151	107	1.3 (1.0–1.7)
				ischemic	125	81	1.4 (1.1–1.9)
				fatal	12	11	1.0 (0.5–2.6) [‡]
WHI, 2006 ²¹	generally healthy (no uterus)	10 739	CE	any	168	127	1.4 (1.1–1.7)
				ischemic	142	95	1.6 (1.2–2.0)
				fatal	17	15	1.2 (0.6–2.3) [‡]
<i>Raloxifene</i>							
MORE, 2002 ³³	osteoporosis	5 133	raloxifene**	any	22	32	0.7 (0.4–1.2)
				fatal	3	6	0.5 (0.1–2.0)
RUTH, 2006 ³⁴	coronary heart disease or coronary risk	10 101	raloxifene**	any	249	224	1.1 (0.9–1.3)
				ischemic	198	171	1.2 (0.9–1.4)
				fatal	59	39	1.5 (1.0–2.2)

CE, conjugated estrogens, 0.625 mg/day; HERS, Heart and Estrogen/progestin Replacement Study¹⁴; MORE, Multiple Outcomes of Raloxifene Evaluation trial³³; MPA, medroxyprogesterone acetate, 2.5 mg/day; RUTH, Raloxifene Use for The Heart trial³⁴; WEST, Women's Estrogen for Stroke Trial¹⁶; WHI, Women's Health Initiative trial for women with a uterus (CE + MPA)²⁰ or without a uterus (CE)²¹

*, Trials with at least 25 events. Table adapted from reference 15; †, the oral estradiol dose was 1 mg/day. Women with a uterus received annually medroxyprogesterone acetate, 5 mg/day for 12 days; ‡, unadjusted relative risks and confidence intervals are estimates from published data; **, results are for raloxifene 60 mg/day; hysterectomy status is not shown

calcium plus vitamin D dietary supplements¹⁷. Participants in these trials were community-dwelling postmenopausal women aged 50–79 years at baseline (mean age 63 years). Principal findings of the WHI hormone therapy trials, published in 2002 and 2004, did not consider the factorial design^{18,19}. Stroke was a secondary outcome in these trials^{18,19}. More detailed analyses of stroke outcomes were published later^{20,21}.

In the WHI estrogen + progestogen trial, women were studied over an average duration of 5.6 years²⁰. The estrogen-alone trial followed women for an average follow-up of 7.1 years²¹. In both trials, about 80% of strokes were classified as ischemic, and in both trials the risk of stroke was increased for women in the hormone therapy arm compared to placebo (Table 1). The magnitude of increase in stroke risk – approximately one-third – was slightly higher than, but consistent with, non-significant increases seen in the Heart and Estrogen/progestin Replacement Study and the Women's Estrogen for Stroke Trial. The excess risk in the WHI corresponded to about nine additional cases of stroke per 10 000 person-years of hormone use²². The increase appeared primarily to affect ischemic stroke, although the study had limited power to evaluate hemorrhagic stroke outcomes. For women with a stroke, severity assessed at the time of discharge with the Glasgow Outcome Scale did not differ between hormone and placebo arms^{20,21}.

AFTER THE WOMEN'S HEALTH INITIATIVE

Since initial WHI publications on stroke^{18,19}, there have been new reports on women who participated in the WHI trials. Other research has helped clarify WHI inferences regarding hormone therapy and stroke. It is also now evident that other hormonally active compounds are associated with increased stroke risk.

A subset of WHI hormone trial participants, 1403 women aged 65–79 years at study onset, underwent magnetic resonance brain imaging²³. Scans were obtained on average 3 years (estrogen + progestogen) or 1.4 years (estrogen alone) after trial termination. The primary outcome was based on an automated measure of ischemic lesion volume, defined by white matter changes attributed to ischemic disease and by lacunar infarction. There were no significant differences between women who had received on-trial hormone therapy and those who had received placebo. This finding was unexpected, as hormone therapy had increased stroke incidence during the WHI trials, although white matter ischemic changes *per se* do not represent frank infarction and are not associated with stroke symptoms.

As might be expected, excess risk of stroke attributed to hormone therapy during the WHI trials tended to decline after the trials were terminated. Group differences (hormone therapy group compared to the placebo group) between the intervention and post-intervention phases were significant for estrogen alone but not for estrogen + progestogen. In both instances, post-intervention stroke risks did not differ significantly between women formerly assigned to hormone therapy

and women formerly assigned to placebo. The 3-year post-intervention relative risk for prior allocation to estrogen + progestogen was 1.2 (95% confidence interval (CI) 0.8–1.6)²⁴; for estrogen alone, the post-intervention relative risk over a 4-year period was 0.9 (95% CI 0.6–1.2)²⁵.

Results of the WHI hormone therapy trial have generally proved consistent with results of other clinical trials. A meta-analysis of 28 randomized, controlled trials (including three trials that included men) suggested a 29% increase in stroke due to hormone use (95% CI 1.1–1.5)²⁶. Risk was confined to ischemic stroke. The major contributors to this meta-analysis, based on number of stroke events, are the four estrogen trials summarized in Table 1. In this meta-analysis, there was no indication that risk was modified by hormone preparation (estrogen + progestogen versus estrogen alone) or type of estrogen (conjugated estrogens versus estradiol)²⁶. Stroke outcomes seemed worse among women who received hormone therapy²⁶.

Interestingly, results from the WHI observational study failed to demonstrate a clear link between hormone therapy use and stroke^{24,25}. Other recent observational findings, however, do support the WHI clinical trial findings^{27,28}.

In the Nurses' Health Study, investigators compared current users of hormone therapy to women who had never used hormone therapy²⁷. These analyses involved 121 700 women aged 30–55 years at baseline in 1976 and followed through 2004. For estrogen + progestogen, risks were increased for any stroke (relative risk (RR) 1.3, 95% CI 1.0–1.6) and for ischemic stroke (RR 1.5, 95% CI 1.2–2.0). For estrogen alone, relative risks were similar (any stroke: RR 1.4, 95% CI 1.2–1.6; ischemic stroke: RR 1.4, 95% CI 1.2–1.7). The population-based General Practice Research Database in the United Kingdom identified 15 710 cases of stroke between 1987 and 2006 among women aged 50–79 years²⁸. For women using oral estrogens, the relative of risk of stroke was 1.3 (95% CI 1.2–1.4); risks were similar regardless of progestogen use.

The effect of dose is not clear, but some evidence points to lower stroke risks with lower doses of oral estrogens. In the Nurses' Health Study, low-dose conjugated estrogens (0.3 mg/day) – unlike higher doses – were unassociated with stroke risk (RR 0.9, 95% CI 0.6–1.4)²⁷. In the General Practice Research Database, however, 'low-dose' conjugated estrogens (defined as ≤ 0.625 mg; note that 0.625 mg/day is usually viewed as standard dose) – like higher doses – were still linked to increased risk (RR 1.3, 95% CI 1.1–1.4)²⁸. Use of transdermal estrogen is addressed below.

HORMONE THERAPY USE AS A FUNCTION OF AGE OR TIMING

The critical window hypothesis – also referred to as the timing hypothesis or window of opportunity hypothesis – posits that effects of exogenous estrogens are modified by a woman's age or by temporal proximity to menopause. It is predicted that some clinical effects are more likely to be beneficial when

hormone therapy is initiated and used by younger women closer to the menopause. A strong biological rationale underpins the critical window hypothesis for atherosclerotic vascular disease^{29,30}, and the clinical literature lends credence to the hypothesis as applied to coronary heart disease²². Contrary to prediction, however, stroke risk does not appear to be modified by a woman's age or the timing of hormone use.

In the WHI hormone therapy trials, *post hoc* analyses considered the relative risk for any stroke among women analyzed by age decade (the youngest being 50–59 years) or time since menopause (analyzed in 10-year increments, the earliest being within 10 years of menopause)²². For women randomized to receive hormone therapy, relative risks for younger women and women closer to menopause – although based on small numbers – were similar to risks for other women allocated to receive hormone therapy²². The WHI was not designed to detect modest age-related differences, but findings are similar from the observational Nurses' Health Study²⁷. Here, comparisons were between women who initiated hormone therapy between ages 50 and 59 years or after age 60 years and between women who initiated hormone therapy within 4 years of menopause or 10 or more years after menopause. There was no evidence that risks differed based on age or timing.

One suggestion for this distinction between coronary heart disease and stroke is that thrombotic mechanisms play a larger role in causing stroke than coronary heart disease in younger postmenopausal women³¹. Oral estrogens are absorbed from the digestive system into the hepatic portal system, where they induce changes in hepatic metabolism of various substrates. The net effect of these changes may be prothrombotic. Indeed, transdermal estrogen is associated with a lower risk of venous thrombosis than oral estrogens³². In the General Practice Research Database, lower doses of transdermal estrogen (≤ 50 $\mu\text{g}/\text{day}$ estradiol) were not significantly associated with stroke (RR 0.8, 95% CI 0.6–1.1), although risks were elevated for higher doses (> 50 $\mu\text{g}/\text{day}$) of transdermal estrogen as well as for oral estrogens²⁸.

OTHER COMPOUNDS THAT INTERACT WITH ESTROGEN RECEPTORS

Other drugs with the ability to interact with estrogen receptors have the potential to affect stroke risk. Raloxifene, a non-steroidal selective estrogen receptor modulator, is an option for postmenopausal women for the treatment and prevention of osteoporosis and for reduction in risk of invasive breast cancer in women with osteoporosis. In large clinical trials of postmenopausal women with osteoporosis³³ or coronary heart disease³⁴, raloxifene did not significantly increase stroke risk, but fatal strokes were more common among women with coronary heart disease at high risk for stroke^{34,35} (Table 1). Tamoxifen is a selective estrogen receptor modulator used to treat breast cancer and to reduce breast cancer incidence in high-risk women. A meta-analysis of clinical trials suggested that tamoxifen increases risk of any stroke (RR 1.4, 95% CI 1.1–1.7) and ischemic stroke (RR 1.8, 95%

CI 1.4–2.4) in women with breast cancer, although absolute risks were small³⁶. Tibolone, a progestogenic steroid with multiple hormonal effects, has been characterized as a selective tissue estrogenic activity regulator. It is used in many countries for treatment of vasomotor symptoms and prevention of osteoporosis. In a study of 4538 older postmenopausal women with osteoporosis followed for a median of 34 months, tibolone increased risk of any stroke compared to placebo (RR 2.2, 95% CI 1.1–4.2)³⁷. Contrary findings are reported from the General Practice Research Database, where tibolone use was unassociated with stroke risk (any stroke RR 1.1, 95% CI 0.2–1.4)³⁸.

CONCLUSIONS

Much has been learned about the relation between hormone therapy and stroke since the initial WHI publications on this topic^{18,19}. Key points based on current understanding are shown in Table 2. Clinical trials and observational studies indicate that hormone therapy in standard doses increases the relative risk of stroke by about one-third, without evidence for substantial risk modification based on type of estrogen, use of a progestogen, age at use, or timing of use. Lower doses of transdermal estradiol (≤ 50 $\mu\text{g}/\text{day}$) may not elevate stroke risk, but evidence is limited²⁸. Other limited evidence suggests that low-dose oral conjugated estrogens (0.3 mg/day) are not associated with elevated stroke risk²⁷.

Because stroke incidence increases with age, the *absolute risk* of stroke associated with standard-dose hormone therapy will be less among women close to the time of menopause, the group of women more likely to consider hormone therapy for vasomotor symptoms. For women in the WHI trials aged 50–59 years, hormone therapy caused two strokes per 10000 person-years. Stated another way, hormone therapy used for 5 years by 1000 women under age 60 would be expected to lead to one additional stroke, on average. In the Nurses' Health Study, attributable risks were almost the same (ages 55–59 years, about two additional strokes per 10000

Table 2 Key points: hormone therapy and stroke

- For healthy postmenopausal women, standard-dose hormone therapy increases stroke risk by about one-third*
- Stroke risk is not modified by age of hormone initiation or use, or by temporal proximity to menopause
- Stroke risks are similar for estrogen + progestogen and for unopposed estrogen
- Limited evidence suggests that lower doses of transdermal estradiol (≤ 50 $\mu\text{g}/\text{day}$) or low-dose oral conjugated estrogens (0.3 mg/day) may not alter stroke risk
- For women aged < 60 years, the absolute risk of stroke from standard-dose oral hormone therapy is about two additional strokes per 10000 person-years, equivalent to one additional stroke among 1000 women using hormone therapy for 5 years. The risk is considerably greater for older women

*, High quality of evidence based on consistent findings from well-performed randomized trials³⁹. Evidence for other key points is of lower quality

person-years; ages 50–54, one or two per 10 000 person-years; below age 50, one per 10 000 person-years)²⁷. These risks, which are rare but not negligible, should be considered by mid-life women and their physicians when discussing hormone therapy initiation and maintenance for treatment of vasomotor symptoms.

Conflict of interest The authors have no conflict of interest to declare. The authors alone are responsible for the content and writing of the paper.

Source of funding V.W.H. was supported in part by National Institutes of Health grant R01-AG023038.

References

1. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol* 2009;8:355–69
2. Lethbridge-Çejku M, Vickerie J. Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2003. *Vital and Health Statistics* 2005;10(225)
3. Kim AS, Johnston SC. Global variation in the relative burden of stroke and ischemic heart disease. *Circulation* 2011;124:314–23
4. O'Donnell MJ, Xavier D, Liu L, *et al.* Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010;376:112–23
5. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *Lancet Neurol* 2003;2:43–53
6. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. *Stroke* 2009;40:1032–7
7. Lisabeth LD, Beiser AS, Brown DL, Murabito JM, Kelly-Hayes M, Wolf PA. Age at natural menopause and risk of ischemic stroke: the Framingham heart study. *Stroke* 2009;40:1044–9
8. Rocca WA, Grossardt BR, Miller VM, Shuster LT, Brown RD Jr. Premature menopause or early menopause and risk of ischemic stroke. *Menopause* 2011 Oct 6. Epub ahead of print
9. Mohr JP, Caplan LR, Melski JW, *et al.* The Harvard Cooperative Stroke Registry: a prospective registry. *Neurology* 1978;23:754–62
10. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. Classification of stroke subtypes. *Cerebrovasc Dis* 2009;27:493–501
11. Ruiz VC, Soler EP. Epidemiology and risk factors of cerebral ischemia and ischemic heart disease: similarities and differences. *Curr Cardiol Rev* 2010;6:138–49
12. Paganini-Hill A. Hormone replacement therapy and stroke: risk, protection or no effect? *Maturitas* 2002;38:243–61
13. Grady D, Rubin SM, Petitti DB, *et al.* Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;117:1016–37
14. Simon JA, Hsia J, Cauley JA, *et al.* Postmenopausal hormone therapy and risk of stroke: the Heart and Estrogen/progestin Replacement Study (HERS). *Circulation* 2001;103:638–42
15. Henderson VW. Alzheimer's disease and other neurological disorders. *Climacteric* 2007;10(Suppl 2):92–6
16. Viscoli CM, Brass LM, Kernan WN, Sarrel SM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001;345:1243–9
17. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials* 1998;19:61–109
18. Rossouw JE, Anderson GL, Prentice RL, *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33
19. Anderson GL, Limacher M, Assaf AR, *et al.* Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701–12
20. Wassertheil-Smoller S, Hendrix S, Limacher M, *et al.* Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA* 2003;289:2673–84
21. Hendrix SL, Wassertheil-Smoller S, Johnson KC, *et al.* Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation* 2006;113:2425–34
22. Rossouw JE, Prentice RL, Manson JE, *et al.* Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465–77
23. Coker LH, Hogan PE, Bryan NR, *et al.* Postmenopausal hormone therapy and subclinical cerebrovascular disease: the WHIMS-MRI Study. *Neurology* 2009;72:125–34
24. Heiss G, Wallace R, Anderson GL, *et al.* Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008;299:1036–45
25. LaCroix AZ, Chlebowski RT, Manson JE, *et al.* Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA* 2011;305:1305–14
26. Bath PM, Gray LJ. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. *BMJ* 2005;330:342
27. Grodstein F, Manson JE, Stampfer MJ, Rexrode K. Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. *Arch Intern Med* 2008;168:861–6
28. Renoux C, Dell'aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ* 2010;340:c2519
29. Umetani M, Domoto H, Gormley AK, *et al.* 27-Hydroxycholesterol is an endogenous SERM that inhibits the cardiovascular effects of estrogen. *Nat Med* 2007;13:1185–92
30. Clarkson TB. Estrogen effects on arteries vary with stage of reproductive life and extent of subclinical atherosclerosis progression. *Menopause* 2007;14:373–84
31. Lobo RA, Clarkson TB. Different mechanisms for benefit and risk of coronary heart disease and stroke in early postmenopausal women: a hypothetical explanation. *Menopause* 2011;18:237–40
32. Laliberté F, Dea K, Duh MS, Kahler KH, Rolli M, Lefebvre P. Does the route of administration for estrogen hormone therapy impact the risk of venous thromboembolism? Estradiol transdermal system versus oral estrogen-only hormone therapy. *Menopause* 2011;18:1052–9

33. Barrett-Connor E, Grady D, Sashegyi A, *et al.* Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *JAMA* 2002;287:847–57
34. Barrett-Connor E, Mosca L, Collins P, *et al.* Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 2006;355:125–37
35. Barrett-Connor E, Cox DA, Song J, Mitlak B, Mosca L, Grady D. Raloxifene and risk for stroke based on the Framingham stroke risk score. *Am J Med* 2009;122:754–61
36. Bushnell CD, Goldstein LB. Risk of ischemic stroke with tamoxifen treatment for breast cancer: a meta-analysis. *Neurology* 2004;63:1230–3
37. Cummings SR, Ettinger B, Delmas PD, *et al.* The effects of tibolone in older postmenopausal women. *N Engl J Med* 2008;359:697–708
38. Renoux C, Dell’aniello S, Garbe E, Suissa S. Hormone therapy use and the risk of stroke. *Maturitas* 2008;61:305–9
39. Santen RJ, Allred DC, Ardoin SP, *et al.* Postmenopausal hormone therapy: an Endocrine Society scientific statement. *J Clin Endocrinol Metab* 2010;95(Suppl 1):s1–66

Estrogen and progestogen effect on venous thromboembolism in menopausal women

D. F. Archer and E. Oger*

Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk, VA, USA; *Pharmacoepidemiology Team, Clinical Investigation Center CIC 0203, National Institute of Health and Medical Research (INSERM), Rennes University Hospital, Rennes, France and Hormones and Cardiovascular Disease (Team 08), Center for Research in Epidemiology and Population Health (UMR-S 1018), National Institute of Health and Medical Research (INSERM), Villejuif, France

Key words: VENOUS THROMBOEMBOLISM, ESTROGEN, PROGESTOGEN, TRANSDERMAL, POSTMENOPAUSAL WOMEN

ABSTRACT

Prior to 1996, the use of postmenopausal estrogen was not believed to increase the risk of venous thrombosis. Subsequent studies, particularly the prospective, randomized, double-blind, clinical trial of the Women's Health Initiative, have clearly shown an increase in the incidence and risk of venous thrombosis in postmenopausal women using conjugated equine estrogens with or without medroxyprogesterone acetate. The risk of venous thrombosis in postmenopausal women is also increased by obesity and age. Oral hormone therapy has been used principally for management of menopausal symptoms. Transdermal estrogens have not been used as extensively in the United States but have a significant use in Europe. Recent observational studies have indicated no increased risk of venous thrombosis with use of transdermal estrogens. Norpregnane derivatives have been associated with an increased risk of venous thrombosis, suggesting that progestins may contribute to the increased risk in postmenopausal women using estrogen plus progestin therapy.

INTRODUCTION

The incidence of venous thrombosis (VT) is estimated to be one to two cases per 1000 woman-years and increases with age and obesity^{1–3}. Venous thrombosis encompasses both deep vein thrombosis and pulmonary embolism. The combination of the incidence of both deep vein thrombosis and pulmonary embolism within the Women's Health Initiative (WHI) is referred to as venous thromboembolism, but, for convenience, this paper will use VT as the descriptor for both deep vein thrombosis and pulmonary embolism.

There is a well-known increased incidence of VT in young women who are using combination oral contraceptives, due to the estrogen component. The estrogens and progestins used in hormone replacement therapy (HRT) for postmenopausal women were initially not associated with an increased incidence of VT thought to be due to 'biologically weaker' estrogens. This concept was overturned in the mid-1990s with evidence of an increased incidence of VT in postmenopausal women using estrogen therapy⁴. The increased incidence of VT was further confirmed in the Heart and Estrogen/progestin

Replacement Study (HERS), which was a randomized, placebo-controlled trial in older women with coronary heart disease⁵.

The progestin component of combination oral contraceptives has recently been implicated as contributing to the occurrence of VT^{6–10}. A similar conclusion implicating progestins in the incidence of VT has been reported in postmenopausal women using HRT^{11,12}. Exogenous estrogen use in postmenopausal women is now a well-established risk factor for VT. Tamoxifen and raloxifene, selective estrogen agonist/antagonists, which were previously known as selective estrogen receptor modulators (SERMS), also increase the incidence of VT by two to three times compared to the incidence in non-users^{2,12,13}.

The WHI is the largest, prospective, randomized, double-blind, clinical trial of HRT using conjugated equine estrogens (CEE, Premarin, Wyeth (now Pfizer), New York, USA) alone and estrogen + progestin therapy (CEE + medroxyprogesterone acetate (MPA)) (Prempro, Pfizer, New York, USA). The results of these studies have clarified the role of HRT in the etiology of VT in postmenopausal women. Subsequent to

Correspondence: Professor D. F. Archer, Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk, VA 23507, USA

the WHI publications, there has been increased interest in the use of transdermal estrogen as a potential means of reducing the risk of VT. The potential of progestin to promote VT has also been postulated. The incidence of VT in postmenopausal women using HRT based on the WHI is reviewed in the following sections.

VENOUS THROMBOSIS AND ESTROGEN WITH OR WITHOUT PROGESTIN

The incidence of VT is higher during the first year of use of CEE and CEE/MPA based on the findings from the WHI prospective, randomized, clinical trials^{1,2,14,15}. The continued use of HRT is associated with an increased incidence of VT in women who continue using CEE or CEE/MPA^{1,15}. Women who stop using HRT rapidly lose their increased risk and are at no greater risk than women who have never used HRT¹⁶. The WHI trials used CEE or CEE/MPA as HRT and, although there are limited data on other estrogenic compounds, it is likely that oral estrogens and probably progestins contribute to the increased occurrence of VT in postmenopausal women. The effect of transdermal estrogen on the incidence of VT is presented in more detail below.

The use of CEE/MPA in the WHI found a statistically significant increase in the incidence of VT with a hazard ratio (HR) of 2.06 (95% confidence interval (CI) 1.57–2.70)². The annualized rate for deep vein thrombosis per 1000 woman-years was 2.6 for the group receiving estrogen + progestin therapy versus 1.3 in the placebo group, with a HR of 1.95 (95% CI 1.43–2.67). The results for deep vein thrombosis and pulmonary embolism were similar in terms of a statistically significant increased incidence with estrogen + progestin therapy (Table 1)². A further evaluation of the incidence of deep vein thrombosis and pulmonary embolism in women associated with a procedure did not find any evidence of an increased risk² (Table 1).

The CEE arm of the WHI had a HR of 1.32 (95% CI 0.99–1.75) for VT associated with estrogen therapy, which was not statistically significant¹. The HR for deep vein thrombosis

Table 1 Rate of venous thrombosis, deep vein thrombosis and pulmonary embolism in postmenopausal women. Data modified from the Women’s Health Initiative clinical trial of conjugated equine estrogen and medroxyprogesterone acetate (Cushman *et al.* JAMA 2004;292:1573–80²)

	Annualized rate per 1000 woman-years		Adjusted hazard ratio (95% confidence interval)
	Estrogen + progestin (n = 8506)	Placebo (n = 8102)	
Venous thrombosis	3.5	1.7	2.06 (1.57–2.70)
Deep vein thrombosis	2.6	1.3	1.95 (1.43–2.67)
Pulmonary embolism	1.8	0.8	2.13 (1.45–3.11)
Procedure related	0.6	0.5	1.09 (0.63–1.91)

was 1.47 (95% CI 1.06–2.06) with estrogen therapy, while the HR for pulmonary embolism again did not reach statistical significance (Table 2)¹. There was no evidence of an increased incidence with any procedure in this study.

VENOUS THROMBOSIS AND AGE

Age is significantly related to the occurrence of VT. Both CEE alone and CEE/MPA WHI trials found an increasing occurrence and HR of VT with age based on the incidence of VT in the placebo arms of the studies^{1,2}. The age-adjusted HR for VT in the placebo arm of the CEE/MPA study was 1.0 (referent), 2.31 (95% CI 1.23–7.72), and 3.37 (95% CI 1.72–6.60) for the 50–59-, 60–69-, and 70–79-year age groups, respectively². The CEE-only study presented HRs for placebo versus age of 1.0 (referent), 2.16 (95% CI 1.20–3.89) and 2.78 (95% CI 1.48–5.22) for the age groups 50–59-, 60–69-, and 70–79-year age groups, respectively. CEE/MPA increased the HR for VT compared to placebo in each age bracket (HR 2.27, 95% CI 1.19–4.33; HR 4.28, 95% CI 2.38–7.22; and HR 7.46, 95% CI 4.32–14.38 in age groups 50–59, 60–69, and 70–79 years, respectively (Table 3)². A similar increase in VT incidence in the CEE arm compared to placebo resulted in HRs of 1.37 (95% CI 0.70–2.68), 2.82 (95% CI 1.59–5.01) and 3.77 (95% CI 2.07–6.89) in the 50–59-, 60–69-, and 70–79-year-olds, respectively (Table 3)¹.

VENOUS THROMBOSIS AND OBESITY

Obesity is an independent risk factor for VT. The incidence of obesity at baseline was 33% in the women who were followed up for 5.7 years in the CEE/MPA study². The CEE study¹ at baseline reported approximately 80% as overweight with a body mass index (BMI) >25 kg/m², and 50% were obese with a BMI of >30 kg/m². Using the occurrence of VT in the placebo arm of the CEE/MPA study, the HRs

Table 2 Hazard ratio of venous thrombosis, deep vein thrombosis and pulmonary embolism based on age and use of conjugated equine estrogen. Data modified from the Women’s Health Initiative study of conjugated equine estrogens in postmenopausal women (Curb *et al.* Arch Intern Med 2006;166:772–80¹)

Age at screening	Hazard ratio (95% confidence interval)		
	Deep vein thrombosis	Pulmonary embolism	Venous thrombosis
<i>Conjugated equine estrogen</i>			
50–59 years	1.64 (0.74–3.60)	1.54 (0.63–3.77)	1.37 (0.70–2.68)
60–69 years	3.02 (1.51–6.06)	2.80 (1.28–6.16)	2.82 (1.59–5.01)
70–79 years	4.54 (2.22–9.31)	2.36 (0.96–5.80)	3.77 (2.07–6.89)
<i>Placebo</i>			
50–59 years	1.00	1.00	1.00
60–69 years	2.17 (1.06–4.45)	1.63 (0.70–3.78)	2.16 (1.20–3.89)
70–79 years	2.94 (1.37–6.30)	2.67 (1.12–6.39)	2.78 (1.48–5.22)

Table 3 Age-specific incidence of venous thrombosis in women using conjugated equine estrogen and medroxyprogesterone acetate. Data modified from the Women's Health Initiative clinical trial of conjugated equine estrogen and medroxyprogesterone acetate (Cushman *et al.* *JAMA* 2004;292:1573–80²)

Baseline age	Placebo	Estrogen + progestin
<i>50–59 years</i>		
Annualized rate/1000 woman-years	0.8	1.9
Hazard ratio (95% confidence interval)*	1.00	2.27 (1.19–4.33)
<i>60–69 years</i>		
Annualized rate/1000 woman-years	1.9	3.5
Hazard ratio (95% confidence interval)*	2.31 (1.23–4.35)	4.28 (2.38–7.72)
<i>70–79 years</i>		
Annualized rate/1000 woman-years	2.7	6.2
Hazard ratio (95% confidence interval)*	3.37 (1.72–6.60)	7.46 (4.32–14.38)

*, Adjusted for prior venous thrombosis, randomized group in the dietary modification trial, age, assignment to estrogen plus progestin or placebo, and the interaction term of age and treatment assignment

were 1.0 (referent), 1.63 (95% CI 0.83–3.20), and 2.87 (95% CI 1.52–5.40) in the women with a BMI <25, 25–30, and >30 kg/m², respectively (Table 4). The CEE study¹ found a similar trend with the HRs being 1.00 (referent), 1.89 (95% CI 0.84–4.19, and 3.39 (95% CI 1.60–7.17), respectively in women with a BMI of <25, 25–29, and >30 kg/m². The use of either CEE/MPA or CEE doubled the risk of VT in women with a BMI >25 kg/m² in each study, while there was no statistically increased HR for VT with either therapy in women whose BMI was <25 kg/m² compared to placebo in both the CEE and CEE/MPA studies^{1,2}. These data indicate that the use of HRT in obese postmenopausal women increases the incidence of VT.

VENOUS THROMBOSIS AND GENETIC MARKERS

The WHI investigated factor V Leiden, prothrombin 20210, prothrombin G 19911A, methylenetetrahydrofolate, coagulation factor XIII Val34Leu, 45/5G polymorphism of plasminogen activator inhibitor-1, and factor V HR2, using standard restrictive fragment length polymorphisms in nested case-controlled studies². Women heterozygous for factor V Leiden using CEE/MPA had an increased risk for VT of 2.6 (95% CI 1.3–5.2), while homozygous women using CEE/MPA had an increased risk for VT of 7.5 (95% CI 0.6–87.8)². There was an increased VT risk with CEE compared to placebo for factor V Leiden but the association was weak ($p = 0.06$), and there

Table 4 Incidence of venous thrombosis by body mass index (kg/m²) in postmenopausal women using conjugated equine estrogens and medroxyprogesterone acetate. Data modified from the Women's Health Initiative clinical trial of conjugated equine estrogen and medroxyprogesterone acetate (Cushman *et al.* *JAMA* 2004;292:1573–80²)

Body mass index	Placebo	Estrogen + progestin
<i><25 kg/m²</i>		
Annualized rate/1000 person-years	0.9	1.6
Hazard ratio (95% confidence interval)*	1.00	1.78 (0.91–3.51)
<i>25–30 kg/m²</i>		
Annualized rate/1000 person-years	1.5	3.5
Hazard ratio (95% confidence interval)*	1.63 (0.83–3.20)	3.80 (2.08–6.94)
<i>>30 kg/m²</i>		
Annualized rate/1000 person-years	2.5	5.1
Hazard ratio (95% confidence interval)*	2.87 (1.52–4.50)	5.61 (3.12–10.11)

*, Adjusted for prior venous thrombosis, randomized group in the dietary modification trial, body mass index, assignment to estrogen plus progestin or placebo, and the interaction term body mass index and randomization group

were similar findings for plasminogen activator inhibitor-1 ($p = 0.08$)¹. Overall, the incidence was low and limited to Caucasians with factor V Leiden mutations.

VENOUS THROMBOSIS FOLLOWING DISCONTINUATION OF HORMONES

During the 2.4 years of follow-up after discontinuation of CEE/MPA, the increased risk of VT disappeared (HR 0.95, 95% CI 0.63–1.44)¹⁷. A further decline in the risk of VT was found in the follow-up of the CEE arm of the WHI (HR 0.63, 95% CI 0.41–0.98)¹⁶.

THE ROLE OF PROGESTOGEN IN VENOUS THROMBOSIS

The large, prospective, randomized, clinical trials of HRT in the United States have found that CEE, with or without MPA, increases the incidence of VT^{5,14,15}. The possibility of the progestin contributing to the increased incidence of VT in these trials was considered. The progestin used in HRT in the United States is principally MPA, while other progestins and progesterone itself are prescribed with estrogens in Europe¹⁸. Progesterone itself does not increase the incidence of VT when used with estrogen¹⁸. MPA has been implicated as increasing the risk of VT in postmenopausal women¹⁸. Norpregnane

derivatives, represented by norgestrol acetate or promegesterone, have been associated with an increased incidence of VT when used as postmenopausal HRT^{11,19}. These data are from a multicenter, case-controlled study and a prospective cohort study and will require confirmation with a prospective, randomized, clinical trial.

TRANSDERMAL ESTROGEN AND THE RISK OF VENOUS THROMBOSIS

Only six observational studies have assessed the risk of venous thrombosis associated with transdermal estrogen replacement therapy (ERT), with point risk estimates ranging from 0.6 to 2.1^{20–25}. It is worth noticing that these results were based on, respectively, two²³, three²⁵, five²⁰ and seven cases²¹ who used transdermal estrogen. Another study observed postmenopausal women predominantly using transdermal estrogen; only six cases used HRT and results according to the route of estrogen administration were not shown²². The EStrogen and THromboEmbolic Risk (ESTHER) study²⁴, a French hospital-based multicenter case-control study, reported data based on 30 cases using transdermal estrogen. By contrast with oral estrogen, no significant association of transdermal estrogen with venous thromboembolism was found (odds ratio 0.9; 95% CI 0.5–1.6). The pooled risk estimate for a first episode of venous thrombosis associated with transdermal ERT, after meta-analyzing those case-control studies, was 1.2 (95% CI 0.9–1.7)²⁶. Following this meta-analysis, other studies have been published which reported no increased risk of venous thrombosis in users of transdermal ERT^{19,27}. The first report was based on the UK's General Practice Research Database and found an adjusted rate ratio for VT in users of transdermal ERT of 1.01 (95% CI 0.89–1.16)²⁷. The second report was a large French cohort study¹⁹. This study showed that the risk of idiopathic VT was not increased in users of transdermal ERT (HR 1.1, 95% CI 0.8–1.8); in addition, this report pointed to an increased risk of idiopathic VT in women using transdermal estrogen combined with norepregnane derivatives, as compared to women using other progestins¹⁹. Altogether, these findings suggest that transdermal ERT might be safer than oral estrogen with respect to venous thromboembolism, but no definite and valid conclusion can be drawn.

Biological evidence supports the observation of an increased venous thromboembolism risk among users of oral ERT and of a difference between routes of estrogen administration^{28–36}. Oral ERT has clear effects on coagulation variables, pointing towards a prothrombotic effect. Activated protein C (APC) resistance is a well-known risk factor for VT^{37,38}. APC resistance detected in the absence of factor V Leiden mutation is also an independent risk factor for venous thromboembolism³⁹. Oral ERT increases resistance to APC^{29,32,33,40}. Oral ERT increased plasma levels of markers for *in vivo* thrombin activation (prothrombin fragment 1 + 2)^{30,32,34,35} and lowered antithrombin activity²⁸ and levels of total protein S in plasma³¹ in postmenopausal women. These deleterious effects on coagulation did not

apply to users of transdermal ERT^{28,32–34,36}. A systematic review of trials comparing the effects of transdermal with oral ERT on coagulation markers concluded that these effects are at least lower with transdermal use⁴¹. These data emphasize the potential importance of the route of estrogen administration in prescribing HRT.

THE FUTURE OF HORMONE THERAPY

The data above suggest that estradiol and progesterone alone or in combination via oral or transdermal routes of administration could be used in postmenopausal women without increasing the risk of VT^{19,26,27}. This does not imply that other combinations and routes of administration of estradiol and progesterone should not be explored. There are two promising studies that are nearing completion that use estradiol and progesterone in postmenopausal women.

The Kronos Early Estrogen Prevention Study (KEEPS) is a multicenter, 5-year, clinical trial that will evaluate the effectiveness of 0.45 mg of CEE orally and of estradiol 50 µg as a weekly transdermal delivery system versus placebo. The treatment regimens will be combined with oral micronized progesterone, 200 mg for 12 days each month. The primary endpoints of the study are the progression of carotid intima-medial thickness and the accrual of coronary calcium in women aged 42–58 years who are within 36 months of their final menstrual period⁴².

The Early versus Late Intervention with Estradiol (ELITE) study is designed to measure progress in carotid intima-medial thickness in postmenopausal women using oral 17β-estradiol versus placebo⁴³. ELITE will use vaginal progesterone gel 4% administered for 10 days each month in women who have an intact uterus.

Both studies plan to enroll a limited number of participants, 720 in KEEPS and 643 in ELITE, which will make it difficult to accurately assess clinical outcomes such as VT. These studies are ground-breaking in that they are investigating 'natural' estradiol and progesterone rather than synthetic progestins or conjugated equine estrogens.

CONCLUSIONS

The overall increases in risk of VT, both deep vein thrombosis and pulmonary embolism, were variable between the oral estrogen and progestin treatment interventions in the WHI. Age and BMI played a major role in the increased incidence of VT in the WHI. The incidence of VT was 3.4 versus 1.6 per 1000 woman-years in the CEE/MPA versus placebo trial, an increase of 1.8 cases per 1000 woman-years, and 2.8 versus 2.1 events per 1000 woman-years, an increase of 0.7 cases per 1000 woman-years, in the CEE versus placebo arm^{2,14,15}. CEE/MPA increased the HRs for VT, deep vein thrombosis and pulmonary embolism, while CEE alone increased significantly the incidence for deep vein thrombosis

but did not lead to a statistically significant increase in VT or pulmonary embolism^{2,14}. Two large studies, one of which was a cohort study, did not find an increased incidence of VT with use of transdermal estrogen in postmenopausal women^{19,27}. These studies and others have concluded that the use of transdermal estrogen might be safer in regard to VT and have less effect on coagulation markers than oral estrogen. The use of progesterone in HRT may abrogate the

increased incidence of VT that has been associated with progestins.

Conflict of interest Professor Archer is a consultant to Pfizer, Agile Therapeutics, and Bayer. Professor Oger reports no conflicts.

Source of funding Nil.

References

1. Curb JD, Prentice RL, Bray PF, *et al.* Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med* 2006;166:772–80
2. Cushman M, Kuller LH, Prentice R, *et al.* Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004;292:1573–80
3. White RH. The epidemiology of venous thromboembolism. *Circulation* 2003;107:14–8
4. Barlow DH. HRT and the risk of deep vein thrombosis. *Int J Gynaecol Obstet* 1997;59(Suppl 1):S29–33
5. Grady D, Wenger NK, Herrington D, *et al.* Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2000;132:689–96
6. Dinger J, Assmann A, Mohner S, Minh TD. Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study. *J Fam Plann Reprod Health Care* 2010;36:123–9
7. Dinger JC, Heinemann LA, Kuhl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. *Contraception* 2007;75:344–54
8. Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. *BMJ* 2011;342:d2151
9. Parkin L, Sharples K, Hernandez RK, Jick SS. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. *BMJ* 2011;342:d2139
10. van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJ, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. *BMJ* 2009;339:b2921
11. Canonico M, Oger E, Plu-Bureau G, *et al.* Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* 2007;115:840–5
12. Haynes B, Dowsett M. Clinical pharmacology of selective estrogen receptor modulators. *Drugs Aging* 1999;14:323–36
13. Cummings SR, Eckert S, Krueger KA, *et al.* The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. *JAMA* 1999;281:2189–97
14. Anderson GL, Limacher M, Assaf AR, *et al.* Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701–12
15. Rossouw JE, Anderson GL, Prentice RL, *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33
16. LaCroix AZ, Chlebowski RT, Manson JE, *et al.* Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA* 2011;305:1305–14
17. Heiss G, Wallace R, Anderson GL, *et al.* Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008;299:1036–45
18. Canonico M, Plu-Bureau G, Scarabin PY. Progestogens and venous thromboembolism among postmenopausal women using hormone therapy. *Maturitas* 2011;70:354–60
19. Canonico M, Fournier A, Carcaillon L, *et al.* Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. *Arterioscler Thromb Vasc Biol* 2010;30:340–5
20. Daly E, Vessey MP, Hawkins MM, Carson JL, Gough P, Marsh S. Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* 1996;348:977–80
21. Perez Gutthann S, Garcia Rodriguez LA, Castellsague J, Duque Oliart A. Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. *BMJ* 1997;314:796–800
22. Varas-Lorenzo C, Garcia-Rodriguez LA, Cattaruzzi C, Troncon MG, Agostinis L, Perez-Gutthann S. Hormone replacement therapy and the risk of hospitalization for venous thromboembolism: a population-based study in southern Europe. *Am J Epidemiol* 1998;147:387–90
23. Hoibraaten E, Abdelnoor M, Sandset PM. Hormone replacement therapy with estradiol and risk of venous thromboembolism – a population-based case-control study. *Thromb Haemost* 1999;82:1218–21
24. Scarabin PY, Oger E, Plu-Bureau G. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428–32
25. Douketis JD, Julian JA, Kearon C, *et al.* Does the type of hormone replacement therapy influence the risk of deep vein thrombosis? A prospective case-control study. *J Thromb Haemost* 2005;3:943–8
26. Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ* 2008;336:1227–31

27. Renoux C, Dell'Aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. *J Thromb Haemost* 2010;8:979–86
28. Conard J, Samama M, Basdevant A, Guy-Grand B, de Lignieres B. Differential AT III-response to oral and parenteral administration of 17 beta-estradiol. *Thromb Haemost* 1983;49:252
29. Hoibraaten E, Mowinckel MC, de Ronde H, Bertina RM, Sandset PM. Hormone replacement therapy and acquired resistance to activated protein C: results of a randomized, double-blind, placebo-controlled trial. *Br J Haematol* 2001;115:415–20
30. Hoibraaten E, Os I, Seljeflot I, Andersen TO, Hofstad A, Sandset PM. The effects of hormone replacement therapy on hemostatic variables in women with angiographically verified coronary artery disease: results from the Estrogen in Women with Atherosclerosis Study. *Thrombosis Res* 2000;98:19–27
31. Marque V, Alhenc-Gelas M, Plu-Bureau G, Oger E, Scarabin PY. The effects of transdermal and oral estrogen/progesterone regimens on free and total protein S in postmenopausal women. *Thromb Haemost* 2001;86:713–14
32. Oger E, Alhenc-Gelas M, Lacut K, et al. Differential effects of oral and transdermal estrogen/progesterone regimens on sensitivity to activated protein C among postmenopausal women: a randomized trial. *Arterioscler Thromb Vasc Biol* 2003;23:1671–6
33. Post MS, Christella M, Thomassen LG, et al. Effect of oral and transdermal estrogen replacement therapy on hemostatic variables associated with venous thrombosis: a randomized, placebo-controlled study in postmenopausal women. *Arterioscler Thromb Vasc Biol* 2003;23:1116–21
34. Scarabin PY, Alhenc-Gelas M, Plu-Bureau G, Taisne P, Agher R, Aiach M. Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial. *Arterioscler Thromb Vasc Biol* 1997;17:3071–8
35. Teede HJ, McGrath BP, Smolich JJ, et al. Postmenopausal hormone replacement therapy increases coagulation activity and fibrinolysis. *Arterioscler Thromb Vasc Biol* 2000;20:1404–9
36. Vehkavaara S, Silveira A, Hakala-Ala-Pietila T, et al. Effects of oral and transdermal estrogen replacement therapy on markers of coagulation, fibrinolysis, inflammation and serum lipids and lipoproteins in postmenopausal women. *Thromb Haemost* 2001;85:619–25
37. Rodeghiero F, Tosetto A. Activated protein C resistance and factor V Leiden mutation are independent risk factors for venous thromboembolism. *Ann Intern Med* 1999;130:643–50
38. Dahlback B. Resistance to activated protein C caused by the factor VR506Q mutation is a common risk factor for venous thrombosis. *Thromb Haemost* 1997;78:483–8
39. de Visser MC, Rosendaal FR, Bertina RM. A reduced sensitivity for activated protein C in the absence of factor V Leiden increases the risk of venous thrombosis. *Blood* 1999;93:1271–6
40. Eilertsen AL, Liestol S, Mowinckel MC, Hemker HC, Sandset PM. Differential impact of conventional and low-dose oral hormone therapy (HT), tibolone and raloxifene on functionality of the activated protein C system. *Thromb Haemost* 2007;97:938–43
41. Hemelaar M, van der Mooren MJ, Rad M, Kluff C, Kenemans P. Effects of non-oral postmenopausal hormone therapy on markers of cardiovascular risk: a systematic review. *Fertil Steril* 2008;90:642–72
42. Harman SM, Brinton EA, Cedars M, et al. KEEPS: The Kronos Early Estrogen Prevention Study. *Climacteric* 2005;8:3–12
43. <http://clinicaltrials.gov/ct2/show/NCT00114517> accessed 19 January 2012

Hormone therapy and breast cancer risk 10 years after the WHI

A. Gompel and R. J. Santen*

UF de Gynécologie, Université Paris Descartes, AP-HP, Hôtel-Dieu, Paris, France; *Division of Endocrinology and Metabolism, Department of Medicine, University of Virginia Health Sciences Center, Charlottesville, Virginia, USA

Key words: BREAST CANCER, HORMONE THERAPY, WOMEN'S HEALTH INITIATIVE, RISK FACTORS, ALCOHOL, LIFESTYLE, PROGESTERONE

ABSTRACT

Ten years after the publication of the first Women's Health Initiative (WHI) report, a substantial decrease in hormone replacement therapy (HRT) has been observed world-wide. Fear of developing breast cancer represents one of the reasons for an important shift toward alternatives for treatment of menopause symptoms or abstinence from therapy altogether. Many publications in the scientific and lay press have emphasized the magnitude of the relative risk of breast cancer but have not focused on excess or attributable risk. Since the original report of the WHI study, new information has been published on risk factors for breast cancer related to hormone therapy use. Accordingly, we believe it important to review current data and examine excess rather than relative or absolute risk. A balanced perspective on excess risk determined from existing data suggests that the benefits of HRT for quality of life can outweigh the risks in management of a large number of postmenopausal women. In addition, alternative strategies for relief of menopausal symptoms are not as effective as HRT in treating the climacteric symptoms.

INTRODUCTION

The first Women's Health Initiative (WHI) publication in July 2002 reported the combined effects of conjugated equine estrogens (CEE) plus a progestogen, medroxyprogesterone acetate (MPA) in postmenopausal women¹. Later reports amplified the initial findings and described an additional trial comparing CEE alone with placebo². These publications had a substantial impact on the use of hormone replacement therapy (HRT), with a decrease of up to 80% world-wide. Most of the women's concerns related to the increase in breast cancer risk, a result emphasized in the lay press. The diagnosis of breast cancer places a large emotional and cost burden on women in western countries and represents a major issue for women of all ages.

Critical analyses of the WHI findings and new data over the past 10 years have added clarity to our understanding of breast cancer risks and modifiable risk factors. Reproductive risk factors have always been considered as major, with relative risks ranging from less than 2 for menopausal hormone therapy to relative risks of 3–5 for plasma estrogen levels

and breast density (Figure 1). Following the WHI report in 2002, only a minority of postmenopausal women now choose to use HRT for climacteric symptoms. Regulatory agencies as well as the lay press regularly discourage women from using HRT for symptoms except in the lowest doses and for the shortest time possible. As a consequence, women favor use of over-the-counter alternatives, generally without medical supervision. The effects of these alternative strategies in terms of quality of life and development of other diseases have not been fully evaluated for the post-WHI generation of postmenopausal women. Untoward consequences may result, as exemplified by a recent report documenting a substantial increase in osteoporotic fractures after cessation of HRT³.

An issue reinforcing the negative perception of HRT is that many publications from western countries have reported a significant decrease in breast cancer incidence following the decline in HRT use and concluded that a cause-and-effect relationship exists. Critical assessment of the HRT cessation/breast cancer reduction link has identified several confounding factors which could have influenced this relationship. Alterations

Correspondence: Professor A. Gompel, UF de Gynécologie, Hôtel-Dieu, 1 Place du Parvis Notre-Dame, Paris, 75004, France

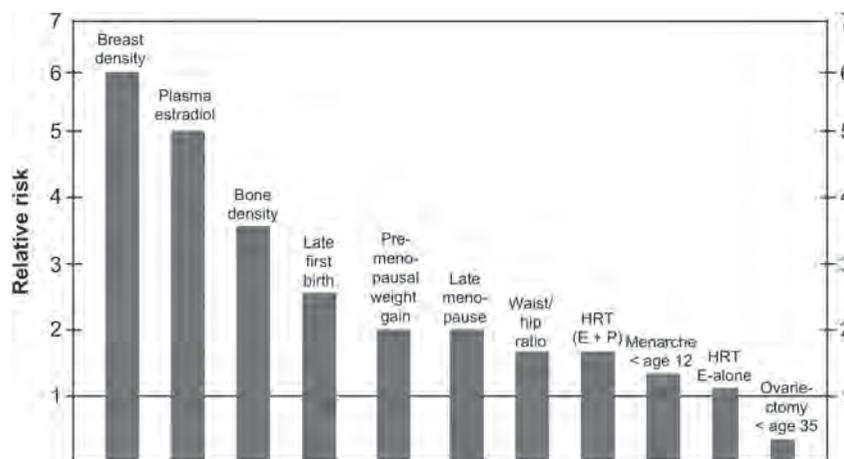


Figure 1 Hormonal factors and the relative risk of breast cancer⁵². HRT, hormone replacement therapy; E, estrogen; P, progesterone

in mammography usage and the timing of initiation of breast cancer screening programs have been cited as potential confounding factors. Another factor regarding adverse perceptions is that an increase in breast cancer risk from use of hormone therapy is biologically plausible based on knowledge of tumor biology and breast physiology. There is little doubt that hormones can promote breast cancer proliferation and prevent programmed cell death.

The focus on breast cancer engendered by the WHI stimulated scientists to point out which environmental and constitutive factors may be modifiable in the general population. Current research has also focused on finding molecules with the beneficial impact of estrogens without their breast-negative impact⁴. While new strategies are being developed, it is important to appreciate that the risk of breast cancer varies substantially between one woman and another. Age of onset of menarche, first live birth, late menopause, high breast density, elevated plasma estradiol levels and presence of hyperplastic benign breast lesions all add to breast cancer risk. Several genetic and lifestyle factors have recently been demonstrated to be important in the risk of breast cancer as well. Development of methods to determine individual risk will be helpful in framing the issues involved in decision-making regarding HRT. Those at low baseline likelihood of breast cancer will experience much less excess risk from HRT than those at high risk. Accordingly, the best candidates for HRT are women at low baseline risk of breast cancer who are experiencing substantial menopausal symptoms.

HRT AND BREAST CANCER RISK

When the WHI was designed, a carefully constructed 'stopping rule' was developed to terminate the trial when risk exceeded benefits as assessed by an integrated health index. Two important components of this health index included cardiovascular events and breast cancer incidence. When the index exceeded the stopping rule, the combined CEE/MPA

arm of the WHI was terminated on this basis. The first WHI report in 2002 unexpectedly demonstrated an increase in cardiovascular events from the combination of CEE and MPA. It should be noted that the mean age of women randomized into the trial was 63 years and the subjects were largely asymptomatic. The reported breast cancer risk confirmed what had been previously found by most of the large observational studies. An excellent overview of observational studies was provided by a collaborative group which pooled 51 previous studies on that topic⁵. This group reported a modest increase in the relative risk of breast cancer with HRT, with a significant trend toward increasing risk with time. The effects were larger with the combined estrogen + progesterone treatment than with estrogen alone. The risk reached statistical significance at approximately 5 years and returned to that of non-users within 4 years of cessation.

The WHI study represented the first large, randomized, controlled trial (RCT) of a combination of estrogen + progesterone, specifically 0.625 mg of CEE plus 2.5 mg of MPA. Involving approximately 16000 women, the WHI trial reported a relative risk of breast cancer of 1.26 (95% confidence interval (CI) 1.00–1.59)¹ for current use of HRT. This observation supports a small promoter role of the combined treatment. Initiation of *de novo* cancers appeared an unlikely explanation since nearly 20 years are required for a *de novo* tumor to reach the clinical detection threshold^{6,7}. The other randomized trial conducted by the WHI included approximately 11000 women who had previously undergone a hysterectomy and compared CEE alone with placebo². This study did not show any increase in breast cancer risk among these women. After a mean treatment duration of 7.1 years, the relative risk of invasive breast cancer for women assigned to estrogen alone was 0.77 (95% CI 0.59–1.01) in the whole population and 0.67 (95% CI 0.47–0.97) in adherent women, which suggested a paradoxical decrease in risk. The results of the estrogen-alone arm differed from most of the observational studies that have been published to date, as these studies reported a slight increase in the risk of breast cancer with estrogen alone⁸. However, the WHI trial was consistent with most other studies which show

a higher risk with the combined estrogen + progestogen therapy than with estrogen alone⁷.

The issue of a decreased risk of breast cancer in the WHI estrogen-alone trial is difficult to interpret in light of the increase with other studies. One consideration is that the risk associated with estrogen alone becomes significant in most of the studies after a longer duration of treatment than with the combined HRT. For example, the Nurses' Health Study reported increases in breast cancer risk when estrogen alone was used for more than 10 and up to 20 years⁹. It is necessary to formally confirm that combined estrogen + progestogen increases risk more than estrogen alone since there are no randomized trials where estrogen + progestogen and estrogen alone have been compared in the same populations. However, as the WHI estrogen-alone and estrogen + progestogen arms were similarly designed, comparison of the data from both arms indicates that the risk associated with estrogen alone appears to be less.

The reasons for the decrease of breast cancer incidence in the estrogen-alone WHI trial remain an object of debate. In this trial, a substantial proportion of women were obese and prior observational data suggest that HRT is associated with breast cancer to a lesser extent in obese women⁷. Given the fact that insulin resistance is decreased by oral estrogens, it is likely that the women in the WHI estrogen-alone trial could have benefited from the treatment by decreasing their risk associated with insulin resistance. Another possible explanation is that CEE contains mixed compounds including some with selective estrogen receptor modulator-like activity, in addition to pure estrogenic derivatives. However, this last hypothesis does not fit with the results from the Nurses' Health Study where CEE was used and an increase in the relative risk of breast cancer was associated with long-term use of CEE⁹. One of the major differences between the two studies was that the body mass index was much lower in the nurses' cohort than in the WHI trials. The nurses could have benefited less from the decrease of insulin resistance and their risk associated with CEE use was significant for a longer use (up

to 20 years) than in the WHI estrogen + progestogen trial⁹. Furthermore, a paper from the WHI suggested that the time when HRT is used after menopause could be associated with a different increase in relative risk. The longer the gap time between menopause and starting combined hormone therapy, the less the breast cancer risk¹⁰. Another explanation, with strong support from basic tumor biology studies, is that estrogen alone might have induced apoptosis in the women deprived of estrogen in the long term. The average age of the participants in the WHI was 63 years, a full 12 years after the average age of menopause. Experimental data demonstrate that estrogen induces apoptosis in breast cancer cells deprived of estrogen long-term by both extrinsic (death receptor-mediated) and intrinsic (mitochondrial-mediated) mechanisms^{11,12}.

The WHI remains unique as a RCT because of the large number of subjects entered and the substantial cost as a result. In the absence of corroborating RCTs, concordance of its findings with well-conducted, observational studies provides further credence of its findings. Several large observational cohorts have been published including the EPIC study from Europe, the E3N study from France, and the Nurses' Health Study from the USA. The EPIC study was composed of cohorts from eight different European countries and included 133 744 women followed up for a mean of 8.6 years. This study clearly showed differences associated with the types of progestogens used within European countries and the USA (Figure 2)¹⁰. In the EPIC study, 4312 breast cancer cases were analyzed and the risk attributed to HRT increased with time of use for the estrogen + progestogen and estrogen-alone therapies. The relative risk appeared lower when comparing the estrogen-alone with estrogen + progestogen therapies¹⁰. There was no difference between oral and transdermal estradiol, or between pregnane derivatives and norsteroid derivatives, but a higher risk for continuous versus sequential regimens, as previously suggested in other studies.

The report from the E3N French cohort was unique in that 25% of the regimens used involved a combination of estradiol plus progesterone (rather than synthetic pregnane

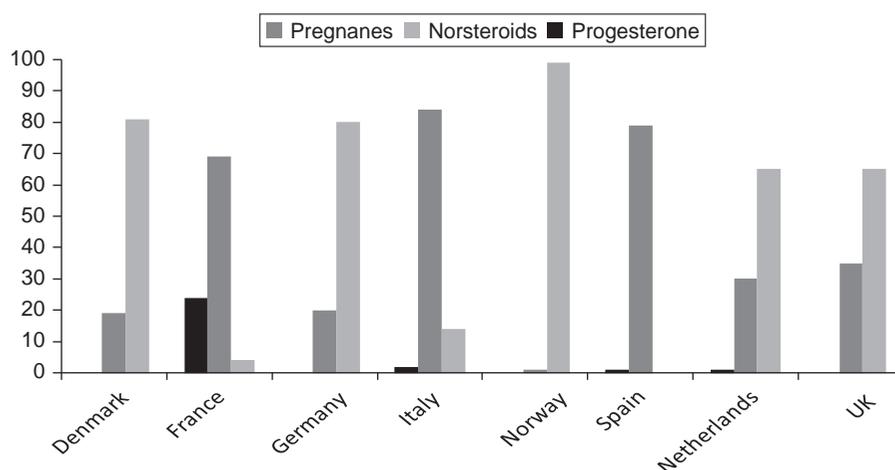


Figure 2 Type of progestin used in Europe (EPIC study) (adapted from reference 10)

or nonsteroid derivatives). In the estradiol + progesterone group, there was no increase in the relative risk of breast cancer, whereas use of estrogen plus a synthetic pregnane or nonsteroid derivative was associated with a relative risk of approximately 1.6. Interestingly, estradiol with dydrogesterone also appeared to confer a lesser risk^{13,14}. A small increase in the risk was also observed with the use of estrogen alone (relative risk 1.3)¹³. Women in the E3N study were leaner than in most of the other populations studied. As noted above, some studies report that the risk from HRT decreases in women with a lower body mass index. As body mass index *per se* constitutes a risk factor, it can be suggested that the risk observed in the French cohort might be lower than in others because of the lean nature of the subjects, a reassuring concept. Confirmation of this beneficial effect of progesterone is not available in other populations since France is almost the only country to use it (Figure 2).

Another publication from Finland also reported no increased risk of breast cancer with dydrogesterone. These data provide additional support for the EPIC study findings¹⁵. Other large observational studies include the Nurses' Health Study from the USA and the Million Women Study in the UK. Data from these studies are largely concordant with the European and French studies and indicate that the risk from estrogen + progestogen appears to be larger than the risk with estrogen alone and is duration-dependent. A very important difference between these observational studies and the WHI RCTs is that most of the women in the observational studies began to use HRT shortly after menopause. In contrast, women in the WHI were randomized to receive HRT at an average age of 63 years, many years after the onset of menopause. Some of these women had never taken HRT prior to the study and others experienced a short 'wash-out' period prior to randomization.

RELATIVE, ABSOLUTE, AND EXCESS RISK

Reports of HRT and breast cancer risk generally emphasize relative risk. This statistic relates the percent increment in an event in one population to that in another. Absolute risk defines the number of events in a population. Excess (or attributable) risk subtracts the underlying risk in one population from that in another population exposed to an agent that increases risk. Relative risk provides meaningful information when the absolute risk is high but not when the absolute risk is low. As an example, one can assume that the risk of dying from a plane crash is one in ten million. With five plane flights, the risk is increased to five per ten million or a relative risk of 5.0. This 500% increase only means that one has an excess risk of four per ten million if taking five plane flights. In this example, relative risk is high, but absolute and excess risks are nearly meaningless.

Based on this reasoning, a scientific statement of the Endocrine Society converted all risks from HRT to excess risk and expressed this as the number of women per 1000 taking HRT

for 5 years that would develop a breast cancer that they would not have developed if not taking HRT⁷. The relative risk of 1.26 with estrogen + progestogen then translates to an excess (attributable) risk of four per 1000 women taking HRT for a 5-year period. This statistic conveys different information than the 26% increase in relative risk imparted by HRT. For this reason, the Endocrine Society Scientific Statement recommends that interpretation of the WHI and observational studies should assess excess rather than relative risk.

DECREASE IN HRT AND DECLINE OF BREAST CANCER INCIDENCE

Following the dramatic decrease in HRT use after 2002, several studies, primarily from Western countries, reported a decrease in breast cancer incidence and generally concluded this to be a cause-and-effect relationship. The first report from Ravdin and colleagues¹⁶ reported a 6.7% fall in breast cancer incidence from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database. The decrease was observed in women over 50 years of age. Between 2001 and 2004, the decrease in estrogen receptor (ER)-positive breast cancers was 11.8% in women between the ages of 50 and 69 years. Comparing the decrease in HRT use and the decline in ER + breast cancers, the authors concluded that the main variation to explain the decrease in breast cancer incidence was the decline in HRT use. From the same registry, other groups reported, however, that the decline in breast cancer preceded the WHI publications. Jemal and colleagues observed that the decrease started in 1999 and involved ER- as well as ER + tumors¹⁷. Li and Daling¹⁸, using data from 13 cancer registries that participated in the SEER database, reported a decrease of the same magnitude as in the previous paper (3–4%/year). However the decline could be detected as early as 1998 and was present for all types of invasive breast cancers before 2002. These data suggest that factors other than the drastic reduction in HRT prescriptions could account for this variation in incidence. As detailed below, other factors could also have influenced the variation in breast cancer incidence.

DECREASE IN MAMMOGRAPHIC SCREENING

A decline in compliance in mammographic screening of 3.2% was reported in women for 2003 by Radvin and colleagues¹⁶. Glass and colleagues¹⁹ reported a 4–5% decrease in compliance from the Kaiser Permanente Northwest cohort in 2001–2004. In addition, a 10% decrease in ER- tumors was observed, suggesting the effect of screening or other unexplained factors. Moreover, in this cohort, as well as that observed by Jemal and colleagues¹⁷, the decrease occurred in 2000 before the WHI publication, with an additional reduction after 2002. These authors suggested the role of both screening and HRT reduction in the decline in breast cancer incidence. A decrease in screening adherence from women

stopping HRT is another possibility. This was reported by Caan and colleagues who showed that women who stop HRT were less willing to continue periodic screening²⁰. However, a change in the frequency of mammographic screening is not the sole explanation for the decline in breast cancer incidence. In the Breast Cancer Screening Detection Program in the USA, a decline in incidence was also observed in women who uniformly underwent serial mammographic screening²¹.

INITIATION OF SCREENING

In a screened population, incidence represents the number of women diagnosed with breast cancer and not the prevalence of tumors in the population. Implementation of national screening is followed by an initial increase in diagnosis of invasive and *in situ* carcinoma. After a certain lag-time, the screening is 'saturated' by the already diagnosed and treated breast cancers and the 'incidence' seems to decrease, as discussed in our previous paper²². In support of this effect, the incidence of *in situ* carcinoma remained stable through 2004 after a sharp increase before 1998/99¹⁸. From their data, Li and Daling¹⁸ concluded, 'The decline predates the publication of the WHI trial; this observation does not support the hypothesis that the marked decline in rates of HRT use is a major contributor to this trend. These trends can be attributable to saturation of mammography.'

CHANGE IN COMPOSITION OF HRT REGIMENS

Concurrently with the French cohort report of a lower risk of breast cancer with transdermal estrogen + progesterone or dydrogesterone²³, these regimens might have been used more commonly. Other reports from the E3N cohort and from an UK database showed no increase in the risk of venous thrombosis²⁴ and stroke with transdermal estradiol + progesterone/pregnane derivatives²⁵. A shift towards increasing use of transdermal estradiol + progesterone was recently reported in France and this could have influenced subsequent breast cancer incidence rates. A decrease of the proportion of treated women at any age²⁶ would also influence incidence. Initiation of HRT fell from 55.8% in two cohorts to 16.8% and the transdermal estrogen + progesterone combination represented 21.9% in the pre-WHI period and 43.6% in the post-WHI period²⁶. As discussed, however, transdermal estradiol is rarely used in the USA.

VARIATION AMONG COUNTRIES

Significant decreases in breast cancer rates were not observed in all of the European studies (UK, Norway, Sweden, Belgium)²⁷⁻²⁹. Similarly, in Canada, the decrease involved only women over 75 years of age and was not seen in younger

women, as reported by some authors^{22,30}. In contrast, a clear decrease was demonstrated by another study³¹, indicating that interpretations may differ even when using the same database. The example of Norway is important since it is a country where extremely accurate registries exist. Screening has been implemented since 1996 and a high rate and stability of participation have occurred. In Norway, HRT use has been extremely frequent, approximating to 50%. The stability of screening and the existence of the registry provide excellent means to better interpret the potential implication of risk factors in breast cancer incidence. In the publication from Zahl and Maehlen²⁷, an increase was apparent following the implementation of screening, but thereafter a decrease to an intermediate level not altered by the decrease in HRT use after 2002. A relative leveling off is now being observed (Figure 3)

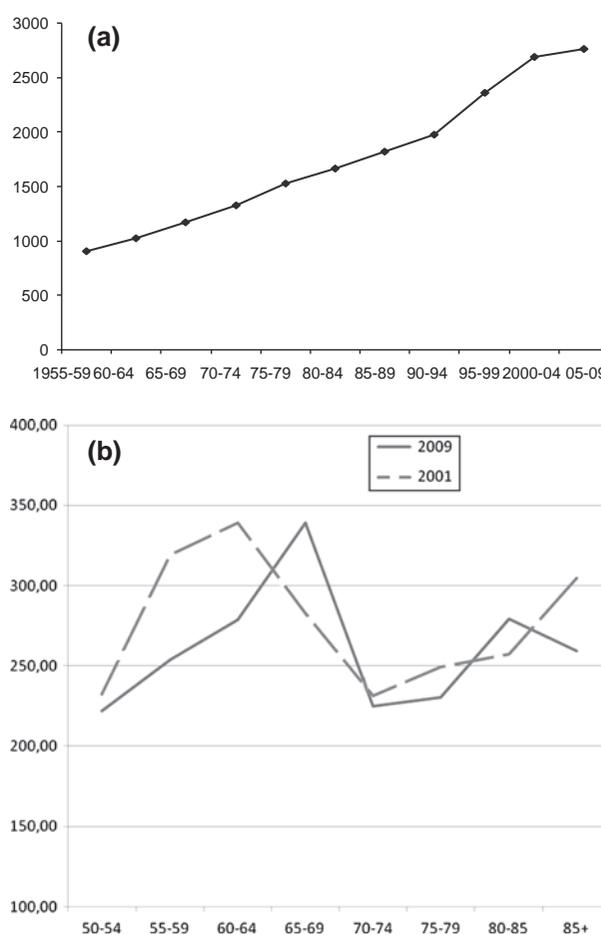


Figure 3 (a) Incidence of breast cancer in Norway between 1955 and 2009 by 5 years of age (<http://www.kreftregisteret.no/en/The-Registries/Cancer-Statistics>). (b) Incidence per 100 000 by age in Norway before the WHI (in 2001) and in 2009 (from <http://www-dep.iarc.fr/nordcan/>). Note the total of incidence per 100 000 women: 1094 in 2009 vs. 1173 in 2001 among the 50–69-year-old women (difference 79) and 1042 vs. 994 in the >69-year-old women (difference 48)

in pooled data from several cancer registries (<http://www.kreftregisteret.no/en/The-Registries/Cancer-Statistics/> and <http://www-dep.iarc.fr/nordcan/>). This may be due to saturation of screening or to a variation in breast cancer risk factors. As previously reported, the breast cancer incidence increased by 102% in women 50–69 years of age in Norway after 1990–2002³². In favor of the screening initiation hypothesis, the annual breast operation rate increased in Norway by 70% (hazard ratio 1.70, 95% CI 1.62–1.7) in 2005–2008 compared to a pre-screening period (1993–1995) as did the annual mastectomy rate ($\times 1.3$)³³. The increase in surgical procedures may have contributed to the fluctuation in breast cancer incidence by initially increasing the levels and decreasing them slightly in the following years by treating *in situ* carcinoma or sub-clinical tumors by mastectomies and/or radiotherapy. In theory, the dramatic decrease of HRT use should have been responsible for at least an 8% decrease in the incidence in Norway, as calculated from the attributable fraction of HRT among breast cancers²². From the cancer registries, a 5.8% decrease in the incidence of breast cancer can be calculated in Norway between 2001 and 2009 in women ≥ 50 years of age but also a 4.1% decrease in women < 50 years of age (from <http://www-dep.iarc.fr/nordcan/>). This could suggest that the decrease in use of HRT is counterbalanced by factors increasing the incidence. Alternatively, the role of HRT might be overestimated. It is extremely difficult to evaluate accurately the contribution of each factor to the overall incidence reported.

MODIFICATIONS OF NON-HRT RISK FACTORS

Alteration of factors other than HRT could also have influenced the incidence of breast cancer during the last 10 years. Alcohol usage is one of the factors that may explain a variation in breast cancer incidence in postmenopausal women. Alcohol consumption has decreased by 40% in France and Italy but remains almost stable in Norway (an increase was recorded but the level of consumption remains low) and increased by 89% in Denmark (Figure 4). The importance of alcohol has been known for many years and the increased risk is mostly observed for lobular breast cancers³⁴. A recent publication from the Nurses' Health Study shows that an intake of as low as three drinks/week is associated with a small relative risk of 1.15 (95% CI 1.06–1.24)³⁵. The most consistent measure is cumulative alcohol intake throughout adult life at any age. Certain reproductive factors have been extremely stable in France such as the mean age at first full-term pregnancy and number of live births. On the other hand, nulliparity has decreased by 50%. Opposite trends have been seen in Norway²². It should be noted that only limited components of the risk factors that can act to increase (or decrease) breast cancer incidence are known and the interaction between them poorly studied.

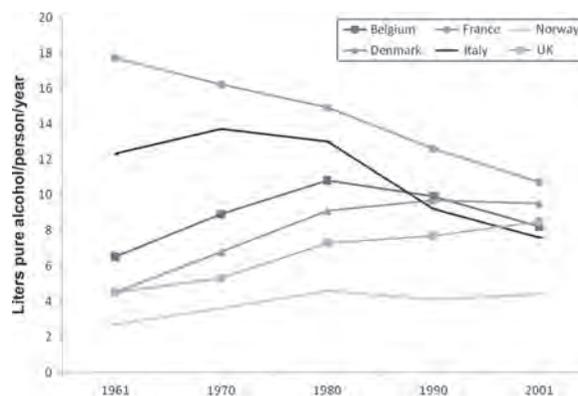


Figure 4 Variation in alcohol consumption in several European countries in the last 40 years. From World drink trends and IREB, 2003

RECENT INCREASE IN BREAST CANCER INCIDENCE

Three publications, two from the USA and one from Canada, report a decline in breast cancer incidence subsequently followed by an increase^{36,37}. In Canada, since 2005, an increase in the incidence rate in all age groups except for those aged 40–49 years was observed³⁸. In the USA using data from the SEER, an increase of 4.8% in the incidence of ER+ tumors in non-Hispanic white women aged 60–69 years was found, whereas the ER+ tumor incidence increased in the 40–49-year-old group³⁷. Interestingly, a parallel decline in women over 70 years and between 50 and 70 years was observed which had started before the summer of 2002³⁷. Another important publication, using five mammography registries within the National Cancer Institute-sponsored Breast Cancer Surveillance Consortium, also showed that, after an initial decrease of lobular and ductal breast cancers, the two types increased by +126% and +12%, respectively in 2006³⁶. These latter observations in women having mammographic screening could be explained by a transitory decrease of a short-term promoter effect of HRT. However, it could also be related to a decrease in screening adherence in this population. The figures are not equivalent in the other studies, where the increase involved only part of the population³⁷. In addition, the data from Norway do not show an increase but a leveling off in the incidence, probably due to the consequences of screening as discussed above.

CONCLUSIONS ABOUT THE DECLINE IN BREAST CANCER INCIDENCE

The fluctuation in the breast cancer rates from one country to another, the variation in mammography screening and the possible confounding risk factors, such as lifestyle, render it difficult to accurately relate the recent decrease in breast cancer incidence and HRT use. This issue has been controversial,

as noted from the discussion above. After assessing all of the evidence, a scientific panel convened by the Endocrine Society concluded that at least a component of the decrease was associated with a cessation of HRT use⁷.

IMPORTANCE OF LIFESTYLE RISK FACTORS

The observation of a possible decline of breast cancer incidence in postmenopausal women over recent years is important positive news. Our aim as clinicians is to help women to decrease their risk of breast cancer and to evaluate as accurately as possible the women in whom the benefits of HRT outweigh the associated risks. Several important studies have been published in the last 2 years that could help to reach this goal. Existing data suggest that HRT acts as a promoter of small, undiagnosed, pre-existing tumors. Accordingly, avoidance of HRT in women who already have transformed cells in their breasts would be beneficial. In those without pre-existing lesions, the benefits of HRT would exceed possible risks. Among risk factors for breast cancer, the most important are genetic alterations and inherited mutations. Women born with a haplo-insufficiency of certain genes have genetically unstable³⁹ breast tissue and are at markedly increased risk of developing breast cancer. A strong family history of breast cancer predicts a high level of risk. Use of HRT is contraindicated in these women except in conditions of prophylactic oophorectomy where HRT can be prescribed according to most of the international consensuses. After the age of 50 years, the climacteric symptoms have to be treated with alternatives in these patients.

Thoracic radiotherapy is also associated with an important relative risk of breast cancer. After a gap time of 20 years, women must be considered as high risk and thus HRT might not be the first choice in this population in case of climacteric symptoms.

Increased density has been shown for many years to be associated with an increased risk of breast cancer and appears to be genetically determined⁴⁰. Few studies have demonstrated that HRT can increase the risk in women with baseline high breast density. Indirect evidence came from the International Breast Cancer Intervention Study (IBIS), a randomized prevention trial of tamoxifen versus placebo. Women observed to have a reduction over 10% in their breast density experienced a 63% reduction in breast cancer risk⁴¹. This suggests that these breast tissues were sensitive to the stimulation of estradiol and this effect was reversed by its antagonist. From these observations, it appears likely that, among women with high breast density, some but not all could experience an increased risk of breast cancer with HRT. Kerlikowks and colleagues showed for the first time that, in women with low breast density, HRT does not increase the relative risk of breast cancer. Using a very large cohort of women participating in a screening program, they observed that high mammographic density was associated with a higher relative risk of breast cancer whether before menopause or after menopause, with or without HRT²¹.

Furthermore, estrogen alone and estrogen + progestogen both increased the incidence of breast cancer at a younger age than without HRT, further demonstrating the promoter effect of HRT in this context.

A recent publication from the WHI reported that mastalgia in association with HRT is a risk factor for breast cancer. In this study, women who experienced mastalgia in response to estrogen + progestogen had a hazard ratio of 1.48 (95% CI 1.08–2.03)⁴². This study found that the risk associated with mastalgia was equivalent in predictive strength to several factors utilized in the Gail index. This concept is in accordance with previous studies which reported an increased relative risk of breast cancer in women experiencing mastalgia^{43,44}. This symptom in association with HRT is a signal of breast intolerance to HRT and the need to decrease the amount of estrogen or to stop altogether. A relationship between increased breast density and mastalgia in association with HRT has also been reported by a small prospective study⁴⁵ as in the WHI⁴². These studies emphasize a clinical issue that was probably not sufficiently considered previously in the clinical evaluation of breast tolerance with use of HRT.

INCREASED RISK WITH ALCOHOL AND OBESITY

Indirect sources of estrogenic effects such as alcohol and obesity are conditions associated with an increased relative risk of breast cancer. The interaction between alcohol and obesity has not been fully studied. After breast cancer is diagnosed, alcohol can increase the risk of recurrence, particularly in obese women⁴⁶. Obesity is also a condition associated with the risk of postmenopausal breast cancer, both through endogenous production of estrogens by aromatization and by insulin resistance⁴⁷. The absence of a clear increase of risk in obese women with an exogenous administration of estrogens, such as in the WHI estrogen-only trial, could be due to their hepatic effect by decreasing the insulin resistance.

PROTECTIVE EFFECT OF PHYSICAL ACTIVITY

Physical activity has been shown in many populations to decrease breast cancer risk⁴⁸. However, the exact role of exercise in women with high risk remains controversial⁴⁸. Whereas some studies suggest that exercise carries a protective effect even in women with a family history⁴⁹, others do not observe such a beneficial effect⁵⁰. Using a predictive model, a new report suggests that alteration of some of the modifiable factors (alcohol consumption, physical activity, body mass index) may decrease the relative risk of breast cancer, especially in women at high risk such as a positive family history of breast cancer, and among women who accounted for the highest 10% of the total population risk⁵¹.

ALTERNATIVES TO HRT

Alternatives to HRT are necessary for some women experiencing climacteric symptoms in whom the risk of breast cancer or heart disease is substantial. For hot flushes, selective serotonin reuptake inhibitor and serotonin norepinephrine reuptake inhibitor agents provide significant relief but not to the degree induced by HRT. Similarly, gabapentin statistically significantly reduces hot flushes but very high doses are needed to achieve parity with HRT and side-effects of drowsiness are common. Bisphosphonates can be used to reduce bone resorption and reduce the incidence of osteoporosis and fractures. Low-dose vaginal estrogens are effective for urogenital atrophy but are associated with limited, but significant systemic absorption. Taken together, use of these agents is not as effective as HRT but can provide some relief of climacteric symptoms.

CONCLUSIONS

The impact of HRT on breast cancer risk remains relatively low but much emphasis has been placed on this issue in the

lay and scientific literature. Use of relative risk statistics overemphasizes the actual excess risks. Conversion of risk estimates to excess (attributable) risks over the time of expected usage provides a more accurate assessment of actual risk that might be expected by a woman taking HRT. An important consideration is that the excess risk of breast cancer from HRT increases with an increase in underlying risk. Accordingly, determination of risk should underlie the decision-making process when considering use of HRT. Those with a low underlying risk of breast cancer and substantial menopausal symptoms will experience benefits which well outweigh possible harm. However, studies are needed to prove this point and to enable a careful weighing of the scale of benefits versus risks. In the meantime, clinicians should evaluate benefit/risk ratios in each individual patient as a decision-making process.

Conflict of interest The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

Source of funding Nil.

References

1. WHI Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 2002;288:321–33
2. Stefanick ML, Anderson GL, Margolis KL, *et al.* Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA* 2006;295:1647–57
3. Karim R, Dell R, Greene D, Mack W, Gallagher J, Hodis H. Hip fracture in postmenopausal women after cessation of hormone therapy: results from a prospective study in a large health management organization. *Menopause* 2011;18:1172–7
4. Arnal J, Lenfant F, Flouriot G, *et al.* From in vivo gene targeting of oestrogen receptors to optimization of their modulation in menopause. *Br J Pharmacol* 2012;165:57–66
5. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997;350:1047–59
6. Santen RJ. Does menopausal hormone therapy initiate new breast cancers or promote the growth of existing ones? *Women's Health* 2008;4:207–10
7. Santen RJ, Allred DC, Ardoin SP, *et al.* Postmenopausal hormone therapy: an Endocrine Society Scientific Statement. *J Clin Endocrinol Metab* 2010;95(Suppl 1):s1–66
8. Foidart J-M, Desreux J, Pintiaux A, Gompel A. Hormone therapy and breast cancer risk. *Climacteric* 2007;10(Suppl 2):54–61
9. Chen WY, Manson JE, Hankinson SE, *et al.* Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Intern Med* 2006;166:1027–32
10. Bakken K, Fournier As, Lund E, *et al.* Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2011;128:144–56
11. Song R, Mor G, Naftolin F, *et al.* Effect of long-term estrogen deprivation on apoptotic responses of breast cancer cells to 17beta-estradiol. *J Natl Cancer Inst* 2001;93:1714–23
12. Ariazi E, Cunliffe HE, Lewis-Wambi J, *et al.* Estrogen induces apoptosis in estrogen deprivation-resistant breast cancer through stress responses as identified by global gene expression across time. *Proc Natl Acad Sci* 2011;108:18879–86
13. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat* 2008;107:103–11
14. Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int J Cancer* 2005;114:448–54
15. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estradiol-progestogen therapy. *Obstet Gynecol* 2009;113:65–73
16. Ravdin PM, Cronin KA, Howlander N, *et al.* The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med* 2007;356:1670–74
17. Jemal A, Ward E, Thun M. Recent trends in breast cancer incidence rates by age and tumor characteristics among U.S. women. *Breast Cancer Res* 2007;9:R28
18. Li CI, Daling JR. Changes in breast cancer incidence rates in the United States by histologic subtype and race/ethnicity, 1995 to 2004. *Cancer Epidemiol Biomarkers Prev* 2007;16:2773–80
19. Glass AG, Lacey JV, Carreon JD, Hoover RN. Breast cancer incidence, 1980–2006: combined roles of menopausal hormone

- therapy, screening mammography, and estrogen receptor status. *J Natl Cancer Inst* 2007;99:1152–61
20. Caan B, Habel L, Quesenberry C, Kushi L, Herrinton L. Re: Declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. *J Natl Cancer Inst* 2008;100:597–98
 21. Kerlikowske K, Cook AJ, Buist DSM, *et al.* Breast cancer risk by breast density, menopause, and postmenopausal hormone therapy use. *J Clin Oncol* 2010;28:3830–7
 22. Gompel A, Plu-Bureau G. Is the decrease in breast cancer incidence related to a decrease in postmenopausal hormone therapy? *Ann NY Acad Sci* 2010;1205:268–76
 23. Canonico M, Fournier A, Carcaillon L, *et al.* Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism. *Arterioscl Thromb Vasc Biol* 2010;30:340–5
 24. Renous C, Dell'aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. *J Thromb Haemost* 2010;8:979–86
 25. Renoux C, Dell'aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ* 2010;340:c2519
 26. Fournier A, Kernaleguen C, Panjo H, Clavel-Chapelon F, Ringa V. Postmenopausal hormone therapy initiation before and after the Women's Health Initiative in two French cohorts. *Menopause* 2011;18:219–23
 27. Zahl P-H, Maehlen J. A decline in breast-cancer incidence. *N Engl J Med* 2007;357:510–11
 28. Antoine C, Ameye L, Moreau M, Paesmans M, Rozenberg S. Evolution of breast cancer incidence in relation to hormone replacement therapy use in Belgium. *Climacteric* 2011;14:464–71
 29. Kumle M. Declining breast cancer incidence and decreased HRT use. *Lancet* 2008;372:608–10
 30. Kliewer E, Demers A, Nugent Z. A decline in breast-cancer incidence. *N Engl J Med* 2007;357:509–10
 31. Neutel CI, Morrison H. Could recent decreases in breast cancer incidence really be due to lower HRT use? Trends in attributable risk for modifiable breast cancer risk factors in Canadian women. *Can J Public Health* 2010;101:405–9
 32. Hery C, Ferlay J, Boniol M, Autier P. Quantification of changes in breast cancer incidence and mortality since 1990 in 35 countries with Caucasian-majority populations. *Ann Oncol* 2008;19:1187–94
 33. Suhrke P, MaehlenJan, Schlichting E, Jorgensen K, Gotzsche P, Zahl P. Effect of mammography screening on surgical treatment for breast cancer in Norway: comparative analysis of cancer registry data. *BMJ* 2011;343:d4692
 34. Li CI, Chlebowski RT, Freiberg M, *et al.* Alcohol consumption and risk of postmenopausal breast cancer by subtype: the Women's Health Initiative observational study. *J Natl Cancer Inst* 2010;102:1422–31
 35. Chen WY, Rosner B, Hankinson SE, Colditz GA, Willett WC. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. *JAMA* 2011;306:1884–90
 36. Farhat GN, Walker R, Buist DSM, Onega T, Kerlikowske K. Changes in invasive breast cancer and ductal carcinoma in situ rates in relation to the decline in hormone therapy use. *J Clin Oncol* 2010;28:5140–6
 37. DeSantis C, Howlader N, Cronin KA, Jemal A. Breast cancer incidence rates in U.S. women are no longer declining. *Cancer Epidemiol Biomarkers Prev* 2011;20:733–9
 38. Canada Public Health Agency 2009, Cancer Surveillance On-Line http://dsol-smed.phac-aspc.gc.ca/dsol-smed/cancer/index_e.html
 39. Rennstam K, Ringberg A, Cunliffe HE, Olsson H, Landberg G, Hedenfalk I. Genomic alterations in histopathologically normal breast tissue from BRCA1 mutation carriers may be caused by BRCA1 haploinsufficiency. *Genes Chromosom Cancer* 2010;49:78–90
 40. Boyd N, Martin L, Yaffe M, Minkin S. Mammographic density and breast cancer risk: current understanding and future prospects. *Breast Cancer Res* 2011;13:223
 41. Cuzick J, Warwick J, Pinney E, *et al.* Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. *J Natl Cancer Inst* 2011;103:744–52
 42. Crandall C, Aragaki A, Cauley J, *et al.* Breast tenderness and breast cancer risk in the estrogen plus progestin and estrogen-alone Women's Health Initiative clinical trials. *Breast Cancer Res Treat* 2012;132:275–85
 43. Plu-Bureau G, Thalabard JC, Sitruk-Ware R, Asselain B, Mauvais-Jarvis P. Cyclical mastalgia as a marker of breast cancer susceptibility: results of a case-control study among French women. *Br J Cancer* 1992;65:945–9
 44. Goodwin P, DeBoer G, Clark R, *et al.* Cyclical mastopathy and premenopausal breast cancer risk. Results of a case-control study. *Breast Cancer Res Treat* 1995;33:63–73
 45. McNicholas MM, Heneghan JP, Milner MH, Tunney T, Hourihane JB, MacErlaine DP. Pain and increased mammographic density in women receiving hormone replacement therapy: a prospective study. *Am J Roentgenol* 1994;163:311–15
 46. Kwan ML, Kushi LH, Weltzien E, *et al.* Alcohol consumption and breast cancer recurrence and survival among women with early-stage breast cancer: the Life After Cancer Epidemiology Study. *J Clin Oncol* 2010;28:4410–16
 47. Pichard C, Plu-Bureau G, Neves-e-Castro M, Gompel A. Insulin resistance, obesity and breast cancer risk. *Maturitas* 2008;60:19–30
 48. Friedenreich CM. The role of physical activity in breast cancer etiology. *Semin Oncol* 2010;37:297–302
 49. Tehard B, Friedenreich CM, Oppert J-M, Clavel-Chapelon F. Effect of physical activity on women at increased risk of breast cancer: results from the E3N cohort study. *Cancer Epidemiol Biomarkers Prev* 2006;15:57–64
 50. Friedenreich CM, Cust AE. Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects. *Br J Sports Med* 2008;42:636–47
 51. Petracchi E, Decarli A, Schairer C, *et al.* Risk factor modification and projections of absolute breast cancer risk. *J Natl Cancer Inst* 2011;103:1037–48
 52. Santen RJ. Endocrine-responsive cancer. In Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, eds. *Williams Textbook of Endocrinology*, 11th edn. Philadelphia: Saunders Elsevier, 2008: 1764

Colorectal cancer in women: hormone replacement therapy and chemoprevention

E. L. Barnes and M. D. Long

University of North Carolina at Chapel Hill, Department of Medicine, Division of Gastroenterology and Hepatology, Chapel Hill, NC, USA

Key words: HORMONE REPLACEMENT THERAPY, COLORECTAL CANCER, COLON CANCER, RECTAL CANCER, CHEMOPREVENTION

ABSTRACT

Colorectal cancer (CRC) accounts for 9.4% of new cancer diagnoses among women world-wide. CRC is the third leading cause of incident cancer among women in the United States and has immense impact on morbidity and mortality. We summarize data on CRC pathogenesis and risk in women. We also review the findings from the Women's Health Initiative (WHI) on CRC risk reduction associated with hormone replacement therapy (HRT) use. We then review observational studies since the WHI which evaluated HRT as a chemopreventive agent for CRC among women. The potential mechanisms behind the association between HRT use and CRC are also reviewed. We then discuss the requirements for implementation of chemopreventive agents, and why HRT should not be used for this indication given current knowledge. Further data on the risk–benefit profile of short-term HRT use are needed and will determine whether there is any future role for HRT use in the chemoprevention of CRC.

INTRODUCTION

Colorectal cancer (CRC) accounts for 9.4% of all new cancer diagnoses among women world-wide, second only to breast cancer. The age-standardized mortality rate for CRC in women is 14.6/100 000 world-wide¹. CRC is the third leading cause of new cancer and cancer death in the United States, with 70 480 incident cases and 24 790 deaths among women in 2010. Current Surveillance Epidemiology and End Results (SEER) data indicate an incidence rate for CRC of 41 per 100 000 and a death rate of 14.5 per 100 000 among women. However, when time trends in CRC are considered, there has been a reduction in both incidence and mortality rates of CRC in women from 1998 to 2008 and from 2001 to 2008, respectively². The noted decrease in CRC incidence rates from 1998 to 2006 has been attributed to increased efforts in CRC screening, with detection and subsequent removal of precancerous polyps³.

Given that the traditionally described pattern of transition from normal mucosa to a precursor lesion (adenomatous polyp) to overt cancer covers a span of approximately 10–20 years, there is an extended opportunity for intervention and thus cancer prevention⁴. Although screening programs have demonstrated an impact on decreasing mortality from CRC^{5–7},

there remains a substantial role for research into alternate and complementary strategies to reduce mortality from CRC⁸. One such strategy is chemoprevention. This strategy uses oral agents to prevent the development of precancerous polyps and thus their progression to CRC via this mechanism. There is a strong suggestion of the potential benefit of hormone replacement therapy (HRT) as a means of chemoprevention of CRC^{9–12}. However, there are specific requirements for chemoprevention that need to be considered prior to application of these therapies at a population-based level.

The aims of this review are (1) to describe CRC risk and pathogenesis, (2) to summarize the association between HRT use and CRC in women, (3) to evaluate potential mechanisms of CRC risk reduction by HRT, and (4) to discuss the applicability of HRT as a form of CRC chemoprevention in women.

COLORECTAL CANCER PATHOGENESIS

Women have a decreased incidence rate of CRC as compared to men (41 vs. 55 per 100 000) as well as a decreased mortality rate from CRC (14.5 vs. 20.7 per 100 000). Among women in the United States, the incidence rate is highest for African

Correspondence: Professor M. D. Long, Campus Box # 7080, University of North Carolina at Chapel Hill, Chapel Hill, NC27599-7080, USA

Americans (51.2 per 100 000), followed by Caucasians (40.2 per 100 000), American Indian/Alaska Natives (40.0 per 100 000), and Hispanics (28.4 per 100 000). The mortality rates associated with CRC follow a similar trend with respect to race². The reduced CRC incidence among women as compared to men argues for the possible protective effect of female hormones.

The traditional adenoma-to-carcinoma sequence remains central in the understanding of the pathogenesis of CRC for both men and women. This sequence is thought to account for the majority of CRCs. Adenomatous polyps are classified as tubular, villous, or tubulovillous, with tubular being the most common type (75–87%). The less common villous adenomas (5–10%) are typically sessile, with a ‘shaggy rug’ appearance and the tubulovillous polyps (8–15%) demonstrate a mix of the two subtypes previously described¹³. Using SEER data from 1988 to 2003, Wasif and colleagues described locations of malignant polyps and found these to be spread throughout the colon. Of the malignant polyps identified in 19 743 patients, 31% were in the ascending colon and cecum, 13% were in the transverse colon and flexures, and 54% were in the descending colon and sigmoid colon¹³. It is thought that this traditional adenoma-to-carcinoma pathway accounts for approximately 70% of CRCs diagnosed in the United States.

Our understanding of the pathogenesis of CRC has advanced in recent years, with the discovery of an alternate pathway to CRC: the ‘serrated pathway’. It is now recognized that hyperplastic or ‘serrated’ polyps are a heterogeneous group that includes premalignant lesions such as the sessile serrated adenoma (SSA)¹⁴. SSAs are associated with distinct genetic and epigenetic defects such as BRAF mutation and CpG island methylation (CIMP)^{14–17}. Several studies have shown that individuals with SSAs have an increased risk of synchronous lesions and CRC, possibly due to a ‘field cancerization’ effect^{18–22}. Serrated pathway cancers are thought to be responsible for 20–35% of CRC cases^{23,24}. The epidemiologies of these lesions differ, consisting of predominantly flat polyps, often on the right side of the colon. These lesions via the ‘serrated pathway’ may play a significant role in ongoing CRC risk.

These mechanisms of development of CRC in women, particularly the potential for an extended time period prior to progression of precursor lesions (whether these be adenomatous or serrated polyps), allow for interventions to prevent CRC. One potential effective intervention could be hormonal therapy among women.

HRT AND COLORECTAL CANCER: THE WHI

The principal results of the Women’s Health Initiative (WHI) were published in 2002. Although the WHI trial of estrogen plus progestin in postmenopausal women identified greater health risks than benefits among women in the exposure group, the use of estrogen plus progestin was associated with a significant decrease in incidence of CRC²⁵. According to intention-to-treat analysis, women in the hormone group had

fewer CRCs of all histologic types (48 vs. 74; hazard ratio (HR) 0.61; 95% confidence interval (CI) 0.42–0.87). When limited to invasive CRC, the effect was similar (HR 0.56; 95% CI 0.38–0.91). The invasive CRCs in the two groups were similar in location, tumor grade, and histologic features²⁵.

The reduction in the risk of CRC in the hormone group was in large part due to a decrease in the risk of local, rather than regional or metastatic disease. Within the category of regional or metastatic disease, those cancers in the hormone group were associated with a greater number of positive nodes than corresponding cancers in the placebo group. Total deaths were similar across groups, with nine deaths due to CRC in the hormone group and eight in the placebo group²⁵. As the women using estrogen plus progestin had fewer overall cancers, yet a greater number of cancers with a more advanced stage, it becomes difficult to explain these results on the basis of a single hormone effect²⁵.

When those with prior hysterectomy on conjugated equine estrogen (CEE)-containing HRT only were compared to those on placebo, there was no difference in incidence of invasive CRC (HR 1.12; 95% CI 0.77–1.63). Mortality outcomes for participants who were diagnosed with CRC were also compared, with cumulative mortality rate of 34% (20 out of 58) in the CEE group and 30% (16 out of 53) in the placebo group (HR 1.34; 95% CI 0.58–3.19)²⁶. Given these findings from the initial WHI data, there seems to be a suggestion that progestin may modify the influence of estrogen on CRC²⁶.

HRT AND COLORECTAL CANCER: BEYOND THE WHI

In the decade following publication of the initial results of the WHI, further studies have investigated the association between HRT and its effects on CRC. Newcomb and colleagues performed a case–control study involving 2066 women to evaluate the relationship between postmenopausal hormone use and CRC. A statistically significant reduction in CRC risk was demonstrated in current HRT users (odds ratio (OR) 0.8; 95% CI 0.6–0.9), with the most significant reduction in CRC risk in those patients who had used HRT for greater than 5 years²⁷. When HRT use was stratified by type of preparation, there was no clear association between estrogen use alone and CRC risk. However, women who were currently using estrogen plus progestin at the time of the study still demonstrated a 40% reduction in CRC risk (95% CI 0.5–0.9)²⁷. Among those women who had used estrogen plus progestin, there was no association between former use and risk of CRC, with benefit only being described in those women currently using estrogen plus progestin²⁷.

The California Teachers Study was a prospective cohort of 56 864 perimenopausal or postmenopausal women under the age of 80, with no previous history of CRC. Of the initial 56 864 women, nearly 76% reported ever using HRT. Those women with any HRT use demonstrated a 28% reduced risk of incident invasive CRC when compared to those without HRT use (relative risk (RR) 0.72; 95% CI 0.58–0.88). This

relative risk did not differ among users of estrogen-only therapy versus estrogen plus progestin therapy or mixed HRT use. On further evaluation, the greatest reduction in colon cancer risk was demonstrated in recent HRT users (RR 0.64; 95% CI 0.51–0.8)²⁸.

Johnson and colleagues evaluated the association between CRC risk and duration and recency of menopausal hormone formulations (unopposed estrogen versus estrogen plus progestin) among 56 733 postmenopausal women participating in the Breast Cancer Detection Demonstration Project²⁹. Among women reporting any use of HRT, there was a modest decrease in the risk of CRC (RR 0.91; 95% CI 0.8–1.04). Among those women using estrogen plus progestin, the greatest reduction in risk of CRC was demonstrated in those women who reported sequential estrogen plus progestin use (RR 0.64; 95% CI 0.43–0.95). The reduction in risk of CRC was most pronounced in those women with moderate use of estrogen plus progestin (2–5 years) compared to never users (RR 0.52; 95% CI 0.32–0.87)²⁹.

Using data from the Molecular Epidemiology of Colorectal Cancer study, Rennert and colleagues identified 2460 peri- or postmenopausal women among 2648 patients with CRC from northern Israel and 2566 controls³⁰. Self-reported use of HRT was associated with a significant reduction in risk of CRC (OR 0.67; 95% CI 0.51–0.89). This reduction in CRC risk remained significant after adjustment for age, sex, aspirin use, statin use, sports activity, family history of CRC, ethnic group, and level of vegetable consumption (OR 0.37; 95% CI 0.22–0.62).

Long and colleagues conducted a population-based, case-control study of incident distal large bowel cancer in North Carolina between 2000 and 2006³¹. In this study, 443 women with distal large bowel cancer were identified. These cases were compared to controls for HRT exposure, defined as ever use for at least 1 year. Ever use of HRT was associated with a reduced risk of distal large bowel cancer (OR 0.52; 95% CI 0.38–0.73). Increased duration of use was associated with further reduction in distal large bowel cancer incidence. ORs demonstrated continuous decrease with subsequent quartiles of HRT, with the highest quartile of use, ≥ 15 years, having an OR of 0.34 for incident distal large bowel cancer (95% CI 0.20–0.58 and p for trend < 0.001)³¹.

The summary results of these observational studies published since the WHI evaluating combined estrogen and progestin HRT use and reduction of CRC are shown in Table 1.

Table 1 Effect size estimates for reduction of colorectal cancer risk with estrogen and progestin-containing hormone replacement therapy in observational studies since the Women's Health Initiative

Author	Date	Effect estimate	95% confidence interval
Newcomb <i>et al.</i> ²⁷	2007	odds ratio 0.6	0.5–0.9
Delellis Henderson <i>et al.</i> ²⁸	2010	relative risk 0.64	0.51–0.8
Johnson <i>et al.</i> ²⁹	2009	relative risk 0.78	0.60–1.02
Rennert <i>et al.</i> ³⁰	2009	odds ratio 0.67	0.51–0.89
Long <i>et al.</i> ³¹	2010	odds ratio 0.52	0.38–0.72

Effect size estimates are comparable to that found in the WHI. While the study designs and descriptions of HRT use were not always uniform across studies (some allowed for self-report, some measured HRT use as ever/never and some measured only current use), markedly similar effect size estimates were found across studies. In general, there was a significant CRC risk reduction of approximately 40% associated with HRT use. Predominantly, increasing benefits for CRC risk reduction were seen in current and recent HRT users. Questions remain as to how long the CRC prevention benefits of HRT persist after discontinuation of these therapies.

In 2008, Heiss and colleagues published a report on health outcomes in the 3 years after intervention was stopped in the WHI, with evaluation of 15 370 women (of the initial 16 308 included in the initial WHI trial of estrogen plus progestin versus placebo)¹². In the post-intervention phase (mean 2.4 years of follow-up), the reduced risk of CRC previously demonstrated in the estrogen plus progestin group converged toward the null. Follow-up data of the WHI estrogen-alone trial was also performed to analyze health outcomes in those women randomized to treatment with CEE. In this study, the 7645 surviving participants from the original population of 10 739 US postmenopausal women were followed for a mean of 10.7 years. There was no demonstrated difference in CRC incidence between the women in the estrogen group and placebo group in the intervention or post-intervention periods³².

Whether changes in HRT prescription patterns will influence CRC incidence becomes an important topic as we advance beyond the WHI. In an analysis of hospital admissions, incidence, and mortality amongst women in England, Martin and colleagues evaluated the immediate impact on population health of the decrease in HRT use following the initial publication and recommendations of the WHI. In their review, little impact on subsequent population trends in rates of CRC was suggested by overall reductions in HRT prescriptions³³. Further information is needed to study the more long-term impact of these prescription pattern changes.

HRT AND COLORECTAL CANCER: MECHANISMS OF ACTION

The exact mechanism behind the association of postmenopausal exogenous hormone therapy and CRC remains unknown at this time. Several potential theories have been identified. Newcomb and colleagues performed a case-control study evaluating microsatellite instability (MSI) and risk of CRC in women using estrogen plus progestin. For women with MSI-low or MSI-stable tumors who were taking estrogen plus progestin HRT, there was a 40% reduction in CRC risk. Of note, no association was found with MSI-high tumors²⁷. Slattery and colleagues have demonstrated that estrogen exposure in women may protect against MSI, while the lack of estrogen in older women increases their risk of MSI³⁴. The biological mechanism of progestin's effect on the colon are unclear, but, given that the protective effects of HRT on CRC have only been demonstrated in combined HRT with estrogen

plus progestin, it is possible that progestin may be acting synergistically to amplify estrogen's effects on the colon³⁵. For example, the conversion of the less potent estrone to the more potent estradiol is catalyzed by the isozyme of 17 β -hydroxysteroid dehydrogenase, which is induced by progesterone³⁵. This could play a role in the efficacy of progestin-containing HRT in prevention of CRC.

Other possible mechanisms of the effect of postmenopausal hormone therapy on the risk of CRC include estrogen's influence on bile acid metabolism^{25,36} and alteration of insulin and insulin-like growth factor 1 (IGF-1)^{37,38}. Laboratory evidence has demonstrated that bile acids appear to cause proliferation and promote colon cancer development in rats. The favorable influence of hormones (endogenous and exogenous hormone preparations) on bile acid secretion may thus lead to reduced risk of CRC³⁵. IGF-1 acts as a potent mitogen and as an anti-apoptotic agent. Prior epidemiologic and *in vitro* laboratory studies have demonstrated that endogenous and exogenous estrogens reduce serum IGF-1^{39,40}, and the possibility exists that these reductions in IGF-1 concentration may play a role in the effects of hormones on CRC risks.

HRT AS CHEMOPREVENTION OF COLORECTAL CANCER

Chemoprevention is defined as the use of drugs or natural compounds to prevent the development of benign or malignant tumors. As CRC is a prevalent disease that is associated with considerable morbidity and mortality, CRC is a disease suitable for chemopreventive interventions. Additionally, the main avenue of CRC development has a natural history of transition from precursor to malignant lesion spanning years to decades. This provides a window where chemopreventive medications could have an effect^{4,8}. In order to study compounds as potential chemopreventive agents, there must be experimental or epidemiological data showing chemopreventive efficacy, safety on chronic administration, and a mechanistic rationale for the chemopreventive activity observed. Of utmost importance is that the agent must promote no harm within the population, as it is being used in healthy individuals. Table 2 describes the necessary components of an ideal chemopreventive agent.

Many other agents have been studied for their chemopreventive effects in CRC, including non-steroidal anti-inflammatory drugs, aspirin, cyclooxygenase-2 inhibitors and supplements such as calcium and folate. While each of these agents appeared promising in epidemiologic and observational studies, a protective effect was not always demonstrated in randomized, controlled trials, often with discovery of harms to the population treated. For example, rofecoxib was studied in a colorectal adenoma chemoprevention trial and was found to be associated with increased cardiovascular risks (RR for thrombotic event 0.92; 95% CI 1.19–3.11)⁴¹. The results of this trial contributed to rofecoxib's removal from the market and it is not used for chemopreventive indications today.

While HRT yielded a statistically significant benefit for development of CRC in the WHI, there are potential harms,

Table 2 Components for an ideal chemopreventive agent

- | |
|--|
| <ul style="list-style-type: none"> • Proven efficacy in controlled trials • Convenient dosing schedule • Safety with chronic administration • Minimal side-effects • Known mechanism of action • Inexpensive |
|--|

including risks of cardiovascular disease and breast cancer, discovered with these medications in women. If the goal of the medication is chemoprevention in a healthy population, the medication must first do no harm. The balance of risks and benefits does not make HRT, or any other currently available chemopreventive agent for CRC, suitable for primary prevention in the general population. Instead, use of chemopreventive agents for CRC prevention should only be considered in groups with a specific increased risk of CRC, where the benefits of therapy may outweigh the risks. These at-risk groups might include those with a prior CRC, those with familial syndromes, and those with advanced adenomas.

NEED FOR FUTURE INVESTIGATION

Prescriptions for HRT have significantly decreased in the United States and Great Britain in the years following the publication of the initial results of the WHI^{42–44}. Although the WHI recommended against prolonged estrogen plus progestin given the poor risk–benefit profile⁴⁵, some populations of women have continued to use HRT for short-term perimenopausal symptom control^{46,47}. What effect these changes on prescribing patterns of HRT have on CRC risk remains to be seen at this time.

While there seems to be a potential protective effect of HRT for the development of CRC, this protective effect is associated with current and ongoing use of these medications. As the risk–benefit ratio of long-term use of HRT may not be appropriate, it will be important to investigate the effects of short-term HRT use on CRC incidence. It will be interesting to see whether future studies investigating both earlier use of HRT, and/or more short-term use of HRT, will demonstrate the same reduction in CRC risk seen in the WHI and other studies. The post-intervention results reported in the WHI follow-up study have already revealed a trend toward the null with respect to the reduced risk of CRC¹², suggesting that short-term therapy may not have long-lasting effects on CRC incidence. The ongoing short-term, early-intervention HRT studies, Kronos Early Estrogen Prevention Study (KEEPS) and Early Versus Late Intervention Trial with Estradiol (ELITE), while powered primarily to assess atherosclerosis endpoints, will be important to assess the impact of early HRT exposure on a multitude of outcomes, including CRC.

As we move forward in the 21st century, we will leave behind the lessons learned from the WHI, apply the concept of weighing the risks and benefits of chemopreventive agents for CRC, and determine the best course for prevention of

CRC in women. Definitely, this course of prevention will contain a central component of a CRC screening program. Ongoing support for CRC screening programs in women will be needed in order to continue to impact (and reduce) the incidence of CRC. Additionally, reduction of known modifiable risk factors for CRC in women should be emphasized. Women should reduce their red meat intake, exercise, quit smoking, and control their weight. There may be a future role

for hormonally mediated chemopreventive agents in the future, although, as of yet, this is not the case.

Conflict of interest The authors have no conflicts of interest to disclose. The authors alone are responsible for the content and writing of this paper.

Source of funding Nil.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893–917
2. SEER cancer statistics review, 1973–2007. National Cancer Institute
3. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010;60:277–300
4. Half E, Arber N. Colon cancer: preventive agents and the present status of chemoprevention. *Expert Opin Pharmacother* 2009;10:211–19
5. Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med* 1992;326:653–7
6. Newcomb PA, Norfleet RG, Storer BE, Surawicz TS, Marcus PM. Screening sigmoidoscopy and colorectal cancer mortality. *J Natl Cancer Inst* 1992;84:1572–5
7. Edwards BK, Ward E, Kohler BA, et al. Annual report to the nation on the status of cancer, 1975–2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer* 2010;116:544–73
8. Janne PA, Mayer RJ. Chemoprevention of colorectal cancer. *N Engl J Med* 2000;342:1960–8
9. Purdue MP, Mink PJ, Hartge P, Huang WY, Buys S, Hayes RB. Hormone replacement therapy, reproductive history, and colorectal adenomas: data from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (United States). *Cancer Causes Control* 2005;16:965–73
10. Potter JD, Bostick RM, Grandits GA, et al. Hormone replacement therapy is associated with lower risk of adenomatous polyps of the large bowel: the Minnesota Cancer Prevention Research Unit Case-Control Study. *Cancer Epidemiol Biomarkers Prev* 1996;5:779–84
11. Peipins LA, Newman B, Sandler RS. Reproductive history, use of exogenous hormones, and risk of colorectal adenomas. *Cancer Epidemiol Biomarkers Prev* 1997;6:671–5
12. Heiss G, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008;299:1036–45
13. Wasif N, Etzioni D, Maggard MA, Tomlinson JS, Ko CY. Trends, patterns, and outcomes in the management of malignant colonic polyps in the general population of the United States. *Cancer* 2011;117:931–7
14. Huang CS, Farraye FA, Yang S, O'Brien MJ. The clinical significance of serrated polyps. *Am J Gastroenterol* 2011;106:229–40
15. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. *Gastroenterology* 2010;138:2088–100
16. Noffsinger AE, Hart J. Serrated adenoma: a distinct form of non-polypoid colorectal neoplasia? *Gastrointest Endosc Clin N Am* 2010;20:543–63
17. Snover DC, Jass JR, Fenoglio-Preiser C, Batts KP. Serrated polyps of the large intestine: a morphologic and molecular review of an evolving concept. *Am J Clin Pathol* 2005;124:380–91
18. Li D, Jin C, McCulloch C, et al. Association of large serrated polyps with synchronous advanced colorectal neoplasia. *Am J Gastroenterol* 2009;104:695–702
19. Lazarus R, Junttila OE, Karttunen TJ, Makinen MJ. The risk of metachronous neoplasia in patients with serrated adenoma. *Am J Clin Pathol* 2005;123:349–59
20. Hiraoka S, Kato J, Fujiki S, et al. The presence of large serrated polyps increases risk for colorectal cancer. *Gastroenterology* 2010;139:1503–10
21. Schreiner MA, Weiss DG, Lieberman DA. Proximal and large hyperplastic and nondysplastic serrated polyps detected by colonoscopy are associated with neoplasia. *Gastroenterology* 2010;139:1497–502
22. Pai RK, Hart J, Noffsinger AE. Sessile serrated adenomas strongly predispose to synchronous serrated polyps in non-syndromic patients. *Histopathology* 2010;56:581–8
23. Snover DC. Update on the serrated pathway to colorectal carcinoma. *Hum Pathol* 2011;42:1–10
24. Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. *Histopathology* 2007;50:113–30
25. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med* 2004;350:991–1004
26. Ritenbaugh C, Stanford JL, Wu L, et al. Conjugated equine estrogens and colorectal cancer incidence and survival: the Women's Health Initiative randomized clinical trial. *Cancer Epidemiol Biomarkers Prev* 2008;17:2609–18
27. Newcomb PA, Zheng Y, Chia VM, et al. Estrogen plus progestin use, microsatellite instability, and the risk of colorectal cancer in women. *Cancer Res* 2007;67:7534–9
28. DeLellis Henderson K, Duan L, Sullivan-Halley J, et al. Menopausal hormone therapy use and risk of invasive colon cancer: the California Teachers Study. *Am J Epidemiol* 2010;171:415–25
29. Johnson JR, Lacey JV Jr, Lazovich D, et al. Menopausal hormone therapy and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2009;18:196–203
30. Rennert G, Rennert HS, Pinchev M, Lavie O, Gruber SB. Use of hormone replacement therapy and the risk of colorectal cancer. *J Clin Oncol* 2009;27:4542–7
31. Long MD, Martin CE, Galanko JA, Sandler RS. Hormone replacement therapy, oral contraceptive use, and distal large bowel cancer: a population-based case-control study. *Am J Gastroenterol* 2010;105:1843–50
32. LaCroix AZ, Chlebowski RT, Manson JE, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal

- women with prior hysterectomy: a randomized controlled trial. *JAMA* 2011;305:1305–14
33. Martin RM, Wheeler BW, Metcalfe C, Gunnell D. What was the immediate impact on population health of the recent fall in hormone replacement therapy prescribing in England? Ecological study. *J Public Health (Oxf)* 2010;32:555–64
 34. Slattery ML, Potter JD, Curtin K, *et al.* Estrogens reduce and withdrawal of estrogens increase risk of microsatellite instability-positive colon cancer. *Cancer Res* 2001;61:126–30
 35. Newcomb PA, Pocobelli G, Chia V. Why hormones protect against large bowel cancer: old ideas, new evidence. *Adv Exp Med Biol* 2008;617:259–69
 36. McMichael AJ, Potter JD. Host factors in carcinogenesis: certain bile-acid metabolic profiles that selectively increase the risk of proximal colon cancer. *J Natl Cancer Inst* 1985;75:185–91
 37. Ma J, Pollak MN, Giovannucci E, *et al.* Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. *J Natl Cancer Inst* 1999;91:620–5
 38. Saydah SH, Platz EA, Rifai N, *et al.* Association of markers of insulin and glucose control with subsequent colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev* 2003;12:412–18
 39. Morimoto LM, Newcomb PA, White E, Bigler J, Potter JD. Variation in plasma insulin-like growth factor-1 and insulin-like growth factor binding protein-3: genetic factors. *Cancer Epidemiol Biomarkers Prev* 2005;14:1394–401
 40. Heald A, Selby PL, White A, Gibson JM. Progestins abrogate estrogen-induced changes in the insulin-like growth factor axis. *Am J Obstet Gynecol* 2000;183:593–600
 41. Bresalier RS, Sandler RS, Quan H, *et al.* Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092–102
 42. Hing E, Brett KM. Changes in US prescribing patterns of menopausal hormone therapy, 2001–2003. *Obstet Gynecol* 2006;108:33–40
 43. Mishra G, Kok H, Ecob R, Cooper R, Hardy R, Kuh D. Cessation of hormone replacement therapy after reports of adverse findings from randomized controlled trials: evidence from a British birth cohort. *Am J Public Health* 2006;96:1219–25
 44. Watson J, Wise L, Green J. Prescribing of hormone therapy for menopause, tibolone, and bisphosphonates in women in the UK between 1991 and 2005. *Eur J Clin Pharmacol* 2007;63:843–9
 45. Rossouw JE, Anderson GL, Prentice RL, *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33
 46. French LM, Smith MA, Holtrop JS, Holmes-Rovner M. Hormone therapy after the Women's Health Initiative: a qualitative study. *BMC Fam Pract* 2006;7:61
 47. Isaacs AJ, Drew SV, McPherson K. UK women doctors' use of hormone replacement therapy: 10-year follow-up. *Climacteric* 2005;8:154–61

Hormone therapy, dementia, and cognition: the Women's Health Initiative 10 years on

P. M. Maki and V. W. Henderson*

Departments of Psychiatry and Psychology, University of Illinois at Chicago, Chicago, Illinois; *Departments of Health Research & Policy (Epidemiology) and of Neurology & Neurological Sciences, Stanford University, Stanford, California, USA

Key words: ALZHEIMER'S DISEASE, COGNITION, DEMENTIA, ESTROGEN, HORMONE THERAPY, MEMORY, MENOPAUSE, PROGESTOGEN, REVIEW, SELECTIVE ESTROGEN RECEPTOR MODULATOR, WOMEN'S HEALTH INITIATIVE

ABSTRACT

Principal findings on dementia from the Women's Health Initiative Memory Study (WHIMS) showed that conjugated equine estrogens plus medroxyprogesterone acetate (CEE/MPA) increase dementia risk in women aged 65 years and above, but not risk of mild cognitive impairment. The dementia finding was unexpected, given consistent observational evidence that associates use of estrogen-containing hormone therapy with reduced risk of Alzheimer's disease. It remains controversial whether hormone use by younger postmenopausal women near the time of menopause reduces dementia risk or whether WHIMS findings should be generalized to younger women. Given the challenges of conducting a primary prevention trial to address that question, it is helpful to consider the impact of hormone therapy on cognitive test performance, particularly verbal memory, for its own sake and as a proxy for dementia risk. The WHI Study of Cognitive Aging (WHISCA) showed that CEE/MPA worsened verbal memory, whereas CEE alone had no influence on cognition. These findings have been replicated in several randomized, clinical trials. The apparent negative effect of CEE/MPA on verbal memory does not appear to be age-dependent. Additional investigations are needed to understand the impact of other hormonally active compounds on dementia and cognitive outcomes.

INTRODUCTION

Principal findings from the Women's Health Initiative (WHI) were published in 2002 and 2004^{1,2}. Subsequently, two ancillary studies, the Women's Health Initiative Memory Study (WHIMS) and the Women's Health Initiative Study of Cognitive Aging (WHISCA), provided important new information on cognitive aging and dementia. An intervention, such as hormone therapy, has the potential to affect cognition as well as dementia. Although mechanisms and effects might be similar in the two instances, they are not necessarily so. For this reason, the following discussion considers hormone effects on dementia risk and dementia symptoms separately from the effects on cognition and cognitive aging.

DEMENTIA

Cognitive skills change across the life span. *Dementia* refers to major cognitive impairment severe enough to affect

occupational, vocational, or social function. In most regions of the world, Alzheimer's disease is the most common cause of dementia^{3,4}. The burden of Alzheimer's disease falls heavily on women, and about twice as many women suffer from this disorder as men. This sex difference is due in large part to the fact that life expectancy is longer for women, and there are therefore more women in the oldest age group, where the risk of Alzheimer's disease is greatest. A second contributor is that women may survive longer than men after an initial diagnosis⁵. Some studies^{6,7}, but not all⁸, also suggest higher incidence rates for women.

Before the WHI

Apparent gender differences in Alzheimer incidence and prevalence, together with observations that women with Alzheimer's disease may have disproportionate difficulty with cognitive tasks viewed as female-advantaged^{9,10}, suggested a possible relation between sex hormones and Alzheimer's disease. Over

Correspondence: Professor P. M. Maki, Departments of Psychiatry and Psychology, University of Illinois at Chicago, Chicago, Illinois, USA

the past two decades, approximately two dozen observational studies have examined associations between a woman's use of estrogen-containing hormone therapy and her risk of developing Alzheimer's disease¹¹⁻¹⁴. Meta-analyses before the WHI linked hormone use to reductions in Alzheimer risk of nearly 40%^{15,16}. These clinical observations were supported by strong biological plausibility, including neurotrophic and neuroprotective effects of estrogens and effects of estradiol on metabolic and biochemical pathways implicated in Alzheimer's disease pathogenesis. There is clear laboratory evidence that brain effects may differ among progestogens (e.g. medroxyprogesterone acetate (MPA) compared to progesterone), among estrogens (e.g. conjugated equine estrogens (CEE) compared to estradiol), between an unopposed estrogen and an estrogen opposed by a progestogen, and between cyclic use of a progestogen compared to continuous use¹⁷⁻¹⁹. As we review below, randomized trials have informed our understanding of the cognitive effects of MPA, but our understanding of other progestins is limited. Physiological differences between oral and transdermal routes of administration might also be important, as might dosage, but we await results from ongoing clinical trials for a direct head-to-head comparison.

Treatment studies of women with dementia due to Alzheimer's disease provided conflicting data. Some observational evidence implied that women with Alzheimer's disease receiving hormone therapy had milder symptoms than women not using hormones²⁰⁻²². Relatively small clinical trials, however, generally failed to show consistent improvement in symptoms of women treated with estrogen compared to placebo^{23,24}.

Dementia and mild cognitive impairment in the WHI

The WHI included a large observational cohort and two parallel clinical trials. The trials were stratified by hysterectomy status and used a partial factorial design²⁵. There were three randomized interventions: low-fat diet, hormone therapy (CEE with or without MPA, depending on hysterectomy status), and calcium plus vitamin D dietary supplements²⁵. Participants in the dual trials were relatively healthy, community-dwelling, postmenopausal women aged 50-79 years at baseline (mean age 63 years).

The WHIMS ancillary study was conceptualized as a double-blind, controlled trial among women in the WHI hormone therapy trials who were at least 65 years of age. The objective was to determine the incidence of 'all-cause dementia' through a four-phase process that included annual cognitive screening. Women who scored below screening cut-points underwent neuropsychological testing and other diagnostic procedures. Mild cognitive impairment was a secondary outcome. WHIMS results were reported in 2003 and 2004^{26,27}. Women, recruited from 39 of 40 WHI centers, included 92% of those potentially eligible. Because the parent WHI trials had been halted prematurely^{18,19}, there were fewer incident cases of dementia than anticipated and consequently reduced power to address study objectives.

In both WHIMS trials combined, there were 108 cases of incident dementia. Exactly half were adjudicated as Alzheimer's disease, but results for Alzheimer's disease were not reported separately. Neither the estrogen + progestogen trial nor the estrogen-alone trial showed the expected reductions in the incidence of all-cause dementia. On the contrary, the dementia rate was increased in women allocated to active treatment. The hazard ratio was approximately doubled for women in the estrogen + progestogen group and increased by about half for women in the estrogen-alone group (Table 1). The difference was significant in the estrogen + progestogen trial but not in the estrogen-alone trial^{26,27}. The absolute risk represents about 12 additional cases of dementia for 1000 women using estrogen + progestogen for 5 years, and six additional cases per 1000 women using estrogen alone for 5 years^{26,27}.

Mild cognitive impairment was defined primarily on the basis of (a) poor performance (10th percentile or lower) on at least one neuropsychological test from an eight-test battery, (b) report of some functional impairment from a designated informant, and (c) absence of adjudicated dementia²⁷. These criteria are similar, but not identical, to other criteria for mild cognitive impairment^{28,29}. The incidence of mild cognitive impairment did not differ between treatment groups (Table 1). Not surprisingly, women who developed dementia were older and had relatively low cognitive performance at the start of the trial.

Dementia: the WHI 10 years on

Since these initial WHIMS trials^{26,27}, new research has explored mechanisms by which estrogens may have affected dementia outcomes and has helped clarify WHIMS inferences regarding dementia risk. Other hormonally active compounds may also be relevant to Alzheimer risk.

Structural brain imaging after WHIMS completion

At the conclusion of the WHIMS trials, an MRI brain imaging study was implemented at 14 WHIMS clinical centers. All former participants were eligible except those with specific contraindications to the procedure (e.g. cardiac pacemaker). A total of 1403 women provided structural MRI data, obtained on average 8 years after randomization and 3 years (estrogen + progestogen trial) or 1.4 years (estrogen-alone trial) after WHIMS ended³⁰. The primary outcome was ischemic lesion volume on structural brain images. Mean differences between women who had received on-trial hormone therapy and those who had received placebo were not significant. Secondary MRI outcomes included total and regional brain volumes assessed on T1 gradient echo images. Here, small but significant differences favored women originally assigned to placebo for frontal lobe volume (2.4 ml difference) and hippocampal volume (0.1 ml difference)³¹. Results were similar for CEE and CEE/MPA. One caveat is that fewer than half (49%) of WHIMS volunteers at participating clinical centers provided MRI data³², leading to

Table 1 Incident dementia and mild cognitive impairment in the Women's Health Initiative Memory Study (WHIMS) and the Multiple Outcomes of Raloxifene Evaluation trial (MORE)

Trial/clinical outcome	Number contributing to analysis	Active intervention	Mean follow-up	Number of events		Hazard ratio (95% confidence interval)
				Active group	Placebo group	
<i>WHIMS/all-cause dementia</i>						
Uterus ²⁶	4532	CEE + MPA	4.1 years	40	21	2.1 (1.2–3.5)
No uterus ²⁷	2947	CEE	5.2 years	28	19	1.5 (0.8–2.7)
Both combined ²⁷	7471	–		68	40	1.8 (1.2–2.6)
<i>WHIMS/mild cognitive impairment</i>						
Uterus ²⁶	4532	CEE + MPA	4.0 years	56	55	1.1 (0.7–1.6)
No uterus ²⁷	2947	CEE	5.1 years	76	58	1.3 (0.95–1.9)
Both combined ²⁷	7471			132	103	1.3 (0.97–1.6)
<i>MORE/all-cause dementia</i> ⁴²	3525	raloxifene*	3.0 years	17	18	0.9 (0.5–1.8)
<i>MORE/Alzheimer's disease</i> ⁴²				8	15	0.5 (0.2–1.2)
<i>MORE/mild cognitive impairment</i> ⁴²				44	63	0.7 (0.5–0.98)

CEE, conjugated equine estrogens, 0.625 mg/day; MPA, medroxyprogesterone acetate, 2.5 mg/day

*Raloxifene 120 mg/day; for standard dose raloxifene (60 mg/day), cognitive outcomes did not differ significantly from placebo (results not shown)

selection bias that undermined the validity of the original randomized design.

Follow-up analyses focused on 53 women with incident dementia or mild cognitive impairment³³. For women originally assigned to hormone therapy, cognitive impairment was significantly associated with smaller mean volumes for total brain (20.7 ml difference) and hippocampus (1.0 ml difference) compared to women without cognitive impairment. There was no difference in the volume of ischemic lesions. The interpretation of these results is not straightforward, as increased hippocampal volume is reported for younger postmenopausal women using hormone therapy³⁴ and smaller brain volumes were not observed for cognitively impaired women in the placebo groups³³. Study investigators concluded that cognitive impairment in women who received CEE is mediated through brain atrophy³³ and not through subclinical ischemic disease^{30,33}.

Critical window in relation to Alzheimer's disease risk

As recognized even before the WHIMS outcomes were reported³⁵, WHIMS results would not necessarily be applicable to hormone therapy prescribed to younger postmenopausal women. Women in this age group were ineligible for WHIMS. The critical window, or timing, hypothesis proposes that effects of exogenous estrogens on dementia risk are modified by a woman's age or temporal proximity to menopause. Thus, hormone use by younger postmenopausal women might reduce dementia risk, but later use might not. This hypothesis is supported by observational research that links hormone therapy use to reduced Alzheimer risk^{15,16}. Most observational

studies compared ever-users to never-users. Because most women who used hormone therapy did so for a limited time close to menopause³⁶, reported associations in these studies primarily reflected past hormone use by relatively younger women.

Several observational studies have specifically considered whether reported associations might vary according to past use versus current use or might vary by age. Shortly before WHIMS results were published, investigators from Cache County, Utah showed that past hormone therapy use was associated with a reduction in Alzheimer risk (hazard ratio (HR) 0.3, 95% confidence interval (CI) 0.2–0.7) but current use was not (HR 1.1, 95% CI 0.6–1.9)¹⁴. After WHIMS, findings from the Multi-Institutional Research in Alzheimer Genetic Epidemiology case-control study demonstrated for the first time a significant interaction between a woman's age and effects of hormone therapy on Alzheimer risk³⁷. When examined by age tertile, younger postmenopausal women (aged 50–63 years) who used hormone therapy were at reduced risk for Alzheimer's disease (odds ratio (OR) 0.35, 95% CI 0.2–0.7). For women in the two oldest tertiles, associations were not significant (ORs of 0.9, 95% CI 0.5–1.5 and 1.0, 95% CI 0.6–1.6)³⁷. Because use of hormone therapy by younger women was necessarily at a younger age closer to the time of menopause, one interpretation of the age interaction is that the results are consistent with the critical window hypothesis. Preliminary analyses of past hormone use by WHIMS participants³⁸ are congruent with Cache County results. Women reporting hormone use prior to the WHIMS trial – independent of the effects of on-trial treatment – were less likely to develop Alzheimer's disease during the WHIMS clinical trial (HR 0.35, 95% CI 0.2–0.9). This protective association contrasts with

deleterious effects of conjugated estrogens during the clinical trial itself (Table 1) but does not detract from the on-trial results²⁷. More recently, investigators from a large managed care organization in northern California examined dementia diagnoses in relation to hormone therapy during midlife and late life. The first assessment was based on self-reported current use, when the mean age was 49 years. The second, three decades later, was based on pharmacy records. Over 1500 women were diagnosed with dementia. Compared to women never on hormone therapy, those reporting hormone use only at midlife showed reduced risk (HR 0.7, 95% CI 0.6–0.9), whereas women receiving hormone therapy only in late life were at increased risk (HR 1.5, 95% CI 1.1–2.0)³⁹.

Together, these observational results are consistent with the critical window hypothesis as applied to Alzheimer's disease risk. Nevertheless, it remains controversial whether results from WHIMS for women aged 65 years and older generalize to younger postmenopausal women, or whether inferences from observational studies are valid in implying reduced Alzheimer risk for younger hormone users⁴⁰. A persistent concern is that observational findings could be flawed by unrecognized confounding, particularly by factors associated with better health and healthier lifestyle practices (the healthy user bias). If the increased relative risk of dementia for older women in WHIMS is generalized to women below age 60, where dementia incidence is rare⁴¹, the absolute risk of dementia would itself be rare, representing about one additional case of dementia among 1000 women using hormone therapy for 5 years.

Other compounds that interact with estrogen receptors

Other drugs with the ability to interact with estrogen receptors have the potential to affect dementia risk. Raloxifene, a non-steroidal selective estrogen receptor modulator (SERM), can be prescribed to postmenopausal women to treat and prevent osteoporosis and to reduce risk of invasive breast cancer in women with osteoporosis. Some brain effects differ from those of estradiol. In a multinational clinical trial of postmenopausal women (mean age 66 years) with osteoporosis⁴², high-dose raloxifene (120 mg/day) was associated with a trend toward lower risk of dementia or mild cognitive impairment compared to placebo (HR 0.7, 95% CI 0.5–1.01) (see Table 1).

Few data address dementia outcomes with other SERMs (tamoxifen, bazedoxifene, lasofoxifene, others), phytoestrogens such as soy isoflavones, which also act as SERMs, or tibolone, a progestogenic steroid characterized as a selective tissue estrogenic activity regulator and having multiple hormonal effects.

COGNITIVE AGING

Cognitive aging in the WHI

As an ancillary study to the WHI, WHISCA was the largest trial of the impact of hormone therapy on standardized tests

of memory and other cognitive functions⁴³. Results from 1416 participants (mean age 74 years) in the estrogen + progestogen arm were published in 2006⁴⁴, and results from 886 participants (mean age 74 years) in the estrogen-alone arm were published in 2009⁴⁵. One considerable limitation of WHISCA is that the cognitive outcomes were first measured 3 years after treatment randomization in the WHI. The trial therefore addressed change in cognitive performance from an on-treatment baseline. The primary outcomes in WHISCA were longitudinal changes in memory for word lists and geometric figures, respectively called verbal and figural memory.

Over 1.35 years of follow-up, verbal learning declined significantly in the active treatment versus placebo arm ($p = 0.009$), with trends for declines in short ($p = 0.016$) and long ($p = 0.015$) free delay recall⁴⁴. In contrast, results on the figural memory test showed a trend for improved performance over time ($p = 0.012$). Overall, these results suggested that the effects of estrogen + progestogen therapy depended on the type of memory tested. The finding that estrogen + progestogen treatment negatively impacted verbal memory replicated previous findings⁴⁶. These results are interesting in light of the finding that estrogen + progestogen also increased dementia risk in WHIMS²⁴ and that deficits in verbal memory are the earliest neuropsychological predictor of Alzheimer's disease^{47,48}.

Findings from the estrogen-alone arm of WHISCA contrasted with those from the estrogen + progestogen arm⁴⁵. After an average follow-up of 2.7 years, there were no significant differences or trends between groups on verbal or figural memory. Secondary analyses revealed worse performance in the estrogen group on a test of visuospatial abilities at the initial WHISCA assessment 3 years post-randomization. This difference did not remain significant over the duration of the study. Overall, these results indicated that estrogen alone did not have any enduring positive or negative impact on cognitive function in older women without a uterus.

Cognitive aging studies following the WHI

Several randomized trials published after WHIMS concluded that estrogen alone had no significant impact on cognitive function in older postmenopausal women. This finding was evident regardless of preparation and dose and included trials of ultra-low-dose transdermal estradiol (0.014 mg/day; $n = 417$)⁴⁹, oral estradiol (1 mg/day; $n = 460$)⁵⁰, oral estradiol (2 mg/day; $n = 115$)⁵¹, and low-dose transdermal estradiol (0.25 mg/day; $n = 57$)⁵². Whether estrogen alone affects memory in younger postmenopausal women is unclear. Small clinical trials in younger surgically menopausal women suggested benefits to verbal memory^{53,54}. Consistent with emerging evidence of possible benefits of estrogen to prefrontal functions⁵⁵, a placebo-controlled study of transdermal estradiol (0.05 mg/day) found benefits to certain outcomes of the California Verbal Learning Test that are sensitive to prefrontal outcomes, but not to verbal learning⁵⁶.

The Cognitive Complaints in Early Menopause Trial (COGENT) addressed the critical question⁵⁷ of whether the

deleterious effects of CEE/MPA on verbal memory might be due to the advanced age of the study participants. With a sample size of 180 women, COGENT represents the largest randomized, placebo-controlled trial of estrogen + progestogen in younger postmenopausal women aged 45–55 years of age. Based on a cognitive test battery similar to that in WHISCA, the primary finding of interest from COGENT was a trend toward a negative impact of estrogen + progestogen on short- and long-delay verbal memory ($p = 0.054$ and $p = 0.066$, respectively). These results indicated that the negative impact of CEE/MPA on memory is evident in younger postmenopausal women, and there appears to be no critical window for the impact of CEE/MPA on verbal memory. That finding was replicated in a randomized clinical trial of women with moderate to severe hot flushes who were randomized to 12 months of treatment with either CEE/MPA, black cohosh, red clover or placebo⁵⁸. In contrast to findings that CEE/MPA decreased memory in COGENT and WHISCA, a small clinical trial using CEE alone ($n = 7$) as the control group found that CEE/micronized progesterone ($n = 8$) decreased delayed verbal memory and improved working memory, but CEE/MPA ($n = 9$) had no effect on either measure.

The Kronos Early Estrogen Prevention Study (KEEPS) will address whether micronized progesterone and a lower dose of MPA affect memory. KEEPS is a multicenter, 5-year randomized, placebo-controlled clinical trial designed to evaluate the effectiveness of 0.45 mg of CEE, 50 µg weekly transdermal estradiol, each in combination with cyclic oral, micronized progesterone, 200 mg for 12 days each month on cardiovascular and cognitive outcomes in women aged 42–58 years who were within 36 months of their final menstrual period. Results are expected in 2012.

In light of findings of a decreased risk of mild cognitive impairment with 120 mg/day of raloxifene (Table 1), it is interesting to consider cognitive findings from randomized trials of raloxifene and other SERMs. Analysis of cognitive outcomes in the raloxifene/mild cognitive impairment study revealed a trend toward less decline with raloxifene on verbal memory and attention⁵⁹. Similarly, raloxifene (60 mg/day) significantly improved verbal memory over a 12-month period in a randomized, placebo-controlled trial involving 213 women aged 70 and older⁶⁰. Consistent with limited neuroimaging data^{61,62}, the finding that SERMs influence verbal memory suggests an estrogen-like action in the hippocampus. The relative effects of SERMs and CEE on cognition have not been directly compared in a head-to-head trial. Cognition in the Study of Tamoxifen and Raloxifene (Co-STAR) assessed cognitive outcomes with the same cognitive test battery used in WHISCA⁶³. The study included 1498 women aged 65 years and older who were randomly assigned to receive raloxifene (60 mg/day) or tamoxifen (20 mg/day). Findings revealed greater benefits with raloxifene compared to tamoxifen on one of four verbal memory measures, suggesting minimal cognitive differences between the two SERMs. One considerable limitation of Co-STAR was that, like WHISCA, the first assessment of cognitive outcomes began after randomization. Another limitation is the lack of a placebo arm. Similarities between the

Table 2 Key points: hormone therapy, dementia and cognition

- Estrogen + progestogen therapy initiated at age 65 or older increases dementia risk*
- Observational evidence, based largely on short-term use by younger women close to the time of menopause, associates hormone therapy with lower risk of Alzheimer's disease risk
- If increased risk from WHIMS is extrapolated to postmenopausal women aged 50–59 years, the absolute risk of dementia from standard-dose hormone therapy would be rare, representing about one additional case among 1000 women using hormone therapy for 5 years
- For healthy young and old postmenopausal women, standard-dose CEE/MPA therapy has a small, but significant adverse impact on verbal memory*
- For healthy older postmenopausal women, standard-dose estrogen therapy does not have a clinically important effect on cognition*

*, High quality of evidence based on consistent findings from well-performed randomized trials. Evidence for other key points is of lower quality

Co-STAR and WHISCA cohorts and methods provided an opportunity to compare the cognitive effects of the two SERMs, CEE and placebo⁶⁴. CEE and the SERMs produced deficits in global cognitive function, particularly among women with poor baseline cognitive function. This finding added to a growing body of evidence^{65,66} that estrogenic agents confer harm when given to women with poor baseline cognitive function and may suggest a healthy cell bias of estrogen⁶⁷.

SUMMARY

Although basic science studies indicate that the effects of hormone therapy on brain function might depend on use and type of progestogen, with the exception of MPA, the clinical relevance of these seemingly important differences remains to be established for dementia and for cognitive aging. Continued investigation of the potential cognitive benefit of SERMs is warranted given clinical trial data demonstrating reductions in mild cognitive impairment and improvements in verbal memory. Findings from clinical trials of cognitive outcomes will not answer long-term questions regarding the risk of Alzheimer's disease, and one cannot conclude from available evidence that hormone therapy should be prescribed at any age to reduce dementia risk. If the relative risk of dementia seen in WHIMS can be validly applied to midlife women who take hormone therapy for treatment of vasomotor symptoms, the absolute risk would be rare (Table 2).

Conflict of interest V. W. H. has no conflict of interest to declare. P. M. received consultant fees from Noven Pharmaceuticals for work unrelated to the content of this paper. The authors alone are responsible for the content and writing of the paper.

Source of funding P. M. was supported in part by NIH grant R01-MH083782-01A1. V. W. H. was supported in part by National Institutes of Health grant R01-AG023038.

References

1. Rossouw JE, Anderson GL, Prentice RL, *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33
2. Anderson GL, Limacher M, Assaf AR, *et al.* Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701–12
3. Plassman BL, Langa KM, Fisher GG, *et al.* Prevalence of dementia in the United States: the Aging, Demographics, and Memory Study. *Neuroepidemiology* 2007;29:125–32
4. Lobo A, Launer LJ, Fratiglioni L, *et al.* Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* 2000;54 (Suppl 5):S4–9
5. Larson EB, Shadlen MF, Wang L, *et al.* Survival after initial diagnosis of Alzheimer disease. *Ann Intern Med* 2004;140:501–9
6. Launer LJ, Andersen K, Dewey ME, *et al.* Rates and risk factors for dementia and Alzheimer disease: results from EURODEM pooled analyses. *Neurology* 1999;52:78–84
7. Plassman BL, Langa KM, McCammon RJ, *et al.* Incidence of dementia and cognitive impairment, not dementia in the United States. *Ann Neurol* 2011;70:418–26
8. Edland SD, Rocca WA, Petersen RC, Cha RH, Kokmen E. Dementia and Alzheimer disease incidence rates do not vary by sex in Rochester, Minn. *Arch Neurol* 2002;59:1589–93
9. Henderson VW, Buckwalter JG. Cognitive deficits of men and women with Alzheimer's disease. *Neurology* 1994;44:90–6
10. Ripich DN, Petrill SA, Whitehouse PJ, Ziol EW. Gender differences in language of AD patients: a longitudinal study. *Neurology* 1995;45:299–302
11. Tang M-X, Jacobs D, Stern Y, *et al.* Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet* 1996;348:429–32
12. Paganini-Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer's disease. *Arch Intern Med* 1996;156:2213–17
13. Kawas C, Gray S, Brookmeyer R, Fozard J, Zonderman A. Age-specific incidence rates of Alzheimer's disease: the Baltimore Longitudinal Study of Aging. *Neurology* 2000;54:2072–7
14. Zandi PP, Carlson MC, Plassman BL, *et al.* Hormone replacement therapy and incidence of Alzheimer's disease in older women: the Cache County study. *JAMA* 2002;288:2123–9
15. Hogervorst E, Williams J, Budge M, Riedel W, Jolles J. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. *Neuroscience* 2000;101:485–512
16. LeBlanc ES, Janowsky J, Chan BKS, Nelson HD. Hormone replacement therapy and cognition: systematic review and meta-analysis. *JAMA* 2001;285:1489–99
17. Liu L, Zhao L, She H, *et al.* Clinically relevant progestins regulate neurogenic and neuroprotective responses in vitro and in vivo. *Endocrinology* 2010;151:5782–94
18. Nilsen J, Deng J, Brinton RD. Impact of clinically relevant progestins on the neural effects of estradiol and the signaling pathways involved. *Drug News Perspect* 2005;18:545–53
19. Morrison JH, Brinton RD, Schmidt PJ, Gore AC. Estrogen, menopause, and the aging brain: how basic neuroscience can inform hormone therapy in women. *J Neurosci* 2006;26:10332–48
20. Henderson VW, Watt L, Buckwalter JG. Cognitive skills associated with estrogen replacement in women with Alzheimer's disease. *Psychoneuroendocrinology* 1996;21:421–30
21. Schneider LS, Farlow MR, Henderson VW, Pogoda JM. Effects of estrogen replacement therapy on response to tacrine in patients with Alzheimer's disease. *Neurology* 1996;46:1580–4
22. Doraiswamy PM, Bieber F, Kaiser L, Krishnan KR, Reuning-Scherer J, Gulanski B. The Alzheimer's disease assessment scale: patterns and predictors of baseline cognitive performance in multicenter Alzheimer's disease trials. *Neurology* 1997;48:1511–17
23. Henderson VW, Paganini-Hill A, Miller BL, *et al.* Estrogen for Alzheimer's disease in women: randomized, double-blind, placebo-controlled trial. *Neurology* 2000;54:295–301
24. Mulnard RA, Cotman CW, Kawas C, *et al.* Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. *JAMA* 2000;283:1007–15
25. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials* 1998;19:61–109
26. Shumaker SA, Legault C, Rapp SR, *et al.* Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study (WHIMS). *JAMA* 2003;289:2651–62
27. Shumaker SA, Legault C, Kuller L, *et al.* Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004;291:2947–58
28. Rapp SR, Legault C, Henderson VW, *et al.* Subtypes of mild cognitive impairment in older postmenopausal women: the Women's Health Initiative Memory Study. *Alzheimer Dis Assoc Disord* 2010;24:248–55
29. Gauthier S, Reisberg B, Zaudig M, *et al.* Mild cognitive impairment. *Lancet* 2006;367:1262–70
30. Coker LH, Hogan PE, Bryan NR, *et al.* Postmenopausal hormone therapy and subclinical cerebrovascular disease: the WHIMS-MRI Study. *Neurology* 2009;72:125–34
31. Resnick SM, Espeland MA, Jaramillo SA, *et al.* Postmenopausal hormone therapy and regional brain volumes: the WHIMS-MRI study. *Neurology* 2009;72:135–42
32. Jaramillo SA, Felton D, Andrews L, *et al.* Enrollment in a brain magnetic resonance study: results from the Women's Health Initiative Memory Study Magnetic Resonance Imaging Study (WHIMS-MRI). *Acad Radiol* 2007;14:603–12
33. Espeland MA, Tindle HA, Bushnell CA, *et al.* Brain volumes, cognitive impairment, and conjugated equine estrogens. *J Gerontol A Biol Sci Med Sci* 2009;64:1243–50
34. Lord C, Buss C, Lupien SJ, Pruessner JC. Hippocampal volumes are larger in postmenopausal women using estrogen therapy compared to past users, never users and men: a possible window of opportunity effect. *Neurobiol Aging* 2008;29:95–101
35. Resnick SM, Henderson VW. Hormone therapy and risk of Alzheimer disease: a critical time. *JAMA* 2002;288:2170–2
36. Brett KM, Chong Y. *Hormone Replacement Therapy: Knowledge and Use in the United States*. Hyattsville, MD: National Center for Health Statistics, 2001
37. Henderson VW, Benke KS, Green RC, Cupples LA, Farrer LA. Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age. *J Neurol Neurosurg Psychiatry* 2005;76:103–5
38. Henderson VW, Espeland MA, Hogan PE, *et al.* Prior use of hormone therapy and incident Alzheimer's disease in the Women's Health Initiative Memory Study. *Neurology* 2007;68(Suppl 1):A205 (abstract)
39. Whitmer RA, Quesenberry CP, Zhou J, Yaffe K. Timing of hormone therapy and dementia: the critical window theory revisited. *Ann Neurol* 2011;69:163–9

40. Henderson VW. Estrogen-containing hormone therapy and Alzheimer's disease risk: understanding discrepant inferences from observational and experimental research. *Neuroscience* 2006;138:1031–9
41. Rocca WA, Cha RH, Waring SC, Kokmen E. Incidence of dementia and Alzheimer's disease: a reanalysis of data from Rochester, Minnesota, 1975–1984. *Am J Epidemiol* 1998;148:51–62
42. Yaffe K, Krueger K, Cummings SR, *et al.* Effect of raloxifene on the prevention of dementia and cognitive impairment in older women: the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. *Am J Psychiatry* 2005;162:683–90
43. Resnick SM, Coker LH, Maki PM, Rapp SR, Espeland MA, Shumaker SA. The Women's Health Initiative Study of Cognitive Aging (WHISCA): a randomized clinical trial of the effects of hormone therapy on age-associated cognitive decline. *Clin Trials* 2004;1:440–50
44. Resnick SM, Maki PM, Rapp SR, *et al.* Effects of combination estrogen plus progestin hormone treatment on cognition and affect. *J Clin Endocrinol Metab* 2006;91:1802–10
45. Resnick SM, Espeland MA, An Y, *et al.* Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy. *J Clin Endocrinol Metab* 2009;94:4152–61
46. Grady D, Yaffe K, Kristof M, Lin F, Richards C, Barrett-Connor E. Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. *Am J Med* 2002;113:543–8
47. Linn RT, Wolf PA, Bachman DL, *et al.* The 'preclinical phase' of probable Alzheimer's disease. A 13-year prospective study of the Framingham cohort. *Arch Neurol* 1995;52:485–90
48. Tierney MC, Yao C, Kiss A, McDowell I. Neuropsychological tests accurately predict incident Alzheimer disease after 5 and 10 years. *Neurology* 2005;64:1853–9
49. Yaffe K, Vittinghoff E, Ensrud KE, *et al.* Effects of ultra-low-dose transdermal estradiol on cognition and health-related quality of life. *Arch Neurol* 2006;63:945–50
50. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. Estrogen therapy and risk of cognitive decline: results from the Women's Estrogen for Stroke Trial (WEST). *Am J Obstet Gynecol* 2005;192:387–93
51. Almeida OP, Lautenschlager NT, Vasikaran S, Leedman P, Gelaviv A, Flicker L. A 20-week randomized controlled trial of estradiol replacement therapy for women aged 70 years and older: effect on mood, cognition and quality of life. *Neurobiol Aging* 2006;27:141–9
52. Pefanco MA, Kenny AM, Kaplan RF, *et al.* The effect of 3-year treatment with 0.25 mg/day of micronized 17beta-estradiol on cognitive function in older postmenopausal women. *J Am Geriatr Soc* 2007;55:426–31
53. Sherwin BB. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. *Psychoneuroendocrinology* 1988;13:345–57
54. Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. *Psychoneuroendocrinology* 1992;17:485–95
55. Maki PM, Sundermann E. Hormone therapy and cognitive function. *Hum Reprod Update* 2009;15:874–86
56. Joffe H, Hall JE, Gruber S, *et al.* Estrogen therapy selectively enhances prefrontal cognitive processes: a randomized, double-blind, placebo-controlled study with functional magnetic resonance imaging in perimenopausal and recently postmenopausal women. *Menopause* 2006;13:411–22
57. Maki PM, Gast MJ, Vieweg AJ, Burriss SW, Yaffe K. Hormone therapy in menopausal women with cognitive complaints: a randomized, double-blind trial. *Neurology* 2007;69:1322–30
58. Maki PM, Rubin LH, Fornelli D, *et al.* Effects of botanicals and combined hormone therapy on cognition in postmenopausal women. *Menopause* 2009;16:1167–77
59. Yaffe K, Krueger K, Sarkar S, *et al.* Cognitive function in postmenopausal women treated with raloxifene. *N Engl J Med* 2001;344:1207–13
60. Jacobsen DE, Samson MM, Emmelot-Vonk MH, Verhaar HJ. Raloxifene improves verbal memory in late postmenopausal women: a randomized, double-blind, placebo-controlled trial. *Menopause* 2010;17:309–14
61. Neele SJ, Rombouts SA, Bierlaagh MA, Barkhof F, Scheltens P, Netelenbos JC. Raloxifene affects brain activation patterns in postmenopausal women during visual encoding. *J Clin Endocrinol Metab* 2001;86:1422–4
62. Goekoop R, Barkhof F, Duschek EJ, *et al.* Raloxifene treatment enhances brain activation during recognition of familiar items: a pharmacological fMRI study in healthy elderly males. *Neuropsychopharmacology* 2006;31:1508–18
63. Legault C, Maki PM, Resnick SM, *et al.* Effects of tamoxifen and raloxifene on memory and other cognitive abilities: cognition in the study of tamoxifen and raloxifene. *J Clin Oncol* 2009;27:5144–52
64. Espeland MA, Shumaker SA, Limacher M, *et al.* Relative effects of tamoxifen, raloxifene, and conjugated equine estrogens on cognition. *J Womens Health (Larchmt)* 2010;19:371–9
65. Espeland M, Rapp S, Shumaker S, *et al.* Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004;291:2959–68
66. Resnick SM, Espeland MA, Jaramillo SA, *et al.* Postmenopausal hormone therapy and regional brain volumes: the WHIMS-MRI Study. *Neurology* 2009;72:135–42
67. Brinton RD. Investigative models for determining hormone therapy-induced outcomes in brain: evidence in support of a healthy cell bias of estrogen action. *Ann NY Acad Sci* 2005;1052:57–74

The WHI: the effect of hormone replacement therapy on fracture prevention

T. J. de Villiers and J. C. Stevenson*

Mediclinic Panorama and Department of Gynaecology, University Stellenbosch, Cape Town, South Africa;

*National Heart & Lung Institute, Imperial College London, Royal Brompton Hospital, London, UK

Key words: WOMEN'S HEALTH INITIATIVE STUDY, HORMONE REPLACEMENT THERAPY, PREVENTION OF OSTEOPOROSIS-RELATED FRACTURES

ABSTRACT

The Women's Health Initiative (WHI) randomized, controlled trial was the first study to prove that hormone replacement therapy (HRT) reduces the incidence of all osteoporosis-related fractures in postmenopausal women, even those at low risk of fracture. The study authors concluded that the bone-friendly aspect of HRT was limited in clinical practice as possible adverse effects outweighed possible benefit. On the strength of these publications, regulatory authorities downgraded the use of HRT for the prevention of fracture to second-line therapy. This article examines the original and subsequent evidence presented by the WHI study and concludes that the restrictions placed on HRT as a bone-specific drug by regulatory bodies have not withstood the test of time and are not supported by the data of the WHI.

INTRODUCTION

Postmenopausal hormone therapy (HRT) with estrogen alone or combined with progestin, was for many years considered as first-line therapy in the prevention of postmenopausal bone loss and osteoporosis-related fractures. This practise was supported by observational data¹ as well as clinical trials showing benefit for bone mineral density (BMD)², although fracture endpoint data in a large randomized, controlled trial (RCT) was absent. The Women's Health Initiative (WHI) RCT of the risks and benefits of estrogen + progestin³ and estrogen alone⁴ in healthy postmenopausal women had, as the primary outcome, coronary heart disease (CHD). Secondary outcomes were invasive breast cancer, hip fracture, stroke, pulmonary embolism, colorectal cancer and death due to other causes. In 2002, the estrogen + progestin arm of the WHI was the first RCT with definitive data to prove the ability of HRT to prevent fractures at the hip, vertebrae and other sites. This was echoed by data from the estrogen-only arm in 2004. Unfortunately, both studies in their primary reports, as well as subsequent detailed reports, concluded that the benefit to bone of estrogen + progestin or estrogen therapy was outweighed by risk^{5,6}. Subsequently, regulatory bodies downgraded both estrogen + progestin and estrogen to second-line therapy in the prevention and treatment of osteoporotic fractures. It is

the aim of this article to examine the evidence leading to these conclusions and to see whether it has stood the test of time after 10 years.

THE ESTROGEN + PROGESTIN TRIAL

Participants ($n = 16\,608$) in the trial were asymptomatic postmenopausal women between the ages of 50 and 79 years (mean age 63 years) with an intact uterus. Participants were randomized to receive 0.625 mg conjugated equine estrogen (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo. Reports of hip, vertebral, and other osteoporotic fractures (including all fractures except those of the ribs, chest/sternum, skull/face, fingers, toes, and cervical vertebrae) were routinely recorded. All fracture outcomes were verified by radiology reports. Study radiographs were not obtained to ascertain subclinical vertebral fractures. The trial was prematurely terminated after 5.2 years of follow-up as the Data and Safety Monitoring Board concluded that the evidence for breast cancer harm had exceeded the predetermined stopping boundary. This was supported by a global index of health suggesting overall harm in the study.

Estimated hazard ratios (HRs) (nominal 95% confidence intervals (CIs)) for all endpoints were as follows: CHD,

Correspondence: Dr T. J. de Villiers, Room 118, Mediclinic Panorama, 1 Rothchilds Boulevard, Parow 7500, South Africa

1.29 (1.02–1.63) with 286 cases; breast cancer, 1.26 (1.00–1.59) with 290 cases; stroke, 1.41 (1.07–1.85) with 212 cases; pulmonary embolism, 2.13 (1.39–3.25) with 101 cases; colorectal cancer, 0.63 (0.43–0.92) with 112 cases; endometrial cancer, 0.83 (0.47–1.47) with 47 cases; hip fracture, 0.66 (0.45–0.98) with 106 cases; and death due to other causes, 0.92 (0.74–1.14) with 331 cases. Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09–1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90–1.17) for total cancer, 0.76 (0.69–0.85) for combined fractures, 0.98 (0.82–1.18) for total mortality, and 1.15 (1.03–1.28) for the global index. The global index was an attempt to summarize important aspects of health benefits vs. risk, but has never been validated as being reliable or clinically applicable⁷. This included earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes. The global index was originally proposed in December of 1996, modified in June of 1997, and again in April of 1998, after formal monitoring had begun, when vertebral fractures were removed from the specifically monitored outcomes of the global index⁸. Thus, the final global index only included hip fractures (no other fractures) and made no provision for measures of quality of life. Surprisingly, the global index was only finally approved after the first interim analysis of the data had been undertaken⁹.

The absolute excess risk of events included in the global index was 19 per 10 000 person-years. The authors concluded that the risk–benefit profile was not consistent with the requirements for a viable intervention for primary prevention of chronic diseases.

The initial report was followed up by a second report in 2003⁵. Although this report contained only adjudicated osteoporotic fracture events, the effect on previously reported fracture reduction was largely unchanged (HR 0.76; 95% CI 0.69–0.83).

BMD was measured by dual X-ray absorptiometry (DXA) in a subgroup ($n = 1024$) at baseline and years 1 and 3. In the subset of women with known BMD, at baseline the mean total hip BMD T -score was -0.94 and the mean spine BMD was -1.3 . In patients treated with estrogen + progestin after 3 years, the percentage difference in BMD compared to the BMD in those receiving placebo was 4.5% and 3.6% at the lumbar spine and total hip, respectively.

It was further reported that the effect of estrogen + progestin therapy did not differ in women stratified by age, body mass index, smoking status, history of falls, personal and family history of fracture, total calcium intake, past use of hormone therapy, BMD, or summary fracture risk score. The authors concluded that estrogen + progestin therapy increases BMD and reduces the risk of fracture in healthy postmenopausal women in all subgroups of women, but, when considering the effects of hormone therapy on other important disease outcomes as measured by the global index, there was no net benefit, even in women considered to be at high risk of fracture (HR 1.03; 95% CI 0.88–1.24).

THE ESTROGEN-ONLY TRIAL

The estrogen-only trial was similar in design to the estrogen + progestin arm, but recruited women with a prior hysterectomy ($n = 10 739$) and treatment was with CEE 0.625 mg or placebo. The trial was prematurely terminated after 6.8 years.

HRs for estrogen vs. placebo were reported as: CHD, 0.91 (0.75–1.12) with 376 cases; breast cancer, 0.77 (0.59–1.01) with 218 cases; stroke, 1.39 (1.10–1.77) with 276 cases; pulmonary embolism, 1.34 (0.87–2.06) with 85 cases; colorectal cancer, 1.08 (0.75–1.55) with 119 cases; and hip fracture, 0.61 (0.41–0.91) with 102 cases. Corresponding results for composite outcomes were: total cardiovascular disease, 1.12 (1.01–1.24); total cancer, 0.93 (0.81–1.07); total fractures, 0.70 (0.63–0.79); total mortality, 1.04 (0.88–1.22), and the global index, 1.01 (0.91–1.12). For the outcomes significantly affected by CEE, there was an absolute excess risk of 12 additional strokes per 10 000 person-years and an absolute risk reduction of six fewer hip fractures per 10 000 person-years. The estimated excess risk for all monitored events in the global index was a non-significant two events per 10 000 person-years.

A follow-up report in 2006 failed to differentiate the effect on hip fracture reduction according to risk stratification⁶. It concluded that application of the global index failed to show significant net benefit even amongst women at highest risk of fracture (HR 1.04; 95% CI 0.88–1.23).

DISCUSSION OF THE ORIGINAL WHI RESULTS

The WHI presented the first evidence based on a large RCT that HRT (estrogen + progestin and estrogen only) is effective in reducing the risk of osteoporotic fractures. This was a remarkable feat as the study subjects in both arms were at low risk of fracture (in the estrogen + progestin arm, the baseline total hip BMD T -score was -0.94 , mean spine BMD was -1.3 and only 14% had experienced a fracture after age 55 years). This is in sharp contrast to other fracture trials that generally only include patients at high risk of fracture (typically a BMD DXA T -score value of ≤ -2.5 or a prevalent fracture or both is needed for inclusion). Indeed, in the fracture intervention trial, alendronate was only effective at a T -score < -2.5 (patients had no previous fractures)¹⁰. Furthermore, in the WHI, fracture protection was consistent for all osteoporotic fractures measured and included hip, clinical vertebral and non-vertebral fractures. This was in contrast to the trials of raloxifene, which failed to show any non-vertebral fracture protection¹¹. Unlike all other modern fracture trials, the most common osteoporotic fracture, radiologically detected fractures (non-clinical fractures) were not captured in the WHI study. This is important as these fractures have been shown to be associated with increased morbidity and mortality and thus should have qualified for inclusion in the global index¹².

So then why was the use of estrogen and estrogen + progestin for the prevention and treatment of osteoporotic fractures not embraced after the WHI? It was simply a matter of solely relying on a single unvalidated instrument, the global index, to judge the safety of estrogen and estrogen + progestin therapy for the prevention of chronic diseases. It is highly questionable to judge a variety of conditions just on the numerical occurrence without weighing the significance of events. The inclusion of the prevention of non-clinical vertebral fractures as well as non-vertebral fractures would have changed the risk profile considerably. It is also questionable to conclude that a statistically significant benefit (prevention of osteoporotic fractures) can be offset by the pooling of a group of non-statistically significant side-effects.

Another limitation of the WHI was the relatively high rates of discontinuation in the active treatment arm (42%) and cross-over to active treatment in the placebo arm (10.7%). This may have underestimated the magnitude of the effect of treatment of bone.

DISCUSSION OF LATER WHI RESULTS

No later publications directly addressed the bone aspects of the WHI RCTs. Later publications indirectly affected the original conclusions regarding bone. The most important subsequent publications were the cardiovascular data stratified according to age or time since menopause, final adjudication of events and other publications drawing attention to the general confusion and lack of consistency in WHI reporting regarding the use of nominal risk vs. adjusted risk (all separately discussed in this issue). A 2011 publication on the health outcomes of patients after stopping the estrogen-only trial and followed up for a mean of 10.7 years showed that the beneficial effect on hip fracture was no longer present¹³. This was in line with some studies suggesting that the beneficial effect of estrogen on bone is lost after cessation of therapy, although this is not supported by other studies.

THE IMPLICATION OF OTHER STUDIES POST-WHI

The publication of the FRAX[®] integrated model of fracture risk analyses has identified a significant group of patients with low bone mass (osteopenia), but not with osteoporosis, at significant risk of fracture over the next 10 years, thus qualifying for bone-specific therapy. This poses a therapeutic dilemma, as only estrogen, estrogen + progestin and strontium ranelate have RCT-derived data to show efficacy under these circumstances. Alendronate has been shown not to be effective in this setting.

Possible side-effects of other bone-specific drugs have been highlighted in recent reports¹⁴. Alendronate specifically, but essentially all bisphosphonates, has been implicated in osteonecrosis of the jaw and atypical subtrochanteric femur fractures.

An association with severe atrial fibrillation has been documented and there are conflicting reports of an association with esophageal cancer. Raloxifene was found to significantly increase the risk of fatal stroke in patients at high risk of CHD. A warning was issued about the association between strontium ranelate and a potentially fatal drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.

THE POSITION OF HRT IN THE PREVENTION OF FRACTURE 10 YEARS AFTER WHI

The position of the regulatory authorities has remained fixed in downgrading estrogen and estrogen + progestin therapy to second-line therapy for the prevention of fractures, as originally decided after publication of the WHI results. Several authors have questioned this stance and have advocated for the re-establishment of HRT as one of the first-line options^{15,16}. The updated position statement of the International Menopause Society (IMS) endeavours to incorporate the earlier and later findings of the WHI¹⁷, a view largely shared by other national and international societies.

'The IMS believes that HRT is effective in preventing bone loss associated with the menopause and decreases the incidence of all osteoporosis-related fractures, including vertebral and hip fractures, even in women not at high risk of fracture. Based on evidence of effectiveness, cost and safety, HRT can be considered as one of the first-line therapies for the prevention and treatment of osteoporosis in postmenopausal women, younger than 60 years, with an increased risk of fracture. The initiation of HRT for the sole purpose of the prevention of fractures after the age of 60 years is not recommended. Continuation of HRT after the age of 60 years for the sole purpose of the prevention of fractures should take into account the possible long-term effects of the specific dose and method of administration of HRT, compared to other proven non-hormonal therapies. The protective effect of HRT on bone mineral density (BMD) declines after cessation of therapy at an unpredictable rate, although some degree of fracture protection may remain after cessation of HRT. If the patient is still considered at risk for fracture after cessation of HRT, additional therapy with proven bone-sparing medication should be given. Evidence of the fracture-protective effect of HRT is limited to standard dosages of conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA), given by the oral route. Evidence for protection against loss of BMD is available for lower than standard doses in oral (CEE and 17 β -estradiol) and transdermal (17 β -estradiol) administration.'

The obvious limitation of HRT for protection against fractures, when applying these guidelines, is the restriction on the initiation of HRT after the age of 60 years, as increasing age

is a strong risk factor for fracture. It is the opinion of the authors that this guideline is in order as a general principle, but that this restriction can be individualized, based on the later results of the WHI.

In summary, it is the opinion of the authors that the restrictions placed on HRT as a bone-specific drug by regulatory bodies have not withstood the test of time and are not supported by the data of the WHI.

Conflict of interest Dr De Villiers has acted as a consultant or speaker for the following companies: Amgen,

Bayer, MSD, Pfizer, Novartis and Servier. Dr Stevenson reports having received research grants from Eli Lilly, Janssen-Cilag, Novo Nordisk, Organon, Schering, Shire, Solvay, Wyeth, the Wellcome Trust and the UK Medical Research Council, and having served on Advisory Boards and/or received honoraria for lectures from Amgen, AstraZenica, Bayer-Schering, Novo Nordisk, Orion, Procter & Gamble, Servier, Solvay, Theramex and Pfizer/Wyeth.

Source of funding Nil.

References

- Weiss NS, Ure CL, Ballard JH, Williams AR, Daling JR. Decreased risk of fractures of the hip and lower forearm with postmenopausal use of estrogen. *N Engl J Med* 1980;303:1195-8
- Genant HK, Baylink DJ, Gallagher JC, Harris ST, Steiger P, Herber M. Effect of estrone sulfate on postmenopausal bone loss. *Obstet Gynecol* 1990;76:579-84
- Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33
- Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701-12
- Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA* 2003;290:1729-38
- Jackson RD, Wactawski-Wende J, LaCroix AZ, et al. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the Women's Health Initiative randomized trial. *J Bone Miner Res* 2006;21:817-28
- Freedman L, Anderson G, Kipnis V, et al. Approaches to monitoring the results of long-term disease prevention trials: examples from the Women's Health Initiative. *Controlled Clin Trials* 1996;17:509-25
- Freedman L, Anderson G, Kipnis V, et al. Guidelines for the statistical monitoring of the Women's Health Initiative clinical trial. *West J Med* 1998;168:236-40
- Anderson GL. WHI results withstand the test of time. *Br Med J* 2010; rapid response 12 March
- Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on the risk of fracture in women with low bone density but without vertebral fracture: results from Fracture Intervention Trial. *JAMA* 1998;280:2077-82
- Ettinger B, Black DM, Mitlak BH, et al. for the Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. *JAMA* 1999;282:637-45
- Kado DM, Browner WS, Palermo L, et al. Vertebral fractures and mortality in older women: a prospective study. Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 1998;159:1215-20
- LaCroix AZ, Chlebowski RT, Manson JE, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA* 2011;305:1305-14
- Stevenson JC. Prevention of osteoporosis; one step forward, two steps back. *Menopause Int* 2011;17:137-41
- Stevenson JC on behalf of the International Consensus Group on HRT and Regulatory Issues. HRT, osteoporosis and regulatory authorities. Quis custodiet ipsos custodes? *Hum Reprod* 2006;21:1668-71
- Studd J. Estrogens as first-choice therapy for osteoporosis prevention and treatment in women under 60. *Climacteric* 2009;12:206-9
- Pines A, Sturdee DW, Birkhäuser MH, et al. IMS updated recommendations on postmenopausal hormone therapy. *Climacteric* 2007;10:181-94

The use of hormone therapy for the maintenance of urogynecological and sexual health post WHI

R. E. Nappi and S. R. Davis*

Research Center for Reproductive Medicine, Department of Obstetrics and Gynecology, IRCCS S. Matteo Foundation, University of Pavia, Italy; *Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

Key words: HORMONE THERAPY, UROGYNECOLOGICAL HEALTH, SEXUAL HEALTH, WOMEN'S HEALTH INITIATIVE

ABSTRACT

Background The loss of estrogen at menopause and the gradual decline in testosterone with age are associated with urogenital atrophy and, as a result, urogenital tract symptoms, including lower urinary tract symptoms and dyspareunia. These symptoms will persist unless treated.

Objective To review the prevalence of urogenital tract symptoms and sexual health problems associated with menopause and the role in the use of hormone therapy for the treatment of symptomatic women, with a specific focus on what has been learned since the first publication of the Women's Health Initiative (WHI) estrogen and estrogen + progestin studies.

Conclusion Studies support the use of local estrogen therapy, but not systemic estrogen therapy, for the treatment of urge urinary incontinence, overactive bladder and to reduce the number of urinary tract infections. The current evidence does not favor a beneficial effect on stress urinary incontinence. Local estrogen therapy is effective for the treatment of dyspareunia caused by vulvovaginal atrophy. Preliminary studies suggest a potential role for both intravaginal dehydroepiandrosterone and testosterone in the treatment of dyspareunia secondary to vulvovaginal atrophy, however, confirmatory studies are required before either therapy can be recommended. Post WHI, there is a need for medical practitioners to proactively raise the topic of urogynecological and sexual health in order to discuss the most suitable treatment option.

INTRODUCTION

Urogynecological and sexual health are important issues throughout menopause and beyond. Approximately 50% of postmenopausal women will experience symptoms relating to urogenital atrophy, with subsequent impact on sexual function and quality of life¹. However, sexual retirement is not an inevitable consequence of the passage of time and a high proportion of women remain sexually active well into later life^{2,3}.

Despite the high prevalence and diversity of symptoms associated with urogenital atrophy, only around one-quarter of symptomatic women seek medical help. Women are often reluctant to consult their doctors about urogenital symptoms, due to embarrassment, cultural values, or acceptance of such

symptoms as an inevitable consequence of aging⁴. Moreover, attitudes and concerns about the use of systemic hormone replacement therapy (HRT) to relief climacteric symptoms and to prevent long-term consequences of hormonal deprivation have recently changed. Prescriptions for oral HRT in the United States declined after July 2002, following publication of the follow-up to the Heart and Estrogen/progestin Replacement Study (HERS II) and the preliminary results of the Women's Health Initiative (WHI)⁵. On the other hand, women are often not aware that local estrogen treatments may be effective in relieving symptoms related to urogenital aging⁴ and that a lack of testosterone might impact on sexual function⁶. The aim of the present short review article is to summarize the evidence available on the impact of HRT on urogynecological and sexual health post WHI.

Correspondence: Professor R. E. Nappi, Department of Obstetrics and Gynecology, IRCCS S. Matteo Foundation, Piazzale Golgi 2, 27100 Pavia, Italy

MENOPAUSE AND LOWER URINARY TRACT SYMPTOMS

Several urogenital complaints correlate with estrogen deprivation at the time of menopause, given the important hormonal influence not only on the genital and gynecologic structures but also on the lower urinary tract and pelvic floor structures⁷. While the impact of estrogen deficiency on genital function may result in vaginal dryness, itching, burning and dyspareunia, the impact on urinary function includes symptoms such as urinary frequency, urgency, nocturia, dysuria, incontinence and recurrent urinary tract infections^{8,9}. The prevalence of such symptoms may vary significantly according to many variables (age, menopausal stage, study design, country), i.e. the prevalence of urinary incontinence (UI) ranges from about 5% for severe to 60% for mild incontinence¹⁰. The mechanisms by which the decline in estrogen may significantly affect urogenital tissues have been elegantly reviewed elsewhere, as well as the potential role of estrogen therapy in the management of urogenital atrophy in postmenopausal women¹¹. The role of HRT in postmenopausal UI remains controversial because lower urinary tract symptoms have only been considered in secondary analyses of large epidemiological studies¹²⁻¹⁵. Recent longitudinal data indicate that annually measured values and year-to-year changes in endogenous estradiol levels are not associated with the development or worsening of incontinence in women during menopausal transition¹⁶. Indeed, menopausal stage has not been associated with developing more frequent incontinence (leaking several times per week or more), whereas worsening anxiety symptoms, weight gain and diabetes have been associated with developing more frequent incontinence¹⁷. These findings are in line with previous studies demonstrating that UI in middle-aged women is more closely associated with mechanical factors than with menopausal transition^{18,19}. The main risk factors for stress UI, the most common form of UI in women at midlife, are obesity and being parous¹⁹. Nonetheless, it is likely that urinary urgency, frequency, and urgency incontinence are symptoms of urogenital atrophy in older postmenopausal women²⁰.

HORMONES AND LOWER URINARY TRACT SYMPTOMS

Differences between systemic and local routes of administration have been outlined for estrogen treatment in the management of lower urinary tract symptoms²¹. In a subgroup *post-hoc* analysis of 1525 women who had at least one episode of incontinence weekly at baseline in the HERS study, Grady and colleagues¹⁵ found that daily HRT was associated with worsening of both stress UI and urge urinary incontinence. No difference in daytime frequency or nocturia was evident between groups. The increased risk was minor (incontinent episodes increased by 0.7 per week in the HRT group and decreased by 0.2 per week in the placebo group) and evident by 4 months of treatment, suggesting no protection of systemic HRT against incontinence. In addition, in those women

($n = 1208$) without loss of urine at baseline in the HERS study, weekly urge UI was reported by 48% of the HRT group and by 36% of the placebo group, while weekly stress UI was reported by 54% of the HRT group and by 38% of the placebo group, causing an excess risk of 12% for weekly urge UI and 16% for weekly stress UI during 4 years of treatment²².

In the subgroup *post-hoc* analysis of the observational Nurses' Health Study¹³, the risk of UI among women taking HRT was greater than that for women who had not taken any estrogen, both orally or transdermally, either alone or in association with a progestin. The risk was mild, with an annual incidence of 1.6% per year and disappeared after therapy discontinuation. An Australian community-based observational study reported an overall prevalence of UI of 42% in women and found no association between HRT use and UI risk for any UI, or stress UI, urge UI and mixed UI when age, weight, parity, hysterectomy and other clinical variables were taken into account¹⁹. Importantly, this study used validated questionnaires to assess UI. In the WHI estrogen + progestin randomized, controlled trial (RCT)¹⁴, incident UI, both stress UI and urge UI, was greater at 1 year among women taking HRT. The risk was highest for stress UI followed by mixed urinary incontinence, while HRT had no effect on developing urge UI, with an increased risk only with estrogen therapy. In addition, among women with incontinence at baseline, those taking HRT, either estrogen alone or in combination with a progestin, reported a greater frequency of incontinence episodes, increased volume of leakage and a greater impact on quality of life. These findings pointed out the need to reconsider the historic evidence suggesting a beneficial effect of estrogen on incontinence, and the most recent European guidelines, based on the 4th International Consultation on Incontinence (ICI), indicate that systemic estrogen, alone or in association with progestins, may not be recommended for treating stress UI or urge UI²³. As far as local estrogen use is concerned, the current evidence does not favor a beneficial effect on stress UI, but supports an improvement of urge UI and overactive bladder symptoms because these are symptoms of urogenital atrophy in older postmenopausal women²⁴. A 2008 Cochrane review²⁵ of the use of estrogen therapy for recurrent urinary tract infections in postmenopausal women did not support the use of systemic estrogen, but indicated that vaginal estrogen reduced the number of urinary tract infections.

SEXUAL FUNCTION AND LOWER URINARY TRACT SYMPTOMS

Stress UI and urge UI/overactive bladder have a negative impact on women's sexual life, not only as a consequence of the impairment of self-image, partner relationship and social activities but mostly because UI during sexual activity may occur, with a prevalence ranging from 10 to 56%²⁶. In spite of the evidence that 46% of a sample of women with lower urinary tract symptoms urodynamically evaluated had concomitant sexual dysfunction with a significant relationship

between stress UI and loss of libido, urge UI and anorgasmia, recurrent urinary tract infections and dyspareunia, the majority (74%) had not even been asked about their sexual life²⁷. At present, some evidence suggests an association between urinary leakage at penetration and USI and urinary leakage during orgasm and urge UI/overactive bladder²⁸. Therefore, it is mandatory to provide early intervention on the lower urinary tract in order to prevent sexual symptoms at menopause. Local estrogen treatment has proven efficacy in preventing urogenital aging and associated conditions⁷.

MENOPAUSE, HT AND SEXUAL FUNCTION

Sexual health has been defined by the World Health Organization (WHO) as 'a state of physical, emotional, mental and social well-being related to sexuality'²⁹. It is not merely the absence of disease, dysfunction or infirmity. Cross-cultural studies demonstrate that the vast majority of women consider sexual activity to be important to them³⁰. The Global Better Health Survey, which involved several Asian countries, reported that over 80% of women considered that physical foreplay, intercourse and the ability to achieve orgasm were each at least somewhat important to very important^{30,31}. Sexual problems in women adversely impact on self-esteem, quality of life, mood and relationships with sexual partners^{31,32}. In a cohort of US adult women, sexual dysfunction has strong positive associations with low feelings of physical and emotional satisfaction and low feelings of happiness³³. Davison and others found general psychological well-being to be inversely related to female sexual satisfaction in premenopausal and postmenopausal non-depressed women in the community who were not necessarily partnered, and who self-identified as being either sexually satisfied or dissatisfied³¹. Others have reported that sexual desire within a relationship is a key determinant of the quality of the non-sexual aspects of the relationship. Women reporting a discrepancy between their own and their partner's sexual desire have lower relationship satisfaction³⁴, and individuals in sexually inactive relationships report less marital happiness³⁵. Women who experience higher levels of physical pleasure in sex are significantly more likely to have higher levels of emotional satisfaction³⁵. These findings fit in well with the WHO statement defining human sexual health.

CHANGES ACROSS THE MENOPAUSE

The most common sexual difficulties reported by women at midlife include loss of sexual desire, inability to relax, dyspareunia, difficulty in becoming aroused and achieving orgasm and anorgasmia³⁶. The importance of sex to women does not appear to change much across the menopause³⁷. In contrast, across the menopause transition, sexual desire diminishes, with approximately 10–15% of perimenopausal women reporting no sexual desire³⁷. Less than 5% of perimenopausal women report never, or almost never, experiencing arousal³⁷.

Dyspareunia increases across the menopause. About 20% of perimenopausal women report occasional dyspareunia, with 5% experiencing this problem on most occasions³⁷. Women with vaginal dryness are more likely to experience dyspareunia, arousal difficulties, more frequent masturbation and less physical and emotional sexual satisfaction³⁷. An important observation of one large study is that, despite the reduction in desire and increase in sexual pain observed across the menopausal transition, the frequency of sexual activity does not seem to change³⁷. Davison and others reported that the frequency of sexual activity was slightly lower for postmenopausal women satisfied with their sexual function than for premenopausal women satisfied with their sexual function³⁸. However, the frequency of sexual activity did not differ between pre- and postmenopausal women dissatisfied with their sexual function, with each having on average five sexual events per month³⁸. Overall, this latter study found that women satisfied with their sexual life had higher frequencies of sexual thoughts, interest, events, and initiation of activity than dissatisfied women.

PREVALENCE OF SEXUAL PROBLEMS IN POSTMENOPAUSAL WOMEN

A recent cross-sectional study of American women has reported that the prevalence of sexual symptoms associated with distress (Female Sexual Distress score >15) amongst women aged 45–64 years is 12.3% for sexual desire, 7.5% for sexual arousal, 5.7% for orgasm and 14.8% overall³⁹. Asian studies suggest high rates of female sexual dysfunction in postmenopausal women. A Malaysian study has reported a prevalence of 30% amongst women with a mean age of 30 years⁴⁰, and a study of postmenopausal Thai women, mean age 56.8 years, revealed that only 14% occasionally reached orgasm and 86% never experienced orgasm after menopause⁴¹. In a survey conducted in six European countries, one-third (34%) of the postmenopausal women reported that they experienced a reduced sex drive⁴², whereas, in a clinical cohort of women between 45 and 59 years of age in South America, low sexual desire (40.5%) was the main reason for sexual inactivity⁴³.

NON-HORMONAL FACTORS THAT CONTRIBUTE TO SEXUAL FUNCTION PROBLEMS

Sexual difficulties at midlife appear to be more common amongst women who are more highly educated, in a significant relationship, experiencing poor personal health, have concurrent urinary incontinence, have depression, or who have a past history of sexual abuse³⁶. Sidi and others observed that sexual problems were more common amongst Malay women who were older, married more than 14 years, had intercourse less than one to two times a week, had more children, married to an older husband and had a higher academic

status⁴⁰. For postmenopausal participants in the WHI study of either estrogen + progestogen or estrogen only, the factors found to be associated with not being sexually active with a partner included low income, chronic health conditions, higher body mass index, use of antidepressants, hysterectomy, daily leakage of urine, and physical examination evidence of vulvovaginal atrophy⁴⁴. Domestic or employment stress may be a factor for some women. Personal illness, or illness of a partner or a change in a partner's sexual function, which may be diminished or enhanced by medication, may alter the dynamics and sexual functioning in a relationship. Poor body image and loss of self-esteem due to weight often contribute to a woman's reluctance to engage in sexual activity.

Impaired sexual function is a common feature of depression. Female sexual dysfunction is frequently reported by women using selective serotonin reuptake inhibitor (SSRI) therapy^{32,45}, the most commonly used antidepressants. SSRI-associated female sexual dysfunction most commonly presents as loss of libido, arousal difficulties or delayed orgasm/anorgasmia. The overall incidence of antidepressant-related female sexual dysfunction is in the order of 55%⁴⁵. Women who have undergone hysterectomy with preserved ovaries are not more likely to experience sexual difficulties; however, women who experience a surgical menopause are more likely to have sexual problems than naturally menopausal women. The WHI observational study attempted to capture correlates of sexual satisfaction among sexually active women aged 50–79 years. The investigators only included women who reported sexual activity with a partner of the preceding year⁴⁶. In this cohort, being older was associated with greater sexual satisfaction, and SSRI therapy was found to be significantly linked with sexual dissatisfaction⁴⁶. In the combined WHI HRT studies, at baseline 62% of partnered women and 42% of women without a partner reported being satisfied with their 'current sexual activity'⁴⁴. Of the women who were dissatisfied with their sexual activity at baseline, 57% indicated that they would have preferred more sexual activity, 8% preferred less⁴⁴. This study did not provide information about masturbation. Avis and co-workers looked at masturbation across the menopause. They found the frequency of masturbation to increase in the early perimenopause and decrease in the postmenopause, relative to the premenopausal years³⁷. This may be related to the increase in the vaginal pain during intercourse experienced by women in the perimenopausal years.

HORMONAL FACTORS THAT INFLUENCE SEXUAL FUNCTION AFTER MENOPAUSE

Hormones and vaginal atrophy

Vaginal atrophy is a consequence of postmenopausal estrogen insufficiency⁴⁷, but as estrogen levels are generally sustained until the final menstrual period, many perimenopausal women

remain unaffected. Vaginal atrophy can present as dryness, irritation, infection and dyspareunia⁴⁸. The Menopause Epidemiology Study in the US provides evidence of an association between vulvovaginal atrophy and overall female sexual dysfunction and its subtypes. Indeed, in a sample of sexually active postmenopausal women ($n = 1480$), the prevalence of vulvovaginal atrophy (57%) and female sexual dysfunction (55%) were high and women with female sexual dysfunction were 3.84 times more likely to have vulvovaginal atrophy than women without female sexual dysfunction (95% confidence interval 2.99–4.94)⁴⁹.

The WHI HRT studies were not undertaken to evaluate the effect of HRT on symptoms but rather on specific disease outcomes. In both WHI HRT trials, the prevalence of vulvovaginal atrophy at baseline was 69%⁴⁴. Overall, women with vulvovaginal atrophy diagnosed clinically were less likely to be sexually active; however, women who reported moderate to severe vaginal dryness were more likely to be sexually active⁴⁴, suggesting that most women need to be sexually active to be aware that they have vaginal atrophy symptoms.

In the WHI estrogen + progestogen study, at baseline, 3.9% of women aged 50–54 years reported vaginal itching and 10.8% reported vaginal dryness⁵⁰. Whereas systemic estrogen + progestogen did not significantly improve vaginal itching versus placebo, it significantly improved symptomatic vaginal dryness⁵⁰. Estrogen therapy restores normal vaginal pH levels and thickens and revascularizes the epithelium. Superficial cells are increased and symptoms of atrophy are alleviated⁵¹. Importantly, low-dose vaginal estrogen improves vaginal atrophy without causing significant proliferation of the endometrium or increase in serum estrogen levels beyond the normal postmenopausal range^{52–54}. Treatment for vaginal atrophy with intravaginal estrogen preparations, either estradiol or estriol, has been shown to be safe and effective in a number of randomized trials, as described in thorough reviews^{51,55}.

The use of androgens to treat vaginal atrophy has been recently explored in small RCTs. Testosterone and dehydroepiandrosterone (DHEA) are estrogen precursors that each provide local combined androgenic and estrogenic effects in the vagina when applied vaginally. Small short-term studies have shown that daily intravaginal application of either low-dose DHEA or testosterone improves objective and subjective measures of vaginal atrophy in women experiencing vaginal dryness and irritation^{56,57}. Further studies are required to verify the effectiveness of these therapies and whether efficacy persists if application is less frequent than daily.

Vaginal dryness in relation to sexual activity may occur in the setting of adequate vaginal estrogenization and be due to failure to be aroused and lubricate. In this setting, treatment with vaginal estrogen does not address the problem. Rather, treatment involves the assessment and management of sexual desire and arousal. Treatment of women in their late reproductive years and postmenopausal women with testosterone has been associated with increased arousal and vaginal lubrication and reduced dyspareunia⁵⁸.

Hormones and sexual desire, arousal and orgasm

In women, both estrogens and androgens are thought to contribute to sexual desire⁵⁹, with subsequent consequences for women during and after the menopause transition due to the significant decline in estradiol levels and with the decline in androgen levels related to aging⁶⁰. Arousal is believed to arise from central and peripheral (genital and non-genital) mechanisms⁶¹. Important elements include hormonal factors, genetic factors, neural factors and the specific influences of culture and context⁶². Hormonal influences in women are thought to be mainly mediated by estrogens and include priming of female sexual tissues, but also sensitizing of neural tissue⁶³. The relationships between steroid hormones and neurotransmitters which are pro-arousal, such as dopamine, norepinephrine, serotonin, histamine and acetylcholine, are pivotal^{62,64,65}. From animal studies, it has been postulated that there is a complex interplay between sex steroid hormones and endogenous and exogenous factors that bind to D1 dopamine, oxytocin, opioid, γ -aminobutyric acid and adrenergic receptors⁶⁶. This interaction involves the maintenance and preparation of sexually responsive tissues including genital tissues, with effects on blood flow and smooth muscle via the sympathetic and parasympathetic nervous system.

In the WHI HRT studies, sexual satisfaction was assessed by a single question, with four answer options: 'very unsatisfied', 'a little unsatisfied', 'somewhat satisfied' or 'very satisfied'. Scores ranged from 1 (worst) to 4 (best)⁶⁷. No significant effect of estrogen + progestogen or estrogen alone on sexual satisfaction was observed⁶⁸. However, this initial analysis was not limited to sexually active women but included all study participants aged 50–79 years at recruitment. Women in the WHI HRT studies were also asked if they were sexually active. Being sexually active at baseline not surprisingly predicted being sexually active in subsequent years of the studies⁴⁴. When an analysis limited to women adherent to therapy was undertaken, HRT use was associated with a higher rate of sexual activity by the 6th study year⁴⁴. However, as several studies have shown, frequency of sexual activity should not be considered to equate with sexual satisfaction or pleasure⁶⁹. In a community-based, observational study, postmenopausal HRT users have reported higher frequencies of sexual thoughts and sexual interest compared to non-users, which may be due to improvements in vaginal dryness but may also be due to estrogen acting centrally⁷⁰.

In contrast to the decline in estrogen following menopause, testosterone levels do not change abruptly across the menopause transition, but fall progressively with age from the mid-reproductive years⁶⁰. The use of tibolone, which exhibits estrogen, progestin and androgen effects, has been associated with improved sexual function⁷¹. An RCT of postmenopausal women demonstrated a greater effect of tibolone over transdermal estradiol–norethisterone therapy on sexual function, as evidenced by the Female Sexual Function Index (FSFI) score, over 24 weeks in the per protocol analysis⁷¹. In this study, tibolone was associated with a significant increase in responsiveness to partner-initiated sexual activity compared with

transdermal estradiol–norethisterone therapy⁷¹. The efficacy of systemic DHEA as a treatment for female sexual dysfunction in postmenopausal women has been investigated in a number of RCTs which have uniformly shown no benefit^{72–75}.

Testosterone, administered either orally as methyltestosterone or as a transdermal patch or gel has been shown to improve sexual function in postmenopausal women presenting with diminished sexual desire^{58,76,77}. Benefits have been seen for both naturally⁷⁸ and surgically⁷⁹ postmenopausal women and for estrogen users⁸⁰ and non-users⁸¹. The transdermal testosterone patch is available in EU countries for the treatment of surgically menopausal women with persistent low libido despite adequate estrogen therapy. A transdermal testosterone cream is available in Australia, with small studies showing efficacy in premenopausal and postmenopausal women^{82,83}. The cardiovascular and breast safety of transdermal testosterone is presently being investigated in a large longitudinal study being conducted in the US⁸⁴. Favorable findings from this study may pave the way towards the approval of transdermal testosterone therapy for women.

CONCLUSION

In summary, the menopause is associated with a reduction in sexual desire and arousal, an increase in dyspareunia, primarily due to vulvovaginal atrophy, but little change in the frequency of sexual activity or the importance of sexual well-being. Women who are not sexually active are unlikely to report vaginal dryness. Vaginal atrophy is effectively treated with local estrogen therapy and the role of intravaginal DHEA and testosterone for the treatment of vaginal atrophy continues to be investigated. Systemic HRT also alleviates vaginal atrophy, but appears to have little additional direct influence on desire, arousal or orgasm. Testosterone therapy has been shown to improve sexual desire, arousal, orgasm and sexual satisfaction and longer-term studies are underway evaluating the breast and cardiovascular safety of transdermal testosterone therapy.

We believe that post WHI there is more need for medical practitioners to proactively raise the topic of urogynecological and sexual health in order to help patients to understand that urogenital aging is a chronic condition resulting from long-term hormonal deprivation. A tailored approach to the variety of symptoms related to vaginal atrophy may be required, as well as a sensible discussion to select the most suitable treatment option for the individual woman.

Conflict of interest During the past 2 years, Professor Nappi had financial relationship (lecturer, member of advisory boards and/or consultant) with Bayer-Schering Pharma, Eli Lilly, Merck Sharpe & Dohme, Novo Nordisk, Pfizer Inc. Dr Davis is a consultant to Trimmel Pharmaceuticals, Warner Chilcott and BioSante Pharmaceuticals, Inc and has received research grant support from BioSante Pharmaceuticals, Inc. and Bayer-Schering Pharma.

Source of funding Nil.

References

- Sturdee DW, Panay N. Recommendations for the management of postmenopausal vaginal atrophy. *Climacteric* 2010;13:509–22
- Bachmann GA, Leiblum SR. Sexuality in sexagenarian women. *Maturitas* 1991;13:45
- Meston CM. Aging and sexuality. *West J Med* 1997;167:285–90.
- Nappi RE, Kokot-Kierepa M. Women's voices in the menopause: results from an international survey on vaginal atrophy. *Maturitas* 2010;67:233–8
- Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA* 2004;291:47–53
- Nappi RE, Lello S, Melis GB, Albani F, Polatti F, Genazzani AR. LEI (Lack of tEstosterone Impact) survey in a clinical sample with surgical menopause. *Climacteric* 2009;12:533–40
- Sturdee DW, Panay N. Recommendations for the management of postmenopausal vaginal atrophy. *Climacteric* 2010;13:509–22
- Barlow DH, Cardozo LD, Francis RM, et al. Urogenital ageing and its effect on sexual health in older British women. *BJOG* 1997;104:87–91
- Pastore LM, Carter RA, Hulka BS, Wells E. Self-reported urogenital symptoms in postmenopausal women: Women's Health Initiative. *Maturitas* 2004;49:292–303
- Sampselle CM, Harlow SD, Skurnick J, Brubaker L, Bondarenko I. Urinary incontinence predictors and life impact in ethnically diverse perimenopausal women. *Obstet Gynecol* 2002;100:1230–8
- Recommendations for estrogen and progestogen use in peri- and postmenopausal women: October 2004 position statement of the North American Menopause Society. Accessed at <http://www.menopause.org/edumaterials/2004HTreport.pdf>
- Cardozo L, Bachmann GA, McClish D, Fonda D, Birgerson L. Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: second Report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol* 1998;92:722–7
- Grodstein F, Lifford K, Resnick NM, Curhan GC. Postmenopausal hormone therapy and risk of developing urinary incontinence. *Obstet Gynecol* 2004;103:254–60
- Hendrix SL, Cochrane BB, Nygaard IE, et al. Effects of estrogen with and without progestin on urinary incontinence. *JAMA* 2005;293:935
- Grady D, Brown JS, Vittinghoff E, Applegate W, Varner E, Snyder T. Postmenopausal hormones and incontinence: the Heart and Estrogen/progestin Replacement Study. *Obstet Gynecol* 2001;97:116–20
- Waetjen LE, Johnson WO, Xing G, Feng WY, Greendale GA, Gold EB. Serum estradiol levels are not associated with urinary incontinence in midlife women transitioning through menopause. *Menopause* 2011;18:1283–90
- Waetjen LE, Ye J, Feng WY, et al. Association between menopausal transition stages and developing urinary incontinence. *Obstet Gynecol* 2009;114:989–98
- Sherburn M, Guthrie JR, Dudley EC, O'Connell HE, Dennerstein L. Is incontinence associated with menopause? *Obstet Gynecol* 2001;98:628–33
- Botlero R, Davis SR, Urquhart DM, Shortreed S, Bell RJ. Age-specific prevalence of, and factors associated with, different types of urinary incontinence in community-dwelling Australian women assessed with a validated questionnaire. *Maturitas* 2009;62:134–9
- Robinson D, Cardozo LD. The role of estrogens in female lower urinary tract dysfunction. *Urology* 2003;62:45–51
- Hillard T. The postmenopausal bladder. *Menopause Int* 2010;16:74–80
- Steinauer JE, Waetjen LE, Vittinghoff E, et al. Postmenopausal hormone therapy: does it cause incontinence? *Obstet Gynecol* 2005;106:940–5
- Thuroff JW, Abrams P, Andersson KE, et al. EAU guidelines on urinary incontinence. *Eur Urol* 2011;59:387–400
- Cardozo L, Lose G, McClish D, Versi E. A systematic review of the effects of estrogens for symptoms suggestive of overactive bladder. *Acta Obstet Gynecol Scand* 2004;83:892–7
- Perrotta C, Aznar M, Mejia R, Albert X, Ng CW. Estrogens for preventing recurrent urinary tract infection in postmenopausal women. *Cochrane Database Syst Rev* 2008:CD005131
- Shaw C. A systematic review of the literature on the prevalence of sexual impairment in women with urinary incontinence and the prevalence of urinary leakage during sexual activity. *Eur Urol* 2002;42:432–40
- Salonia A, Zanni G, Nappi RE, et al. Sexual dysfunction is common in women with lower urinary tract symptoms and urinary incontinence: results of a cross-sectional study. *Eur Urol* 2004;45:642–8
- Serati M, Salvatore S, Uccella S, Nappi RE, Bolis P. Female urinary incontinence during intercourse: a review on an understudied problem for women's sexuality. *J Sex Med* 2009;6:40–8
- World Health Organization. Sexual health. In *Health Topics*. Geneva: WHO, 2011
- Tan HM, Marumo K, Yang DY, Hwang TI, Ong ML. Sex among Asian men and women: the Global Better Sex Survey in Asia. *Int J Urol* 2009;16:507–14
- Davison SL, Bell RJ, La China M, Holden SL, Davis SR. The relationship between self-reported sexual satisfaction and general wellbeing in women. *J Sex Med* 2009;6:2690–7
- Williams VS, Baldwin DS, Hogue SL, Fehnel SE, Hollis KA, Edin HM. Estimating the prevalence and impact of antidepressant-induced sexual dysfunction in 2 European countries: a cross-sectional patient survey. *J Clin Psychiatry* 2006;67:204–10
- Laumann E, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999;281:531–44
- Davies S, Katz J, Jackson JL. Sexual desire discrepancies: effects on sexual and relationship satisfaction in heterosexual dating couples. *Arch Sex Behav* 1999;28:553–67
- Breznyak M, Whisman MA. Sexual desire and relationship functioning: the effects of marital satisfaction and power. *J Sex Marital Ther* 2004;30:199–217
- Addis IB, Van Den Eeden SK, Wassel-Fyr CL, Vittinghoff E, Brown JS, Thom DH. Sexual activity and function in middle-aged and older women. *Obstet Gynecol* 2006;107:755–64
- Avis NE, Brockwell S, Randolph JF Jr, et al. Longitudinal changes in sexual functioning as women transition through menopause: results from the Study of Women's Health Across the Nation. *Menopause* 2009;16:442–52
- Davison SL, Bell RJ, LaChina M, Holden SL, Davis SR. Sexual function in well women: stratification by sexual satisfaction, hormone use, and menopause status. *J Sex Med* 2008;5:1214–22
- Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress in United States women: prevalence and correlates. *Obstet Gynecol* 2008;112:970–8
- Sidi H, Puteh SE, Abdullah N, Midin M. The prevalence of sexual dysfunction and potential risk factors that may impair sexual function in Malaysian women. *J Sex Med* 2007;4:311–21

41. Tunghpaisal S, Chandeying V, Sutthijumroon S, Krisanapan O, Udomratn P. Postmenopausal sexuality in Thai women. *Asia-Oceania J Obstet Gynaecol* 1991;17:143–6
42. Nappi RE, Nijland EA. Women's perception of sexuality around the menopause: outcomes of a European telephone survey. *Eur J Obstet Gynecol Reprod Biol* 2008;137:10–16
43. Blumel JE, Castelo-Branco C, Cancelo MJ, Romero H, Aprikian D, Sarra S. Impairment of sexual activity in middle-aged women in Chile. *Menopause* 2004;11:78–81
44. Gass M, Cochrane BB, Larson JC, et al. Patterns and predictors of sexual activity among women in the hormone therapy trials of the Women's Health Initiative. *Menopause* 2011;18:1160–71
45. Montejo AL, Llorca G, Izquierdo JA, Rico-Villardemoros F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. *J Clin Psychiatry* 2001;62(Suppl 3):10–21
46. McCall-Hosenfeld JS, Jaramillo SA, Legault C, et al. Correlates of sexual satisfaction among sexually active postmenopausal women in the Women's Health Initiative observational study. *J Gen Intern Med* 2008;23:2000–9
47. Crandell C. Vaginal estrogen preparations: a review of safety and efficacy for vaginal atrophy. *J Womens Health (Larchmt)* 2002; 10:857
48. Bachmann GA, Nevadunsky NS. Diagnosis and treatment of atrophic vaginitis. *Am Fam Physician* 2000;61:3090–6
49. Levine KB, Williams RE, Hartmann KE. Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women. *Menopause* 2008;15:661–6
50. Barnabei VM, Cochrane BB, Aragaki AK, et al. Menopausal symptoms and treatment-related effects of estrogen and progesterin in the Women's Health Initiative. *Obstet Gynecol* 2005;105: 1063–73
51. The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of The North American Menopause Society. *Menopause* 2007;14: 355–69
52. Weisberg E, Ayton R, Darling G, et al. Endometrial and vaginal effects of low-dose estradiol delivered by vaginal ring or vaginal tablet. *Climacteric* 2005;8:83–92
53. Rioux JE, Devlin C, Gelfand MM, Steinberg WM, Hepburn DS. 17beta-estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis. *Menopause* 2000;7:156–61
54. Simon J, Nachtigall L, Ulrich LG, Eugster-Hausmann M, Gut R. Endometrial safety of ultra-low-dose estradiol vaginal tablets. *Obstet Gynecol* 2010;116:876–83
55. Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev* 2006:CD001500
56. Witherby S, Johnson J, Demers L, et al. Topical testosterone for breast cancer patients with vaginal atrophy related to aromatase inhibitors: a phase I/II study. *Oncologist* 2011;16:424–31
57. Labrie F, Archer D, Bouchard C, et al. Intravaginal dehydroepiandrosterone (Prasterone), a physiological and highly efficient treatment of vaginal atrophy. *Menopause* 2009;16:907–22
58. Somboonporn W, Davis S, Seif M, Bell R. Testosterone for peri- and postmenopausal women. *Cochrane Database Syst Rev* 2005, updated 2009:CD004509
59. Riley A, Riley E. Controlled studies on women presenting with sexual drive disorder. I. Endocrine status. *J Sex Marital Ther* 2000;26:269–83
60. Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. *J Clin Endocrinol Metab* 2005;90:3847–53
61. Levin RJ. Human male sexuality: appetite and arousal, desire and drive. In Legg C, Boott D, eds. *Human Appetite: Neural and Behavioural Bases*. New York: Oxford University Press, 1994: 127–64
62. Schober JM, Pfaff D. The neurophysiology of sexual arousal. *Best Pract Res Clin Endocrinol Metab* 2007;21:445–61
63. Pfaff D, Frohlich J, Morgan M. Hormonal and genetic influences on arousal – sexual and otherwise. *Trends Neurosci* 2002;25: 45–50
64. Kapp B, Cain M. The neural basis of arousal. In Smelser N, Baltes P, eds. *The International Encyclopedia of Social and Behavioral Sciences*. Oxford: Elsevier Science, 2001:1463–6
65. Lee AW, Pfaff DW. Hormone effects on specific and global brain functions. *J Physiol Sci* 2008;58:213–20
66. Giraldi A, Marson L, Nappi R, et al. Physiology of female sexual function: animal models. *J Sex Med* 2004;1:237–53
67. Hays J, Okene J, Brunner R, Kotchen J, Manson JE, Patterson R. Effects of estrogen plus progesterin on health-related quality of life. *N Engl J Med* 2003;348:1839–54
68. Brunner RL, Gass M, Aragaki A, et al. Effects of conjugated equine estrogen on health-related quality of life in postmenopausal women with hysterectomy: results from the Women's Health Initiative randomized clinical trial. *Arch Intern Med* 2005;165: 1976–86
69. Dennerstein L, Lehert P, Burger H. The relative effects of hormone and relationship factors on sexual function of women through the natural menopause transition. *Fertil Steril* 2005;84:174–80
70. Davison SL, Bell RJ, Lachina M, Holden SL, Davis SR. Sexual function in well women: stratification by sexual satisfaction, hormone use, and menopause status. *J Sex Med* 2008;5:2690–7
71. Nijland EA, Weijmar Schultz WC, Nathorst-Boos J, et al. Tibolone and transdermal E2/NETA for the treatment of female sexual dysfunction in naturally menopausal women: results of a randomized active-controlled trial. *J Sex Med* 2008;5:646–56
72. Panjari M, Bell RJ, Jane F, et al. A randomized trial of oral DHEA treatment for sexual function, well-being, and menopausal symptoms in postmenopausal women with low libido. *J Sex Med* 2009;6:2579–90
73. Kritz-Silverstein D, von Muhlen D, Laughlin GA, Bettencourt R. Effects of dehydroepiandrosterone supplementation on cognitive function and quality of life: the DHEA and Well-Ness (DAWN) Trial. *J Am Geriatr Soc* 2008;56:1292–8
74. Morales AJ, Nolan JJ, Nelson JC, Yen SS. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. *J Clin Endocrinol Metab* 1994;78:1360–7
75. Mortola JE, Yen SS. The effects of oral dehydroepiandrosterone on endocrine-metabolic parameters in postmenopausal women. *J Clin Endocrinol Metab* 1990;71:696–704
76. Lobo R, Rosen RC, Yang H-M, Block B, Van der Hoop R. Comparative effects of oral esterified estrogens with and without methyl testosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire. *Fertil Steril* 2003;79:1341–52
77. Warnock JK, Swanson SG, Borel RW, Zipfel LM, Brennan JJ. Combined esterified estrogens and methyltestosterone versus esterified estrogens alone in the treatment of loss of sexual interest in surgically menopausal women. *Menopause* 2005;12: 374–84
78. Panay N, Al-Azzawi F, Bouchard C, et al. Testosterone treatment of HSDD in naturally menopausal women: the ADORE study. *Climacteric* 2010;13:121–31
79. Simon J, Braunstein G, Nachtigall L, et al. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab* 2005;90:5226–33

80. Shifren J, Davis SR, Moreau M, *et al.* Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 study. *Menopause* 2006;13:770–9
81. Davis SR, Moreau M, Kroll R, *et al.* Testosterone for low libido in menopausal women not taking estrogen therapy. *N Engl J Med* 2008;359:2005–17
82. Goldstat R, Briganti E, Tran J, Wolfe R, Davis S. Transdermal testosterone improves mood, well being and sexual function in premenopausal women. *Menopause* 2003;10:390–8
83. El-Hage G, Eden JA, Manga RZ. A double-blind, randomized, placebo-controlled trial of the effect of testosterone cream on the sexual motivation of menopausal hysterectomized women with hypoactive sexual desire disorder. *Climacteric* 2007;10:335–43
84. Snabes MC, Berry SD, Berry DA, Zborowski JD, White WB. Low cardiovascular event rate in postmenopausal women with increased cardiac risk: initial findings from the ongoing blinded Libigel (testosterone gel) cardiovascular safety study. Presented at 92nd Annual Meeting of the Endocrine Society, San Diego, USA, 2010

Shock, terror and controversy: how the media reacted to the Women's Health Initiative

S. Brown

Freelance medical writer, Harrogate, UK

Key words: WOMEN'S HEALTH INITIATIVE, HORMONE REPLACEMENT THERAPY, MEDIA, PRESS

ABSTRACT

Results from the first publication of the Women's Health Initiative trial were announced by press release and press conference in July 2002. The announcement explained that the combined hormone trial had been terminated early because of 'increased breast cancer risk'. The dramatic nature of the announcement set the tone for the early news reporting from the study and introduced a note of confusion into the media's perception of hormone replacement therapy (HRT). Such a tone persisted until July 2007, when the trial revised its findings on cardiovascular risk. Despite investigators' protests to the contrary, the results were perceived by the press as a U-turn, and reinforced the media's confused interpretation of the safety and benefits of HRT. We argue that the WHI's melodramatic presentation of its results explains the media response.

INTRODUCTION

It is said that a medical journalist working on a prominent daily newspaper will receive around 50 story tips a day. They arrive by phone, by e-mail, by press release, by press conference, and even by word of mouth. Most will be non-starters; but even if two or three of these stories are actually written and filed, there is still no guarantee that they will find their way into print. All stories must compete for limited space.

But, when a press release from the *Journal of the American Medical Association (JAMA)* pinged into in-boxes during the first week of July 2002, there was every reason that this story would make it through the log-jam. The *JAMA* press release ('Hormone therapy study stopped due to increased breast cancer risk') was followed immediately by a similarly headlined release from the National Heart, Lung and Blood Institute (NHLBI) and a flurry of earnest statements from investigators saying that trial subjects had been told to stop their medication.

The *JAMA* announcement, which like the rest had carried an embargo for 08.30 US Central Time on Tuesday, 9th July 2002, recounted more than just salient facts and investigator comment. Reporters were also invited that day to a press conference in the ballroom of the National Press Club in Washington DC, where speakers would include no less than the director of the NHLBI and the acting director of the Women's Health Initiative (Figure 1). *JAMA* was also

planning to feed a video release of proceedings via Telstar satellite 6.

However, even without the press conference and the satellite feed, the Women's Health Initiative (WHI) had all the ingredients of a big story. Indeed, by the year's end, the international news agency Associated Press had dubbed it the 'top medical story of 2002', describing the fall-out – in the words of WHI investigator JoAnn Manson – as 'the most dramatic sea change in clinical medicine that I have ever seen'. And certainly, the story was bursting with drama, even in the very wording of that first press release: 'a major study . . . stopped because of health safety concerns . . . because of the importance of the researchers' findings . . . 16 608 menopausal women . . . stop prescribing estrogen plus progestin . . . treatment not beneficial overall.'

And to pile drama on drama, just one day after the press embargo was lifted – on Wednesday 10th July – the Committee on Safety of Medicines (CSM) in Britain issued new advice on the use of hormone replacement therapy (HRT), that it should not be used for the prevention of cardiovascular disease and that women who did use it 'should have a regular check-up'. A day later, the warning was repeated in Australia, and a week later the American Heart Association issued similar advice that physicians should avoid HRT for the prevention of cardiovascular disease. (An FDA statement was not issued until 13th August, noting a need to reassess risks and benefits.)

Correspondence: Dr S. Brown, Harrogate, UK

SPECIAL EMBARGO FOR RELEASE: 8:30 A.M. (CT) TUESDAY, JULY 9, 2002

News Conference

Hormone Therapy Study Stopped Due to Increased Breast Cancer Risk

When: 9:30am ET July 9, 2002

Where: Ballroom, National Press Club

529 - 14th Street, NW 13th floor

Washington, DC 20045

For More Information: Contact National Heart, Lung and Blood Institute at 301/496-4236.

EMBARGOED JAMA INFORMATION: 8:30 A.M. (CT) Tuesday, July 9, 2002

Media Advisory: To contact Jacques E. Rossouw, M.D., call the NHLBI Communications Office, 301/496-4236.

To contact Suzanne W. Fletcher, M.D., M.Sc., call Donna Burtanger at 617/432-3991.

Health Risks Outweigh Benefits for Combined Estrogen plus Progestin Clinical Trial Stopped Early in Major Study

CHICAGO -- Researchers have stopped the estrogen plus progestin portion of the Women's Health Initiative, a clinical trial designed to assess the major health benefits and risks of the most commonly used hormone preparation in the United States on healthy menopausal women, after overall health risks were found to exceed the health benefits, according to an article to be published in the July 17 issue of *The Journal of the American Medical Association (JAMA)*. The study is being released early on the JAMA website (www.jama.com) because of the importance of the researchers' findings.

Figure 1 The press announcement from *JAMA* – ‘Hormone Therapy Study Stopped Due to Increased Breast Cancer Risk’ – inviting reporters to a news conference at the National Press Club, Washington DC

PHASE 1: SHOCK AND TERROR

But by then the story was out, and for most of the press, as explicitly indicated in the headlines of the co-ordinated *JAMA/NHLBI* press releases, the story was indeed breast cancer – even though, as the published paper made clear, ‘the primary outcome for the trial [was] coronary heart disease’. The press release itself explained that ‘the trial was stopped because of apparent increased risks in invasive breast cancer, as well as coronary heart disease, stroke, and pulmonary embolisms in study participants’. So the story that journalists prepared for the mornings of 9th and 10th July when the embargo lifted was the increased risk of breast cancer caused by HRT. ‘HRT linked to breast cancer’, was the unambiguous BBC headline (Figure 2). Moreover, every ingredient for a big story was there – unexpected results (‘met with shock and disbelief’, according to the *New York Times*), inevitable public health implications, the makings of a health scare (‘Alarm over HRT cancer risk’, headlined the *Sydney Morning Herald*), and controversy by the bucket load. This indeed was 21st century news: shocking, terrifying and controversial.

Coverage, in both broadcast and print, was wall-to-wall, with the emphasis on risk and public health. To avoid any confusion over the statistical relative risks, the NHLBI press release (unlike *JAMA*’s) had helpfully expressed the hazard ratios in plain man’s language: ‘that during 1 year, among 10 000 postmenopausal women with a uterus who are taking estrogen plus progestin, eight more will have invasive breast cancer, seven more will have a heart attack . . . than

will a similar group of 10 000 women not taking these hormones’.

The NHLBI press release had also explained the emphasis on breast cancer – that, for the trial’s monitoring board, it was the breast cancer cases which had risen beyond an acceptable limit (even though the relative risk of breast cancer in the published paper was marginally less than that of myocardial infarction). Also quoted in the press release was the WHI statistician Garnet Anderson, who reported: ‘Because breast cancer is so serious an event, we set the bar lower to monitor for it. We pre-specified that the change in cancer rates did not have to be that large to warrant stopping the trial. And the trial was stopped at the first clear indication of increased risk.’

However, these caveats did little to hold back the flood. According to *Newsweek* magazine, ‘the announcement caused a near panic among the more than 13 million American women now on hormone replacement therapy. Doctors’ offices were overwhelmed by calls, and Wyeth Pharmaceuticals, the maker of Prempro, saw its stock price plunge by 25% overnight’.

PHASE 2: DON’T PANIC

So much for shock and terror. Controversy came in the next few days, when the menopause establishment slowly came to life and experts at home had time to consider the findings. The initial press reports had simply followed the WHI line – that



Figure 2 'HRT linked to breast cancer'. How the BBC reported the story on the morning of Wednesday 10th July

the trial had been stopped on the grounds of safety and that women had been told to halt their medication and see the doctor. How else could the story be reported? But over the following days, as the study details were analyzed and the editorials digested – and as news desks demanded follow-up to the story – these simple facts reported verbatim were now challenged, and among the challengers prepared to stand up and be quoted were the professional and consumer menopause societies, especially in Britain and the USA. Among those widely quoted in the UK were the osteoporosis specialist David Purdie ('no British women should stop taking HRT on the basis of these results') and a succession of leading gynecologists; even the Oxford epidemiologist Valerie Beral – whose Million Women Study would cause even more controversy just 13 months later – said 'there is no need to panic'. Indeed, looking back in a 2009 interview, Rowan Chlebowski, principal investigator of the trial, said that the greatest support for HRT came more from the gynecologists than from general medicine or oncology. 'The gynecology community tends to focus more on heart problems than . . . breast or lung cancer,' said Chlebowski, who added with pejorative innuendo that the manufacturers of HRT preparations were 'big supporters of the gynecological community'¹.

However, it is also worth noting that even the regulatory announcements which had followed so dramatically hard on the heels of the initial WHI report did not in fact cry havoc about the results. The CSM, for example, seemed underwhelmed, saying in its statement that the new findings confirm what is already known about breast cancer and HRT, and that HRT should not be used for any cardioprotective effect. The Chairman of the CSM added: 'This is no cause for alarm.'

As these press follow-ups began to emerge, the subjects of most controversy were the progestogen component of the combined HRT (medroxyprogesterone acetate, deemed

by some to be excessively androgenic in its metabolism), the diagnostic definition of 'breast cancer', and the age range of the trial subjects (50–79 years, and the likelihood that age and not hormones would explain the cardiovascular findings).

And on this question of age, it's also worth considering just what journalists 'knew' at this stage and what they did not know (both the known unknowns and the unknown unknowns). The 'facts', as universally and faithfully reported at the end of the embargo period, were that a major NIH trial of combined HRT had been stopped on the grounds of safety, with increased relative risks of coronary heart disease (1.29), breast cancer (1.26), stroke (1.41), and pulmonary embolism (2.13); risks of hip fracture and colorectal cancer were reduced, but there was no significant effect on all-cause mortality. Unknown at the time was the effect of age on the risk of coronary heart disease and stroke, or whether the findings with combined HRT were replicated with estrogen alone. Such matters could only be left to speculation, or ignored.

In fact, and notwithstanding a 2003 publication on combined HRT and coronary disease risk, it would not be until 2007 and a 'secondary' analysis of all the cardiovascular data that the age factor would be addressed – when the WHI investigators formally acknowledged that 'women who initiated hormone therapy closer to menopause tended to have reduced CHD risk compared with the increase in CHD risk among women more distant from menopause'^{2,3}. As a counterpoint to any accusation that this might constitute a U-turn on coronary heart disease – as the UK's *Daily Mail* would prominently charge – the NIH press release said that the effect *may* vary by age and that these findings 'are consistent with the primary publications from the WHI trials'.

PHASE 3: STANDING UP FOR READERS

On 21st July 2002, less than 2 weeks after the WHI news first broke, the US magazine *Newsweek* ran an article on the fall-out titled 'What's a woman to do?'. It was a sentiment echoed in many more publications across the world, as the story shifted from the news to the feature pages. At the heart of these features were women themselves, women who, like so many readers and TV viewers, had had to abandon their HRT without adequate explanation. And what they resented, as they recounted their own short-lived experiences, was that nothing had been recommended to take the place of HRT. The keyword of these articles, as well as many which followed, was 'confusion'. Indeed, that *Newsweek* story of 21st July had begun with 'No doubt you're confused about hormone replacement therapy', and went on to quote a 60-year-old who had been on HRT for 7 years and had now decided to stop. 'I think there should be clear, definitive answers,' she said, 'but of course there aren't. I hate these studies.'

Thus, as this momentous year moved on, coverage of the menopause in the media took on a theme of self-help, to help women make their own decisions about HRT and manage their symptoms for themselves. A rather dry and convoluted

analysis of 'major' media coverage of the WHI, commissioned by the Hormone Foundation of the Endocrine Society and published in 2009, found that the media 'did a good job of telling women what to be concerned about if they were using HT, but a poor job of providing the information women need to determine if the latest findings apply to them'⁴. Such conclusions, derived only from US press and broadcast coverage, suggest that more emphasis was placed on risk than on benefit, but that those risks were inadequately quantified.

No other year since has seen anything like the coverage that HRT received in 2002. The same Hormone Foundation review counted 139 major stories in 2002, but only 49 in 2003, despite the UK frenzy over the Million Women Study, more WHI data on HRT and dementia (WHIMS), and a growing interest in alternative and complementary therapies. And despite the abrupt end of the WHI's estrogen-alone trial in March 2004, coverage that year remained similarly restrained.

THE WINDOW OF OPPORTUNITY

Media coverage during the 5 years following the first WHI report remained largely negative, with study after study announcing relatively 'harmful' effects. There was a note of added confusion when individual specialists challenged these findings (particularly of the Million Women Study), but overall the press seemed to accept that the days of HRT were numbered. In September 2006, Britain's National Institute for Health and Clinical Excellence (NICE) excluded HRT altogether from its draft guidance on the prevention of osteoporosis, presumably on the grounds of safety and not efficacy, and with that HRT appeared to have little place in the provision of women's health, a fact which the press now seemed – albeit reluctantly – to accept. Indeed, as the bad news about HRT continued to accumulate, a Dutch study claimed that 'media coverage' had largely contributed to the rapid decline in HRT prescribing in the Netherlands⁵. The investigators found that prescribing levels fell suddenly after August 2003 when the Million Women Study was published; the number of new users fell by 29% and continuing users by 42%. While the WHI report of 2002 had failed to have much impact in the Netherlands, where it received little or no press attention, coverage of the Million Women Study, 'which included the front pages of six national newspapers . . . definitely played a role in reducing the number of women using, and being prescribed, HRT'.

While this Dutch investigation may well have been yet another study of the blindingly obvious, it does nevertheless support the adage that news is only news if the journalist chooses to report it; news does not exist as a predefined abstract. So wars have been fought and tragedies endured without them ever being news. In their publicity for the WHI and Million Women Study, *The Lancet* and *JAMA* were also in the news business, in packaging their material in such a way that it *was* reported and did make the headlines.

The WHI did not bounce back onto the news pages until April 2007 when the investigators published – yet again in *JAMA* – results of a secondary analysis of HRT's effects on cardiovascular disease. These findings would largely shape the regulatory and public position of HRT today and shift the focus of attention back to the study's original objective. The report proposed that women who began HRT within the first 10 years following the menopause actually reduced their risk of coronary heart disease (a hazard ratio of 0.76). Those who started 10–19 and more than 20 years after slightly increased their risk (HR 1.10 and 1.28, respectively). The data also showed that hormone users aged 50–59 had a 30% lower risk of all-cause mortality than those given placebo. Thus, with a continuing recognition of HRT's unequivocal effect on climacteric symptoms, the concept of a window of prescribing opportunity began to take shape. Indeed, Jacques Rossouw of the NHLBI told the *New York Times* that 'we were as clear as could be that there seems to be a window of opportunity to use it in that short interval'.

This apparent flip-flop of the WHI was greeted by howls of protest in the media, especially in the UK and USA; in London the *Daily Mail* in a front-page splash said that 'millions of women may have been scared into abandoning HRT unnecessarily', while many others took a similar line (Figure 3). As noted earlier, the press releases accompanying the publication had stressed that the findings were 'trends' and not statistically significant, and thus 'consistent with the primary publications'. However, in the USA the *Wall Street Journal* reported that the 'conservative' *p*-value of the study (0.01) was not the same as the more conventional 0.05 value applied when the paper was first submitted for publication. Once the latter value was applied, the findings became statistically significant⁶.

The decision to lower the standard for statistical significance to 0.01, Rossouw told the *Wall Street Journal*, was on the recommendation of both 'internal reviews and the journal reviews'. Both he and *JAMA* played down the importance of the late *p*-value change (it's the overall tone of the paper that matters, said Rossouw), but Wulf Utian, Executive Director of the North American Menopause Society, was quoted as saying that the study's claim of non-significance was nothing but a 'statistical game'. 'It's like a half-hearted apology,' Utian told the *Wall Street Journal*. 'They did the analysis, but then they say it isn't really statistically valid. Before, they were happy with 0.05 with every other study they wrote, but now they say it should be 0.01.'

Rossouw was also dismissive about the results reversing the WHI's initial findings, insisting that hormones should still not be taken to prevent heart disease. 'I understand some people are going to say we've reversed course,' he said. 'But the data are the data.' The press, however, did not agree. 'Hormone therapy redeemed', headlined *Time* magazine, while the news agency Reuters reported that hormone therapy was 'safe' for younger women. 'A major government study that once warned that menopause hormones raised heart risk has now concluded that they don't,' was how the *Wall Street Journal* saw it.

answered. And this may be one reason why the menopause and HRT seem now of only minority interest to journalists, kept at arm's length in a mist of potential risk and definite maybes. For her part, Barbara Alving, a former acting director of the NHLBI, also told Tara Parker-Pope that the WHI results were presented 'in a very dramatic fashion'. 'There should have been less drama and more thought,' she went on. 'What we learned is that we need to work much better in the communication of risk, so people can understand it.'

ACKNOWLEDGEMENT

Tom Parkhill, Press Officer of the International Menopause Society, provided background information for this report.

Conflict of interest The author reports no conflict of interest. The author alone is responsible for the content and writing of this paper.

Source of funding Nil.

References

1. See http://epoch-archive.com/a1/en/us/lax/2010/04-Apr/01/B3_EET.pdf
2. Manson JE, Hsia J, Johnson KC, *et al.* Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523–34
3. Rossouw JE, Prentice RL, Manson JE, *et al.* Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465–77
4. See <http://www.hormone.org/Menopause/upload/media-analysis-081309.pdf>
5. Faber A, Bouvy ML, Loskamp L, *et al.* Dramatic changes in prescribing of hormone replacement therapy in the Netherlands after publication of the Million Women Study: a follow-up study. *Br J Clin Pharmacol* 2005;60:641–7
6. The Wall Street Journal. Matter of Timing: New Study Reassures Most Users of Hormones. 4 April 2007
7. The Wall Street Journal. How NIH misread hormone study in 2002. 9 July 2007
8. Cardiff School of Journalism, Media and Cultural Studies, 2008. The quality and independence of British journalism
9. Parker-Pope T. *The Hormone Decision*. Rodale Press, 2007

Evidence-based assessment of the impact of the WHI on women's health

H. G. Burger, A. H. MacLennan*, K-E. Huang[†] and C. Castelo-Branco[‡]

Prince Henry's Institute of Medical Research, Clayton, Victoria, Australia; *The Discipline of Obstetrics & Gynaecology, The University of Adelaide, Adelaide, Australia; [†]Department of Obstetrics & Gynecology & Centre for Menopause & Reproductive Medicine, Kaohsiung Chang Gung Memorial Hospital & Chang Gung University School of Medicine, Kaohsiung, Taiwan; [‡]Institut Clinic of Gynecology, Obstetrics and Neonatology, Faculty of Medicine-University of Barcelona, Hospital Clinic-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

Key words: WOMEN'S HEALTH INITIATIVE, WOMEN'S HEALTH, IMPACT, HEALTH-RELATED QUALITY OF LIFE, FRACTURES, CARDIOVASCULAR DISEASE, BREAST CANCER

ABSTRACT

Following the announcement of the first results of the Women's Health Initiative (WHI) to the media in 2002, prior to their scientific publication, the resulting panic headlines had an immediate and lasting negative effect on use of menopausal hormone replacement therapy (HRT) around the world. Rates of use dropped by 40–80%. Symptomatic women then sought multiple alternative therapies but the majority of these have no greater effect than the effect seen from placebo in well-conducted trials of HRT. Some of these therapies have risks.

Although anecdotally most menopause practitioners after 2002 can attest to having to counsel large numbers of women with debilitating menopausal symptoms who were too frightened to consider HRT, it is difficult to document loss of health-related quality of life in large population studies as they were not conducted. Similarly, the positive or negative effects of the marked decline in HRT on long-term morbidities and mortality have yet to be fully assessed. Recent studies have shown an increase in postmenopausal fractures and in some, but not all, populations a small temporary decline in breast cancer. Cardiovascular outcomes may not be apparent for another decade. Short-term, randomized, placebo-controlled trials confirm that HRT is the only therapy that effectively improves health-related quality of life in symptomatic women through a reduction in vasomotor and urogenital symptoms, joint pains and insomnia, while improving sexuality. The results of the re-analyses of the WHI data and new data from other studies do not justify the continuing negative attitude to HRT in symptomatic women who start HRT near menopause.

INTRODUCTION

In July 2002, at a press conference convened in Washington DC, the first, then unpublished results of the Women's Health Initiative (WHI) randomized, controlled trial of combined continuous menopausal hormone therapy¹ were announced. They received world-wide attention, with emphasis on the finding of a 26% increase in breast cancer risk in treated women. Little attempt was made to explain what a 26% increase meant (actually less than one additional case of breast cancer per 1000 women taking menopausal hormone replacement therapy (HRT) above the baseline risk of three to four per 1000 per year, and 'technically not statistically significant'

at the time of announcement). Relatively little media attention followed the mostly reassuring results of the estrogen-only arm of the WHI published in 2004² that showed a 'technically not statistically significant' reduction in breast cancer after 7 years of estrogen-alone HRT. Not alluded to was the fact that 76% of the approximately 10 000 participants in each arm had never used HRT previously and, in them, no increase in breast cancer risk was seen.

Furthermore, it was announced that HRT increased the risk of heart disease and that both increased risks were observed across the entire age spectrum, 50–79 years, of participants in the study. This was later found not to be true. Thus, the first and major negative impact on women's health was to

Correspondence: Professor H. G. Burger, PO Box 5152, Clayton, Victoria 3168, Australia

engender unnecessary anxiety and fear in all those menopausal women who read and heard the results and in the majority of practitioners involved in their care. There was a consequent cessation by many of the HRT on which they were previously established, with recurrence of menopausal symptoms in many instances. The first paper¹ was published soon after the press conference, in the *Journal of the American Medical Association (JAMA)*. In stark contrast to the initial announcement, a further analysis by the same investigators, also published by them in the *JAMA* in April, 2007³ stated 'there were no significant increases in risk due to hormone therapy for any outcome at ages 50–59 years'. It was also stated 'there was a reduction in total mortality in the age group of 50–59 years (hazard ratio (HR) 0.70, 95% confidence interval (CI) 0.51–0.96)'. In that age group, there were 10 fewer deaths per 10 000 person years in the treated group. This compared with 16 additional deaths at ages 70–79 years. Such a contradiction indeed stretches credulity and invites speculation as to what the investigators' true motives were for the initial devastating announcements.

The first casualty following the announcement of the first results of the WHI to the media was WISDOM, the Women's International Study of long Duration Oestrogen after Menopause. This was to have assessed similar HRT for 15 years but in a younger age group (50–69 years). Cardiovascular disease (CVD) was one of WISDOM's main outcomes and, when the WHI investigators initially and wrongly announced that an increase in CVD was seen in all age groups, this was one of the main reasons that the funding for WISDOM was withdrawn⁴. Had WISDOM continued, the effect of earlier onset of HRT on cardiovascular and cognitive function and many other outcomes such as sexuality and quality of life would have been now becoming apparent. The WHI effectively torpedoed WISDOM, its main 'competitor', and science and women have suffered. New studies such as KEEPS and ELITE have had to be designed, funded and run to help answer the questions that the WHI and WISDOM left unanswered^{5,6}.

HRT, given to symptomatic women, usually in their early fifties (and not in the sixties or seventies) is known to improve menopausal symptoms and hence quality of life, to reduce mortality, as shown above, to reduce cardiovascular risk, to reduce fracture risk, to reduce risk of colorectal cancer and endometrial cancer with combined continuous therapy and to reduce the incidence of diabetes⁷. It thus seemed likely that these benefits would be lost in women discontinuing their therapy on the basis of fear and anxiety. Discontinuation rates were as high as 80% in some countries. On the other hand, in the light of evidence, primarily from observational studies, that breast cancer and venous thromboembolism risks were increased with the use of HRT, it seemed likely that those two risks may decrease after discontinuation. We do not presume that all those who stopped HRT without medical advice were disadvantaged. For some who had been on long-term HRT, it was appropriate to stop to see whether debilitating symptoms returned and resume only if annoying symptoms returned. However, those who developed severe

symptoms around menopause and were too frightened to start HRT were probably the most disadvantaged.

IMPACT ON GLOBAL USAGE AND PERCEPTION OF HRT

Over the past 10 years, numerous publications from many countries have documented the effects of the publication of the first WHI data on HRT usage. In the USA, in the first 5 months after the publication, the prevalence of HRT use among 169 586 women aged 40–80 years, enrolled in five health maintenance organizations, declined by 46% (from 14.6% to 7.9%), while estrogen-only use fell by 28% (from 12.5 to 9.1%)⁸. Other authors reported on various aspects of the decrease, e.g. in minority women⁹, in women in a Mammography Registry¹⁰ and in women in an internal medicine practice¹¹.

Reports from many other countries corroborated the decreased HRT usage following WHI, including publications from the United Kingdom¹², Canada¹³, Thailand¹⁴, Germany¹⁵, Israel¹⁶ and Hong Kong¹⁷.

In Australia, MacLennan and colleagues¹⁸ obtained data on HRT use from nine South Australian Omnibus Surveys, over 17 years. These surveys involved representative population face-to-face interviews. Associated with the timing of the media reporting of the WHI, current HRT use rates dropped from 28% in women over 50 in 2000 to an estimated 10.2% in 2002 but, by October 2003, current use rates had returned to 18.8% in this age group (Figure 1). The media had been the main influence in the women's decision-making and half of those who restarted changed to another type of HRT. One study¹⁹ assessed the reasons for the use of HRT among postmenopausal Spanish women after the WHI publication. The most frequent reasons given were medical recommendation, improvement of menopausal symptoms and quality of life. Most HRT users were satisfied with this therapy (78.9%), with 11.7% being unconcerned and 9.4% reluctant to use HRT. Reasons for such reluctance included adverse effects (29%), dislike of hormone therapy (47%), fear of cancer (24%), advice from a friend or relative (6%), negative information in the media (6%) and cost (6%). Of these reluctant HRT users, 47% said they remained on therapy for medical indications, 24% for the relief of symptoms and 24% due to an improvement in life quality (several women declared more than one reason). As for the impact of the media on HRT compliance, 26% of HRT users indicated that negative data from published studies strongly influenced their opinion of this therapy, and 57% of them had expressed their wishes to reduce the time during which they used HRT.

There are scant data regarding the effect of the WHI on HRT prescription in South America. A recent study done in Ecuador²⁰ demonstrated that the percentage of HRT users was surprisingly very low (1.7%). The authors related this low use to low socioeconomic status and therefore lower knowledge regarding HRT and that anxiety regarding the WHI among physicians had been transmitted to nursing staff,

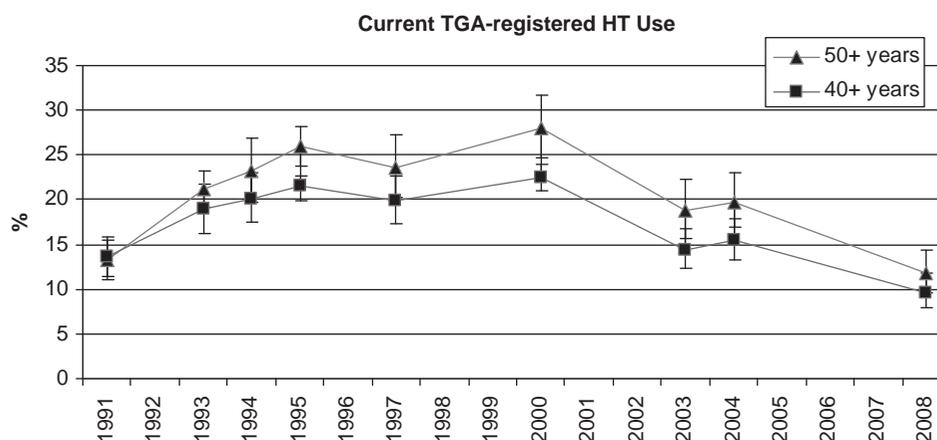


Figure 1 Current hormone therapy (HT) use by age group, women aged ≥ 40 years and women aged ≥ 50 years, over time (South Australian Health Omnibus Surveys 1991–2008)¹⁸. TGA, Therapeutic Goods Administration

as 27.2% recommended not to use HRT. The relation between low socioeconomic status and low HRT use appears to be common in South America²¹. Another study reported similar data regarding use among low socioeconomic groups in Chile²². Among physicians, 97.2% were aware of the WHI study, and 64.7% modified their clinical approach. Decreased prescribing was more pronounced for conjugated equine estrogen and medroxyprogesterone acetate. In contrast, prescription of transdermal estrogens and tibolone increased by 5.2% and 16%, respectively.

Although studies about the frequency of use of HRT after the WHI in many countries have been published, it is not known whether women are well informed about the risks and benefits of using HRT. Several studies have revealed insufficient information from physicians^{15,23–26}. They demonstrated that social trust is affected by images expressed in the media and it may affect certain patients' attitudes and behavior, including satisfaction with care and motivation to follow doctors' recommendations.

In Asian countries, the impact of the WHI report on menopause treatment was more obvious in those developed countries/regions such as Japan, Korea, Taiwan, Singapore, and Hong Kong, compared to the other areas. HRT use rate dropped dramatically immediately after the WHI report, for instance, from 33% to 10% in Taiwan and from 25% to 12% in Thailand²⁷. Women often experienced recurrence of menopausal symptoms and also became distrustful of the doctors who had prescribed HRT for them.

A multinational menopause survey²⁷ of 1000 women from China, Malaysia, Taiwan, Thailand and Hong Kong in 2006 showed that, on average, 54% had heard, seen or read about HRT. Awareness was generally higher in Taiwan (90%) and Thailand (95%) compared with other countries. Fifty-three percent of Chinese women reported having no knowledge of any type of treatment for menopausal symptoms. Forty-three percent of the women aware of HRT had negative perceptions of it. Fifty-five percent of respondents were unwilling to try HRT because of a fear of breast cancer. More

than 85% said that their doctors had never advised HRT. All these data reflect the negative impact of the WHI report. Health-care providers are concerned by the development of breast cancer among their patients using HRT and had a fear of medicolegal consequences.

THE INCREASE IN USE OF COMPLEMENTARY AND ALTERNATIVE THERAPY

Menopausal women are targeted by the alternative medicine industry and, since the media scares that followed the WHI, many alternative products have alluded to the dangers of HRT and the safety of 'natural' remedies. The use and cost of alternative medicines in most Western countries have greatly increased in the last decade, particularly amongst menopausal women²⁸. The efficacy of any alternative therapy for menopausal symptoms, especially vasomotor symptoms, has not been shown to be better than the average effect for placebo seen in well-conducted, double-blind, placebo-controlled, randomized trials of HRT²⁹. Of particular concern has been the increasing use of so-called 'natural' or 'bioidentical' hormones to treat menopausal symptoms. On the internet, they are commonly touted as being side-effect-free, but their variable combinations of estrogens, progesterone, DHEA, testosterone and sometimes thyroxine, melatonin and growth hormone remain untested for long-term safety and efficacy. In the 2008 Australian population sample, 37% of women on hormone therapy in the 50–59-year age group, and thus likely to have commenced HRT since the WHI, were using unregistered, imported and unaudited 'bioidentical' hormones compounded in local pharmacies and made into buccal troches or creams¹⁸. The estrogens used can cause endometrial proliferation and the progesterone added (if at all) may not inhibit this endometrial stimulus. To date, the authors are aware that four cases of endometrial cancer (including one subsequent death) have followed the use of unregistered HRT in Australia. Symptomatic women and

sometimes their attendants who have an exaggerated fear of HRT are being driven towards the false promises, lack of efficacy and potential dangers of alternative therapies. These therapies are being sold at high cost for financial rather than altruistic reasons.

THE LONG-TERM IMPACT OF THE GLOBAL REDUCTION IN HRT USE

In the introduction to this paper, the list of benefits and risks ascribed to HRT was presented with the conclusion that it was likely that those benefits and risks would be lost in women discontinuing their therapy on the basis of fear and anxiety. The WHI results had clouded perceptions of the effects of HRT on the risk of cardiovascular disease, with the initial report indicating an increase in risk, but subsequent reports suggesting that that increase was confined to women over the age of 70.

Fractures

The most detailed reports so far published of health outcomes after cessation of HRT concern osteoporotic fracture risk. Two US studies have documented an increase in osteoporosis-related fractures following the publication of the WHI. Islam and colleagues³⁰ found significantly higher age-adjusted incidence rates of osteoporosis-related fractures among 40–69-year-old women between 2004 and 2005, as compared with 2000 and 2001. Karim and colleagues³¹ reported a longitudinal observational study of 80 955 postmenopausal women using HRT as of July 2002 who were followed up through December 2008. After 6.5 years of follow-up, those who discontinued HRT were at 55% greater risk of hip fracture, compared with those who continued using HRT (HR 1.55, 95% CI 1.36–1.77). The risk increased as early as 2 years after HRT was ceased and increased incrementally with longer duration of cessation. Longer duration was also correlated with lower bone mineral density (BMD). Thus, the authors concluded that women who discontinued postmenopausal HRT had significantly increased risks of hip fracture and lower BMD, compared with continuing users. The protective association of HRT with hip fracture disappeared within 2 years of stopping. The WHI combined hormone therapy trial had shown significant reductions in hip, lower arm/wrist, vertebral and total fracture incidence by 33%, 29%, 35% and 24%, respectively, amongst women assigned to active therapy in comparison to placebo during the 5.6-year trial period. There was a 35–39% reduction in hip fracture in the estrogen-only trial and an improvement in BMD. The WHI cohort was not selected for low BMD or previous fracture and the results therefore have general application to all postmenopausal women seeking HRT in order to prevent bone fracture. Gambacciani and colleagues³² estimated that a 50% increased risk of bone fracture associated with a 50% decrease in HRT usage in the United States would result in

43 000 extra bone fractures per year. Thus, the increase in fracture rates is an important and evidence-based impact of the reduction in HRT usage following the WHI. This study includes information on the poor use of other bone-protective strategies after HRT discontinuation. While HRT use substantially decreased between July 2002 and December 2008 from 85% to 18%, use of the bisphosphonate drugs increased from 8% to 23% during the study period.

Cardiovascular disease

Data on cardiovascular outcomes are preliminary and very limited. Shetty and colleagues³³ examined the relationship between HRT use and cardiovascular outcomes, including deaths and non-fatal hospitalizations in the entire US population of women aged 40–79 years. Decrease in HRT use was not associated with statistically significant changes in hospitalizations or deaths due to acute stroke, but was associated with a decrease in the incidence of acute myocardial infarction, with 25 events less per 10 000 person years. In contrast, Martin and colleagues³⁴ reported a time series analysis of hospital admissions, incidence and mortality amongst women aged 50–69 years in England over the period 1997–2006. They observed no relationship between reduced HRT prescribing after 2002 and trends in breast cancer, colorectal cancer or hip fracture. Among 50–59-year-olds, the annual percentage change in venous thromboembolism hospitalizations fell by 5.7% between 2000 and 2006 and of considerable concern was the annual change in endometrial cancer mortality, which increased from 0.7% between 1997 and 2003 to 11% after 2003. Previously falling acute myocardial infarction hospitalizations (annual change –6.8% and stroke –3%) stabilized (–0.4%) or increased (+0.8%), respectively, around 2001, but this makes any relationship with discontinuation of hormone therapy difficult to evaluate. Karim and colleagues³¹, in their paper on osteoporosis-related fractures, foreshadowed reports on cardiovascular and other outcomes, but to date no substantial publications have appeared that would allow an assessment of the impact of discontinuation of HRT use after the WHI.

Breast cancer

As indicated above, HRT use declined substantially by up to 80% following the publication of the first WHI report. Several publications documented an apparent decrease in breast cancer incidence occurring in association with the decrease in HRT use. Clarke and colleagues³⁵ documented a 68% drop in combination HRT use and a 10% decline in breast cancer incidence in the Kaiser Permanente's Northern Californian region. Similar data were observed in the SEER database³⁶. Kerlikowske and colleagues³⁷ analyzed data from more than 600 000 women who had undergone mammography and again showed a decline of 34% in HRT use and of 5% in breast cancer incidence, with a 13% decline in invasive

estrogen receptor-positive breast cancer. Sprague and colleagues³⁸, in a further analysis of the US database, calculated that the decline in HRT use would account for only 43% of the decline in breast cancer diagnosis rates between 2002 and 2003 in women aged 40–79 years. Other explanations would need to be considered. Despite the widespread decline in HRT use, a decline in breast cancer incidence was not reported in other countries, e.g. as noted above in the United Kingdom. It is also apparent that the decline has not been sustained and has levelled off despite continuing low HRT usage rates. The short-lasting decline is consistent with a late promoter effect of combination HRT on pre-existing breast cancers.

In contrast to the apparent fall in breast cancer incidence in the United States, breast cancer incidence rates in Asia actually increased, even after the significant decrease in HRT use^{39,40}. Whether this is the result of more extensive breast cancer screening in recent years is unclear. Nevertheless, the increased incidence of breast cancer in Asian countries has been predominantly in women younger than comparable Western populations. The reason is suspected to be the westernized lifestyle in young Asian women. It should be noted that breast cancer incidence rates peak at ages 47–48 years in Asian countries and subsequently level off, in contrast to the situation in Western countries where the rates continue to rise until 80 years and older⁴¹.

Other morbidities

In the WHI, other statistically significant and non-significant trends were described such as a reduction in newly diagnosed diabetes, a reduction in colorectal cancer, a reduction in endometrial cancer, an increase in stroke and, in the first year or two of therapy, an increase in thromboembolism on oral HRT. It is not possible to conclude whether the marked reduction in HRT use is directly related to any increase or decrease in these morbidities or indeed to overall mortality, which is decreased in HRT users commencing under age 60⁴². To assess the health impact of the cessation of HRT, millions of women in longitudinal studies would have been required from before 2002 in continuing users, those who ceased HRT and never-users of HRT as well as those who did subsequently develop debilitating symptoms and did or did not accept HRT.

Menopausal symptoms, sexuality and health-related quality of life

Menopausal symptoms, sexuality and health-related quality of life are the main indications for HRT and were not adequately assessed in the WHI. Only 3.4% of women in the WHI were under age 55 years and were symptomatic. The WHI did not try to effectively assess this major benefit of HRT and yet the WHI results and the media's interpretation of these results have probably had the most impact on symptomatic women since 2002. Approximately 50% of menopausal Western women profess to moderate to severe menopausal symptoms

and are candidates for the option of HRT. Particularly since 2002, any practitioner of menopausal medicine can attest to the huge numbers of unhappy symptomatic women in their clinics who have tried to avoid HRT because of their understanding or lack of understanding of the WHI results. They usually have tried unsuccessfully many alternative therapies and require lengthy counselling about the mythology surrounding conventional and unconventional menopause therapies. Some practitioners have found it too hard and non-remunerative and have opted out of offering help. Like the other outcomes above, it is hard to find population data to verify what one has heard daily in clinical practice. Although terminated prematurely, the WISDOM trial enrolled sufficient numbers to show that HRT compared to placebo significantly reduced vasomotor symptoms, sleep problems, aching joints and muscles, insomnia and vaginal dryness. Sexual functioning significantly improved⁴³. It does not take longitudinal trials to convince those who have practised menopausal medicine since 2002 that the WHI has disadvantaged many deserving women who have suffered incapacitating menopausal symptoms to the detriment of their own quality of life, their families and their role in the work place.

A recent UK survey⁴⁴ of 1100 women showed that, in the early 2000s, 754 decided to stop HRT, mostly without medical advice, and 56% had been influenced by the media. Symptoms returned in many that affected their ability to work (37%), make decisions (45%), and affected relationships negatively (54%). Overall, 46% would not have stopped HRT given their current understanding of risk.

In particular, women who have had a premature or early menopause are the most disadvantaged if they have been dissuaded from taking HRT because of the media image of the WHI results. They will be at increased risk of osteoporotic fractures, premature cardiovascular disease, premature dementia and a major decrease in sexuality and quality of life.

CONCLUSION

The re-analyses of the WHI results and the addition of all other quality data on HRT still have not done enough to reverse the media excesses of 2002. All of us, including the media, the WHI investigators, and responsible clinicians, should give evidence-based information appropriate to the individual and facilitate symptomatic women around menopause to have the option of low-dose HRT regimens tailored to their needs and tailored to reduce the known risks of HRT without reducing the overall benefit that is seen for most women starting HRT under age 60. It can be argued that, since 2002, untreated symptomatic women have lost the best years of their lives.

Conflict of interest Professor MacLennan was a Chief Investigator in the WISDOM trial.

Source of funding Nil.

References

1. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Randomized controlled trial. *JAMA* 2002;288:321–33
2. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the WHI randomized controlled trial. *JAMA* 2004;291:1701–12
3. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465–77. Erratum in *JAMA* 2008;299:1426
4. MacLennan AH, Sturdee D. The end of WISDOM. *Climacteric* 2002;5:313–16
5. Harman SM, Brinton EA, Cedars M, et al. KEEPS: The Kronos Early Estrogen Prevention Study. *Climacteric* 2005;8:3–12
6. Hodis HN for the ELITE study group. <http://clinicaltrials.gov/ct2/show/NCT00114517>
7. Sturdee DW, Pines A, On behalf of the International Menopause Writing Group. Updated IMS recommendations on postmenopausal hormone therapy and preventative strategies for midlife health. *Climacteric* 2011;14:302–20
8. Buist DS, Newton KM, Miglioretti DL, et al. Hormone therapy prescribing patterns in the United States. *Obstet Gynecol* 2004;104:1042–50
9. Helenius IM, Korenstein D, Halm EA. Changing use of hormone therapy among minority women since the Women's Health Initiative. *Menopause* 2007;14:216–22
10. Haas JS, Kaplan CP, Gerstenberger EP, Kerlikowske K. Changes in the use of postmenopausal hormone therapy after the publication of clinical trial results. *Ann Intern Med* 2004;140:184–8
11. Ness J, Aronow WS, Newkirk E, McDanel D. Use of hormone replacement therapy by postmenopausal women after publication of the Women's Health Initiative Trial. *J Gerontol A Biol Sci Med Sci* 2005;60:460–2
12. Menon U, Burnell M, Sharma A, et al. Decline in use of hormone therapy among postmenopausal women in the United Kingdom. *Menopause* 2007;14:462–7
13. Guay MP, Dragomir A, Pilon D, Moride Y, Perreault S. Changes in pattern of use, clinical characteristics and persistence rate of hormone replacement therapy among postmenopausal women after the WHI publication. *Pharmacoepidemiol Drug Saf* 2007;16:17–27
14. Chaikittisilpa S, Jirapinyo M, Chaovitsaree S, et al. Impact of Women's Health Initiative study on attitude and acceptance of hormone replacement therapy in Thai women attending menopause clinics. *J Med Assoc Thai* 2007;90:628–35
15. Heitmann C, Greiser E, Dören M. The impact of the Women's Health Initiative randomized controlled trial 2002 on perceived risk communication and use of postmenopausal hormone therapy in Germany. *Menopause* 2005;12:405–11
16. Silverman BG, Kokia ES. Use of hormone replacement therapy, 1998–2007: sustained impact of the Women's Health Initiative findings. *Ann Pharmacother* 2009;43:251–8
17. Leung KY, Ling M, Tang GW. Use of hormone replacement therapy in the Hong Kong public health sector after the Women's Health Initiative trial. *Maturitas* 2005;52:277–85
18. MacLennan AH, Gill TK, Broadbent JL, Taylor AW. Continuing decline in hormone therapy use: population trends over 17 years. *Climacteric* 2009;12:122–30
19. Castelo-Branco C, Ferrer J, Palacios S, Cornago S, Peralta S. Spanish post-menopausal women's viewpoints on hormone therapy. *Maturitas* 2007;56:420–8
20. Leon-Leon P, Chedraui P, Hidalgo L, et al. Hormone therapy for the management of the menopause in Ecuador: perception, use and knowledge among middle-aged women. *Gynecol Endocrinol* 2008;24:580–5
21. Blümel JE, Castelo-Branco C, Riquelme R, et al. Use of hormone replacement therapy among Chilean women: a comparison between socioeconomic levels. *Menopause* 2002;9:377–80
22. Blümel JE, Castelo-Branco C, Kerrigan N, et al. Influences of hormone replacement therapy on postmenopausal women's health perceptions. *Menopause* 2003;10:235–40
23. Coe H, O'Connor KS, Hunter D. Women's knowledge of hormone therapy. *Patient Educ Couns* 2001;45:295–301
24. Breslau ES, Davis WW, Doner L, et al. The hormone therapy dilemma: women respond. *J Am Med Womens Assoc* 2003;58:33–43
25. Pan HA, Wu MH, Hsu CC, Yao BL, Huang KE. The perception of menopause among women in Taiwan. *Maturitas* 2002;41:269–74
26. Rolnick SJ, Kopher RA, Defor TA, Kelley ME. Hormone use and patient concerns after the findings of the Women's Health Initiative. *Menopause* 2005;12:399–404
27. Huang K-E, Xu L, Masari IN, et al. The Asian Menopause Survey: knowledge, perception. Hormone treatment and sexual function. *Maturitas* 2010;65:276–83
28. MacLennan AH. Death by 'natural' causes! Placebos, poisons and potions. In Genazzani AR, ed. *Menopause State of the Art: Proceedings of the 13th Congress on Menopause 2011*. CIC Edizioni Internazionali, 2011:118
29. MacLennan AH. Evidence-based review of therapies at the menopause. *Int J Evid Based Health* 2009;7:112–23
30. Islam S, Liu Q, Chines A, Helzner E. Trend in incidence of osteoporosis-related fractures among 40- to 69-year-old women: analysis of a large insurance claims database, 2000–2005. *Menopause* 2009;16:77–83
31. Karim R, Dell RM, Greene DF, et al. Hip fracture in postmenopausal women after cessation of hormone therapy: results from a prospective study in a large health management organization. *Menopause* 2011;18:1172–7
32. Gambacciani M, Ciapponi M, Genazzani AR. The HRT misuse and osteoporosis epidemic: a possible future scenario. *Climacteric* 2007;10:273–5
33. Shetty KD, Vogt WB, Bhattacharya J. Hormone replacement therapy and cardiovascular health in the United States. *Med Care* 2009;47:600–6
34. Martin RM, Wheeler BW, Metcalfe C, Gunnell D. What was the immediate impact on population health of the recent fall in hormone replacement therapy prescribing in England? Ecological study. *J Public Health (Oxf)* 2010;32:555–64
35. Clarke CA, Glaser SL, Uratsu CS, et al. Recent declines in hormone therapy utilisation and breast cancer incidence: clinical and population based evidence. *J Clin Oncol* 2006;24:e49–50
36. Ravdin P, Cronin KA, Howlader N, et al. The decrease in breast cancer incidence in 2003 in the United States. *N Engl J Med* 2007;356:1670–4
37. Kerlikowske K, Miglioretti DL, Buist DS, Walker R, Carney PA. Declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. National Cancer Institute-sponsored Breast Cancer Surveillance Consortium. *J Natl Cancer Inst* 2007;99:1335–9. Erratum in *J Natl Cancer Inst* 2007;3;99:1493

38. Sprague BL, Trentham-Dietz A, Remington PL. The contribution of postmenopausal hormone use cessation to the declining incidence of breast cancer. *Cancer Causes Control* 2011;22: 125–34
39. Owen OG. Breast cancer incidence rising in Asian women at younger age: Sunitinib shows potential as treatment for metastatic disease. *Med News Today* February 18, 2008
40. Yip CH. Breast cancer in Asia. *Methods Mol Biol* 2009;471: 51–64
41. Chia K-S, Relly M, Tan C-S, et al. Profound changes in breast cancer may reflect changes into a Westernised lifestyle: a comparative population-based study in Singapore and Sweden. *Int J Cancer* 2005;11:302–6
42. Salpeter SR, Walsh ME, Greyber E, Ormiston TM, Salpeter EE. Mortality associated with hormone therapy in younger and older women. *J Gen Intern Med* 2004;19:791–804
43. Welton AJ, Vickers MR, Kim J, et al. Health related quality of life after combined hormone replacement therapy: randomised controlled trial. *BMJ* 2008;337:1190
44. Cumming GP, Currie HD, Panay N, et al. Stopping hormone replacement therapy: where women ill advised? *Menopause Int* 2011;17:73–4

Future long-term trials of postmenopausal hormone replacement therapy – what is possible and what is the optimal protocol and regimen?

B. Purbrick, K. Stranks, C. Sum and A. H. MacLennan

The Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia

Key words: HORMONE REPLACEMENT THERAPY, LONG-TERM RANDOMIZED CONTROLLED TRIALS, FEASIBILITY, PROTOCOL, TRANSDERMAL ESTROGEN, BAZEDOXIFENE, KEEPS, ELITE

ABSTRACT

The ideal long-term, randomized, placebo-controlled trial of hormone replacement therapy (HRT) from near menopause for up to 30 years to assess major morbidity and mortality is impractical because of high cost, participant retention, therapy compliance, and continuity of research staff and funding. Also the trial regimen may become outdated. It is nihilistic to demand such a long-term trial before endorsing HRT. However, medium-term trials using surrogate measures for long-term morbidity and mortality are possible and two are near completion. If these studies have been able to maintain reasonable participant retention, therapy compliance and minimal breach of protocol, they will set standards for trials of new HRT regimens. This paper discusses lessons learnt from past attempts at long-term trials and suggests the currently optimal protocol and cost of assessing new HRT regimens to optimize potential benefits and minimize adverse effects. A 5–7-year randomized, placebo-controlled trial of a flexible transdermal estrogen regimen \pm either a selective estrogen receptor modulator, e.g. bazedoxifene, or micronized progesterone is discussed. Mild to moderately symptomatic women, 1–4 years post menopause, can be recruited via general practice and group meetings. Future trials should be funded by independent agencies and are high priority in women's health.

INTRODUCTION

Hormone replacement therapy (HRT) is an effective treatment for menopausal women to improve menopausal symptoms and quality of life¹. It is still controversial whether long-term HRT from near menopause reduces cardiovascular events and cognitive decline and increases life expectancy. Results from the Women's Health Initiative (WHI) and Women's International Study of long Duration Oestrogen after Menopause (WISDOM) were relevant to asymptomatic women starting HRT many years after menopause, but the effects of HRT commenced near menopause in symptomatic women were not adequately explored^{2–5}. Some, but not all, studies suggest that there may be a therapeutic window of cardioprotection and possibly neuroprotection if HRT is started soon after

menopause^{6–8}. It is still necessary to conduct a high-level study on a more appropriate population of newly menopausal, symptomatic women with a modern regimen to explore the hypothesis that early initiation of hormone therapy will decrease cardiovascular disease and cognitive decline without a clinically significant increase in other morbidities. An 'ideal' 30-year randomized, double-blind, placebo-controlled trial (RCT) from menopause would be best to measure all outcomes but it is impractical for the reasons listed in Table 1. This paper discusses whether or not it is feasible to conduct a medium-term trial (5–7 years) of postmenopausal HRT to study overall health outcomes and surrogate markers of cardiovascular disease progression and cognitive decline. Nearing completion are two such trials, namely, KEEPS (The Kronos Early Estrogen Prevention Study) and ELITE

Correspondence: Professor A. H. MacLennan, Head of the University of Adelaide Discipline of Obstetrics and Gynaecology, The Women's & Children's Hospital, 72 King William Rd, North Adelaide, South Australia, Australia 5006

Table 1 Reasons why a 30-year trial of hormone replacement therapy (HRT) from menopause is impractical

1. The total cost would be very high
2. Funding agencies would require results before 30 years
3. Participant withdrawal rates by 30 years would likely be high.
The WHI trial suffered nearly 50% in the combined HRT arm²
4. Treatment and placebo compliance rates by 30 years would likely be low
5. Continuity of research staff and investigators would be difficult
6. The proposed HRT regimen might be out-dated by 30 years
7. Results from other studies might compromise funding⁹
8. The pharmaceutical company providing the HRT and placebo could withdraw support due to changes in this industry over 30 years
9. A generation of women would miss knowledge of the results

(Early versus Late Intervention Trial with Estradiol)^{10,11}. These 4- and 7-year trials using surrogate outcomes for cardiovascular disease and cognitive decline will test whether such trials are practical, can maintain the integrity of their protocols throughout the trials, and are cost effective. Both trials have the potential to provide important information and may set the standard required to test new HRT regimens. As new and potentially better HRT regimens evolve, this paper explores what may be the best protocol and HRT regimen to use to obtain scientifically and clinically valid results.

WHAT MAY BE THE OPTIMAL REGIMEN FOR FUTURE TRIALS?

Route of administration

To date, there are no reported long-term, randomized, placebo-controlled trials of transdermal HRT. The ELITE trial is studying only oral estradiol but the KEEPS study has a transdermal arm with cyclical oral progesterone^{10,11}. Oral estrogen is known to have a number of procoagulant effects, which could explain the two- to threefold increased risk of thrombotic events in women taking oral HRT^{2,12}. Oral estrogen has first-pass liver metabolism. This increases hepatic production of clotting factors and decreases anti-clotting factors, and these favor intravascular thrombus formation^{13–15}. The ESTHER studies found transdermal estrogen to be a safer route of administration even in obese women and in those with thrombophilia¹⁶.

Transdermal estrogen may also potentially reduce the risk of stroke and transient ischemic attacks that have been associated with oral HRT^{17,18}. Thus, from the point of view of reducing two major morbidities, thromboembolism and stroke, the transdermal route deserves further study¹⁹. However, transdermal estrogen is associated with a different lipid profile from oral estrogen²⁰. The potential cardioprotective increase in levels of high density lipoproteins, seen with the oral route, is absent when the transdermal route is used. On the other hand, triglyceride levels are not elevated, as seen

with the oral route. The ability of transdermal estrogen to slow arterial intimal thickening and calcification is more relevant; it is currently the best predictor of cardiovascular events and deserves study.

Choice of HRT regimen

Although there are inadequate data to show that one estrogen is better than another, estradiol has been shown to be well absorbed transdermally and gives effective symptom control¹⁹. However, it is likely that all progestogens are not equal and, in particular, the androgenic progestogens may undermine the potential cardioprotective actions of estrogen^{21,22}. Micronized progesterone appears to have the safest profile of the current progestogens but a selective estrogen receptor modulator (SERM), e.g. bazedoxifene, would potentially avoid the disadvantages of progestogens²³. Such a SERM should give the needed endometrial protection and potentially reduce the risk of breast cancer and mood disturbance associated with some progestogens in some women. Oral bazedoxifene in conjunction with estrogen effectively reduces menopausal symptoms and improves quality of life when compared to placebo²⁴. A combined transdermal estrogen and SERM would be the ideal regimen to study if future research can show that the SERM was effective transdermally.

Flexible regimen

It is important that the regimen chosen is flexible as, in clinical practice, tailoring of the dose to the individual greatly improves the efficacy/side-effect ratio and subsequent compliance. This will help reduce drop-out rates from the two common start-up side-effects of HRT, namely early uterine bleeding and breast tenderness, that were seen in trials with fixed HRT regimens²⁵.

Entry criteria

The cardiovascular effects of HRT vary depending on the age at baseline²⁶. Women less than 65 years old had a 45% decreased risk for all-cause mortality but, for women over 75 years, the risk was similar to that of never-users. Also, meta-analyses of randomized, controlled trials show a decrease in both cardiovascular events and mortality in those commencing HRT under the age of 60 compared to placebo^{27,28}. This suggests that time since menopause modifies the relationship between HRT and ischemic heart disease. Similarly, women commencing HRT at menopause (mean age 48.7 years) had a 26% decreased risk of developing dementia, while women starting HRT later in life (mean age 76 years) had a 48% increased risk⁸. In clinical practice, nearly all HRT users are women with menopausal symptoms who commence HRT near menopause. In the WHI, only 3.4% of the participants were symptomatic and under the age of 60 years. The length

of the potential therapeutic cardioprotective window is not known. The combined results of ELITE and KEEPS may shed some light on this. The need for estrogenic cardioprotection may begin before the final menstrual period and, as in the KEEPS protocol, a cyclical progestogenic regimen needs to be used if perimenopausal women are included. A flexible regimen could allow a postmenopausal continuous combined regimen to supersede the perimenopausal cyclical regimen after about 2 years in symptomatic women entering the trial at perimenopause. However, the practical administration of such a trial would be simplified by including only recently postmenopausal women with the use of only a combined continuous HRT regimen and identical placebos.

If the estrogen is given separately from the progesterone or SERM, then flexibility of the estrogen and placebo dose is possible to try to minimize breast tenderness should the starting dose of estradiol be too high for any individual. This improves compliance.

A study of symptomatic women is recommended as currently this is the main indication for therapy and it may be that symptomatic women have the most cardiovascular benefit^{29,30}. Women with severe symptoms (the top quartile) will not be enrolled to reduce drop-out in the placebo group and women with few or no menopausal symptoms (the lowest quartile) would be excluded.

PROPOSED RESEARCH PLAN

Design and setting

The trial should be designed as a randomized, placebo-controlled, double-blind trial of 5–7 years. The setting should be in general practices in collaborating international countries.

Recruitment

Research nurses would send letters to eligible women in participating practices from their general practitioner inviting them to local group meetings to discuss the trial. Details of the trial would be included in the letter. After the information meeting, interested women would be individually screened by a research nurse before trial entry and a run-in period. This method of recruitment was successfully used in WISDOM³¹.

Inclusion and exclusion criteria

To be included in the trial, women would be postmenopausal (1–4 years since last period or hysterectomized), symptomatic, under age 55, and self-rated in the 25–75th percentile of menopausal symptom severity (Greene score), to avoid asymptomatic and severely symptomatic groups³². Exclusion criteria would be a history of estrogen-dependent cancer, ischemic

heart disease, stroke, thromboembolism, major neurological disease or unresolved gallbladder disease. Women with or without a uterus would be separately randomized by central computer randomization after trial entry.

Interventions

Interventions would be a modern and flexible regimen consisting of a transdermal estradiol patch and an oral/transdermal SERM, e.g. bazedoxifene. Identical transdermal/oral placebos would be used. For hysterectomized women, the intervention would be an estradiol patch (25, 50, 75, or 100 µg) or placebo patch using flexible doses starting at 50 µg, 50 µg/24 h.

Outcome measures

Primary outcome measures would be progression of cardiovascular disease as measured yearly by carotid artery intimal thickness³³ and coronary artery calcium scores³⁴. Secondary outcome measures would be yearly symptom scores, quality of life scores³⁵, cognitive function tests³⁶, all cancers including breast cancer, bone density, fractures, cerebrovascular disease, venous thromboembolism and all-cause mortality.

Ethnicity, run-in phase and pre-trial screening

Symptomatic eligible women of any ethnicity should be eligible as HRT is indicated for symptomatic women of all cultures. At trial entry, a 2-month run-in phase using placebo is proposed to assess compliance and exclude patch allergy and skin adherence issues. Pre-trial screening would consist of mammography, cervical smears, and general examination; baseline hematology and biochemistry would help to exclude detectable baseline morbidity.

Statistical analysis

Carotid artery intimal thickness

With a significance level of 0.05 and 99% level of detection, a group size of 145 in each of the treatment and placebo groups finishing the study would detect a difference of -0.017 mm after 5 years. This is based on published data on the effects of hormone treatment on carotid artery intimal thickness measurements in postmenopausal women¹¹. The published underlying population progression rate is 0.0036 mm/year and the estimated minimum effect of the treatment is 0.0002 mm/year, a minimum rate of progression that would be clinically significant.

Coronary artery calcium scores

In published data from large observational studies, the extent of apparent HRT protection against coronary heart disease

ranged between 40 and 50%³⁷. Assuming an 18% progression rate per year in untreated women, a group size of 150 would allow detection of a 50% rate of reduction in calcium progression in treated women with a significance of 0.03 by the χ^2 test³⁸.

The three arms of the study would require a total of 450 participants to complete the study. With an estimated drop-out rate of 44% in the placebo group and 32% in the two treatment groups, the total number of participants required would be 612³⁹. To help increase recruitment and minimize drop-out, yearly group meetings of participants would be proposed in their locality³¹.

Logistics

Central computerized randomization, a safety monitoring committee and an outcome adjudication committee would be required.

Ethical clearance

The main ethical considerations would include informed consent, trial insurance, conflict of interest (especially in regard to funding) and beneficence and non-maleficence to trial participants. In order for the trial to be adequately powered, it would be run internationally across multiple centers, with ethical approval from all sites, as in WISDOM³⁹. The involvement of a pharmaceutical company would be necessary to provide the trial therapies and identical placebo. Ideally, main trial funding should be independent of the pharmaceutical industry.

DISCUSSION

There are several potential limitations to long-term RCTs of HRT and to those using surrogate end-points of major disease (Table 2). However, RCTs help to eliminate the potential selection, detection and recall biases of observational studies.

Table 2 Study limitations of medium-term trials

1. Surrogate end-points for cardiovascular disease and dementia and fractures are not precise predictors of these morbidities or mortality
2. The cardio-deleterious process and optimal therapeutic window may start with ovarian decline in perimenopause or before that time
3. Optimal regimens may change over 7 years
4. Volunteers for randomized, controlled trials may not be representative of the population usually treated
5. A randomized, controlled trial can study only one or two regimens in circumstances limited by their entry and exclusion criteria
6. Retention and compliance rates may compromise the trial over time

Currently, two randomized trials of HRT from near menopause are in progress, i.e. the ELITE and KEEPS trials^{10,11}. ELITE is a 7-year study of 643 women receiving oral estradiol and vaginal progesterone versus placebo. The comparative groups in the ELITE study are those initiating HRT less than 6 years post menopause versus those taking trial therapies more than 10 years after menopause. Surrogate markers of cardiovascular disease such as carotid artery intimal thickness, coronary artery calcification and cognitive function are the outcomes. This is an important trial and results may be available in 2013. Potential limitations are that the group being treated from near menopause extends up to 6 years from menopause and the length of the potential 'therapeutic window' is not known; only oral HRT is being studied, not allowing study of whether transdermal estrogen reduces thromboembolism and stroke risk, and women in the late-therapy group may have had HRT prior to trial entry, possibly confounding the results.

The KEEPS study of 728 postmenopausal women is studying both oral and transdermal estrogen along with cyclical progesterone. It has a narrower 3-year window for entry near menopause and is following the progress of cardiovascular disease for 4 years, using the same surrogate markers as ELITE. This study is well designed to answer many questions concerning these HRT regimens for up to 4 years of use.

Both ELITE and KEEPS should add valuable information to support or refute the 'critical window' hypothesis. Methodological lessons can be learnt from these trials about trial recruitment, therapy compliance, and cost. It is likely that regulatory agencies, the medical profession and the public will want to see the results of medium-term trials of new HRT regimens such as transdermal estrogen and oral or transdermal SERMS, micronized progesterone or intrauterine progestogen before endorsing or registering such therapies. These trials will show if studies of up to 4–7 years are feasible in terms of subject retention and therapy compliance. Our suggestions to minimize drop-out and increase compliance may further help participant retention. A conservative estimate of the cost of a 7-year trial, as described here, is approximately AUD \$41 million (Table 3).

Table 3 Costing for a 7-year study with surrogate outcomes for cardiovascular disease, mental and bone health (in AUD \$)

Per patient

B-mode ultrasound (carotid-intimal thickness) = \$37.85 × 8

Coronary artery calcification scores (CT chest/abdomen) = \$295 × 8

Bone densitometry = \$100 × 2

Hematology, lipids, biochemistry = \$40 × 10

Cognitive function tests = \$150 × 8

Mammogram = \$150 × 5

Annual costs = \$5000 per patient based on projected clinical trial costs

Central costs (shipping and administration) = \$2,000,000/year

Total estimated cost of a 7-year trial based on a study of 612 participants = AUD \$ 41,088,833

It is not appropriate to call for the impossible 30-year HRT trial that assesses major adverse event outcomes and mortality, before being prepared to prescribe HRT to symptomatic women for the duration of their debilitating symptoms, which can last for many years. However, medium-term trials such as KEEPS and ELITE are proving that these trial durations are possible and the success of these trials or otherwise in maintaining the integrity of their protocols will be as interesting as their results. New trial protocols, such as the one described here, should take into account the lessons learnt from past medium- and long-term RCTs. They are feasible,

much needed and should be funded by health authorities rather than industry. The time, effort and costs of such trials should not inhibit the development of better therapeutic regimens for postmenopausal women, as potentially they may reduce major and costly morbidity in later life and improve the health-related quality of life of women.

Conflict of interest Alastair MacLennan was the Chief Investigator of the Australian arm of WISDOM.

Source of funding Nil.

References

- MacLennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database of Systematic Reviews* 2004, Issue 4. Art. No.: CD002978
- Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33
- Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701–12
- Vickers MR, MacLennan AH, Lawton B, et al. Main morbidities recorded in the Women's International Study of long Duration Oestrogen after Menopause (WISDOM): a randomised controlled trial of hormone replacement therapy in postmenopausal women. *BMJ* 2007;335:234–44
- Welton AJ, Vickers MR, Kim J, et al. Health related quality of life after combined hormone replacement therapy: randomised controlled trial. *BMJ* 2008;337:a1190
- Pal L, Hailpern SM. Cardio-deleterious implications of declining premenopausal ovarian reserve. *Sexuality, Reprod Menopause* 2009;17:S11–12
- Sowers M, Randolph Jr J, Jannausch M, et al. Levels of sex steroid and cardiovascular disease measures in premenopausal and hormone-treated women at midlife. Implications for the timing hypothesis. *Arch Intern Med* 2008;168:2146–53
- Whitmer RA, Quesenberry CP, Zhou J, Yaffe K. Timing of hormone therapy and dementia: the critical window theory revisited. *Ann Neurol* 2011;69:163–9
- MacLennan AH, Sturdee D. The end of WISDOM. *Climacteric* 2002;5:313–16
- Harman SM, Brinton EA, Cedars M, et al. KEEPS: The Kronos Early Estrogen Prevention Study. *Climacteric* 2005;8:3–12
- Hodis HN for the ELITE study group. <http://clinicaltrials.gov/ct2/show/NCT00114517>
- Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism. A systematic review and meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002;136:680–90
- De Lignieres B, Basdevant A, Thomas G, et al. Biological effects of estradiol-17 beta in post-menopausal women: oral versus percutaneous administration. *J Clin Endocrinol Metab* 1986;62:536–41
- Scarabin PY, Alhenc-Gelas M, Plu-Bureau G, Taisne P, Agher R, Aiach M. Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial. *Arterioscler Thromb Vasc Biol* 1997;17:3071–8
- Alkjaersig N, Fletcher AP, de Ziegler D, Steingold KA, Meldrum DR, Judd HL. Blood coagulation in postmenopausal women given estrogen treatment: comparison of transdermal and oral administration. *J Lab Clin Med* 1988;111:224–8
- Canonica M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* 2007;115:840–5
- Renoux C, Dell'Aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. *J Thromb Haemost* 2010;8:979–86
- Arana A, Varas C, Gonzalez-Perez A, Guterrez L, Bjerrum L, Garcia Rodriguez LA. Hormone therapy and cerebrovascular events: a population-based nested case-control study. *Menopause* 2006;13:730–6
- Speroff L. Transdermal hormone therapy and the risk of stroke and venous thrombosis. *Climacteric* 2010;13:429–32
- Crook D. The metabolic consequences of treating postmenopausal women with non-oral hormone replacement therapy. *Br J Obstet Gynaecol* 1997;104:4–14
- Sitruk-Ware R. New progestogens: a review of their effects in perimenopausal and postmenopausal women. *Drugs Ageing* 2004;21:865–83
- Hermesmeyer RK, Thompson TL, Pohost GM, Kaski JC. Cardiovascular effects of medroxyprogesterone acetate and progesterone: a case of mistaken identity? *Nat Clin Pract Cardiovasc Med* 2008;5:387–95
- Ronkin S, Northington R, Baracat E, et al. Endometrial effects of bazedoxifene acetate, a novel selective estrogen receptor modulator, in postmenopausal women. *Obstet Gynecol* 2005;105:1397–404
- Utian W, Yu H, Bobula J, Mirkin S, Olivier S, Pickar JH. Bazedoxifene/conjugated estrogens and quality of life in postmenopausal women. *Maturitas* 2009;20:329–35
- MacLennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database of Systematic Reviews* (Online) 2004:CD002978
- Stram DO, Liu Y, Henderson KD, et al. Age-specific effects of hormone therapy use on overall mortality and ischemic heart disease mortality among women in the California Teachers Study. *Menopause* 2011;18:253–61
- Salpeter SR, Walsh JM, Greyber E, Salpeter EE. Coronary heart disease events associated with hormone therapy in younger and older women. *J Gen Intern Med* 2006;21:363–6

28. Salpeter SR, Walsh ME, Greyber E, Ormiston TM, Salpeter EE. Mortality associated with hormone therapy in younger and older women. *J Gen Intern Med* 2004;19:791–804
29. Pines A. Vasomotor symptoms and cardiovascular disease risk. *Climacteric* 2011;14:535–6
30. Lee SW, Jo HH, Kim MR, Kwon DJ, You YO, Kim JH. Association between menopausal symptoms and metabolic syndrome in postmenopausal women. *Arch Gynecol Obstet* 2011 August 19. Epub ahead of print
31. Paine BJ, Stocks NP, MacLennan AH. Seminars may increase recruitment to randomised controlled trials: lessons learned from WISDOM. *Trials* 2008;9:5 doi:10.1186/1745-6215-9-5
32. Greene JG. Measuring the symptoms dimension of quality of life: general and menopause-specific scales and their subscale structure. In Schneider HPG, ed. *Hormone Replacement Therapy and Quality of Life*. Lancaster: Parthenon Publishing, 2002:35–43
33. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med* 1999;340:14–22
34. Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium for all-cause mortality. *Radiology* 2003;228:826–33
35. Schneider HPG, MacLennan AH, Feeny D. Assessment of health-related quality of life in menopause and aging. *Climacteric* 2008; 11:93–107
36. MacLennan AH, Henderson VW, Paine BJ, et al. Hormone therapy, timing of initiation, and cognition in women older than 60 years: the REMEMBER pilot study. *Menopause* 2006;13: 28–36
37. Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. *Ann Rev Pub Health* 1998;19: 55–72
38. Raggi P, Callister TQ, Cooil B, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 2000;101: 850–5
39. Vickers MR, Martin J, Meade TW. The Women's International Study of long-Duration Oestrogen after Menopause (WISDOM): a randomised controlled trial. *BMC Women's Health* 2007; 7:2

