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# CLIMACTERIC

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The Journal of the International Menopause Society

Editors-in-Chief

David W. Sturdee      Alastair H. MacLennan



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The Journal of the International Menopause Society

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## Hormone replacement therapy in the post-Women's Health Initiative era

A Report of a meeting held in Funchal, Madeira  
February 24–25, 2003

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**Book** Whitehead MI, Cooper A. *An Atlas of the Menopause*. London: Parthenon Publishing, 2002:94–6

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**Published abstracts** Christiansen JS. Growth hormone, growth hormone secretagogues and ageing. Presented at *The First World Congress on the Aging Male*, Geneva, February, 1998. *Aging Male* 1998;1:6, Abstr 11

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The meeting was chaired by Professor Henry Burger

The following participants at the Meeting contributed to this Report:

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**Martin Birkhäuser**, University of Bern, Switzerland

**Henry Burger**, Prince Henry's Institute of Medical Research, Australia

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**John Stevenson**, Royal Brompton Hospital and Imperial College, London, UK

**Malcolm Whitehead**, King's College Hospital, London, UK

## Meeting Report

# Hormone replacement therapy in the post-Women's Health Initiative era

Henry Burger, *Chairman of the Meeting*

### SUMMARY

Over 24–25 February 2003 in Funchal, Madeira, Novo Nordisk gathered together 25 of the top international hormone replacement therapy (HRT) experts, in order to debate the results of the Women's Health Initiative<sup>1</sup> (WHI) and interpret its possible implications for the future use of HRT. The meeting covered many interesting and controversial areas, addressing the complex and multifaceted issues with insight and realism.

Some of the areas covered at the meeting were the use of HRT as a short- or long-term therapy for hot flushes, for general menopausal symptom relief and in osteoporosis prevention; the overall risk–benefit profile and specific breast cancer concerns were also discussed. The WHI data were reviewed and summarized, and, although it was generally agreed that the study was well designed and executed, its relevance to standard hormone therapy for clinical practice must be seriously called into question. The target population used in the WHI is not representative of the target population for whom menopausal HRT is normally considered. It is important to note that randomized controlled trials such as the WHI are really scientific tools for a group of research participants, not a form of individualized medical management. Since their publication, the relevance of the WHI study results for everyday clinical practice has been the subject of controversy. The WHI targeted a group of women who were much older than those normally treated and who had numerous other risk factors. These were not women for whom a practicing clinician would think about initiating hormone therapy with the regimen that was used. Putting a high-risk 70-year-old woman on 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate would not seem appropriate for any indication. With this in mind, we reviewed statements and guidance that followed the release

of the WHI to the media, putting them in context with the actual results. Focusing on data taken out of context and without reference to subject profiles, the media created an emotive wave of uncertainty for patients and physicians, which needs to be addressed through realistic, factual communication.

It is clear that hormone therapy is effective for postmenopausal symptoms and osteoporosis prevention. Timing is critical for the initiation of therapy and length of treatment. The individual's unique personal profile must be assessed. This leads to the paradox of osteoporosis prevention: therapy should be long-term, but it is long-term therapy that may increase breast cancer risk.

The meeting reviewed the uncertain nature of the risks for breast cancer, although the evidence is becoming stronger that combinations of estrogen and progestogen cause a modest increase in risk after 5 years, while this seems not to be true for estrogen alone. Cardiovascular disease issues were also reviewed and discussed. This is perhaps the most misinterpreted result that came out of the WHI, given the population of women studied. Considering the vascular biology and effects of early interventions, the WHI finding that hormone therapy has no place in primary cardiovascular protection is an unwarranted conclusion.

Other issues regarding the risk–benefit profile of HRT for the individual patient were also discussed. Additionally, presenters explored the possibility of class effects against the potential risk factors associated with particular estrogen and progestogen types. It is quite clear that CEE and 17 $\beta$ -estradiol differ with respect to their source and composition; pharmacokinetic and metabolic data indicate that they differ in their total estrogenic potency, with CEE possessing greater estrogenic potency. Using 17 $\beta$ -estradiol at the lowest dosage level can provide safe and effective therapy for most indications.

The evidence for progestogen differences is even more clear. Medroxyprogesterone acetate and norethisterone acetate have different pharmacokinetic profiles and different activities on steroid receptors. Evidence from preclinical and clinical studies supports the conclusion that these differences result in different pharmacological and clinical effects in favor of norethisterone acetate.

Having comprehensively discussed and reviewed all available evidence, a consensus was achieved with regard to appropriate therapy: HRT should be given to women with menopausal complaints to meet their individual needs, taking into account their individual risk profile and the overall therapeutic objectives.

## INTRODUCTION

During 24–25 February 2003 in Funchal, Madeira, Novo Nordisk gathered together 25 of the top international hormone replacement therapy (HRT) experts in order to debate the results of the Women's Health Initiative<sup>1</sup> (WHI) and interpret its possible implications for the future use of HRT. Reviewing WHI data, it was generally agreed that the study was well designed and executed, but its relevance to standard clinical practice must be called into question. The use of HRT as a short- or long-term therapy for hot flashes, for general menopausal symptom relief and in osteoporosis prevention, and the overall risk–benefit profile and specific breast cancer concerns were discussed. Additionally, presenters explored the differences between estrogen and progestogen types, highlighting the importance of correct dosage levels and individually tailored treatments. Of particular significance is the positioning in context of the WHI findings by assessing all currently available data before considering a patient's individual treatment program. Participants also evaluated the sensational popular media coverage following the WHI. Focusing on data taken out of context and without reference to subject profiles, the media created a wave of uncertainty for patients and physicians. This needs to be addressed through realistic, factual communication.

## SUMMARY OF MAJOR FINDINGS FROM THE WHI RANDOMIZED CONTROLLED TRIAL

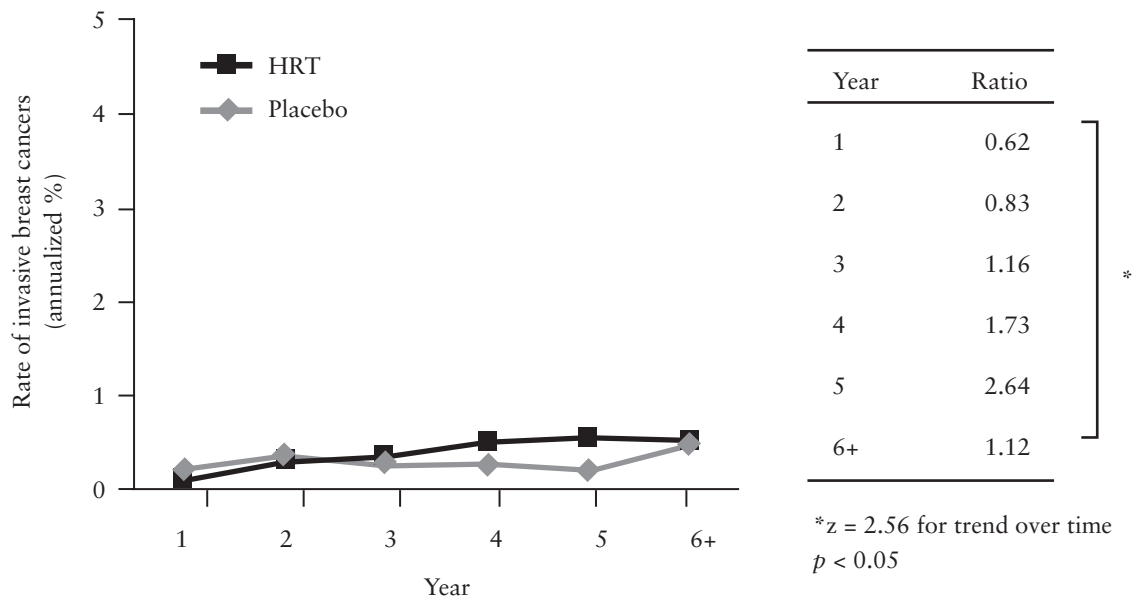
The meeting chairman, Professor Henry Burger from the Prince Henry's Institute of Medical Research, Australia, summarized the WHI's major findings with a concise overview, noting the reactions of several authorities and interested groups to the study. Designed by epidemiologists and statisticians, not clinicians, the WHI's aim was to study the preventive effects of the combination of conjugated equine estrogens (CEE, 0.625 mg) and medroxyprogesterone acetate (MPA, 2.5 mg) on healthy postmenopausal women. Several mitigating factors should be taken into account when assessing the trial results. Considering the baseline characteristics of the 16 608 study participants, Professor Burger pointed out that 66% of the participants were over the age of 60 years, about a decade above the usual candidate age for HRT, and 69% had a body mass index (BMI) above the normal

25 kg/m<sup>2</sup>. Additionally, 36% were hypertensive, 12.5% were hypercholesterolemic and on treatment, 6.9% were statin users, 40% were previous smokers and 10.5% continued to smoke during the trial. 'Not exactly what you might call a clean subject selection for looking at the effects of long-term hormone therapy', he said.

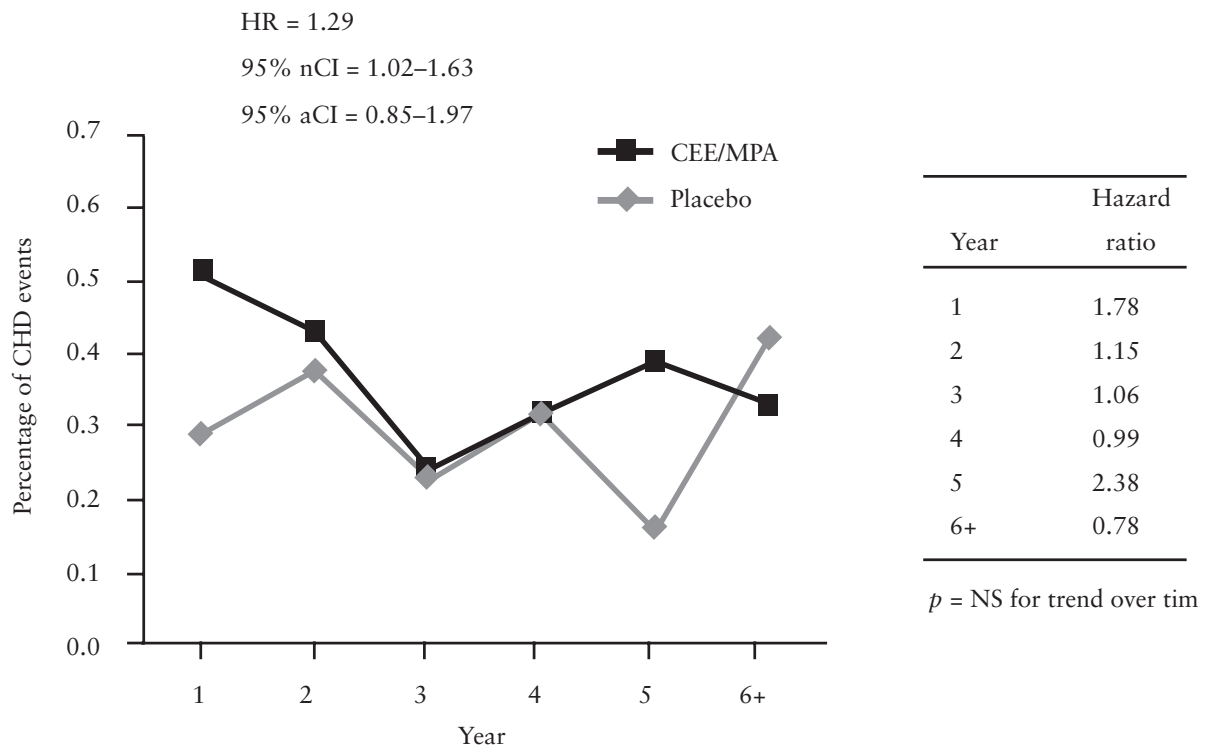
Perhaps the most publicly emotive aspect, and what terminated the study prematurely, was the effect of HRT on increased risk of invasive breast cancer (hazard ratio 1.26, nominal 95% confidence interval (CI) 1.00–1.59). Although the risk exceeded the set limit, it actually was not statistically significant with a lower boundary of 1.00. A comparison of the hazard ratios for the placebo and therapy groups reveals rates that are virtually the same up to year 4, diverging and then overlapping again at year 6 (Figure 1). This suggests a small increase in risk with HRT use for 4 years or more, but the proportion of women who developed breast cancer in both groups was very small. Additionally, the hazard ratio for previous non-users of HRT was only 1.06 (95% CI 0.81–1.38); thus, the increase in risk was almost entirely in the previous-user population.

Assessing the effects on coronary heart disease (CHD; hazard ratio 1.29, nominal 95% CI 1.02–1.63), the most significant increase was seen in year 1 of the WHI, similar to the Heart and Estrogen/progestin Replacement Study (HERS)<sup>2</sup>. In years 2–4, the HRT and placebo groups closely paralleled each other, with a divergence in year 5 and crossing in year 6 (Figure 2). Professor Burger commented, 'A recurrent observation in these annualized plots is the curious behavior of what happened in year 5, with a drop in the placebo group well below the otherwise fairly horizontal trend for the data . . . and making you wonder about the wisdom of premature termination of the study.' Results for global index, stroke and venous thromboembolism also showed statistically significant increases in risk among HRT users, but a significant number of subjects had cardiovascular risk factors or pre-existing cardiovascular disease. The WHI showed positive indications for CEE–MPA use in reducing colorectal cancer, hip fractures and total fractures.

The International Menopause Society (IMS) gave a considered response to the WHI, underscoring a number of issues related to the study. Entry criteria did not reflect standard clinical practice, and there was preferential selection of older first-time HRT users, biasing the study against beneficial effects because of age-dependent cardiovascular risk factors. There was a high



**Figure 1** Women’s Health Initiative (WHI) annual invasive breast cancer rates for hormone replacement therapy (HRT) versus placebo. Adapted from reference 1



**Figure 2** Women’s Health Initiative (WHI) annual coronary heart disease (CHD) events rate for hormone replacement therapy (HRT) versus placebo; CHD events include eight silent myocardial infarctions. HR, hazard ratio; nCI, nominal confidence interval; aCI, adjusted confidence interval; CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate; NS, not significant. Adapted from reference 1

differential unblinding rate (40.5% HRT, 6.8% placebo), and, if adjusted for multiple testing, the number of significant outcomes was dramatically lowered. The trial period of 5.2 years was too short to implicate CEE-MPA as a carcinogen, and the general trends of breast cancer mortality were not reflective of the bleak public perception of the WHI results. The IMS emphasized that HRT's primary indication remains symptom relief, that HRT should remain a focus of cardiovascular trials, that the WHI can only be related to CEE-MPA prescription to elderly, obese women with characteristics similar to the WHI subject pool, and that doctors should continue to counsel patients individually.

The North American Menopause Society (NAMS) also provided a measured assessment, but with somewhat different recommendations. While stating that estrogen-progestogen therapies and estrogen-alone therapy should be primarily for symptomatic treatment for the shortest duration to achieve treatment goals, they cautioned that no estrogen-progestogen therapy should be used for CHD prevention, and alternatives should be considered for osteoporosis prevention. The NAMS stressed that data from both the WHI and HERS trials cannot be extrapolated to symptomatic perimenopausal women or those with an early menopause. Additionally, they suggested that alternative methods of administration could offer advantages, and of primary importance is that each patient has her individual risk profile assessed before beginning any estrogen-progestogen or estrogen-alone treatment. No consensus was reached on acceptable treatment duration, reasons for extension of treatment, premature menopause or ovarian failure as indicators for estrogen-progestogen or estrogen-alone therapy and best methods of discontinuing therapy.

A number of other influential groups published recommendations in the wake of the WHI. The US Preventive Task Force stated that there was enough evidence against routine use of estrogen and progestogen for the prevention of chronic conditions in postmenopausal women, but there was insufficient evidence to make a decision for or against using unopposed estrogen in women who have had hysterectomies. The American College of Obstetricians and Gynecologists concluded that HRT should not be used for CHD, advised caution in using it for osteoporosis prevention and, while accepting its use for symptom relief, advised against prolonged use. The American Heart Association was also negative on the use of

HRT for CHD prevention. Reflecting upon the WHI data and the diverse interpretations and responses, Professor Burger provided a key introduction to a lively discussion on the future of HRT.

## WHI: A CRITICAL REVIEW

Professor David Archer, Director of the CONRAD (Contraceptive Research and Development) Clinical Research Center in Norfolk, Virginia, USA, assessed the WHI's impact, and the manner in which the results were released by the media. Although the WHI study was a well-designed, randomized study, he noted that there were inevitable biases; some associations were weak or could be due to chance and other studies could have very different outcomes. 'The concern now is that, because of the WHI results, no other study will be done', said Professor Archer. This is a significant issue, as the results could be left unchallenged.

When interpreting the WHI data, it is important to consider participant behavior and treatment outside the trial. HERS trial results were released in the middle of the WHI, with subjects receiving this information, and participation itself can alter individual behavior. Furthermore, medication changes may have occurred through the subjects' private practitioners, who were not involved in the trial. Another key aspect is the high drop-out rate in the WHI, potentially modifying the outcomes. 'There is a huge attrition rate during the course of the trial, from about 8000 women at the beginning to 1500 at the end', said Professor Archer.

One question that the WHI trial investigators have not addressed is the incidence rate compared with underlying disease. Although the news media presented the subjects as 'healthy women', Professor Archer underscored Professor Burger's earlier points that obesity, diabetes, smoking and hypertension were present in a significant number of participants. While the investigators point out that randomization should overcome any differences, Professor Archer argued that it is possible that there could have been longer use of insulin, a difference in the type of hypertension and a disparity in statin use between the two trial groups, which could influence the study results as previous investigations have demonstrated (Figure 3). He also highlighted the lack of socio-economic breakdown, an important factor in cardiovascular disease.

Addressing the nominal 95% CI, Professor Archer stated that epidemiologists agree that it should be used only for one or two outcomes. Once it is adjusted for multiple interactions, the statistical significance disappears for all WHI results, except venous thromboembolism (Table 1). He also emphasized that most cardiovascular adverse events occurred in the first year, after which the comparison curves are parallel.

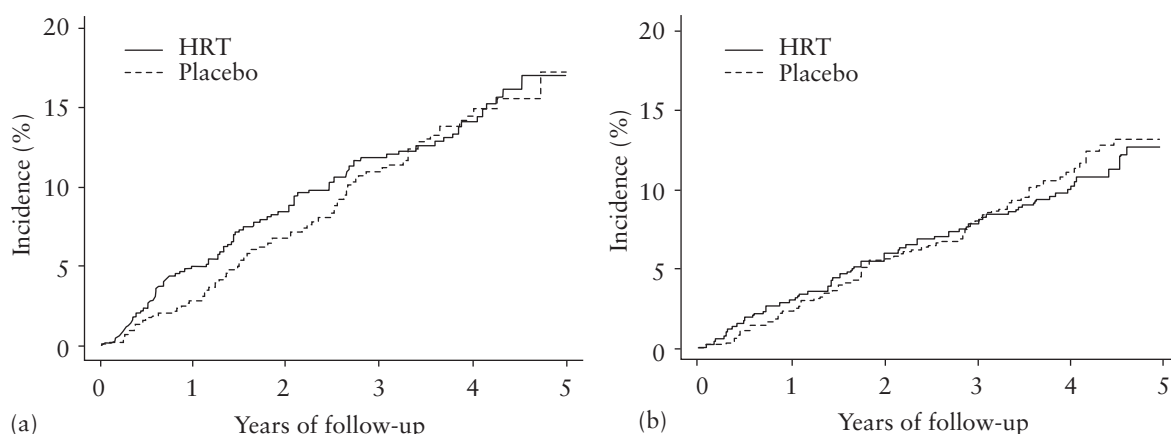
The dramatic impact of the WHI upon HRT prescriptions resulted more from sensational media reporting than from actual data. Consumers now believe that they should not use HRT, and the use of alternative therapies has increased. Professor Archer said, 'Several months ago *The National Enquirer* listed ten different medications that can be used to substitute for hormone therapy, none of which have been ever clinically proven to do anything, some of which potentially can cause harm.' He believes that the average drop in HRT prescriptions is coming from the primary care doctors who write approximately 30% of US prescriptions. Time constraints and lack of

knowledge contribute to HRT cessation, as it is the easiest course of action. 'In the few talks I have given to a non-obstetrician/gynecologist audience, I would estimate from the audience interaction that probably less than 0.01% have read anything other than headlines of the local newspaper', said Professor Archer. Consumers and doctors are getting their information from the media.

The post-WHI reality is that perhaps HRT may not be appropriate for some women, lower doses may be better, other delivery routes should be explored and other steroids could have different outcomes. The risk–benefit profile should be evaluated sensibly, with further research to identify accurately the at-risk population.

### HORMONE REPLACEMENT THERAPY FOR HOT FLUSHES

Mr Whitehead began by profiling the typical woman who uses HRT in Europe and the United States: they tend to be Caucasian, have a normal BMI, be in the perimenopausal transition or early



**Figure 3** Effects of statin use on cardiovascular events in women using hormone replacement therapy (HRT). (a) Women not on statin at baseline; (b) baseline statin users. Adapted from reference 3

**Table 1** Women's Health Initiative (WHI) results: summary of main outcomes. Data from reference 1

Outcome	Relative risk vs. placebo (95% nCI)	Increased absolute risk per 10 000 women/year	Increased absolute benefit per 10 000 women/year
CHD	1.29 (1.02–1.63)	+7	—
Invasive breast cancer	1.26 (1.00–1.59)*	+8	—
Stroke	1.41 (1.07–1.85)	+8	—
VTE	2.11 (1.58–2.82)	+18	—
Colorectal cancer	0.63 (0.43–0.92)	—	–6
Hip fracture	0.66 (0.45–0.98)	—	–5
Global index	1.15 (1.03–1.28)	—	—

\*Not significant; CHD, coronary heart disease; VTE, venous thromboembolism; nCI, nominal confidence interval

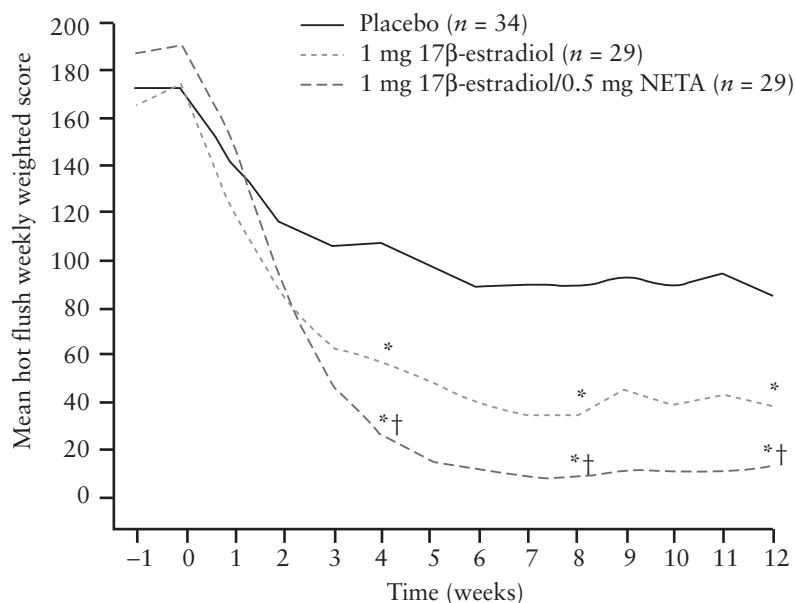
menopause, and symptomatic. He then explained that, globally, there is going to be a huge shift in female life expectancy over the next 50 years and this will result in much larger numbers of postmenopausal women. It is predicted that the average age for the onset of menopause will remain about 50 years. He emphasized that some studies report that up to 40% of women begin to have episodes of hot flushing and night sweating at least 10 years prior to menopause. Flushing episodes cause profound physiological changes that cause discomfort in one out of four women. There is a peripheral skin temperature change of between 5 and 9°C and there can be a change in basal heart rate of up to 12–20 beats/minute. Women can experience up to ten flushes per day and chronic sleep disturbance results if intense night sweats wake the patient four to five times each night. The resultant sleep deprivation may be associated with psychological changes and these, typically, are difficulty in making decisions, anxiety, irritability, and a loss of confidence. The psychological problems tend to be self-limiting for most women, but 25% of symptomatic women still experience hot flushes and night sweats 5 years after the menopause.

HRT is the most effective therapy to treat typical estrogen deficiency symptoms and the most important point of debate is the duration of therapy. In women with an intact uterus, a combination of estrogen and progestogen therapy is required and it is now recognized that the added

progestogen enhances the beneficial effects of estrogen in relieving frequent and severe flushes (Figure 4). Thus, lower estrogen doses can be used and these are effective in the majority of women<sup>6</sup>. It often takes 3 months for the benefits of therapy to be realized fully, and the first follow-up visit should take place at this time. Thereafter, Mr Whitehead suggested that patients be seen after a further 6 months and then annually. He emphasized that each patient should be regarded as being unique and should be treated individually. In some women, flushes and sweats resolve spontaneously within 2 years of menopause; however, many other women continue to experience symptoms for more than 5 years and, in some cases, it was well known that flushes and sweats could last for as long as 40 years. Mr Whitehead emphasized that, in his opinion, patients should be allowed to decide the duration of therapy after a full discussion of all benefits and risks of HRT. In patients with symptoms lasting many years, he posed the question, 'Are we God and do we make the patient symptom-free for 5 years and then withdraw treatment because the regulators say you can't use HRT long-term?'

## HORMONE REPLACEMENT THERAPY FOR HOT FLUSHES AND MORE

Outlining the need for a long-term treatment perspective, Professor Andrea Genazzani from the



**Figure 4** Hot flush reduction for 17β-estradiol versus placebo. \* $p < 0.05$ , significantly different from placebo; † $p < 0.05$ , significantly different from 1 mg 17β-estradiol. NETA, norethisterone acetate. Adapted from reference 5

University of Pisa, Italy, explained that, while women seek HRT primarily for symptomatic relief of hot flushes, the hot flushes themselves reveal the brain's susceptibility to estrogen reduction and a myriad of additional negative effects. In conjunction with hot flushes, lack of estrogen affects the brain, leading to other quality-of-life modifications including mood changes, anxiety, memory impairment and altered sexual behavior. Quality of life deteriorates on several levels. There are many similarities between the perimenopause and depression, with decreased libido, sleep disturbance, mood swings, concentration/memory problems, irritability, general loss of interest in life and fatigue (Figure 5). HRT may provide a stabilizing effect during the perimenopause and improve mood.

Estrogen has a positive effect on neurofunction, improving neurotransmission, neuroprotection, neurite branching synaptogenesis, cerebral blood flow and trophic factor expression. Its depletion may impair memory and cognitive function and accelerate the onset of Alzheimer's disease. According to the Cache County Study<sup>6</sup>, estrogen treatment may halt degeneration and provide some cognitive protection (Figure 6). This defensive brain effect depends on the duration of treatment and how early treatment is initiated. Estrogen-progestogen did not improve the condition of study participants who already had Alzheimer's disease. Professor Genazzani suggested that there is a need for more studies of estrogen use and improved cognitive function in postmenopausal women. He called for double-blind, randomized, controlled trials to confirm the long-term effects of estrogen and HRT on age-related decline in cognitive function and improvement in verbal memory.

Just as previous speakers emphasized the need for individualized treatment programs, Professor Genazzani also stressed the need for personalized patient profiles. Women may differ in age, years since onset of menopause, health status, disease development and concomitant medications. He made the case for early intervention with HRT, to prevent cardiovascular disease before myocardial infarctions, osteoporosis before fractures occur and dementia ahead of neuronal loss. Professor Genazzani closed with the forceful argument, 'On the basis of the Women's Health Initiative study [and] on the basis of the weight of these results, to start with the phrase that women should not be treated if they do not have any specific indications and, in such a case with the lower dose and

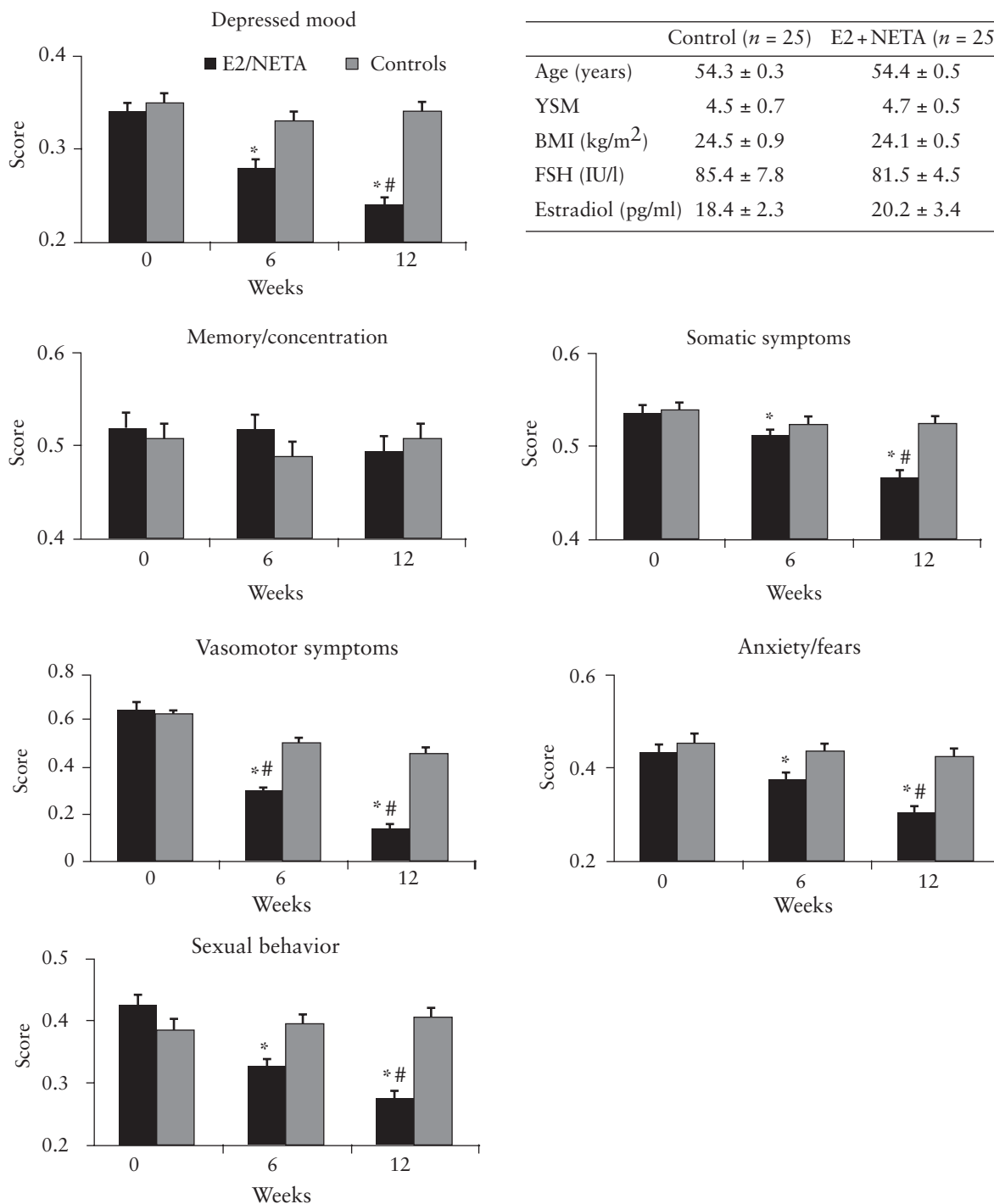
with the shorter time, I think is an anticultural attitude.'

## HORMONE REPLACEMENT THERAPY FOR OSTEOPOROSIS PREVENTION: WHEN TO START?

Dr Peyman Hadji from the Philipps-University of Marburg, Germany, presented a compelling case for early interventional use of HRT in osteoporosis prevention. Considering hip fractures, not only do they have a devastating effect for the individual with 50% never regaining previous mobility and 5–20% dying within 1 year, but also there is a cost to the public care system related to greater care requirements. Loss of bone mineral density (BMD) in the spine has equally dramatic consequences. The menopause greatly increases the risk, with possibly every second postmenopausal woman experiencing a fracture due to osteoporosis. 'More than 90% of osteoporotic fractures are related solely to estrogen deficiency', said Dr Hadji. He emphasized the question of timing in treatment, and outlined two preventive approaches: early and late intervention. Using an early approach with a low-dose combination of 17 $\beta$ -estradiol and norethisterone acetate (NETA), HRT is started immediately after the menopause to maintain BMD (Figure 7) and to retain trabecular connectivity. Using this approach, it is necessary to give HRT long-term. 'Five to ten years is the minimum, because you will not see an effect [if administered] later on', he said. On HRT discontinuation and the consequences for BMD, Dr Hadji stated that it is currently unclear whether there is any sustained benefit, but it is clear that bone loss resumes after therapy is withdrawn.

The late interventional approach is based on the rationale that treatment begins when the risk of fracture is greatest. Yet, as Dr Hadji pointed out, this is really too late. At this stage, the BMD has already deteriorated to a level where HRT, or any agent, including selective estrogen receptor modulators (SERMs) and bisphosphonates, will probably make very little difference to the microarchitectural structure of the bone. 'Today we do not have a rationale any more for the late approach', he concluded.

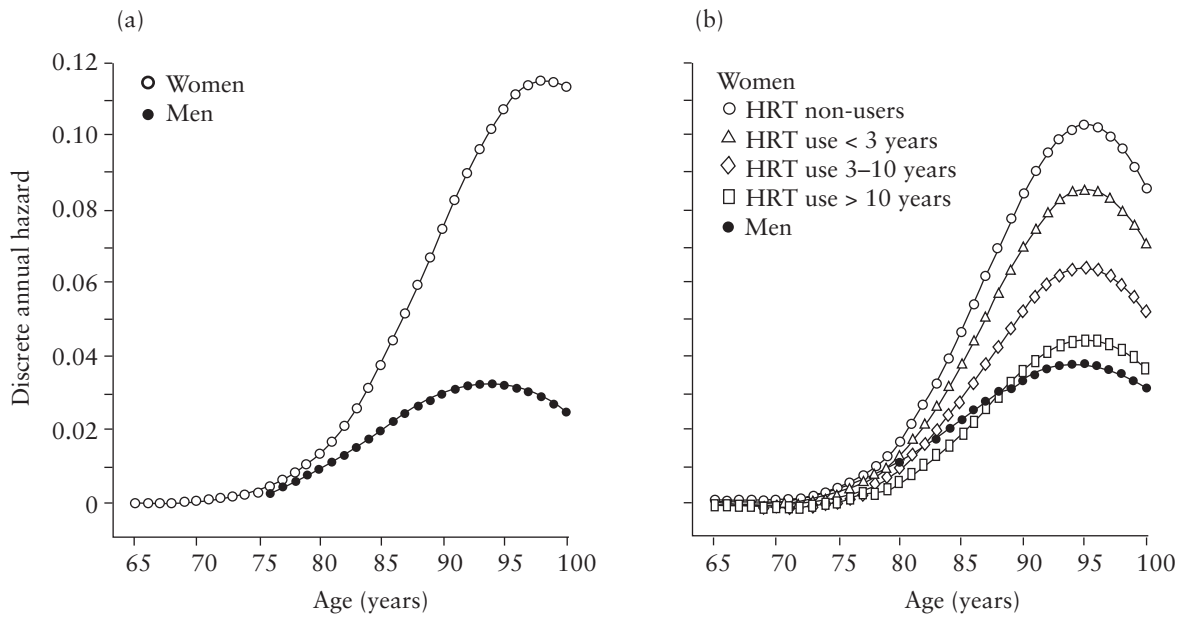
Dr Hadji also suggested the possible option of using BMD as a surrogate marker in identifying women suitable for HRT therapy. Women with high BMD have a high risk of breast cancer, as shown by numerous studies in recent years,



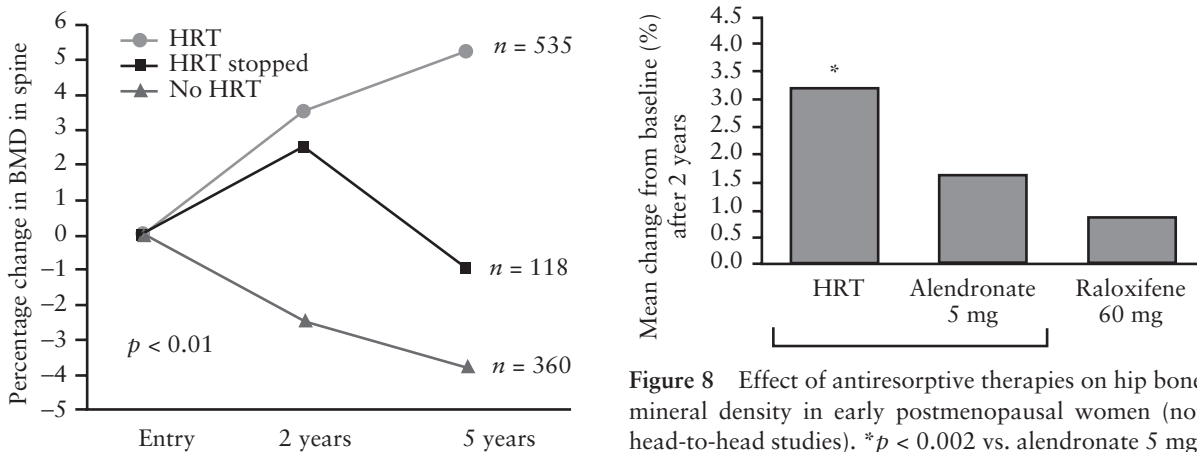
**Figure 5** Mood, memory, somatic symptom, anxiety, sexual behavior and vasomotor symptom scores for low-dose estradiol (E2) + norethisterone acetate (NETA) versus placebo. \**p* < 0.05 vs. corresponding basal values; †*p* < 0.05 vs. corresponding control group values; YSM, years since menopause; BMI, body mass index; FSH, follicle stimulating hormone. Adapted from reference 4

including one performed at the Philipps-University of Marburg using matched-pair analysis. Despite the participants being equal in all aspects, the Marburg study found significantly

higher BMD in women with breast cancer compared with controls. Dr Hadji proposed, ‘If women with osteoporosis or osteopenia really have a decreased risk of breast cancer, would this



**Figure 6** Alzheimer's disease incidence rates for hormone replacement therapy (HRT) versus placebo, Cache County Study. Men:  $n = 1357$ , mean age 73.2 years; women:  $n = 1889$ , mean age 74.5 years. Adapted from reference 6



**Figure 7** Influence of discontinuation of hormone replacement therapy (HRT) on bone mass. BMD, bone mineral density. Adapted from reference 7

**Figure 8** Effect of antiresorptive therapies on hip bone mineral density in early postmenopausal women (not head-to-head studies). \* $p < 0.002$  vs. alendronate 5 mg. Data from reference 8 and Evista® approval package

mean that these women are relatively safe for HRT?'

### HORMONE REPLACEMENT THERAPY FOR OSTEOPOROSIS PREVENTION: WHEN TO STOP?

Dr Marco Gambacciani from the University of Pisa proposed that the number of fractures is still very high when the BMD is still in the normal

range according to World Health Organization (WHO) criteria. Primary prevention for fractures should therefore begin long before pathological BMD values have developed. Additionally, there are other risks related to fractures, beyond BMD, showing the need to treat patients with drugs that offer multiple benefits, not just bone-specific medications. While improving BMD, HRT also enhances bone quality and muscle strength, helping to prevent both falls and fractures. Compared with other antiresorptive agents such as SERMs and bisphosphonates, HRT has significantly higher efficacy in retaining BMD (Figure 8). Dr Gambacciani went on to dismiss the myth that

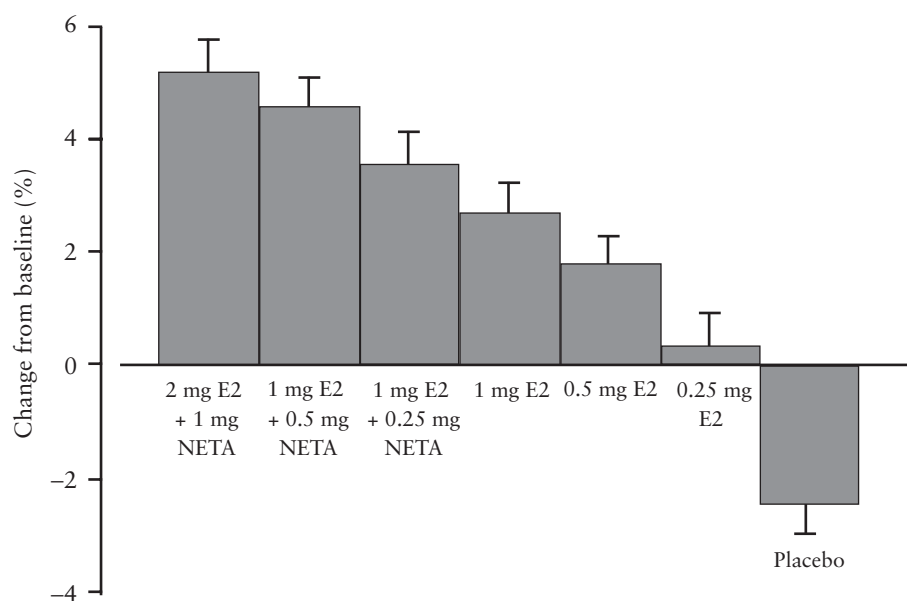
only high-dose therapy is effective, showing that doses as low as 0.5 mg of 17 $\beta$ -estradiol have a preventive effect on bone loss for postmenopausal women. 'We can select doses and types of hormone replacement therapy according to age and needs, knowing that even lower dosages are able to protect the bone', he said (Figure 9).

Citing several studies that included early postmenopausal women, Dr Gambacciani highlighted that fractures were reduced with HRT for all groups, not just the elderly. Looking at the WHI, HRT was associated with a significant decrease of risk of osteoporotic fractures, considering total as well as vertebral and hip fractures. Hip fractures were reduced by 30% (hazard ratio CI 0.45–0.98), even after 1 year in women who were not selected for prior diagnosis of osteoporosis (Table 2). While this is comparable to the efficacy of bisphosphonates, it is important to note that neither alendronate nor risedronate are effective for fracture prevention in patients who do not already suffer from osteoporosis.

Although many case-controlled studies have shown that the fracture prevention benefit of HRT ends 5 years after therapy ceases, a more sporadic approach may be the solution for long-term treatment, as revealed by a recent study<sup>10</sup>. 'It means that women [who] stop estrogen for a couple of months, or for 6 months [and then resume] hormone replacement therapy for years,

are not losing the effect of protection with hormone replacement therapy', Dr Gambacciani said. Estrogen-using participants who suffered fractures were slightly older, more likely to smoke and to take sedative or anxiolytic medications. He stressed the importance of taking patient selection into account when evaluating study results and, as a corollary, that it is vital in clinical practice to tailor hormone therapy regimens individually.

Evaluating the WHI data, the high number of adverse events in the first year of HRT administration would suggest that clinicians should not be concerned about long-term use of HRT for the stand-alone indication of osteoporosis, if the majority of the negative effects disappeared by the second year, even in elderly, obese, hypertensive, diabetic women. While in the first months of HRT the possible procoagulant effects must be borne in mind, the benefits of symptom relief and quality of life, along with improved bone density, turnover and architecture, should also be considered. In terms of long-term therapy, a variance between previous studies and the WHI and HERS is that the latter show a slight, but not significant, breast cancer risk increase as a group, and this issue must always be considered. The long-term benefits of symptom relief, improved quality of life and cognitive function, and reduced risk of colon cancer and fractures should be evaluated continuously, taking into account any possible harm.



**Figure 9** Hormone replacement therapy (HRT) dose effect on bone mineral density (BMD): spine BMD after 26 months of treatment. E2, estradiol; NETA, norethisterone acetate. Adapted from reference 9

**Table 2** Women's Health Initiative (WHI) annual hip fracture incidence for hormone replacement therapy (HRT) versus placebo: relative risk 0.66 (confidence interval 0.45–0.98). Adapted from reference 1

Year	HRT n (%)	Placebo n (%)	Hazard ratio
1	6 (0.07)	9 (0.11)	0.64
2	8 (0.10)	13 (0.16)	0.59
3	11 (0.13)	12 (0.15)	0.87
4	8 (0.10)	11 (0.15)	0.69
5	5 (0.08)	8 (0.14)	0.58
6+	6 (0.12)	9 (0.21)	0.55

## RISKS OF HORMONE REPLACEMENT THERAPY

Beginning with a general overview of the South African situation, Professor Franco Guidozi from the University of Witwatersrand in Johannesburg stated that, despite human immunodeficiency virus (HIV) being the country's primary clinical concern, the HRT industry is still worth \$30 million. Unopposed oral estrogen accounts for 50% of prescriptions, opposed oral estrogens for 35–40% and other delivery methods for the remainder.

Reviewing the WHI data and the resulting HRT risk indicators, Professor Guidozi outlined that invasive breast cancer, cardiovascular adverse events, stroke, venous thromboembolism, pulmonary emboli, ovarian cancer and gall-bladder disease were the serious harms to emerge from the study. He added the caveat that this pertains only to a particular combination therapy, and the unopposed-estrogen arm of the study is still ongoing.

The essential breast cancer finding was a 26% increase in invasive breast cancer, but no increase for *in situ* cancers. The increasing risk was apparent only after 4 years, and applied only to patients with prior usage of hormone therapy. Comparing these results with the findings of the Collaborative Group on Hormonal Factors in Breast Cancer<sup>11</sup>, this confirmed that, if patients use HRT for up to 4 years, there is no increased risk. The real risk increases only at year 5. Furthermore, the review of Dr Trudy Bush and colleagues<sup>12</sup> of 46 studies stated that the evidence did not support the notion that estrogen alone increases the risk of breast cancer, or that combined HRT increases the risk even more. While a longer duration of HRT (more than 15 years) may increase breast cancer risk, this is still a weak asso-

ciation (Figure 10). In fact, Dr Bush found that HRT users were less likely to die from breast cancer than non-users. 'If the patient is likely to get the breast carcinoma, it is likely to be better differentiated, at an earlier stage, with a protective effect on survival and mortality', said Professor Guidozi. He went on to state that, although combined HRT does increase breast cancer risk, it possibly increases the risk only of lobular carcinoma, while there may be a neutral effect on ductal carcinoma.

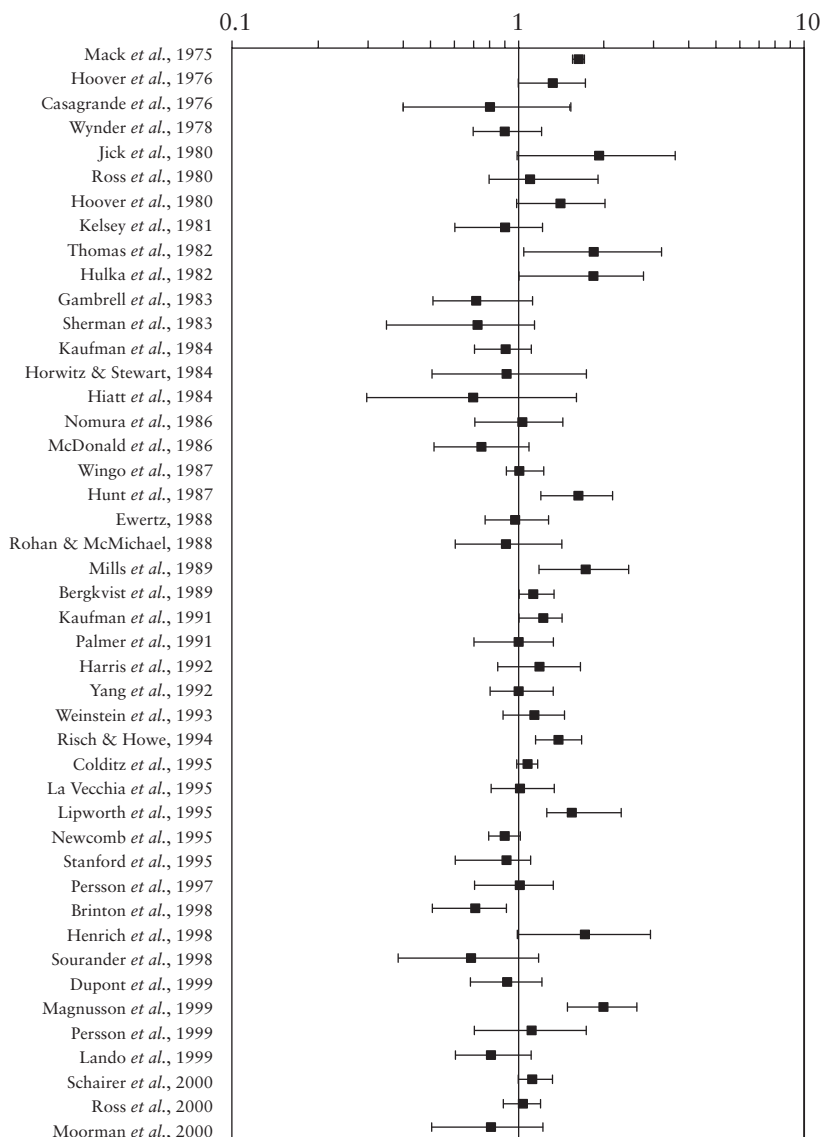
Turning to coronary heart disease, Professor Guidozi reasoned that the epidemiological evidence in many case-controlled, cohort studies shows that estrogen alone and in combination with progestogens provides an approximately 30–34% protective effect, respectively. Yet, several recent studies conflict with this conclusion, and a review of the original observational studies<sup>13</sup>, with removal of secondary-prevention and socioeconomic factors, showed no cardio-protection in using HRT (Figure 11). Stroke studies show similar conflicting evidence, making assessment difficult.

Professor Guidozi also revealed that ovarian cancer risk increases, but this depends on time, usage and type of therapy. While patients may be at risk with estrogen-only and sequential HRT, combined HRT does not pose a risk. Gall-bladder pathology from HRT has been noted in some studies, but not in the WHI.

To summarize, Professor Guidozi took the WHI data and assessed the absolute risk of having an adverse event by using HRT. Using information from the South African Department of National Statistics, he equated this risk of dying to a woman driving a car in Johannesburg for 5 years. 'It is horrendous if our patients were to take [on board] the WHI [results] and media coverage, [when] our patients just purely by driving a car were to exceed [the risk]', he said.

## BENEFITS OF HORMONE REPLACEMENT THERAPY

Examining the positive reasons for using HRT, Professor Martin Birkhäuser from the University of Bern, Switzerland, began from the patient's perspective. The sequence of the many reasons that patients cite for taking HRT is as follows: menopausal symptoms (47%), osteoporosis and bone fracture prevention (32%), treatment prescribed or recommended by doctor (30%), prevention of cardiovascular disease (15%) and psychological symptom relief (about 10%).

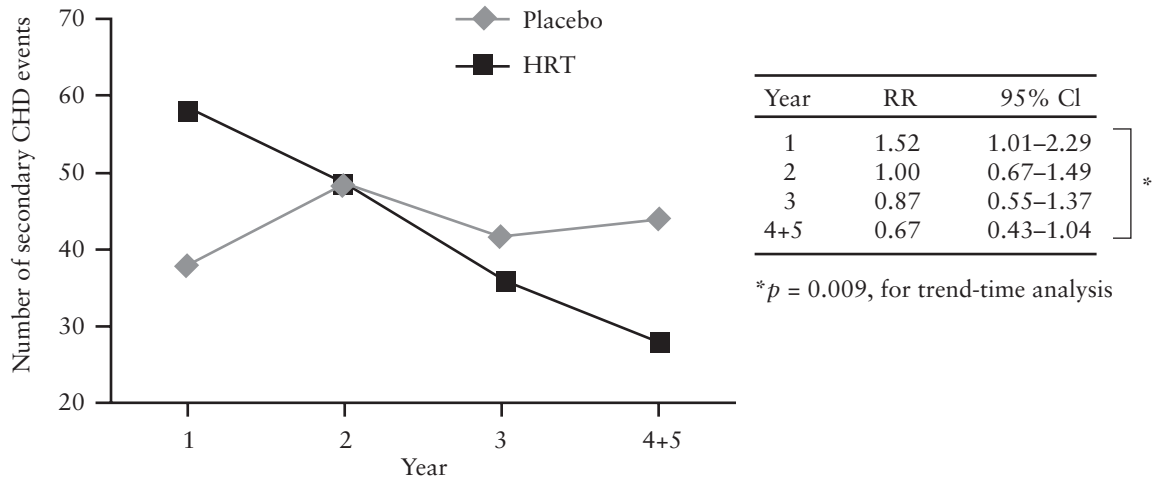


**Figure 10** Meta-analysis of hormone replacement therapy (HRT) use and risk of invasive breast cancer: ever-users compared with never-users of unopposed estrogen replacement therapy. Adapted from reference 12

Looking at menopausal symptom relief, Professor Birkhäuser stated that a combination of low-dose estradiol (1 mg) and NETA (0.5 mg) significantly reduces the Kupperman score (Figure 12). The Women’s Health, Osteoporosis, Progestogen and Estrogen (HOPE)<sup>15</sup> study also showed symptom reduction with different combinations of CEE-MPA. This again suggests that low-dose therapy should be used. Transdermal HRT administration is also effective for a variety of physical and psychological symptoms. ‘We have an impact with HRT that is clear for very different symptoms’, said Professor Birkhäuser, ‘including backache, anxiety and depressive moods’. Other studies have also shown that there is increased quality of life and sexual satisfaction

with HRT (Figure 13). An additional benefit is increased skin thickness, and, while not a justification for therapy, this is appreciated by patients.

Osteoporosis prevention is another important HRT benefit. BMD is increased at both the lumbar spine and femoral neck, with HRT preventing bone deterioration and decreasing the risk of fractures. This is confirmed by the WHI. In favor of low-dose treatment, even a dose of estradiol at 1 mg has a significant effect on deterring bone loss. Professor Birkhäuser emphasized that treatment must be tailored to suit each patient’s individual requirements, with appropriate dosage adjustments. Comparing raloxifene with HRT for osteoporosis prevention, Professor

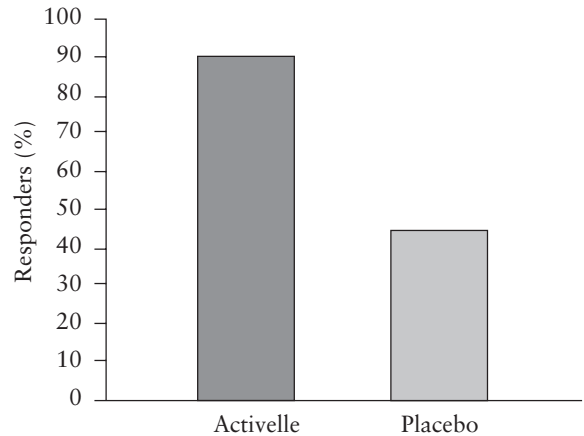


**Figure 11** Effect of hormone replacement therapy (HRT) versus placebo on secondary coronary heart disease events, Heart and Estrogen/progestin replacement study (HERS). RR, relative risk; CI, confidence interval. Adapted from reference 14

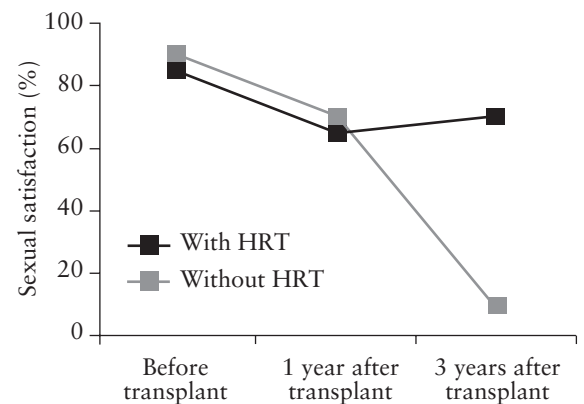
Birkhäuser stated that raloxifene decreases the risk of new clinical vertebral fractures and provides an alternative, but it does not reduce non-vertebral fractures. He also stressed the importance of beginning HRT early for this indication. ‘I think if you start late, you will not have the same benefit and there we could use the alternatives’, he said.

In the case of CHD, Professor Birkhäuser was positive about true primary prevention, starting HRT immediately after the menopause. Unfortunately, the WHI has been conducted in a population corresponding more to the definition of secondary rather than of primary prevention. Looking at the WHI data, he said that it is a matter of interpretation. If one uses the nominal CI, the risk of CHD events appears significant, but, if one takes the adjusted CI, it appears minor. He also explained that the WHI patient profile is not what clinicians see in women starting HRT. Patients were older, had a high BMI and were not an example of a healthy population. ‘I think it is a good study, but done in the wrong population, and we cannot deduce something for real primary prevention’, he said. Considering other studies, Professor Birkhäuser concluded that HRT for primary CHD prevention might still be useful, but randomized prospective data using modern treatment regimens are still lacking and urgently needed. Therapy must be started immediately after the menopause or the clinician is facing secondary prevention.

Using HRT to prevent the development of colorectal cancer is questionable. While the WHI shows some benefit, it is not significant, and there



**Figure 12** Menopausal symptom relief with 1 mg 17β-estradiol/0.5 mg norethisterone acetate (Activelle®) versus placebo: Kupperman score (12 weeks). From Novo Nordisk Clinical Trial PD/1/N



**Figure 13** Effect of hormone replacement therapy (HRT) versus placebo on sexual satisfaction after bone marrow transplant. Adapted from reference 16

is no proof that it is the same for all forms of administration. The results for Alzheimer's disease are more convincing. A number of studies have shown that, with early treatment and long-term use, HRT provides a protective effect in delaying the onset of Alzheimer's disease. To conclude, Professor Birkhäuser said, 'As long as the patient has a real profit concerning the quality of life, then she has the right to continue [with HRT], even if she is 80–84'.

### **WOMEN'S HORMONE INTERVENTION SECONDARY PREVENTION PILOT STUDY**

Presenting the results of the new Women's Hormone Intervention Secondary Prevention (WHISP) pilot study, Dr John Stevenson and Professor Peter Collins from the Royal Brompton Hospital and Imperial College, London, UK, showed that, for postmenopausal women with acute coronary syndrome, continuous combined, low-dose 17 $\beta$ -estradiol (1 mg) and NETA (0.5 mg) therapy is safe following myocardial infarction, and may even have the potential to bring benefit. The subject group of 100, the majority (more than 80%) having recently suffered a myocardial infarction, were randomized to placebo or the low-dose combined HRT and followed for 12 months. Treatment began within 2–28 days following the acute event. 'Unlike some of the other secondary prevention studies, these women aren't just hot, they're on fire', said Dr Stevenson. The patient pool baseline characteristics are similar to those of the HERS, with a slightly lower BMI. The primary efficacy parameters were a benefit in lipoprotein changes and a lack of adverse effects in terms of hemostasis. Emphasizing the importance of low dosage level, Dr Stevenson said, 'Uniformly all of these [previous] studies have been using too high a starting dose of estrogen for the age of the population they're studying.' The majority of the patients were already on statin therapy, but, while both groups showed a reduction in total cholesterol, there was a significant difference in the HRT group's decrease in triglycerides and increase in high-density lipoprotein (HDL), confirmed by a decrease in apolipoprotein A1, compared with the placebo group.

Looking at changes in hemostasis, there were several interesting differences between the two groups. While there was an unexplained drop in the placebo group's fibrinogen level, there was no increase in fibrinogen levels for the HRT group.

For factor VII and antithrombin III, the well-known HRT effect of decreasing levels occurred. There was no increase in activated protein C resistance, prothrombin fragments 1 + 2 and D-dimers. 'There was no increase in coagulability in these patients and therefore, most likely no increase in thrombogenesis', said Dr Stevenson.

Professor Peter Collins explained the cardiovascular end-points of the study, reviewing the investigations undergone by both groups during the first 3 months, including angiography, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, exercise stress testing, echocardiography and mammography. In virtually all of the evaluations, the event rate was less in the HRT group than in the placebo group, and for angiography this was statistically significant. '[It is] very difficult to claim that these are true differences, but it is very interesting that every single trend was in favor of the HRT group', said Professor Collins. Cardiovascular outcomes and adverse events requiring hospitalization at 12 months again showed extremely positive indications for the active group. There were few serious adverse events, and there was a marked favorable effect for the HRT group. Compliance is always an issue in HRT trials, and WHISP had an approximately 40% drop-out rate in the active group at 180 days. But further education about HRT may improve this. With the caution that this is a small pilot study with a high-risk group, making statistical significance difficult to assess, it does provide interesting indicators for further study. 'With this different low-dose hormone therapy, there may indeed, in this high-risk group of patients, be a potential reduction in cardiovascular investigations and events', concluded Professor Collins.

### **ESTROGENS: ARE THEY ALL EQUAL?**

Presenting the case for estrogen equivalence, Professor David Archer, Director of the CONRAD Clinical Research Center, said that CEE has been the most popular estrogen formulation in the USA for the past 30–40 years. Although 17 $\beta$ -estradiol has been available for some time, to date it has not accounted for a large number of prescriptions in the USA. While the currently available estrogens are quite similar, Professor Archer predicted, 'I think what we are going to see in the future [are] advances in changing the estrogen formulation.'

Comparing the three approved HRT products, 17 $\beta$ -estradiol, CEE and ethinylestradiol, he reviewed configuration, safety and side-effect profiles. In terms of molecular structure, ethinylestradiol differs from estradiol by having an ethinyl group at the 17th position. While basically the two are the same, the extra group found on ethinylestradiol makes it more readily absorbed in the gastrointestinal tract, unchanged, and prolongs its mechanism of action. CEE include ten known biologically active estrogens, primarily estrone and equilin. More than 200 substances have been identified over the last few years. Owing to US pharmacological approval requirements, all estrogen formulations are equally potent for clinical parameters with effects of equal duration, and have an estrogen receptor interaction. 'The question is, do other estrogens, estrone or estriol, have subtle alterations in the receptor when they bind into that pocket and therefore that change their downstream message?', Professor Archer asked. Recently, clinicians have begun to appreciate that, once the estrogen and estrogen receptor response element bind, within the nucleus, they are coactivators, activators and repressors. Looking at serum levels of ethinylestradiol and 17 $\beta$ -estradiol, it is clear that, in oral formulations of 17 $\beta$ -estradiol, there is a more rapid conversion in the intestinal tract to estrone, which is rapidly sulfated. With oral estradiol, the converted estrone sulfate pool continues to increase with treatment and, through sulfatase activity, provides a maintenance effect, with the estrone level steadily pushing into the estradiol level in the target tissue. Professor Archer explained that it was more difficult to obtain accurate serum level measurements for CEE. 'Essentially, if you try to measure estradiol in the blood of women [taking Prempro®], you get a level, but it is due to the cross-reactivity with the equilins and equilenins in the assay systems', he said. Each of the estrogenic substances binds differently and has a different half-life, although they produce similar estrogenic effects.

The primary evaluation of estrogens for the American market is efficacy in the reduction of hot flushes. All three forms of estrogen are highly effective in this indication, with dose-related responses in both oral and transdermal administration. Another target tissue is the endometrium. Professor Archer demonstrated by citing several studies that the endometrial hyperplasia rates for unopposed CEE and estradiol are similar, and both have comparable dose-response effects. 'Anytime you give estrogen, for any length of

time, the dose and the duration are the impactor in terms of [endometrial] hyperplasia', he said (Figure 14). There are also similar lipid effects with all forms of unopposed estrogen, with the HERS trial showing dose-related effects for CEE. In terms of BMD, studies have also proved the same effectiveness over time in preventing bone deterioration for unopposed and combination therapies of estradiol and CEE. 'So, in the United States, [for] hot flushes, lipids, endometrium and bone, all estrogens look like an estrogen', Professor Archer reasoned.

It is well known that, in the postmenopausal endometrium, estrogen increases the estrogen receptor content. Estrogen binds to a receptor in the nucleus, a dimer form. When the estrogen binds with the dimer, the receptor configuration is altered. Data indicate that, with a SERM, the configuration of the estradiol receptor actually alters. This complex binds to the hormone response element and then begins to encode downstream a variety of structural genes. Although the equivalent clinical effects of estrogens have been well demonstrated, it is less certain what are the exact molecular effects of each type. 'It is perfectly plausible that various estrogens have subtle, and as yet unidentified, interactions here in the nucleus where you change activators, coactivators and corepressors and you end up with a different downstream response element', he explained. While currently we see no clinical differences between estrogens, there may be molecular differences yet to be explored.

## ESTRADIOL AND CEE: DIFFERENT ESTROGENS, DIFFERENT EFFECTS

Challenging the premise that all estrogens are the same, Dr Morris Notelovitz from the USA highlighted the differences between 17 $\beta$ -estradiol and CEE. When evaluating the function and bioequivalence of the available hormone therapies, there are three responses that should be addressed: clinical symptoms, organ function and changes at the tissue and cellular levels of the organs. While exploring all of these indicators, it is important to consider the patient as a complete individual, meeting all of the potential targets, not just relying on primary symptoms.

While 17 $\beta$ -estradiol is a fairly simple compound and native to humans, in contrast, CEE (Premarin®) are extremely complex, with many different forms of estrogen, and are native to pregnant mares. 'When you are choosing between these two preparations, you can either decide to

use something which is more physiologic, in the sense that it is an estrogen type normally found in women, versus something which is pharmacologic', said Dr Notelovitz. Unlike with CEE, the synthesis and metabolism of 17β-estradiol are well documented (Figure 15). Frequently ignored, but vital for a proper assessment of the individual, are the levels of estrone sulfate and dehydroepiandrosterone sulfate (DHEAS). The onset of

the menopause and the progression of symptoms depend upon the genetic make-up of the patient and her sulfatase, aromatase and dehydrogenase activities in specific tissues. Commenting on one of the major faults with the WHI, Dr Notelovitz said, 'Menopause is a generic clinical sign, but it is not a generic clinical condition.' It is important to treat each woman as a biologically unique patient.

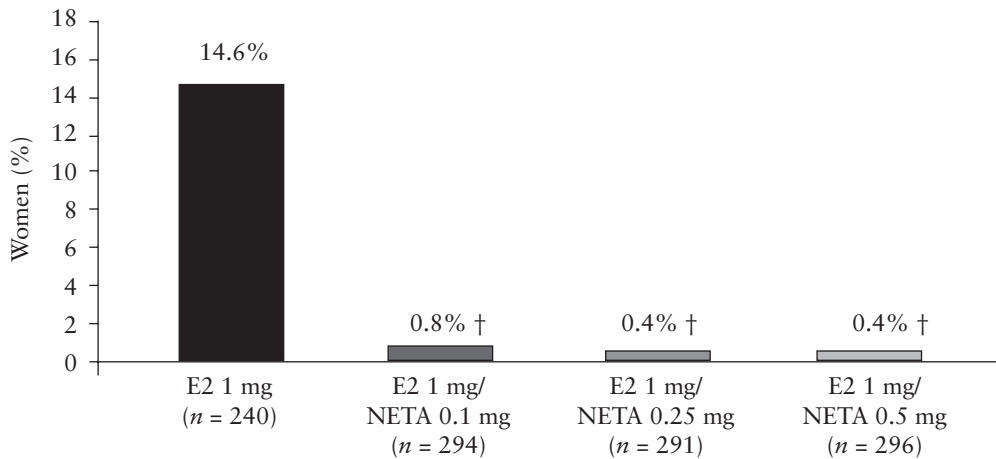


Figure 14 Endometrial hyperplasia incidence rates with 17β-estradiol and various doses of continuous combined 17β-estradiol (E2) + norethisterone acetate (NETA). †p < 0.001 vs. E2 1 mg. Adapted from reference 17

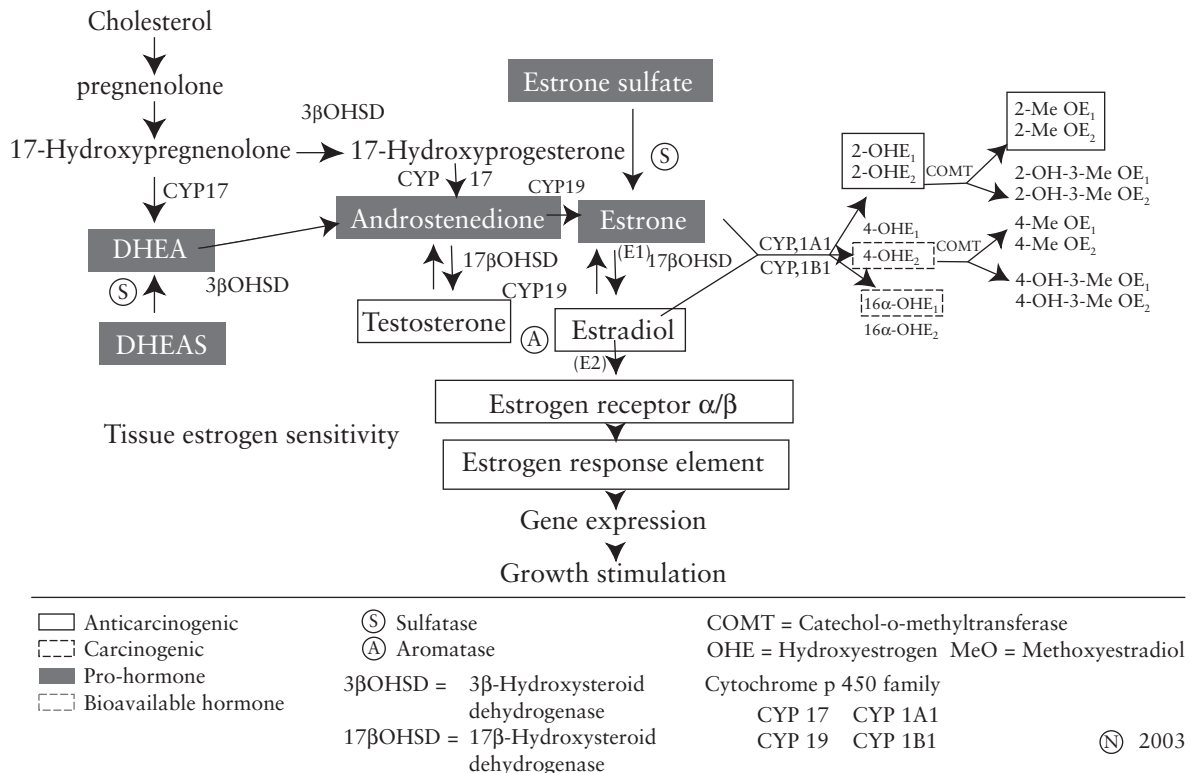


Figure 15 Synthesis and metabolism of estrogen. DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate. Copyright, Dr Morris Notelovitz

The liver plays a principal role in synthesizing sex hormone binding globulin (SHBG), and offers clinicians the opportunity to make treatment choices in administration and hormone therapy via modulation. Looking at estradiol dose equivalents through different administration routes and the effects on SHBG, free estradiol and estrone, oral (2 mg) compared with transdermal (50 µg) administration greatly increases the levels of serum SHBG and estrone, but serum free-estradiol levels are almost identical. While this does not make a difference in most healthy postmenopausal women, it could be extremely important in women with a high level of sulfatase activity in the breast. In the case of oral CEE (0.625 mg), there is over 100% increase of serum SHBG levels after 4 months, while oral 17β-estradiol (1 mg) shows a 45% increase and transdermal estradiol (50 mg) only a 12% increase. Measurements for free estradiol in the same population reveal a 32% increase with oral CEE, a 19% increase with oral 17β-estradiol and a 22% increase with transdermal estradiol. Considering the influence of estrogenic metabolites on breast cancer, it has been clearly demonstrated by a number of studies that women with breast cancer have much higher levels of sulfatase, aromatase and dehydrogenase activity in the breast tissue. While the numbers of women who developed invasive breast cancer in the WHI were quite small, it is vital for individual assessment of patients that these factors be taken into account.

The dimerization of the type of estrogen used in treatment characterizes the menopausal patient profile. As clinicians gain more knowledge about exactly what estrogen receptors ERα and ERβ do, it is possible to recognize that, in addition to the intervention of coactivators and corepressors, there are up to six subtypes of ERβ which can modulate the activity of ERα. 'It is a very, very complex process, and we have oversimplified it again by making menopause generic, treatment generic: one dose does not fit all people', stressed Dr Notelovitz. Looking at the estrogen receptor binding versus the biological potency of Premarin's formulation, the 8,9-dehydroestrone has a low binding ability, but has a high biological potency. With so many potential variables in the formulation, he commented, 'We don't really know what Premarin does because it is a very complex hormone and it is not native to women.'

A comparison study using patient assessment of 17β-estradiol and CEE hormone therapies at different dosage levels produced some interesting observations. Both groups taking 17β-estradiol

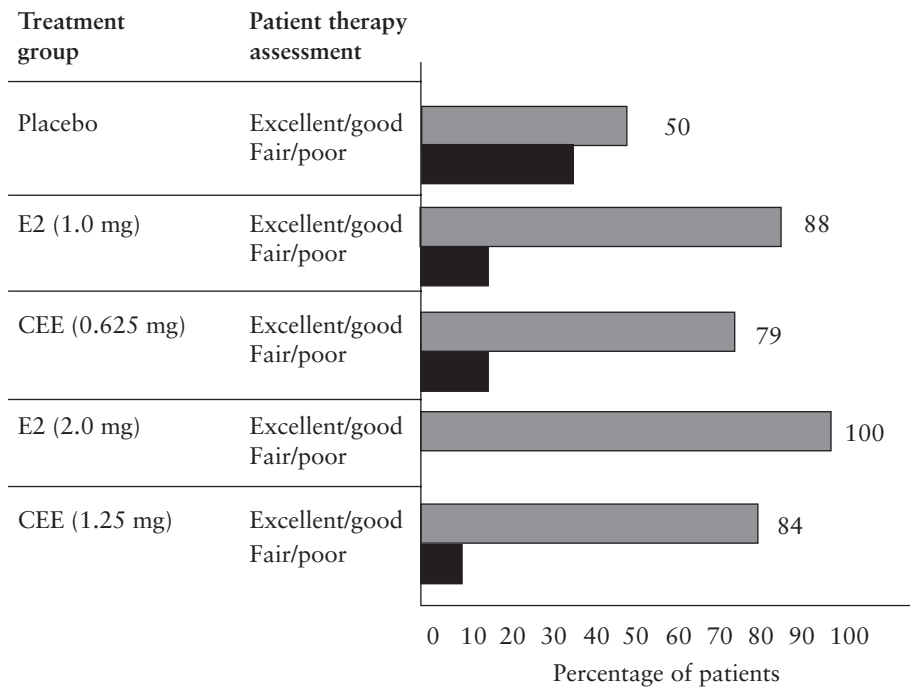
had the highest satisfaction ratings, with that of the 1-mg group at 88% and that of the 2-mg group at 100%. The CEE groups were less satisfied, with the 0.625-mg group having a 79% satisfaction rating and the 1.25-mg group having 84% (Figure 16). Although the ratings for 17β-estradiol (1 mg) and CEE (0.625 mg) are similar, this does not mean that they are equivalent. Biological potency is quite different. Looking at the effects of the hormone therapies on the pituitary gland, 17β-estradiol (1 mg) gives a 34.6 mIU/ml decrease in follicle stimulating hormone (FSH) level from baseline while CEE (0.625 mg) gives a 50.3 mIU/ml reduction in FSH level. Thus, at this end-organ, the lower-dose 17β-estradiol is less potent.

Considering combined hormone therapies, it is established that, for symptom relief, estrogen and progestogen treatments are more effective than estrogen alone. Dr Notelovitz suggested that this could be due partially to the blood-brain barrier. In two studies by Yaffe and colleagues, a comparison of estrogen levels and cognitive function showed that, while there does not seem to be a relationship between total estradiol levels and cognitive function, there does appear to be a link between free estradiol levels and improved cognitive function<sup>19</sup> (Figure 17). This suggests that the estrogen must be able to cross the blood-brain barrier to have a positive effect.

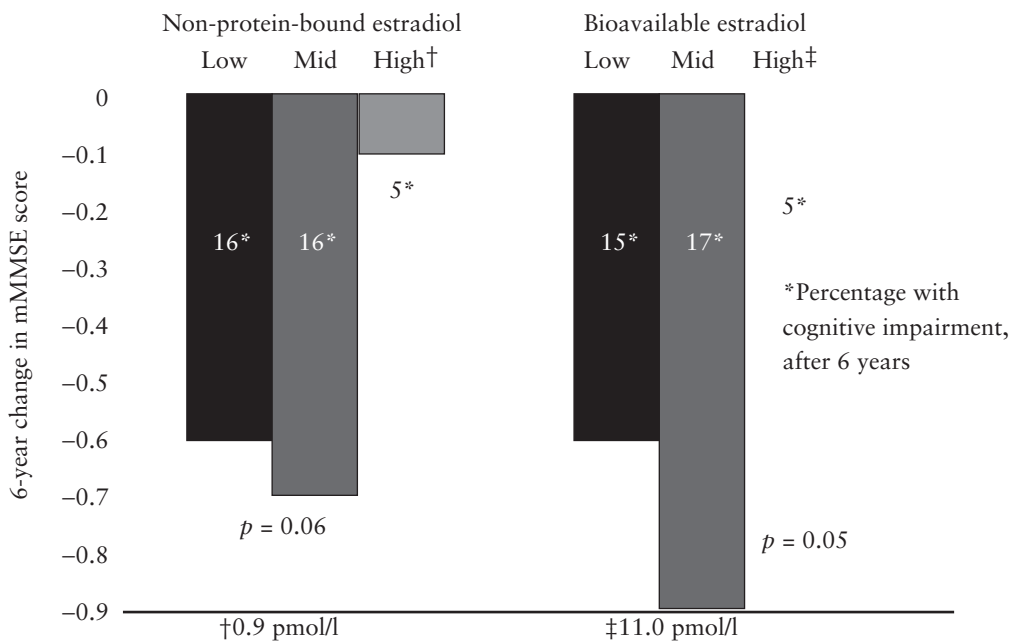
Dr Notelovitz reiterated the message that hormone therapy can be very effective in the prevention of bone deterioration and cardiovascular protection, but again emphasized that each patient must be assessed carefully, taking symptoms and potential hazards into account. The paradigm for treatment design should include the goals of the therapy, the dose rate, side-effects, patient preference and route of administration, monitoring periodically with plasma estradiol testing. Dr Notelovitz concluded by saying that it is not possible to determine the best therapy without selective testing, and this individual approach should then continue, with appropriate monitoring over time with treatment adjustment as necessary.

## MPA AND NETA: ARE THEY THE SAME?

Dr Marco Gambacciani from the University of Pisa explored the similarities between the various progestogens and their risk-benefit profiles. While progestogens have a variety of unwanted effects including androgenic actions, somatic symptoms



**Figure 16** Dose response to estrogen therapy: patient assessment of therapy, estradiol (E2) versus conjugated equine estrogens (CEE). Adapted from reference 18



**Figure 17** Endogenous bioavailable estradiol prevents cognitive decline in women (mean age over 70 years). Six-year decreases in modified Mini-Mental State Examination (mMMSE) score according to tertile of estradiol concentration. Adapted from reference 19

and psychological symptoms, they also offer endometrial protection and bleeding control. All progestogens are not the same, requiring different doses to elicit endometrial secretory response, with 200 mg progesterone, 0.35 mg NETA,

0.075 mg norgestrel, 5 mg MPA and 10 mg dydrogesterone being roughly equivalent. While this allows crude comparison between different progestogens, the dose, type and route of administration are factors that should be considered.

For lipid effects, it is clear from the Postmenopausal Estrogen/Progestin Interventions (PEPI)<sup>20</sup> trial that a combination of CEE with micronized progesterone has a greater efficacy by increasing HDL and triglycerides, while lowering low-density lipoprotein (LDL) and total cholesterol, more than CEE-MPA or CEE alone. This is also seen with dydrogesterone, and, in fact, MPA seems to diminish the positive effects of estrogen on LDL level. Comparing a combination of estradiol-dydrogesterone with estradiol-NETA, dydrogesterone again appears to increase HDL, while NETA negates positive effects. The effects of different progestogens on glucose tolerance, insulin action and insulin sensitivity also reveal that they are not all the same. Combined therapy of CEE-MPA influences fasting insulin and glucose differently from CEE-dydrogesterone (Figure 18). It also has been shown that combined 17 $\beta$ -estradiol-NETA therapy does not have an adverse effect on insulin sensitivity.

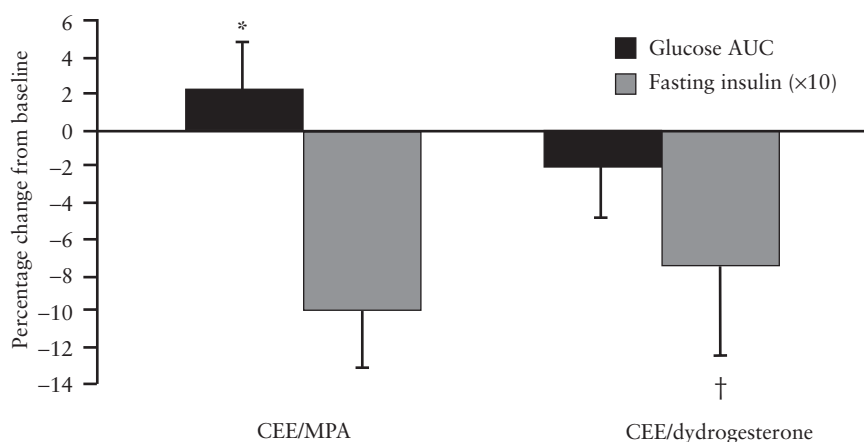
Looking at body fat distribution 12 months after women begin taking combined HRT, Dr Gambacciani stated that, after the menopause, untreated women experience a weight that is higher than that measured in hormone-treated women. In addition, it needs to be considered that HRT maintains a gynoid body fat distribution, preventing the central accumulation of fat that occurs in the legs and not in the trunk. This is important, not only for body appearance, but also for assessing the likelihood of adverse cardiovascular events. Flow-mediated dilatation declines in postmenopausal women, and here the combination therapy CEE-MPA appears to be beneficial, with MPA (2.5 mg) not affecting the positive effects of CEE (0.625 mg), while, in the combination estradiol-NETA, NETA (1 mg) counteracts

the positive effects of estradiol (2 mg). This is also seen in forearm vascular resistances, with the same combination dosage of CEE-MPA achieving a significant reduction, while the same combination dosage of estradiol-NETA results in an increase. Examining the vascular effect of the combination estradiol-dydrogesterone against the same dosage of estradiol alone, there is no moderating effect at all by dydrogesterone on estradiol. 'In all these studies, MPA attenuated the effect of conjugated equine estrogen alone', said Dr Gambacciani.

Turning to progestogen use in HRT and its effect on blood pressure, there is a significant positive effect for combined therapy. This is shown in the use of estradiol-dydrogesterone and CEE-MPA combinations; however, in one study, 2 mg estradiol-1 mg NETA appears to induce a slight increase of blood pressure. Dr Gambacciani cautioned that, while interesting, the studies perhaps were using combination products that were not exactly equivalent. 'When we are making a head-to-head comparison, we must use comparable dosages of different products. Otherwise we are doing something that we cannot really compare', he said. To conclude, he advised that there is a fine-tuning between the various estrogen and progestogen options, considering respective dosages and potencies and schedules of administration.

### MPA AND NETA: BIOLOGICAL DIFFERENCES AND CLINICAL IMPACT

Considering whether the differences between NETA and MPA are clinically relevant, Professor Herbert Kuhl from the J. W. Goethe University of



**Figure 18** Effect of different progestins on glucose tolerance and insulin action. \* $p < 0.05$  vs. baseline; † $p < 0.05$  vs. conjugated equine estrogens (CEE) alone; AUC, area under the curve; MPA, medroxyprogesterone acetate

Frankfurt/Main, Germany, gave a comprehensive direct comparison of the two progestogen derivatives. A list of estrogen clinical effects and the influence of the two progestogens showed that, while both have a favorable effect in reducing hot flashes, their similarity quickly ends. In terms of osteoporosis prevention, NETA is favorable, but MPA has no effect. For changes in lipid metabolism, MPA has nearly no effect, while NETA may antagonize the effect of estrogens on HDL and triglycerides, but may enhance the effect on LDL. NETA does not inhibit estrogen's protective properties against atherosclerosis and vasospasm, and does not lead to an increased risk of thrombosis; MPA is unfavorable for these parameters. MPA's role in the proliferation of breast tissue is well known, but NETA's role is less clear as there are insufficient data. Concerning endometrial protection, NETA's positive effect is sufficient in low doses, in contrast to MPA.

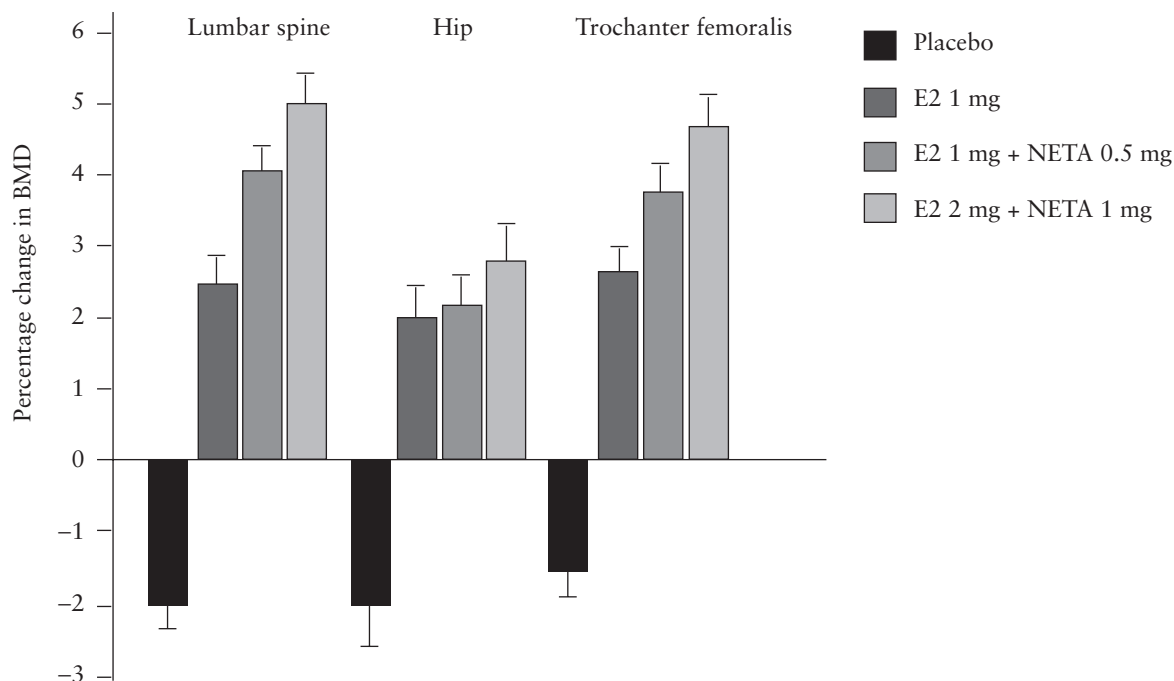
Hormonal patterns show that both are anti-estrogenic. NETA is also a weak estrogen because a small amount of it is aromatized. MPA has a weak and NETA a moderate androgenic effect, but NETA also has a certain antiandrogenic effect, similar to progesterone, but this is not mediated by the androgen receptor; similar to progesterone, NETA inhibits the activity of 5 $\alpha$ -reductase. The two compounds have no anti-

mineralocorticoid side-effects, and only MPA has glucocorticoid side-effects.

There are several studies, both *in vivo* and *in vitro*, which have examined the glucocorticoid and antiglucocorticoid effects of MPA. MPA may enhance procoagulatory activity, inhibit the function of T-lymphocytes and potentially cause bone resorption through its glucocorticoid activity. High doses of MPA suppress the release of adrenocorticotrophic hormone and cortisol, and can cause Cushing's disease-like symptoms. On the positive side, MPA has been shown to be a respiratory stimulant, and to slow down glucocorticoid-induced bone resorption in asthma patients. Additionally, MPA up-regulates  $\beta$ -adrenoreceptors in healthy women, but down-regulates and desensitizes  $\beta$ -adrenoreceptors in female asthmatics.

Looking at the positive effects of NETA, in osteoporosis prevention, it is almost the only progestogen that enhances the effect of 17 $\beta$ -estradiol on bone, increasing bone mass (Figure 19).

The progestogen influence on the estrogen-dependent prevention of atherosclerosis development is shown by a comparison of estrogen-only treatment and combined treatments. While 17 $\beta$ -estradiol decreases the number of plaques in the abdominal aorta, and carotid and iliac arteries, when it is combined with levonorgestrel



**Figure 19** Effect of estradiol (E2) and various doses of continuous combined E2 + norethisterone acetate (NETA) on bone mineral density (BMD). Adapted from reference 21

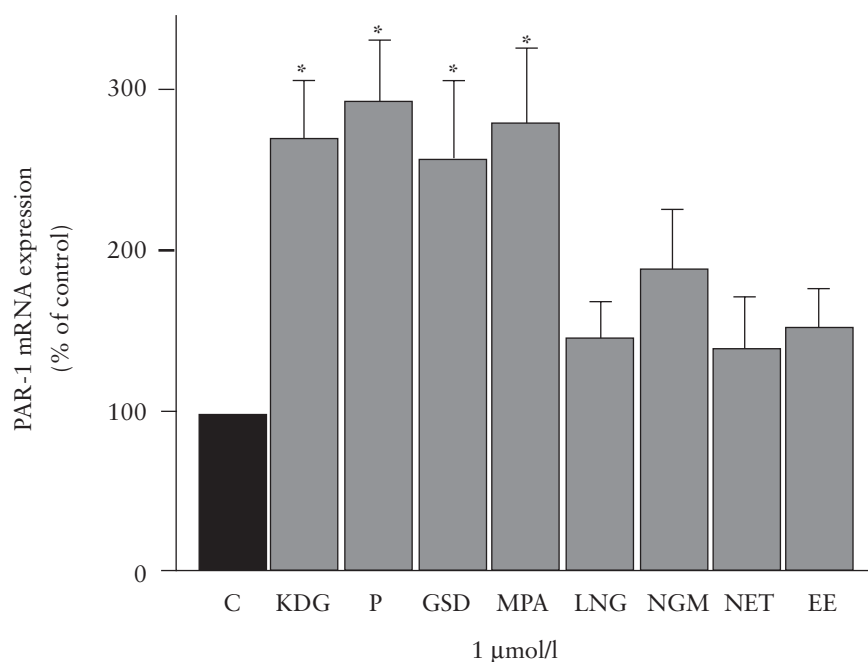
(LNG), this decrease is not significant. In contrast, the addition of MPA to CEE counteracts the positive direct effect of estrogens on the arterial wall and may also cause vasospasms.

These changes may be traced to thrombin receptor activity. The thrombin receptor is found in vascular smooth muscle cells (VSMC) in macrophages, platelets and the endothelium. Activation of the thrombin receptor by thrombin stimulates the extrinsic coagulation cascade that is important for injured endothelium, involved in the development of thrombosis, atherosclerosis and restenosis. Furthermore, this activation causes the proliferation and movement of VSMC and stimulates platelet activity and monocyte chemotaxis, as well as an increase in endothelial production of adhesion molecules, prothrombotic factors and antithrombotic factors. The unfavorable effects of certain progestogens such as MPA may be mediated by an up-regulation of thrombin receptor expression in VSMC by progestogens. This effect was observed in VSMC from human or rat aorta after incubation with low concentrations of dexamethasone, 3-keto-desogestrel, progesterone, gestodene and MPA because of a binding affinity with the glucocorticoid receptor (Figure 20). In contrast, NETA, LNG, norgestimate and ethinylestradiol do not bind to the glucocorticoid receptor and do not up-regulate the thrombin receptor. Thus, it is the glucocorticoid, not the

androgenic, activity of progestogens that influences vascular disease development. Turning to cardiovascular disease, Professor Kuhl reviewed the results of the HERS trial using a combination therapy of CEE (0.625 mg) with MPA (2.5 mg), the recent ESPRIT<sup>23</sup> study (Estrogen Therapy for Prevention of Reinfarction), which used estradiol valerate (2 mg) alone, and the WHISP study with the active-group dose of estradiol (1 mg) and NETA (0.5 mg) (Table 3). 'If you compare [the ESPRIT study] with the HERS study, this shows that estradiol is in all probability capable of protecting the arteries from secondary events', he said. The WHISP study then shows that the addition of NETA to estradiol probably does not increase the cardiovascular risk.

Concerning breast cancer, Professor Kuhl compared seven studies, including the WHI. The overall results reveal that HRT combinations increased the rate of breast cancer, while estradiol and CEE alone had no significant effect. A French study comparing relatively high doses of NETA (8–10 mg) with progesterone or norethisterone derivatives found that NETA at higher doses can even reduce the incidence of breast cancer. This effect has not been observed with progesterone or norethisterone derivatives.

Professor Kuhl then evaluated endometrial cancer risk with progestogen use. The sequential addition of progestogens to the estrogen for less



**Figure 20** Effect of steroid hormones on thrombin receptor expression in vascular smooth muscle cells. \* $p < 0.05$  vs. control (C); KDG, 3-keto-desogestrel; P, progesterone; GSD, gestodene; MPA, medroxyprogesterone acetate; LNG, levonorgestrel; NGM, norgestimate; NET, norethisterone; EE, ethinylestradiol. Adapted from reference 22

than 10 days per month does not reduce the estrogen-dependent increase in endometrial cancer risk. If used for more than 10 days per month, the risk decreases, but remains elevated during long-term use. This was confirmed in another study, but, pivotally, the long-term risk increased only with estrogen combined with progesterone derivatives, not with estrogen and nortestosterone derivative combinations. ‘I think we have clear differences between NETA and MPA, which might be clinically relevant’, Professor Kuhl concluded.

### IS THERE A CLASS EFFECT FOR BREAST CANCER?

Addressing one of the primary concerns raised by media coverage of the WHI, Professor Joaquim

**Table 3** Women’s Hormone Intervention Secondary Prevention (WHISP) pilot study of cardiovascular disease (2–28 days after myocardial infarction). 3–12 months: 1 mg estradiol (E2) + 0.5 mg norethisterone acetate (NETA) or placebo

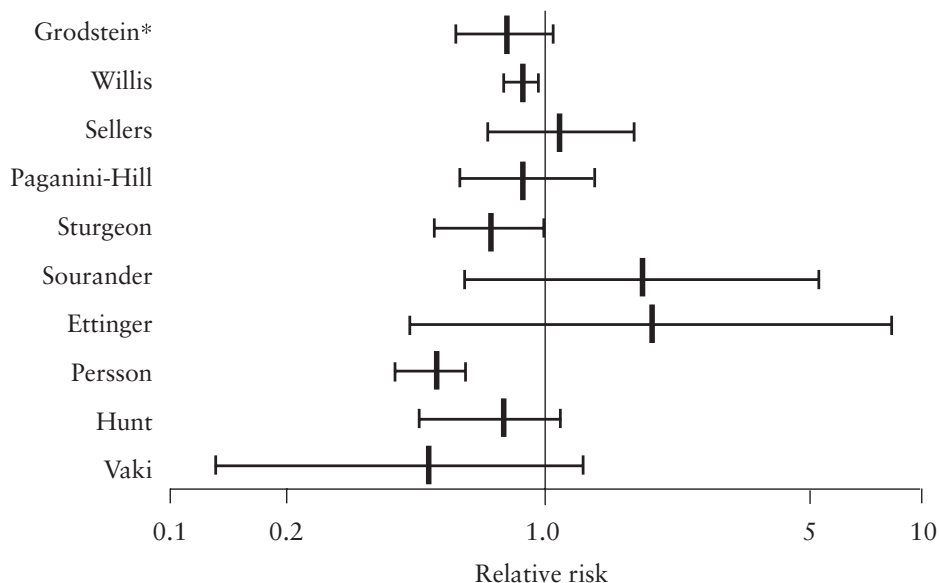
Outcome	HRT (n = 47)	Placebo (n = 48)
Death, MI, stroke	2 (4.3%)	3 (6.3%)
Death, all CHD, stroke	8 (17%)	12 (25%)
Gynecological events	1 (2.1%)	0 (0.0%)
Pulmonary embolism	1 (2.1%)	1 (2.1%)

MI, myocardial infarction; CHD, coronary heart disease; HRT, hormone replacement therapy

Calaf-Alsina from the Hospital de la Santa Creu Sant Pau at the University Autònoma, Barcelona, Spain, explored whether the risk of breast cancer with HRT is a class effect. Individualized therapy is the key to any HRT regimen. ‘I think the right thing is to apply different therapeutic approaches with different women’, he said.

While the incidence of breast cancer is increasing, mortality is decreasing, but varies from country to country. The absolute risk has to be related to the incidence found in each country. It follows that an increase in relative risk is very different in terms of absolute number of deaths. This can vary by more than 50%. It is important to note that there is an inflection point at the menopause, and this varies from country to country. Testing at this early stage could be vital for profiling the patient’s probability of future disease. ‘The information you have at the time of menopause will determine your ability to estimate the risk’, said Professor Calaf-Alsina. The lack of this essential data has biased some studies if they were unable to determine or exclude cases when they did not know the time of menopause, making an accurate calculation impossible (Figure 21).

There has been much debate on whether estrogen is a cause or simply a promoter of breast cancer. Assuming that estrogen is a promoter, it is logical to ask why it takes 5 years before detection of tumors via mammography. Pre-existing levels of serum estradiol undoubtedly play a role in the cancer risk. As a recent systematic review of many studies reveals, breast cancer risk increases



**Figure 21** Relative risk of breast cancer mortality with hormone replacement therapy use. \*Current use. Adapted from reference 24

with the level of bioavailable sex hormones. Obesity is an additional risk factor for breast cancer, and must also be taken into account.

Looking at Premarin, the product pharmacokinetic profile has changed over the years, with the majority of studies of breast cancer having been done with a product that has not always been the same, varying even from batch to batch. Premarin also contains many active substances, with varying estrogenic potencies at the different target organs. At certain levels, all estrogens are the same, but at the molecular level there are distinctions.

Different progestogens also have different effects. *In vitro* studies must be looked at very carefully for clinical significance. As only the substance is examined, eliminating peripheral microenvironmental influences, they are not a true reflection of treatment. *In vitro* studies show that NETA and MPA significantly reduce estradiol-stimulated proliferation of MCF-7 cells, and that tibolone promotes tumor cell-growth while combination estradiol-NETA therapy slightly inhibits it, but these results may not be clinically relevant. 'What happens in the *in vitro* environment has nothing to do with what happens at the level of the breast tissue', said Professor Calaf-Alsina. It is clear that CEE combined with various progestogens *in vivo* increases breast density when compared with CEE alone. Comparing treatment regimens, it is possible that sequential administration may confer a lower

breast cancer risk than continuous combined, but there is much disagreement over this hypothesis. He noted, 'Estrogen plus progestogen, whatever kind of combination you are using, possibly carries more risk than estrogen alone.'

Using mammographic density to determine breast cancer risk can be difficult in a clinical setting, with the variety of available systems inhibiting direct comparisons. Even if regimens produce different levels of breast density, there is an underlying genetic susceptibility that should be taken into account. A comparison of monozygotic and dizygotic twins with breast cancer risk showed that there is a very clear correspondence between genetic profile and predisposition to high breast density. Being able to identify the molecular markers that will lead the tissue to be denser is a challenge for the future. There also is the question of whether the increased density associated with short-term HRT carries the same risk as the underlying genetic tendency for breast density. 'Treatment probably plays a very small role as compared to heredity in this situation', said Professor Calaf-Alsina.

Assessing the relationship of breast cancer types and severity of disease is complex, as there are many opposing views. Using a histological classification, the adjusted relative risks for ductal, invasive ductal and lobular cancers are quite similar for HRT users and non-users, but the adjusted relative risks for papillary and tubular tumors are much higher with HRT (Figure 22).

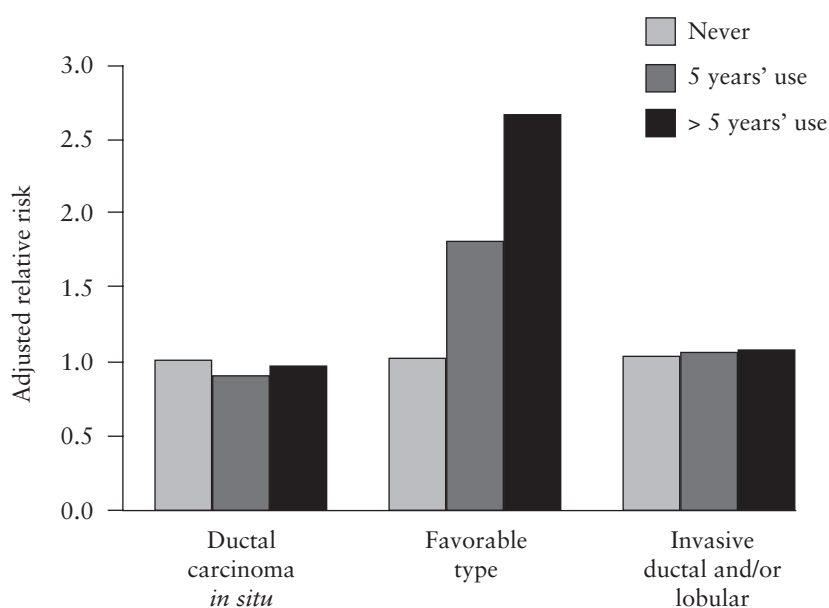


Figure 22 Breast cancer histology and relative risk with hormone replacement therapy use. Adapted from reference 25

However, the reverse is shown with the high S phase more frequently represented in current users than in never users. Despite this disagreement on breast cancer risk with HRT, the majority of studies show that the mortality rate in HRT users is lower than in non-users, even when incidence is increased. The cumulative risk of using HRT appears only after 4 years of treatment and gradually lessens 5 years after treatment has stopped, so duration of treatment must also be taken into account.

In conclusion, there are still no clear answers about HRT and breast cancer risks, even after 50 years of experience. The topic has many aspects and potential influencing factors, making quality, experimental designs difficult to perform. The WHI confirms the small increased breast cancer risk with combined CEE-MPA therapy, as identified in previous observational studies, but continued research is needed, particularly at a molecular level.

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