THE MANAGEMENT OF THE MENOPAUSE

THIRD EDITION

EDITED BY John Studd

Also available as a printed book see title verso for ISBN details
THE MANAGEMENT OF THE MENOPAUSE

THIRD EDITION
Contents

List of principal contributors vii
Foreword xii

1 The future of hormone replacement therapy 1
   H.G.Burger, S.Davison and S.R.Davis

2 National Osteoporosis Society statement, February 2003: hormone replacement therapy and the Women’s Health Initiative study 15
   D.Barlow

3 Estrogen therapy for cardiovascular disease 19
   G.Samsioe

4 Urogenital atrophy 31
   D.Robinson and L.Cardozo

5 Urogenital collagen turnover and hormone replacement therapy 49
   C.Falconer

6 Progestins in premenopausal women 63
   A.E.Schindler

7 Effects of progestogen on the breast 73
   E.Lundström and B.von Schoultz

8 Mammographic density and breast cancer 83
   G.Svane

9 Estrogen replacement therapy in the endometrial- and breast-cancer patient 95
   W.T.Creasman and M.F.Kohler

10 Oral contraceptives and ovarian cancer: a review 106
    C.La Vecchia

11 Mood and the menopause 118
    P.Klein

12 Premenstrual syndrome and the menopause 137
    S.O’Brien, K.M.K.Ismail and K.Jain

13 Women, hormones and depression 146
    J.Studd

14 The use of hormonal intrauterine systems in menopausal women 162
    C.Ng, J.Hockey and N.Panay

15 Clinical use of bone density measurements 172
    J.A.Kanis

16 Prevention and correction of osteoporosis 188
    D.I.Crosbie and D.M.Reid
17 Bleeding patterns and hormone replacement therapy
   *F.Al-Azzawi and M.Wahab*

18 Immunological changes after the menopause and estrogen replacement
   therapy
   *S.Ocampo de Ruiz*

19 Contribution of assisted reproduction technology to the understanding of
   early ovarian aging
   *D.Nikolaou and G.Trew*

20 Efficacy of and tolerance towards different kinds of hormone replacement
   therapy
   *J.Donát*

21 Vaginal estrogens: is there a role for their use?
   *W.H.Cronje and J.Studd*

22 Pulsed estrogen therapy: a new concept in hormone replacement therapy
   *N.Panay and J.Studd*

23 Dyspareunia: clinical approach in the perimenopause
   *A.Graziottin*

24 Menopause and the internet
   *H.Currie and G.Cumming*

25 Nutrition and the menopause
   *S.Palacios and C.Rueda*

26 Alternative therapies for postmenopausal women
   *L.Speroff*

Index
List of principal contributors

**Farook Al-Azzawi**  
Gynaecology Research Unit  
Department of Obstetrics and Gynaecology  
Leicester Warwick Medical School  
University of Leicester  
RK Clinical Sciences Building  
Leicester Royal Infirmary  
Leicester LE2 7LX  
UK

**David Barlow**  
Nuffield Department of Obstetrics and Gynaecology  
Level 3, The Women’s Centre  
The John Radcliffe Hospital  
University of Oxford  
Oxford OX3 9DU  
UK

**Henry Burger**  
Prince Henry’s Institute of Medical Research  
Level 4 Block E  
Monash Medical Centre  
246 Clayton Road  
Clayton  
Victoria 3168  
Australia

**Linda Cardozo**  
King’s College Hospital  
Denmark Hill  
London SE5 9RS  
UK

**William T.Creasman**  
Department of Obstetrics and Gynecology  
Medical University of South Carolina  
Charleston SC 29425  
USA

**Wilhelm H.Cronje**  
The Menopause and Premenstrual Syndrome Trust
Academic Department of Obstetrics and Gynaecology
Chelsea and Westminster Hospital
369 Fulham Road
London SW10 9NH
UK
David I. Crosbie
Department of Rheumatology
Aberdeen Royal Infirmary
Foresterhill
Aberdeen AB25 2ZN
UK
Heather Currie
Department of Obstetrics and Gynaecology
Dumfries and Galloway Royal Infirmary
Bankend Road
Dumfries DG1 4AP
UK
Josef Donát
Department of Obstetrics and Gynecology
School of Medicine of Charles University
500 05 Hradec Kralove
Czech Republic
Christian Falconer
Division of Obstetrics and Gynecology
Karolinska Institute
Danderyd Hospital
SE-182 88 Danderyd
Sweden
Alessandra Graziottin
Center of Gynecology and Medical Sexology
Hospital San Raffaele Resnati
Milan
Italy
John Kanis
Centre for Metabolic Bone Diseases at Sheffield
(WHO Collaborating Centre)
University of Sheffield Medical School
Beech Hill Road
Sheffield S10 2RX
UK
Pavel Klein
Department of Neurology
Georgetown University Medical Center
Bles Building-1
3800 Reservoir Road NW
Washington DC 20007
USA

Chun Ng
The Menopause and Premenstrual Syndrome Centre
Department of Obstetrics and Gynaecology
Queen Charlotte’s and Chelsea Hospital
Du Cane Road
London W12 0HS
UK

Dimitios Nikolaou
Chelsea and Westminster Hospital
369 Fulham Road
London SW10 9NH
UK

Shaughan O’Brien
Women and Children’s Division
Maternity Unit
City General Hospital
North Staffordshire NHS Trust
Stoke on Trent ST4 6QG
UK

Santiago Palacios
Instituto Palacios Salud y Medicina de la Mujer
Calle Antonio Acuña 9
28009 Madrid
Spain

Nick Panay
The Menopause and Premenstrual Syndrome Centre
Department of Obstetrics and Gynaecology
Queen Charlotte’s and Chelsea Hospital
Du Cane Road
London W12 0HS
UK

Sonia Ocampo de Ruiz
Sociedad Boliviana del Climaterio
Av. Moñoz Reyes No. 100 Cota Cota
La Pa
Bolivia
South America

Goran Samsioe
Department of Obstetrics and Gynecology
Lund University Hospital
S-221 85 Lund
Sweden

Adolf E. Schindler
Director of Institute of Medical Research and Education
Department of Obstetrics and Gynecology
University of Essen
Hufelandstrasse 55
D-45147 Essen
Germany

Bo von Schoultz
Department of Obstetrics and Gynecology
Karolinska Hospital
SE-171 76 Stockholm
Sweden

Leon Speroff
Department of Obstetrics and Gynecology
Oregon Health Sciences University
3181 Sam Jackson Park Road
Portland OR 97201
USA

John Studd
Chelsea and Westminster Hospital
369 Fulham Road
London SW10 9NH
UK

Gunilla Svane
Mammography Section
Department of Diagnostic Radiology
Karolinska Hospital
S-171 76 Stockholm
Sweden

Carlo la Vecchia
Instituto di Ricerche Farmacologiche Mario Negri
20157 Milan
Italy

and

Instituto di Statistica Medica e Biometria
Università degli Studi Milano
20133 Milan
Italy
Foreword

Five years ago, consensus concerning hormone replacement therapy (HRT) and the menopause was fairly straightforward. Estrogens helped symptoms, prevented osteoporosis, prevented heart attacks and probably prevented strokes and Alzheimer’s disease. There was a problem with a possible small increase in breast cancer, but this was somewhat nullified by the view that the prognosis was so much better and that fewer HRT users died of breast cancer than a comparable group of non-users. It was all good news.

The Heart and Estrogen/progestin Replacement Study (HERS) secondary prevention study removed much optimism that estrogens would improve the prognosis of women who already had coronary artery disease. Stopping the trial at 5 years was certainly a wasted opportunity as the slight increase in cardiovascular events in the first year compared with placebo was being replaced by a clear benefit in years 3 and 4. Such is the wisdom of epidemiologists.

But it gets worse: the Women’s Health Initiative (WHI) study has had a devastating effect upon patients’ confidence in HRT. The media, quite correctly, made a great issue of these results. In spite of warnings from many clinical ‘menopausologists’, the WHI proceeded with a vastly expensive study using a standard dose of HRT whether the women were aged 50 or 79. They used, in my view, the wrong estrogen, probably the wrong route, and certainly the wrong population with an average age of 63 (range 50–79). Sixty-eight percent of patients were recruited over the age of 60 and 22% over the age of 70, with some recruited aged 79. Seven-point-seven percent had a past history of cardiovascular disease and 35% were taking hypertensives, but they were still prescribed 0.625 mg Premarin® and 0.25 mg Provera®. Only a clinical optimist would do this but this was the standard treatment in this group.

At $100 million and still spending the WHI trial is the most expensive, and in my personal opinion, the most inappropriate and probably the worst clinical trial in the history of medicine. Approximately 40% of American and European women have stopped taking HRT and the North American Menopause Society Advisory Panel (03.10.02) recommend that estrogens should be reserved for the treatment of severe vasomotor symptoms and atrophy and should not be first choice for the prevention or treatment of osteoporosis.

The British Medical Research Council (MRC) spent almost £10 million reproducing the WHI study which was already underway using the same estrogen despite protests from individual experts from the British Menopause Society, and from some members of the Council of the Royal College of Obstetricians and Gynaecologists. Epidemiologists certainly know how to spend money whether they are American or British. The MRC WISDOM study was discontinued with hardly a murmur of protest nor a hint of apology.

I am constantly amazed at the reaction of the commentators to this study. Although recognizing its faults, their reaction is to advocate very-low-dose estrogens on the assumption that this must be safer and perhaps even better. We must be aware that our
responsibility to peri-and postmenopausal women is to be sure that specific symptoms are treated correctly and that these women feel better without side-effects. The message is so simple: if women feel better, they will continue with estrogen therapy but they are unlikely to achieve this with a quasihomeopathic dose of the fashionable American oral estrogen.

Older women certainly need a very low starting dose, perhaps given on alternate days. The recently postmenopausal woman will need a low-to-moderate dose with the appropriate progestogen for relief of symptoms and prevention of osteoporosis. The woman with osteoporosis needs estrogen that will produce plasma estradiol levels of at least 300 pmol/l. The perimenopausal woman with depression and even premenstrual syndrome symptoms requires moderately high doses of transdermal estrogens which will produce plasma estradiol levels of at least 600 pmol/l (note the normal range is 150–1500 pmol/l so we are not going too high), together with cyclical progestogen. Women with libido problems need higher doses of estrogen with the addition of testosterone, and those with estrogen-responsive depression with progestogen intolerance need moderately high doses of transdermal estrogens, probably with the use of a Mirena® intrauterine system. All these patients do not need the standard low dose of estrogen. None of these patient groups needed the standard low dose of estrogen as used in the WHI study.

Not surprisingly, a subsequent paper from the WHI showed that there was no improvement in quality-of-life scores on this dose of Premarin® in this age group. Once again this was the wrong dose for the wrong patient.

This is such an important issue that I am grateful for the chapters on this subject from Henry Burger and colleagues, David Barlow and Goran Samsioe in the early pages of this volume. Passing on quickly to the end of the book, Santiago Palacios and Leon Speroff have produced scholarly accounts on the value—or lack of it—of alternative therapies for the postmenopausal woman.

I am grateful to all of the authors for their timely contributions and I can reassure my friends who haven’t quite been able to make the deadline that they will not be forgotten for the Fourth Edition next year. I must also acknowledge my thanks to the staff at Parthenon who are, at whatever level, always totally reliable. I particularly thank Jean Wright and Stephen Nicholls for their work on this volume.

John Studd, DSc, MD, FRCOG
Chelsea & Westminster Hospital, London
www.studd.co.uk
INTRODUCTION

The future of hormone replacement therapy (HRT), more appropriately described as postmenopausal hormone therapy (PHT), has become an extremely topical issue with the recent publication of the first report from the Women’s Health Initiative randomized controlled trial of estrogen plus progestin in ‘healthy’ postmenopausal women\(^1\). The field had been thrown into substantial controversy by the earlier publication of another prospective randomized controlled trial, the Heart and Estrogen/progestin Replacement Study (HERS)\(^2\), in which the benefit of PHT for the secondary prevention of cardiovascular disease in women was shown to be lacking.

The latter, combined with major recent reports of the increased risk of breast cancer, had already begun to cast significant doubts about the advisability of long-term hormone therapy in particular. This chapter aims to give a current perspective on the future applications of PHT by considering the indications for such therapy, the preparations available now and likely to be modified in the future, dosages, methods of administration and availability of compounds such as tibolone and the selective estrogen receptor modulators (SERMs). Other potential new methods are mentioned briefly, and the potential role of androgens in future PHT is considered.

INDICATIONS FOR POSTMENOPAUSAL HORMONE THERAPY

Currently available preparations and dosages of estrogen with or without a progestin are prescribed both for the short-term relief of symptoms associated with the peri-and early postmenopause and for long-term risk reduction, specifically for osteoporotic fracture and, until recently, for cardiovascular disease. Other possible reasons for long-term therapy have included reduction in the risk of cognitive decline and prevention of Alzheimer’s disease, and reduction in the risk of colorectal cancer. Each of these indications is reviewed in the light of current knowledge.

Short-term use for symptom relief

The vasomotor symptoms of hot flushes and night sweats, which are characteristic of the peri-and early postmenopause, can be satisfactorily relieved with an estrogen or an
estrogen plus a progestogen. Appropriate attention to life-style factors such as exercise, diet and stress reduction may also contribute to relief. Urogenital atrophy occurs commonly and responds to local estrogen administration as well as systemic therapy. Other symptoms that are commonly experienced, but are not specific to the menopause, include depression, anxiety, palpitations, headaches, insomnia, lack of energy, fluid retention, backache, difficulty in concentrating and dizzy spells. These are usually not highly correlated with menopausal status, although they are strongly correlated with each other and are more common among women who experience severe flushing. The severity of menopause-associated symptoms varies widely between women within the same culture, and even more widely among those from different cultures. Hormone therapy is effective for symptom relief and is indicated when a woman seeks this for moderate or severe complaints. With appropriate choice of dose and regimen, such therapy is generally regarded as non-controversial. The only significant risk of such short-term therapy is a small increase in the incidence of thromboembolism, estimated as an excess of about 1 in 5000 events per year in women early in their sixth decade. The results of studies such as the Women’s Health Initiative (WHI) and HERS are not generally relevant to consideration of the short-term use of hormones, as the subjects were predominantly substantially older than women with symptoms. Once symptom relief has been obtained, it is common practice to continue therapy for 2, 3 or 4 years. The possibility of long-term therapy arises if symptoms recur when treatment is withdrawn. Treatment withdrawal should be staged and not abrupt, as the latter is more likely to cause recurrence. If symptoms persist each time hormone therapy is withdrawn, women may request ongoing therapy. However, the benefits and risks of long-term therapy must then be carefully considered so that each woman can make an informed choice to continue, as discussed below.

**Long-term therapy**

*Results of the Women’s Health Initiative randomized controlled trial*

Long-duration PHT would generally be regarded as therapy lasting for more than 5 years. In that context, the results of the WHI to some extent become relevant. The WHI was initiated to define the risks and benefits of long-term PHT with particular reference to the incidence of heart disease and breast cancer, but with reference to other outcomes such as fracture and colorectal cancer. The study enrolled 161,809 postmenopausal women aged 50–79 years for various trials including PHT, low-fat diet and supplementation with calcium and vitamin D. One arm of this study was prematurely terminated in 2002 because the preset limit for the occurrence of invasive breast cancer ‘exceeded the stopping boundary for this adverse effect’. This randomized controlled primary-prevention trial included 16,608 postmenopausal women recruited in 40 American clinical centers between the years 1993 and 1998. Women were recruited by population-based direct mailing campaigns, were required to be postmenopausal and to have an intact uterus, and not to have medical conditions likely to be associated with only short-term survival. Some women were using postmenopausal hormones at their initial screening, and for these a 3 month wash-out period was required. The regimen evaluated
consisted of conjugated equine estrogen (CEE) 0.625 mg and medroxyprogesterone acetate (MPA) 2.5 mg or a matching placebo.

The average age of participants at screening was 63.2 years. One-third were in the age group 50–59, 45% were 60–69 and 21% were 70–79. The majority were White women, but the study included small numbers of Blacks, Hispanics, American Indians and Asians/Pacific Islanders. Almost 20% of the subjects were past users of hormones, and a further 6% were current users. The majority of these had used hormones for less than 5 years, although 19% of the previously treated women in the active treatment arm and 17% of the controls had used hormones previously for 5–10 years and 12% in each group for more than 10 years. Average body mass index (BMI) was 28.5 kg/m², and fewer than one-third of women had a normal BMI <25 kg/m². One-third of the women were overweight, and one-third had a BMI >30 kg/m², i.e. they were obese. Yet, overall, the subjects were described by the authors as ‘healthy’ postmenopausal women. Fifty per cent of the women had never smoked, 40% were past smokers and 10% current smokers. In each group 4.4% had been treated for diabetes, and 7% in each group had used statins at baseline, while approximately 20% had used aspirin. A very small number of women had a history of either coronary artery disease or prior thromboembolic events. The latter is generally considered a strict exclusion criterion for studies of postmenopausal estrogen therapy. The group were in general not at increased risk of breast cancer.

At the time of the report all women had been enrolled for at least 3.5 years and the average duration of follow-up was 5.2 years, with a maximum of 8.5 years. Forty-two per cent of women had stopped using hormones, and 38.5% had stopped using placebo at some time; 10.7% of the placebo group initiated hormone therapy. The authors provided data about the absolute numbers of various clinical outcomes by randomization assignment and presented their results in particular as annualized percentages, from which annual rates per 10 000 women were calculated. For purposes of clarity, the results from this study have been recalculated, as shown in Table 1, as events per 1000 women over the average 5.2 years of follow-up, together with the increased or decreased number of cases in the active group compared with placebo in that interval.

Many of the results in this first report from the WHI were in accord with the results of previous observational studies. Somewhat unexpected, however, was an increase rather than a decrease in the frequency of coronary heart disease events, with an excess risk of 4.2 cases per 1000 women over 5.2 years. It is noteworthy that the excess of coronary heart disease events occurred primarily in the first year of the study when the ratio of events in the treated versus placebo arms was 1.78, comparable to what was seen in the first year of the HERS trial. There was also an excess of cases in year 5, 23 of 5964 participants compared with nine of 5566, although the trend was negative over time.

Stroke risk was somewhat higher than anticipated, while the risks of venous thromboembolism and pulmonary embolism were relatively high, but not unexpected for a group of women of average age 63 years, of whom most were overweight. The rate of increase in cases of invasive breast cancer was in line with the results of previous studies, and again showed an excess of 4.2 cases per 1000 women over 5.2 years. This can also be expressed as an excess risk of 1:240 over 5 years. Of considerable importance, but not highlighted in the publication, is that there was no increase in breast cancer risk among the 6280 women treated with active therapy for a mean duration of 5.2 years who had not used hormone therapy prior to commencing the study, compared with
the 6204 prior non-users treated with placebo (hazard ratio for active therapy being 1.06, 95% confidence interval (CI) 0.81–1.38). This reconfirms the results of previous studies indicating that hormone therapy for less than 5 years is not associated with increased breast cancer risk⁵.

**Table 1 Women’s Health Initiative¹: events per 1000 women over 5.2 years (average)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Active treatment</th>
<th>Placebo treatment</th>
<th>Excess/deficiency in active groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>19.3</td>
<td>15.1</td>
<td>4.2 more</td>
</tr>
<tr>
<td>Stroke</td>
<td>14.9</td>
<td>10.5</td>
<td>4.4 more</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>17.8</td>
<td>8.3</td>
<td>9.5 more</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>8.2</td>
<td>3.8</td>
<td>4.4 more</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>19.5</td>
<td>15.3</td>
<td>4.2 more</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>5.3</td>
<td>8.3</td>
<td>3 fewer</td>
</tr>
<tr>
<td>Total fractures</td>
<td>76</td>
<td>97</td>
<td>21 fewer</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>5.2</td>
<td>7.7</td>
<td>2.5 fewer</td>
</tr>
<tr>
<td>Total deaths</td>
<td>27</td>
<td>27</td>
<td>–</td>
</tr>
<tr>
<td>Global index</td>
<td>88.3</td>
<td>76.9</td>
<td>11.4 greater</td>
</tr>
</tbody>
</table>

In contrast, in those who had used hormones for less than 5 years previously, the hazard ratio was 2.13 with 95% CI 1.15–3.94.

Of interest was a reduction in colorectal cancer risk by three cases, and a reduction in total fractures by 21 and hip fractures by 2.5. Total deaths in both arms of the study were identical, but a global index comparing risk with benefit proved to be in the adverse direction in the actively treated women.

It was noteworthy that the absolute excess risks attributable to the therapy were low, and that the trial tested an oral drug therapy regimen usually used for symptomatic treatment in early postmenopausal women, not in women 10–25 years postmenopausal. The authors and other commentators have indicated that this combined hormone therapy regimen should not be initiated or continued for the primary prevention of coronary heart disease, and that the substantial risk for coronary heart disease and breast cancer must be weighed against benefit for fracture, in selection of the available agents to prevent osteoporosis. Recommendations have been made that clinicians should stop prescribing this combination for long-term use. A limitation of these recommendations is that event rates were not published per decade of age. One would strongly suspect that cardiovascular events would have been rare in women under 65 years of age in this study, and thus recommendations may not be applicable to younger women.

The authors were careful to point out that ‘this trial tested only one trial regimen, CEE 0.625 mg per day, plus MPA 2.5 mg per day, in postmenopausal woman with an intact
uterus. The results do not necessarily apply to lower dosages of these drugs, to other formulations of oral estrogens and progestins, or to estrogens and progestins administered through the transdermal route. It remains possible that transdermal estradiol with progesterone, which more closely mimics the normal physiology and metabolism of endogenous sex hormones, may provide a different risk-benefit profile. The authors also pointed out that the trial was unable to distinguish the effects of estrogen from those of progestin, the latter perhaps being particularly important for breast cancer and perhaps atherosclerotic disease. A separate trial within the WHI is testing the hypothesis of whether oral estrogen alone will prevent coronary heart disease in 10,739 hysterectomized women. The latter trial is continuing at the time of this writing.

Primary prevention of cardiovascular disease

The results of the WHI, as discussed in detail above, have been interpreted as indicating that long-term PHT has no place in the primary prevention of cardiovascular disease. This conclusion had also been drawn by some writers from the results of the HERS trial and a limited number of other randomized trials. It may be argued that this is too strong a generalization on the basis of the published data. Women in the HERS trial were chosen deliberately to evaluate the place of PHT in secondary prevention, i.e. they were women with existing, clinically manifest coronary artery disease. Women in the WHI were chosen to be ‘healthy postmenopausal women’, as only 7.7% of the participants reported having had prior cardiovascular disease. However, this study population cannot realistically be characterized as ‘healthy’ considering the high rates of obesity and current and past smoking, that 35% were being treated for hypertension, 12% had hypercholesterolemia requiring therapy and 20% had an indication for aspirin use. Although the participants were in general free of clinical coronary artery disease, it seems highly probable that many had significant subclinical disease. That there were more coronary events in the treated group than in the controls is consistent with this interpretation. It could be argued that true primary prevention of coronary heart disease involves the treatment of women at risk, but without significant coronary disease at the time such preventive therapy is initiated. There is substantial literature indicating that modification of endothelial function plays a major role in the cardioprotection afforded by estrogen, but that this is attenuated in women with pre-existing endothelial dysfunction. This, in turn, may in part explain the disappointing results of prospective estrogen intervention studies in women at high cardiovascular risk.

The work of Clarkson’s group in the cynomolgus monkey model of postmenopausal atherosclerotic vascular disease suggests strongly that, in animals in which advanced atherosclerosis has been allowed to develop, sex-steroid therapy is ineffective in reducing progression. In animals with moderate disease, some reduction in progression can be anticipated, but the striking results in terms of primary prevention are seen in animals with minimal or absent lesions. A large body of evidence indicates that estrogen influences vascular function via genomic and non-genomic mechanisms, and therefore that sex-steroid administration to postmenopausal women should clearly be cardioprotective. Extensive epidemiological data also indicate that current usage of PHT is associated with a reduction in the relative risk (RR) of cardiovascular events (current users RR 0.56, 95% CI 0.4–0.8; past users: RR 0.83, 95% CI 0.65–1.05). The women
most likely to benefit are those with the most significant cardiovascular risk factors. At best, in the WHI, this criterion might have applied to the group of women aged <60 years at the time therapy was initiated. It could be postulated that a true primary prevention trial should randomize women within the first 3–5 years after the menopause, and should perhaps use the most physiologically relevant type of hormone, namely estradiol itself, given parenterally, preferably associated with progesterone, a progestin closely resembling it, or a progestin administered directly to the uterus (for example by an intrauterine device) and thus avoiding systemic exposure. Only in those circumstances could true primary prevention be evaluated. This type of study is one which the authors would hope to see carried out in the context of the ‘future of HRT’. Thus, although such observational studies are known to be limited by various biases, the design of the WHI is not such that it would allow an unequivocal conclusion that long-term PHT has no place in primary cardiovascular protection. The issues of dosage are considered below.

### Secondary prevention of cardiovascular disease

While the results of the HERS trial have been widely interpreted as indicating that long-term PHT has no place in the secondary prevention of heart disease, it is again noteworthy that observational studies such as the Nurses’ Health Study have suggested that some long-term protection may be afforded, as have several studies of women undergoing surgical procedures for coronary disease. The HERS trial was conducted among volunteers of average age 68 years who were commenced abruptly on a regimen of CEE 0.625 mg per day and MPA 2.5 mg per day. Most clinicians would regard as inappropriate clinical management the abrupt initiation of therapy with doses actually appropriate for early-postmenopausal women, but not for those 10–25 years past the menopause. It could be postulated that such abrupt hormone dosage might have adverse effects on pre-existing atherosclerotic plaques, thus accounting for the increased event rate in the first year of active therapy. While it may be that extensively diseased arteries could never be affected favorably by long-term hormone therapy, a trial in which very low doses of therapy were administered initially and gradually built up to low therapeutic levels could be worthwhile if the issue was to be studied rigorously. Nevertheless, the availability of several other measures for cardiovascular protection makes it most unlikely that such a trial would ever be conducted. On current evidence, the appropriate measures for secondary prevention of coronary disease include life-style changes, avoidance of smoking, regular exercise, and specific treatment of hypertension and dyslipidemia.

### Osteoporosis prevention and management

A major dilemma posed by the WHI findings concerns the long-term use of PHT for women at increased risk of osteoporotic fracture, including those who have already suffered such an event. A woman may be considered at sufficient risk to warrant intervention, for example with PHT, if her bone mineral density indicates a T-score below −2.5 standard deviations from the mean in the absence of other risk factors, or a T-score at −1.5 to −2.5 standard deviations in the presence of other risk factors such as a maternal history of osteoporotic fracture. For such women, many clinicians have