Effects of HT on bone

A number of randomised controlled trials have evaluated the effects of systemic estrogen on BMD and fracture in postmenopausal women. The beneficial effects of estrogen and progestogen (EPT), or estrogen only (ET) for women without a uterus, are considered below.

Bone mineral density (BMD)

A 2002 meta-analysis of 57 randomised clinical trials comparing ET/EPT with placebo in postmenopausal women found consistent BMD increases with ET/EPT at all sites. In trials of 2 years’ duration, the mean difference in BMD after ET/EPT was 6.8% at the lumbar spine and 4.1% at the femoral neck.

The two largest and best controlled studies support these findings. In the Postmenopausal Estrogen/ Progestin Interventions trial (N=875), standard daily doses for 3 years of 0.625 mg conjugated equine estrogens (CEE), with or without a progestogen (either medroxy-progesterone acetate (MPA) or micronised progesterone), significantly increased spinal BMD by 3.5% to 5.0%, with a 1.7% increase in hip BMD. More recently, the WHI, a 5-year randomised controlled trial in postmenopausal women aged 50 - 79 years (N=16 608), reported that standard doses of daily EPT (0.625 mg CEE plus 2.5 mg MPA) significantly increased spine and total hip BMD by 4.5% and 3.7%, respectively, relative to placebo.

Effects of lower-than-standard doses of ET/EPT on BMD have been investigated. Randomised controlled trials using doses as low as 0.3 mg/day oral CEE, 0.25 mg/day oral micronised 17β-estradiol, and 0.014 mg/day transdermal 17β-estradiol reported significant increases in spine and hip BMD relative to placebo. These trials were conducted either in populations of early postmenopausal women (mean age 51 - 52 years) or in older postmenopausal women (mean ages 67 and 74 years). Changes in lumbar spine BMD were in the range of 1% to 3% – significantly better than placebo.

Significant BMD improvements have also been noted...
with systemic estrogen doses delivered via a vaginal ring (Femring). In a randomised controlled trial of 174 postmenopausal women <65 years, daily doses of 0.05 and 0.1 mg of estradiol acetate delivered via the ring significantly increased hip BMD (1.7% and 1.9%, respectively) and lumbar spine BMD (2.7% and 3.3%) compared with baseline.

**Fractures**

Evidence from both randomised controlled trials and observational studies indicates that standard doses of ET/EPT (including 0.625 mg CEE/day or the equivalent) reduce fracture risk in postmenopausal women. Two meta-analyses have found that ET/EPT significantly reduces the risk of fracture by up to 27%. Two recent, large observational studies support these data. The National Osteoporosis Risk Assessment (NORA) study followed 200,160 postmenopausal women and reported that current estrogen use was associated with a significantly reduced risk of new fracture. Participants were at least 50 years old and had no previous diagnosis of osteoporosis. The Million Women Study, a prospective observational study of 138,737 postmenopausal women, reported that current ET/EPT use provided a significant relative risk reduction in incidences of fracture. These findings were confirmed in the WHI study. In both the EPT arm and the ET arm, significant reductions were seen for hip fractures, vertebral fractures, and total fractures compared with placebo. The EPT arm of the WHI trial was the first randomised trial to show a statistically significant reduction on HT in both hip and vertebral fracture (Table I). HT remains the only evidence-based therapy shown to reduce fracture risk in unselected populations. The selection criteria and outcomes evaluated in the WHI (i.e. women were not selected based on an established osteoporosis risk factor or BMD level; fracture outcomes included hip, wrist/lower arm, and clinically identified vertebral and total fractures) are in contrast to the design of studies of fracture risk reduction with bisphosphonates or selective estrogen receptor modulators (SERMs), etc. In those studies, women were selected based on high risk of osteoporosis (i.e. prevalent vertebral fracture and/or low BMD); radiologically detected vertebral fractures were often a primary outcome.

The Million Women Study, although observational in design, addressed issues related to ET/EPT and the risk of fracture that could not be ascertained in the WHI trials, such as comparison between different EPT formulations, doses, and routes of administration. When the overall fracture risk reduction was examined by type of hormone, no difference was found between ET and EPT. Sequential or continuous progestin use also did not significantly affect the results. Furthermore, the relative risk of fracture was not different when specific estrogen or progestin products were compared (i.e. CEE v. estradiol, MPA v. norethisterone, or norgestrel v. levonorgestrel). Neither this nor any other study to date specifically report on the possible fracture protection afforded by a low estrogen dose (i.e. 0.3 mg), but did find that risk reductions for doses greater than 0.625 mg were similar to those for doses of 0.625 mg or less.

**HT benefits v. risks**

The therapeutic envelope of any intervention is defined by the ratio of benefit to risk. This is especially true in the case of menopausal HT that is used in the prevention or treatment of osteoporosis.

**Background**

The US Food and Drug Administration (FDA) approved marketing of diethylstilbestrol in 1941 and conjugated equine estrogens (CEE) in 1942 for treatment of menopausal symptoms. Estrogen sales doubled and tripled in the mid-1960s to mid-1970s, until 1975, when reports of increased endometrial cancer in estrogen users resulted in a dramatic decline. Estrogen use increased again, with evidence of protective effects of progestins on estrogen-induced endometrial changes. HT received even more support from a 1982 report that CEE retained bone mass, and from a 1984 National Institutes of Health (NIH) statement that estrogens were the most effective means for preventing bone loss. The use of HT further increased till 2001, at which time approximately 15 million US women were using HT. The increasing popularity of HT was primarily fuelled by observational studies suggestive of reduced coronary heart disease (CHD) in women on HT. The 2002 WHI report of greater harm than benefit in EPT users resulted in a precipitous decrease in HT use.

**WHI report**

The WHI report redefined the therapeutic envelope of HT and osteoporosis in the following ways:

- It was the first large randomised controlled trial (RCT) to prove that HT (EPT and ET) reduces the

| Table I. The effect of HT on the reduction of fracture (WHI) |
|-----------------|-----------------|------------------|
| EPT             | ET              |
| **Hip**         | **Vertebrae**   | **Total**        |
| 0.67 (0.47 - 0.96)* | 0.65 (0.48 - 0.92)* | 0.60 (0.42 - 0.90)* |
| 0.65 (0.49 - 0.92)* | 0.62 (0.42 - 0.93)* | 0.70 (0.63 - 0.79)* |

*p<0.05.
risk of all osteoporotic fractures, including hip fractures. This was even more remarkable, as the patients were generally regarded to be at low risk of fracture with the average BMD in the osteopenic range. The effect on radiological fractures is underestimated, as routine X-rays of the spine were not done.

- The WHI study failed in the primary endpoint to demonstrate a reduced risk of CHD in HT users. In the EPT arm, an increase in non-fatal CHD was found in patients started on HT on average more than 10 years after start of menopause (WHI: excess cases of CHD 7/10 000 women per year).
- The WHI study failed to demonstrate a beneficial effect of HT on Alzheimer’s disease or dementia. Furthermore, women >65 years should be made aware that commencement of HT at such a late stage could result in a worsening of cognitive capacity. Generally, HT should not be recommended for the preservation of cognitive function or the prevention of dementia.
- The risk of venous thromboembolism (VTE) is doubled with HT. The absolute risk of VTE is increased by 18 cases per 10000 women per year (EPT arm, WHI). The effect is maximal in the first year of treatment and more pronounced with advancing age, obesity and previous VTE. The risk of VTE in the age group 50 - 60 years is very small.
- The WHI study reported an increased risk of stroke accompanying HT (HR 1.39 in the EPT arm and 1.39 in the ET arm), which is consistent with results from the Nurses Health study. In contrast to VTE, the effect was not confined to the first year, but was maintained throughout the study. However, the Danish Nurse Study found that in 13 122 healthy postmenopausal women followed for 5 years, unopposed estradiol 1 mg daily was not associated with an increased risk of stroke (risk ratio (RR) 0.80 (0.40 - 1.61)). It is possible that the effect of HT on stroke is dose-related. Smaller doses may be protective, and larger doses harmful.
- EPT is associated with a modest increase in risk of invasive breast cancer, if used for more than 5 years. Although the relative risk is in the order of 1.35, the absolute increase in risk is small (e.g. WHI: 8/10 000 per year – or less than 0.1% per year), but increases with duration of treatment if initiated after age 50. The increased risk disappears 5 years after cessation of therapy. (It is possible that this does not imply causality, but rather modification of pre-existing malignancy.) The effect is more pronounced in lean patients. The increased risk is associated with the addition of progestogen and is not apparently increased when estrogen is used alone. The initial report on the estrogen-only arm concluded that there was no significant decreased risk for breast cancer in ET users, but subgroup analyses now reveal that first lifetime exposure to ET at entry to the trial was associated with significantly fewer breast cancer cases as compared with placebo (RR 0.76; 95% confidence interval (CI) 0.58 - 0.99; p<0.05); women who took ET had significantly fewer breast cancers with localised disease and significantly fewer breast cancers with ductal carcinoma (RR 0.71; 95% CI 0.52 - 0.99).

Conclusion from initial WHI reports

It was concluded that estrogen plus progestogen increases BMD and reduces the risk of fracture in healthy postmenopausal women. The decreased risk of fracture attributed to estrogen plus progestogen appeared to be present in all subgroups of women examined. When considering the effects of hormone therapy on other important disease outcomes in a global model, there was no net benefit, even in women considered to be at high risk of fracture. The effect did not differ in women stratified by age, body mass index, smoking status, history of falls, personal and family history of fracture, total calcium intake, past use of hormone therapy, BMD, or summary fracture risk score. It must be noted that the global index as used by the WHI investigators, is not a validated system and does not take into account quality-of-life issues. The fracture reduction effect of HT in WHI is underestimated when compared with other RCTs in osteoporosis as radiological vertebral fractures were not recorded. The benefit/risk profile for prevention of fracture has not been calculated for the EHT arm of WHI.

The reaction of regulatory authorities to WHI 2002

- The FDA (USA) restricted the use of HT to the prevention of osteoporosis. When used only for this indication, other approved medication should be considered, and the risk of osteoporosis should exceed possible risks.
- EMEA (Europe) removed HT as first-line therapy for prevention or treatment of osteoporosis.
Timing hypothesis (therapeutic window)

A number of recent clinical reports, including a further analysis of WHI, support the data (from primate, rodent and in vitro studies) that the timing of HT introduction plays a crucial role in cardiovascular outcomes. The hypothesis is that when atherosclerosis is at an early stage (e.g. fatty streaks), HT is beneficial, but in older unstable plaque it is deleterious.

The original WHI report in 2002 showed an increased risk of coronary heart disease (CHD), but the average age of starting HT was 63 years (some 12 years into menopause). Support for the timing hypothesis came from the report on the ET arm of WHI, which showed a trend to decreased events versus placebo in younger women. Last year, the WHI working group published the analysis of CHD according to decade of age at entry into the study; results from both arms of the WHI were combined. There was a significant trend (p=0.02) for CHD events on HT to be lower, the shorter the period since menopause. A recent analysis of the Nurses Health Study showed even more encouraging results: for women starting HT near the menopause, there was a significantly reduced risk of CHD (RR=0.66, 95% CI 0.54 - 0.80) for estrogen alone; RR=0.72, 95% CI 0.56 - 0.92 for estrogen with progestogen.

The most recently published sub-analysis of the WHI looked at coronary artery calcium scores (CACS) in 1,064 subjects, who entered the ET arm (or placebo) at age 50 - 59 years. CACS (a marker of calcified plaque and predictive of future CHD events) was measured in these subjects on average 1.3 years after the trial was stopped. The calcified plaque burden was lower in women who had been on ET (average of 7.4 years) versus placebo, and this difference was highly significant.

Taking all these recent pieces of evidence together, it is reasonable at present to consider that the healthy, early postmenopausal female is at very low risk on HT. The International Menopause Society (IMS) has always promoted a more upbeat outlook on HT and, even in 2003, cautioned that the seminal WHI report was not the last word on this subject. In the latest update of their position statement, the overall balanced tone is in sharp contrast to some unsubstantiated points, e.g.: ‘There are no reasons to place mandatory limits on the length of treatment’. The American Association of Clinical Endocrinologists (AACE) position statement on HT and cardiovascular risk is somewhat more conservative and reflects the general view of non-gynaecologists. Their position paper of January 2008 recognises that the evidence presently available is such that young females in early menopause can be safely counselled ‘… to use estrogen for the relief of menopausal symptoms’.

Common ground

The present areas of consensus can be divided into those where HT is recommended and those where it should definitely not be started.

A. HT indicated
1. Premature menopause
2. Significant vasomotor symptoms
3. Early postmenopause with above average risk of future fracture and menopausal symptoms (use up to the age of 60).

B. HT NOT indicated
1. Universal treatment at menopause
2. Initiation of HT after the age of 60
3. Purely as strategy to prevent CVD.

The two major points of contention are:
1. Where HT has been appropriately initiated, should it be continued after the age of 60?

Once HT is no longer required for menopausal symptoms, it should generally be stopped. If ongoing bone protection is indicated, bisphosphonates and other agents have been shown to be highly effective cross-over therapies and prevent the often rapid bone loss which occurs on stopping HT.

2. ‘HT is an appropriate first-line therapy in early postmenopausal women presenting with an increased risk of fracture’ (IMS 2007) – WITHOUT other indications?

Finally, although the IMS suggests that lower doses of HT (as well as, presumably, types and formulations different to CEE) may further reduce risks and side-effects, they agree that the prospective evidence regarding fracture risk and CVD is still lacking. Furthermore, the difference in benefit/risk assessment between women on EPT (the majority) versus ET still has to be defined adequately. The potential benefits of younger postmenopausal women receiving HT will hopefully become clearer in two ongoing trials: Kronos Early Estrogen Prevention Study (KEEPS) and the Early versus Late Intervention Trial with Estradiol (ELITE).