OPINION

HRT, osteoporosis and regulatory authorities
Quis custodiet ipsos custodes?

John C. Stevenson on behalf of the International Consensus Group on HRT and Regulatory Issues

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HRT has been widely used for the relief of menopausal symptoms and the prevention and treatment of post-menopausal osteoporosis. However, following the publication of the Women’s Health Initiative (WHI) and the Million Women Study (MWS), regulatory authorities issued an urgent safety restriction on HRT use in preventing post-menopausal osteoporosis, recommending that it now be considered a second-line treatment. Are such recommendations justified? Treatments for osteoporosis, in women with increased future risk for fractures but who have not yet developed the disease, should prevent all types of osteoporotic fractures. Of the available therapies, none other than HRT has been clearly demonstrated to prevent hip fractures in such women. Thus, HRT should be recommended as first-line treatment for osteoporosis prevention. Potential risks of HRT, such as increased development of breast cancer and increased thromboembolism, have long been known. The WHI showed risks in less than 0.3% of women studied, and the MWS appears to have overestimated the risk of breast cancer. Thus, no new safety issues have been identified, and the regulatory authorities may have misinterpreted the data from these recent studies. When given for the correct indications, HRT is of major benefit to many women.

Introduction

Hip fracture is the most serious consequence of osteoporosis, but other fractures also contribute to morbidity and cost. HRT is a well-established and proven strategy for the prevention of osteoporosis and osteoporosis-related fractures. Nevertheless, since December 2003 its use has been discouraged by regulatory authorities on the grounds of safety. It is our view that the recommendations of the European Agency for the Evaluation of Medicinal Products (EMEA) and UK Committee on Safety of Medicines (CSM) are not justified. Whilst osteoporotic fractures are commonest in the elderly, a substantial number occur in women who do not have very low bone density (Siris et al., 2001) and many are below 65 years of age. For prevention of fractures in these women with increased risk, initiation of HRT is often an appropriate approach for that age group. For these women, no alternatives to HRT have been demonstrated to reduce the incidence of hip fracture. Concerns regarding the safety of HRT have arisen inappropriately, firstly, from a large randomized clinical trial showing only minor risks and secondly, from an observational study that appears to have overestimated the risk of breast cancer.

Regulatory position on HRT

Despite efforts by the European Committee for Proprietary Medicinal Products (CPMP) to harmonize prescribing information for all HRTs, the Summaries of Product Characteristics (SPCs) for HRTs remain inconsistent throughout the European Union. A provisional core SPC was first agreed in February 2002 under the auspices of the Mutual Recognition Facilitation Group (MRFG). This process was disrupted by publications from the Women’s Health Initiative (WHI) in July 2002 (Writing Group for the Women’s Health Initiative Investigators, 2002) and subsequently the Million Women Study (MWS) in 2003 (Million Women Study Collaborators, 2003). In August 2003, following publication of the MWS, the CPMP was asked to examine public health concerns related to the safe and effective use of HRT in osteoporosis indication. An ad hoc expert group was formed by the EMEA. This committee had very few members with clinical expertise in the management of osteoporosis. On 3rd December 2003, following the recommendations of this expert group, the EU’s Heads of Agencies issued the new advice. They stated that, for the treatment of menopausal (climacteric) symptoms, which adversely affect quality of life, the balance of risks and benefits of HRT is generally favourable. They also stated that for the prevention of osteoporosis in women with an increased risk of fractures the benefit–risk balance of HRT with different kinds of estrogens and estrogen–progestogen combinations is, on the basis of available evidence, not favourable. Hence, HRT would not be the first-line treatment for this indication. On the same day, the CSM issued advice to doctors and information for press and patients reiterating the Heads of Agencies’ position. The regulatory action to restrict the osteoporosis indication was taken via an Urgent Safety Restriction (USR) issued to all member
states on 4th December 2003. This resulted in a revised version of the core SPC for all HRTs in February 2004. The revised text states that clinicians should only prescribe HRT for the prevention of osteoporosis ‘in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis’. Thus, it is recommended that HRT should no longer be prescribed freely for the prevention of osteoporosis. Indeed, clinicians are advised to prescribe alternative therapies for osteoporosis unless there is a contraindication to, or intolerance of, such therapies. However, it should be pointed out that no large safety study lasting several years has been carried out on the current bisphosphonates.

The regulatory actions and attendant publicity have resulted in a loss of confidence in HRT use amongst doctors and their patients. Even for the treatment of menopausal symptoms, the CPMP has advised that HRT should be used at the minimum effective dose for the shortest duration. No advice has been given as to what is the minimum effective dose or how to establish it for individual women nor has any advice been given as to how to establish the shortest duration of therapy, and this has been left to the judgment of the individual clinician. However, this has resulted in doctors being even more confused.

**Prevention of osteoporosis**

Primary prevention of osteoporosis is directed at women identified as being at increased risk for the disease but without established disease. HRT has been shown to reduce postmenopausal bone loss and reduce fracture incidence. Lower doses then previously thought necessary are now proving effective (Lees and Stevenson, 2001; Lindsay et al., 2002; Ettinger et al., 2004), and a very low dose estrogen product has recently been licensed for osteoporosis prevention by the US Food and Drugs Administration. The WHI trials, using a fixed combination of conjugated equine estrogens 0.625 mg and medroxyprogesterone acetate 2.5 mg, have confirmed the fracture reduction efficacy of HRT, including hip and spine fractures (Cauley et al., 2003; Women’s Health Initiative Steering Committee, 2004). The studies were of women aged between 50 and 80 years, who were not known to have increased fracture risk and who were supposed to be in general good health. The benefits and risks of HRT for the primary prevention of osteoporosis in women with increased risk of fractures have not been studied in any large randomized clinical trial. Thus, it is difficult to understand how the statement made by the Heads of Agencies that the balance is unfavourable is justified. The currently licensed alternatives to HRT for the secondary prevention of osteoporosis, preventing fractures in women who have existing osteoporosis, include bisphosphonates, raloxifene, teriparatide, strontium ranelate, calcitonin and anabolic steroids. Calcium supplements are licensed as an adjunct to therapy. Of these, only alendronate and risedronate have been shown to reduce the incidence of hip fractures, yet hip fracture is the most important osteoporotic fracture. However, both alendronate (Cummings et al., 1998) and risedronate (McClung et al., 2001) have only been shown to prevent hip fracture in elderly women, mean age above 65 years, who already had osteoporosis, with bone density T-score in either hip or spine below –2.5, and in many cases had already sustained a fracture. These agents have not been shown in prospective studies to prevent hip fractures in younger women with increased risk rather than established disease, although the existing studies were not designed to investigate fracture reduction in such women. Of course, hip fractures occur most commonly in elderly women, and bisphosphonate use in such women is often more appropriate than the current HRT regimens. Furthermore, although it is likely to be effective, no appropriately sized studies to evaluate hip fracture prevention have been conducted with HRT in women with established osteoporosis. Whether very low dose unopposed estrogen, with its minimal endometrial stimulation and relative freedom from other side effects (Ettinger et al., 2004), will prove an effective and cheaper alternative for fracture prevention in these women remains to be determined. Thus, there is no doubting the efficacy of HRT for the primary prevention of osteoporosis in post-menopausal women, but its current role in prevention of fractures seems best suited to those younger post-menopausal women with increased risk. In such a population, HRT use for osteoporosis prevention would be cost-effective (Lamy et al., 2003).

**Safety of HRT**

The concerns of the regulatory authorities over the safety of HRT arise from their interpretation of the WHI estrogen/progestogen study and the MWS. The WHI estrogen/progestogen arm showed a small increase in absolute risk of breast cancer, stroke and pulmonary embolism. Using a ‘global index’, created by the study Data Safety and Monitoring Board, to summarize important aspects of health benefit versus risk, an adverse outcome of HRT was demonstrated [hazard ratio (HR) 1.15, 95% confidence intervals (CI) 1.03–1.28]. In absolute terms, this represented risk in 19 women per 10 000 women-years (<0.2%). However, an increased risk of CHD or stroke was not found in women less than 10 years beyond menopause. In the estrogen-alone arm of WHI, no adverse outcome in terms of global index was found (HR 1.01, CI 0.91–1.12). The use of this global index, which does not incorporate any menopausal symptoms, has not been validated. If all clinical outcomes recorded in the WHI studies are considered (cardiovascular disease, cancer, fractures and death), a different pattern emerges. The estrogen–progestogen arm shows an overall benefit in 17 women per 10 000 women-years (0.17%) (Table I), whilst the estrogen-alone arm shows an overall benefit in 36 women per 10 000 women-years (0.36%) (Table II).

| Table I. Comparison of events (excess or reduction) per 10 000 women-years from clinical outcomes between estrogen–progestogen HRT and placebo (Writing Group for the Women’s Health Initiative Investigators, 2002) |
|-------------------------------------------------|-----------------|
| **Risks** | **Benefits** |
| All CVD | 25 |
| All cancers | 3 |
| All fractures | 44 |
| Deaths | 1 |
| Overall balance = +17 |

CVD, cardiovascular disease.
A major concern about HRT has been an increase in the incidence of breast cancer associated with its use. This concern is not new (Colditz et al., 1995). The estrogen–progestogen arm of WHI found a small increase in risk of invasive breast cancer (HR 1.24, CI 1.01–1.54) but not in situ cancer (Chlebowski et al., 2003). The risk of breast cancer was increased significantly only in women with a history of HRT exposure prior to study entry, supporting a duration effect. In women not previously exposed to HRT, the risk of breast cancer was not increased (HR 1.09, CI 0.86–1.39). The MWS reported a greater incidence of breast cancer with estrogen–progestogen HRT (HR 2.00, CI 1.88–2.12). However, there are concerns about the findings of the MWS (Whitehead and Farmer, 2004). Inclusion and surveillance biases, together with treatment misclassification, make the study outcomes uncertain. The findings of a complete disappearance of risk 14 months after discontinuation of HRT are biologically implausible. Furthermore, MWS reported an increased incidence of breast cancer with estrogen-alone therapy (HR 1.30, CI 1.21–1.40), which is in complete contradiction to the reduced incidence found in the WHI randomized clinical trial (HR 0.77, CI 0.50–1.01) and in many other studies (Bush et al., 2001). It therefore seems that the MWS has overestimated the breast cancer risk with HRT. Thus, it seems most improbable that the USR issued by the CPMP could have been justified on the grounds of breast safety. The significant increased risk of CHD (HR 1.29, CI 1.02–1.63) reported by the WHI estrogen–progestogen arm in the first publication (Writing Group for the Women’s Health Initiative Investigators, 2002) was not confirmed in the subsequent full publication after final adjudication of events (HR 1.24, CI 1.00–1.54) (Manson et al., 2003). In the WHI estrogen-alone arm, there was no increase in risk (HR 0.91, CI 0.75–1.12). The early increased risk seen in the WHI study could be dose related (Stevenson, 2004) and therefore avoidable. The increased risk of stroke seen in WHI could also be dose related (Grodstein et al., 2000) and is found more in the older (70–79 years) women in the estrogen-alone arm. This is not an age group targeted for HRT, where menopausal symptoms are extremely uncommon and effective alternatives for hip fracture prevention exist. The final safety concern is venous thromboembolism (VTE), again not a new concern (Daly et al., 1996). A significant increase in VTE was reported in the WHI estrogen–progestogen arm (Cushman et al., 2004), although not in the estrogen-alone arm. However, the VTE risk (HR 2.06, CI 1.57–2.70) was lower than that found in previous observational studies and particularly in women aged 50–59 years who were not overweight. VTE risk could again be dose related. In contrast to the risks, there is a possible benefit in terms of a reduction in colorectal cancer seen in HRT users (Writing Group for the Women’s Health Initiative Investigators, 2002), although this was not seen in the estrogen-alone arm of WHI (Women’s Health Initiative Steering Committee, 2004).

**Recommendations for HRT**

A main indication for HRT remains the relief of post-menopausal symptoms, which brings a major improvement in quality of life. No other therapy has proved to be more effective than HRT in this respect. It is also quite clear that HRT is an effective treatment for prevention of osteoporotic fractures in women without established disease. These women tend to be younger, since older women have an increasing prevalence of osteoporosis as defined by bone density criteria (Kanis et al., 2001). Are younger women with osteopenia, rather than osteoporosis, at increased fracture risk? In the age group 50–80 years, around 36% of classical osteoporotic fractures occur in those below age 65 years (Singer et al., 1998; Kanis et al., 2004). In the UK, this amounts to over 100 000 fractures per year in women aged 50–65 years, over 9000 of which are hip fractures (Singer et al., 1998; Kanis et al., 2004; www.uk2u.net). HRT is less expensive than any of the alternatives, and thus its use for primary prevention should be actively encouraged targeting post-menopausal women at high risk for fracture, such as those with osteopenia, with a family history of hip fracture, with a low body mass index or with a history of corticosteroid use. Prevention of hip fracture later in life could require long-term therapy, since there is evidence from large but short-term observational studies that it is only current HRT use which reduces the risk of fracture (Barrett-Connor et al., 2003). Bisphosphonates may be the most cost-effective intervention for elderly osteoporotic women. However, new data from a long-term prospective study suggest that even limited HRT use in women during early menopause may result in fracture reduction later (Bagger et al., 2004). A recent analysis of the WHI study data also showed that overall fracture benefit was maintained 16 months after discontinuation of estrogen plus progestogen (Jackson et al., 2004). Both these findings need to be confirmed.

It is our view that HRT should be considered a first-line option for the primary prevention of osteoporosis-related fracture in post-menopausal women with increased risk, even if asymptomatic. It should also be available to those older women with increased risk who either have persisting menopausal symptoms or who make an informed choice to use it. With regard to safety issues, the regulatory authorities may have misinterpreted the new data from the recent studies. These studies do not identify a new safety issue. The WHI was a chronic disease prevention trial aimed primarily at determining whether hormone therapy initiated at any age would be protective against heart disease. The participants had no clinical indication to take HRT and not surprisingly the treatment resulted in neither benefit nor harm for more than 99%. It is logical to recommend that HRT should not be used in women who do not need it. Because of its inherent weaknesses, we believe that the MWS should not be used as part of an evidence base for HRT and should be discounted by regulatory authorities.
Whether HRT regimens, which will reduce cardiovascular risk, can be devised remains to be seen, but the potential is there. However, this is not a licensed indication at present, and the regulatory authorities are right to highlight this. The current recommendations produced by the regulatory authorities have undermined confidence in the use of HRT and have led to the avoidance or discontinuation of such treatment in many women who need it, resulting in a major detriment to female health care and well-being. These recommendations about HRT need to be revisited and revised as a matter of urgency.

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References

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