HRT and osteoporosis

What's the controversy? What are the alternatives?

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Estrogen, either alone or in combination with progesterone, has been a cornerstone in the management of osteoporosis for more than 50 years. Estrogen was accepted as the gold standard to prevent and treat osteoporosis. Over the past several years, Canada's Health Protection Branch and the U.S. Food and Drug Administration introduced a new requirement — drug therapies were required to document the prevention of bone loss and fractures in well-designed randomized clinical trials prior to approval for the prevention and treatment of osteoporosis.

Data from the Women's Health Initiative (WHI) was expected to shed light on the potential risks and benefits of estrogen on cardiovascular disease, breast cancer and stroke. It was also expected to confirm the efficacy of estrogen with respect to fracture risk.

What was the outcome?

The primary outcome of the WHI trials evaluating the combination of estrogen and progesterone was coronary heart disease (non-fatal myocardial infarction and fatal coronary heart disease). Breast cancer was the primary adverse outcome. Other risks and benefits were also evaluated (see Table 1). There is currently no evidence of increased breast cancer risk in women taking estrogen alone in the WHI. The National Institutes of Health (NIH) recommended that women in the estrogen monotherapy arm continue to take estrogen

and continue in the study. The NIH is closely monitoring this data. It is important to provide this information to our patients who are on estrogen alone. See Table 1 for an overview of the WHI results.[1]

A number of valuable antiresorptive therapy options are available for the prevention and treatment of osteoporosis. These options should be considered.

What are the alternatives to HRT?

Selected Estrogen Receptor Modulators (SERMs) are a valuable treatment option for the prevention and treatment of postmenopausal osteoporosis. Raloxifene is an estrogen receptor antagonist in the breast and the uterus. It has estrogen receptor agonistic effects in bone and on serum lipid concentrations.[2] Data from the multiple outcome of raloxifene evaluation trial (MORE) showed raloxifene to have a significant effect on the incidence of new vertebral fractures by three years with a 55% reduction in new morphometric vertebral fractures in the 60 mg/day dosage.[3] Raloxifene decreased the risk of cardiac events in high-risk women.[4] Breast cancer has been seen to decrease by 62% with raloxifene.[5]

Bisphosphonates are another valuable alternative to HRT in the prevention of osteoporosis. Bisphosphonates are synthetic analogues of pyrophosphate and inhibit osteoclast-mediated bone resorption.[6] The two amino bisphosphonates, alendronate and risedronate, have been shown to be effective in the prevention of vertebral and non-vertebral fracture.

In the Fracture Intervention Trials (FIT), alendronate was effective in decreasing the incidence of new vertebral fractures by 47% in patients with a pre-existing ver-

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Table 1

Results of the WHI

Estrogen and Progestin Use

- The risk for development of **cardiac events** was **increased** by **29%** in comparison to placebo.
- The **rates of stroke** were **increased** by **41%** in comparison to placebo.
- The incidence of **thromboembolic events** was significantly **increased** with a **twofold rise** vs. placebo.
- The **risk of breast cancer** was **increased** by **26%**.
- The development of **hip and vertebral fractures** were **reduced** by **34%** and these benefits were seen after 3 years of use.
- The development of **colorectal cancer** was **reduced** by **37%** and these benefits were seen after 3 years of use.

Overall the study has been cited to have more harmful, than beneficial, effects. Over one year, 10,000 women taking HRT compared to placebo would experience:

- 7 more cardiac events
- 8 more strokes
- 8 more pulmonary emboli
- 8 more invasive breast cancers
- 5 fewer hip fractures
- 6 fewer colorectal cancers

The WHI clinical trials were conducted between 1993 and 1998 and involved post-menopausal women in the age range of 50 to 79 years. The women received a daily tablet combining 0.625 mg conjugated equine estrogen and 2.5 mg medroxyprogesterone acetate or placebo daily.

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tebral fracture.[7] The incidence of multiple new vertebral fractures was decreased by 90% in the alendronate-treated arm in comparison to placebo.[7] In patients with a pre-existing vertebral fracture, the incidence of hip fractures was decreased with alendronate therapy by 51% at year three.[7] Alendronate is a potent bisphosphonate which has consistently demonstrated effectiveness in preventing hip and vertebral fractures. Alendronate, 70 mg once weekly, is now available and is a more convenient option for patients.

Alternatives to HRT

- SERMs (*i.e.,* raloxifene)
- Bisphosphonates (*i.e.,* etidronate, alendronate and risedronate)
- Salmon calcitonin

In The Vertical Efficacy with Risedronate Trials (VERT), a 41% reduction in vertebral fracture was seen with the 5 mg dose of risedronate in comparison to placebo.[8] Non-vertebral fractures were decreased by 39% at three years. A 65% reduction in vertebral fractures was seen in the first year of therapy. The risk of hip fracture was evaluated in the hip trial involving more than 9,000 women and risedronate significantly decreased the overall risk of a hip fracture by 30%. A 40% reduction in hip fractures was seen in women with osteoporosis. Also, a 60% reduction was seen in the risk of hip fractures in women with osteoporosis, by BMD criteria and the presence of prevalent vertebral fractures. There was no reduction in the risk of hip fractures in women who enrolled on the basis of clinical risk factors for fracture. Risedronate has demonstrated vertebral fracture efficacy and hip fracture efficacy in elderly women with confirmed osteoporosis.[8,9,10] With etidronate, there were demonstrated reductions in vertebral fracture only in high-risk patients. No reductions in hip or non-vertebral fractures have been seen.[11]

Salmon calcitonin is effective in preventing osteoclast-mediated bone resorption.[12] The Prevent Recurrence Of Osteoporotic fractures (PROOF) trial evaluated calcitonin nasal spray in doses of 100, 200 and 400 i.u. per day. The risk of fracture in postmenopausal women with low bone density evaluated at the spine and one to five vertebral fractures were studied.[13] The 200 i.u. per day dose was effective in reducing the relative risk of new morphometric vertebral fractures by 33% at five years.[13] Calcitonin had modest effects on the lumbar spine bone density. Calcitonin has been shown to have a bone analgesic effect and is of significant benefit in relief of pain in association with vertebral fractures.[14] Salmon calcitonin has been very well tolerated. The only adverse effect reported has been rhinitis occurring in 37.5% vs. 17.3% in the placebo group. The drug has been extremely well-tolerated and is safe in patients even with osteomalacia, renal or liver disease.

New treatments on the horizon?

Parathyroid hormone (PTH) has been approved in the U.S., but has not yet been approved for use in Canada. PTH has the ability to stimulate new bone formation. Large randomized placebo-controlled clinical trials using low-dose intermittent PTH administration have confirmed this finding. Increases in bone mineral density (BMD) by 7%-10% on an annual basis have been seen with dual energy X-ray absorptiometry (DXA). Increases of 40% were seen, however, when bone was measured by quantitative computed tomography (QCT). Impressive reductions in fracture

have been seen. PTH is an anabolic agent which is able to improve bone quality as well as bone quantity and can reverse micro architecture deterioration. It may be used in combination with antiresorptive agents in the future.[15-17]

What now?

HRT is a valuable treatment option for women who are experiencing menopausal symptoms. HRT is certainly of benefit in preventing bone loss and fractures, as was confirmed by the WHI. This benefit, however, must be considered with the potential harmful effects seen with the use of conjugated equine estrogen and progestin. We should reconsider using HRT on a long-term basis, in particular over five years in light of the WHI results. Women who are at an increased risk for coronary artery disease, breast cancer, or stroke may not be suitable candidates even for short-term hormone replacement. Other formulations and lower doses may be safer for the prevention and treatment of osteoporosis. It is necessary for physicians to inform our patients regarding the risks and benefits of therapy and individualize therapy to best suit the patients' needs. **Dx**

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