Is HRT on the way out?

By Paul Bessette, MD, FRCSC

Margaret's dilemma

Margaret, 51, has had more than 10 hot flashes a day for four months, with amenorrhea. She also presents with vaginal dryness and secondary insomnia. She smokes a little, does not drink much milk or do much exercise. There is no known arteriosclerotic heart disease. Her family history shows an aunt who had breast cancer at 60. She would be happy if she no longer menstruated.

1. What is this patient's main problem?

2. What pre-treatment assessment would you carry out for this patient?

3. What is the treatment of choice for this patient's principal problem?

She has now been on HRT for four years, even though she doesn't really like taking medication every day. She has heard that there are alternatives to HRT. Her neighbour had breast cancer and died a week ago and her older sister (68) had surgery for a hip fracture three weeks ago. This worries her a great deal.

4. What are the patient's two main concerns?

5. What are the therapeutic choices for this patient's principal problem?

For the answers, please go to page 62.

In this article:

A number of clinicians consider an interview and a clinical examination routine practice for many women over 50 (Figure 1).

If the patient agrees that hormone replacement therapy (HRT) is indicated to relieve her severe hot flashes, for example, the physician will initiate HRT with estrogen alone if the patient has already had a hysterectomy. If she has an intact uterus and wants predictable administration, cyclical estrogen-progestin HRT should be prescribed.

If the patient prefers to try a regimen where she will have a 60% to 80% chance of no longer having withdrawal bleeding after four to six months of occasional spotting, continuous estrogen-progestin therapy should be instituted (Figure 2). Several types of HRT are available. However, a simple regimen that encourages compliance, has the fewest possible side-effects, and is efficacious in alleviating symptoms over the short-term and with the fewest adverse

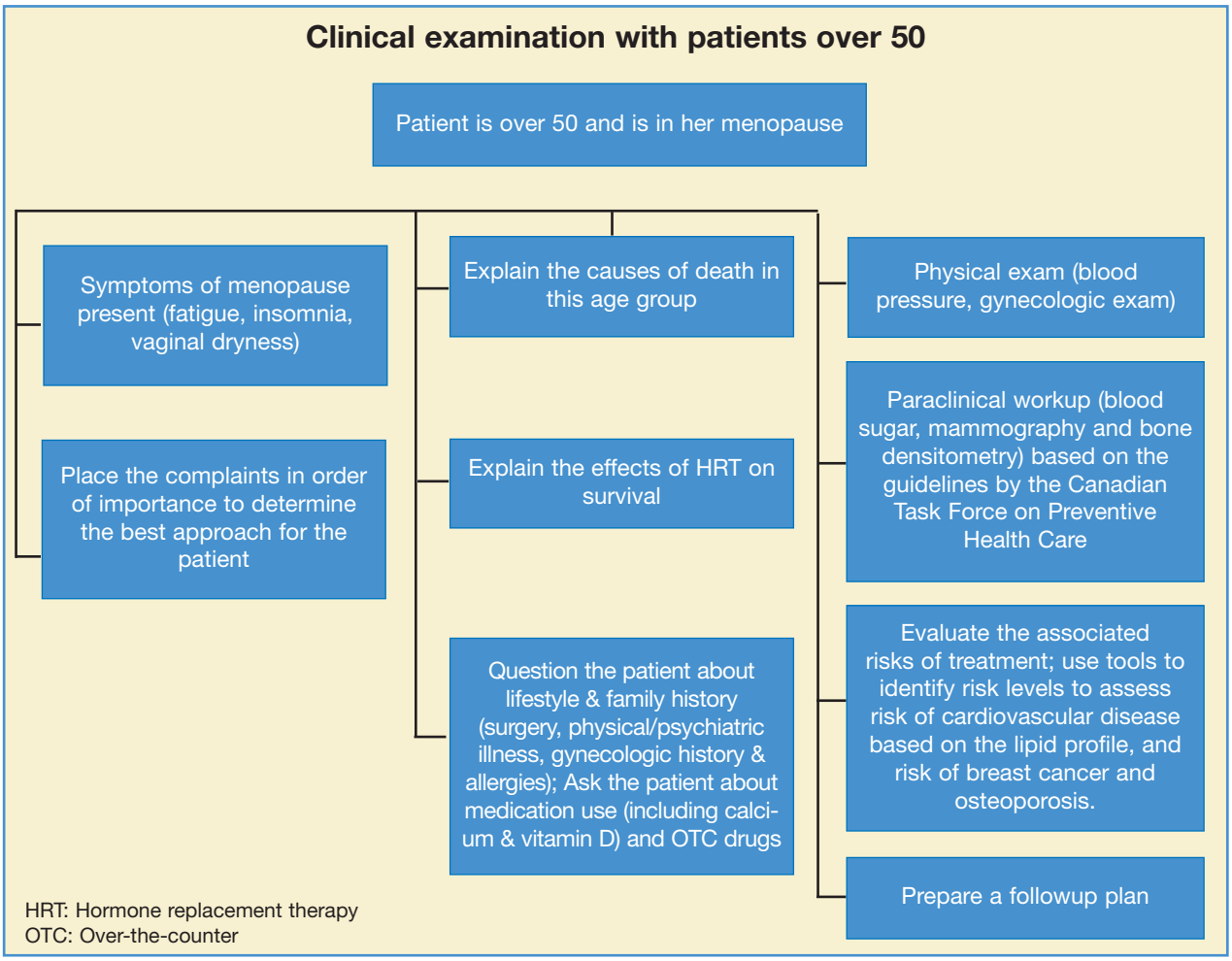

Figure 1.

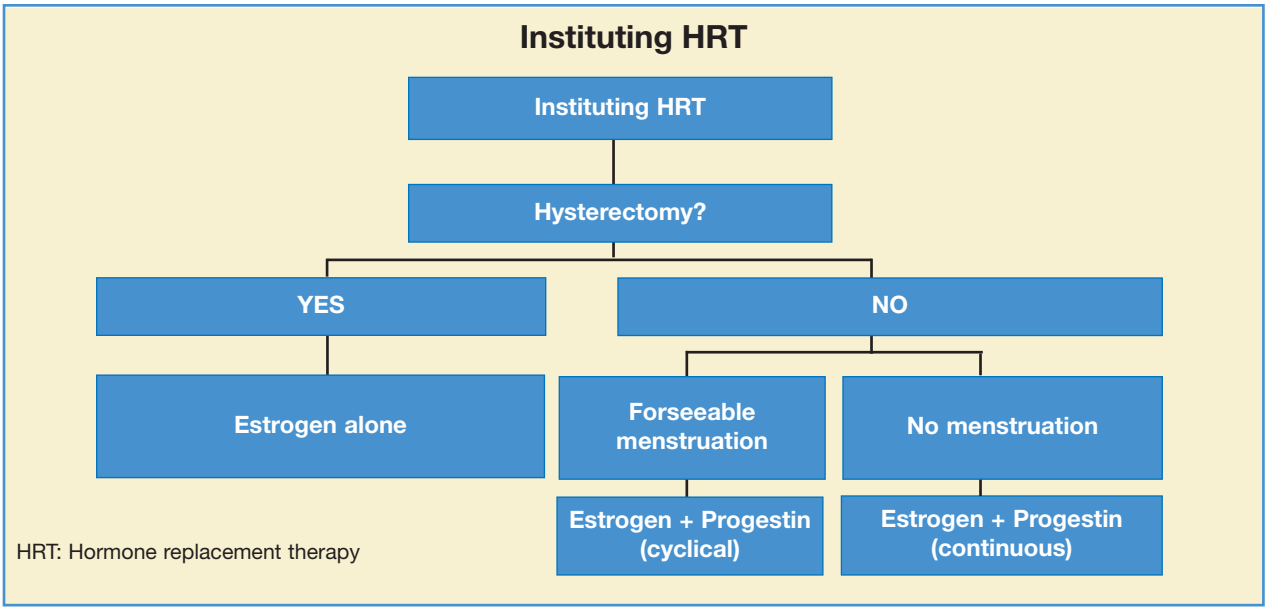

Figure 2.

effects over the short- and long-term, would be a reasonable choice for this patient. There is a great deal of debate on whether a more physiologic type of HRT, with consistent estradiol levels and less effect on coagulation, would be a better choice than the conventional oral route. Given equivalent efficacy, reasonable cost is also an important criterion in the choice of HRT.

There are various types of treatment regimens available (Table 1): estrogens alone (vaginal, oral, or transdermal route) and progestins alone or combined (oral and transdermal route). We will not be dealing with androgen therapy, as there are only small studies on this. However, some patients may benefit from such treatment, particularly if libido is lowered despite the use of standard HRT.

Are transdermal and oral estrogens very different?

A study of 250 postmenopausal women, averaging 66 to 77, randomized to placebo or transdermal estrogen (80 mcg/day) ± 4 mg norethisterone following an angiogram (performed after an ischemic coronary problem) did not show that the transdermal route was safer.[1] Fifty-three events were reported in the HRT group (cardiac death, nonfatal myocardial infarction, and hospitalization for unstable angina) versus 37 in the placebo group (Relative risk [RR]=1.49 with 95% confidence interval of 0.93 to 2.36). This gives 15.4% versus 11.9% of events for the HRT group versus the placebo (RR=1.29 with 95% confidence interval of 0.84 to 1.95).

However, transdermal HRT has the advantage of substances entering the circulation immediately, without having passed through the digestive tract or liver.[2] This would be useful in cases of hypertriglyceridemia, oral route intolerance, a previous history of venous thromboembolism, liver, or gallbladder problems. Oral estrogens can, in fact, trigger the production of numerous liver proteins, such as angiotensinogen, the protein that carries sexual steroids (testosterone and estrogens) (sex hormone binding globulin [SHBG]), as well as increase metabolic load and the number of active metabolites. Liver dysfunction can potentially result in hyperestrogenemia, with a higher incidence of side-effects for the patient. Conversely, smoking is an inducer of liver enzymes, increas-

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ing the metabolism of oral estrogens. A reduction in estradiol levels might be accompanied by a corresponding reduction in associated side-effects. As far as testosterone SHBG is concerned, a decrease in free-circulating testosterone could result in a decreased libido.

Table 1
Available Treatment Regimens

Estrogen alone
- Vaginal: ring (estring), pill form (vagifem), or cream (Premarin®)
- Oral: Premarin, ogen, ces, estrace, ethynyl-estradiol
- Transdermal patch: estraderm, vivelle, climara, oesclim and estradot
- Percutaneous gel: estrogel

Progestin alone
- Oral only: Provera®, prometrium, megace, colprone and norethindrone
- Transdermal: norethindrone

Estrogen (E) + Progestin (P) Combination
- *Two separate medications:*
  E cyclical (1-25) or continuous
  P cyclical (1-10 to 14) semi-continuous (21-25), or continuous
- *One medication including two products:*
  E continuous and P cyclical (1-14): estracomb or estalis-vivelle (estalis Sequi) transdermally
  E continuous and P continuous: FemHRT (orally) or Estalis (transdermally)

As far as headaches and HRT are concerned, a recent study included 50 women who were randomized into two groups according to whether they had migraine with no aura or tension headache.[3] The treatments were transdermal HRT (50 mcg weekly with 10 mg medoxyprogesterone acetate [MPA] from day 15 to 28) versus oral HRT with 0.625 mg Premarin® and the same dose of MPA. No difference in tension headache was noted between the two groups, but, with the oral treatment, there was an increase in migraine attacks without aura (incidence 8.5, $p<0.001$) and the number of days with headache (incidence 6.9, $p<0.001$). Analgesic consumption also increased (incidence 6.3, $p=0.01$).

What are the side-effects?

Estrogens can cause side-effects in certain patients. Other than bleeding, the most common complaints are mastalgia with or without increase in volume, nausea (rarely with vomiting), headache, cramps, and abdominal bloating. Increased pigmentation (chloasma or melasma) also occurred occasionally, as did hair loss, dizziness, depression, intolerance to contact lenses, weight variation, carbohydrate intolerance, and edema.

The side-effects are often dose-related and can be relieved with continuous use or a lower dosage. Side-effects may vary

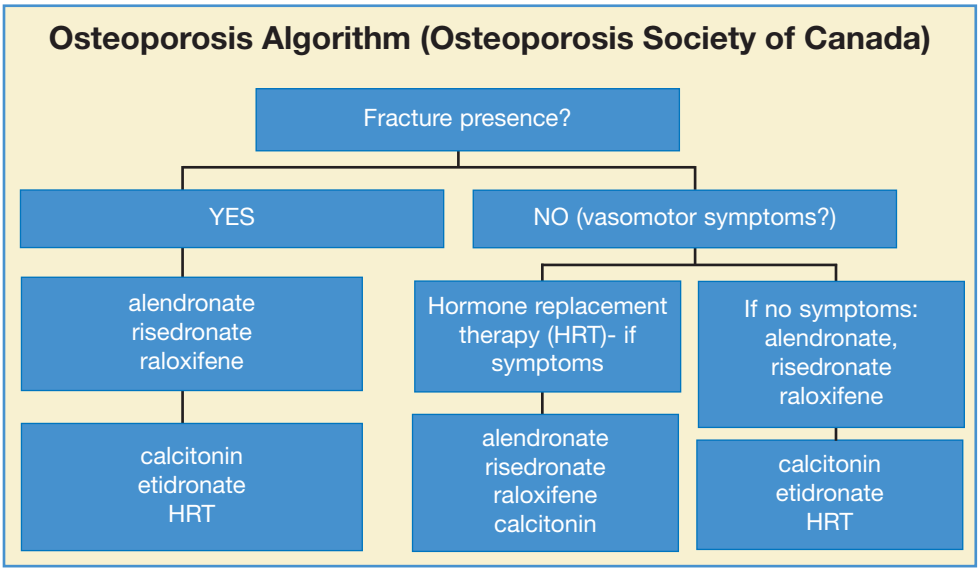

Figure 3.

depending on the estrogen preparations used. Substituting one preparation for another or changing the administration route in the event of intolerance would therefore be a reasonable strategy. Estrogens should be titrated to control symptoms. Breast sensitivity and leukorrhea may require a reduction in the dose. Progestin side-effects include mood changes (including those similar to premenstrual syndrome), mastalgia, bloating, abdominal discomfort, nausea, fatigue, headache, and musculoskeletal pain in the legs. A few instances of galactorrhea, acne, and hirsutism have been noted. Changing the progestin in such cases might also be considered. Prometrium is similar to natural progestin.[4] It also has an antialdosterone effect, with less water retention and fewer premenstrual symptoms than MPA. It also appears to have a positive effect on sleep when taken at bedtime. It is, however, contraindicated in patients allergic to peanuts. Side-effects are more frequent when a progestin is added to an estrogen. Certain cyclical HRT side-effects can be reduced or eliminated by changing to continuous use.

How can you monitor HRT?

The physician must make sure the patient is seen in the weeks following the initiation of HRT. Exactly when will depend on the patient's needs, and may vary from two weeks to four months. If there is abnormal or unexpected bleeding, diagnostic methods, such as endometrial biopsy, sonohysterography, or hysteroscopy should be employed. Curettage is rarely necessary today. Blood pressure must be checked periodically. Blood sugar can be monitored in women with a predisposition to diabetes, as should triglycerides in hyperlipidemia patients, and calcium and phosphorus if certain bone diseases are present. Using ultrasound, any change in the volume of uterine fibroma can also be monitored, if applicable. The patient must be told to consult if severe or serious symptoms develop (*e.g.,* visual problems or symptoms suggestive of thromboembolism).

HRT in osteoporosis

HRT prevents both vertebral[5,6] and non-vertebral[5] fractures, including the hip (level 1 evidence). In its 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada, the Osteoporosis Society of Canada recommends (Figure 3):

1. HRT should be used as first line care for the prevention of osteoporosis in post-menopausal women with low bone density, provided the benefits outweigh the risks (grade A) and in premenopausal women (< 45: grade D).

2. HRT should be used as second line care for the treatment of osteoporosis (grade B).[7]

What happened with Margaret?

1. *What do you consider this patient's main problem to be?*
   Hot flashes
2. *What pre-treatment assessment would you carry out for this patient?*
   - Update her risk factors (osteoporosis, ASHD, breast and uterine cancer) and lifestyle.
   - Physical exam, blood pressure, breast and gynecologic exam, including Pap smear.
   - Mammography, bone mineral density test and lipid profile.
3. *What is the treatment of choice for this patient's principal problem?*
   Continuous HRT with estrogen + progestin is the treatment of choice. Local treatment with a lubricant or local estrogen could also be useful. She must be helped to stop smoking and to get dietary advice. Calcium carbonate 500 mg and vitamin D, 400 units twice daily, as needed, should be suggested.
4. *What do you consider this patient's two main concerns to be?*
   She is afraid of breast cancer and the risk of osteoporosis.
5. *What are the therapeutic choices for this patient's principal problem?*
   Start weekly biphosphonate (Fosamax®, 70 mg or Actonel®, 35 mg), raloxifen, 60 mg daily, or continue her HRT. If the HRT is to be stopped, it should be done by gradually reducing the dose.

Exercise and a sufficient intake of calcium and vitamin D are obviously recommended as basic preventive measures. Biphosphonates (risedronate, etidronate, and alendronate) and raloxifen are the drugs of choice for the prevention and treatment of osteoporosis in women with no vasomotor menopausal symptoms. HRT is no longer the gold standard treatment. Estrogen combined with artificial or natural progestin is, therefore, one of the first choices with regard to prevention and a second choice for the treatment of post-menopausal osteoporosis. While intranasal calcitonin is also a second choice for the treatment of osteoporosis, it is the drug of choice for pain associated with acute vertebral fractures. Parathyroid hormone would be the drug of choice for severe osteoporosis.

Indications for starting HRT

Today, the indication for initiating HRT is the relief of moderate to severe menopausal symptoms, *i.e.,* hot flashes, night sweats, vaginal dryness, mood problems, insomnia, and lowered libido. According to the North American Menopause Society, the treatment of vasomotor and urogenital menopausal symptoms remains the main indication for HRT.[8] According to the Food and Drug Administration, moderate to severe hot flashes, vaginal dryness, and pruritus, as well as the prevention of osteoporosis, are the only indications for HRT. Some think that menopause before age 45 could nonetheless represent a normal indication for initiating HRT. Osteoporosis prevention using HRT should, therefore, take into account the risks and short- and long-term benefits in women with low bone density and menopausal symptoms (without too high a risk of breast cancer and/or arteriosclerotic heart disease), as well as women at risk for osteoporosis who are unable to tolerate other (second line) treatment options. Studies on the prevention of colorectal cancer and cognitive loss are ongoing.

Appropriate dosage in HRT

Are low doses just as efficacious and desirable as high doses?[9] A recent review concerning hot flashes showed that all dosages, preparations, and forms of HRT can be effective in reducing vasomotor symptoms.[10] Low-dose HRT, however, is not homeopathy!

It is efficacious and has fewer side-effects, while encouraging greater patient compliance.[11] This has led to a major change in the concept of HRT: The goal nowadays is to make symptomatic patients comfortable by using the lowest possible dose, rather than provide complete relief from symptoms. The HOPE study (Women's Health, Osteoporosis, Progestins, Estrogens) on 822 women, 40 to 65, showed that conjugated equine estrogen doses of 0.45 mg and 0.3 mg per day, with or without MPA at 1.5 mg per day, provided relief of vasomotor symptoms and vaginal atrophy, preserved bone density, and did not increase endometrial hyperplasia.[12] According to a number of experts, lower than standard doses should be considered.

How long should patients undergo HRT?

A second important change in concept is that HRT should be used for the shortest time possible based on treatment goals, benefits, and risks in each individual case. The concept of short-term (three to five years) and long-term HRT is now outdated and should, consequently, be abandoned. It should be reassessed based on age and the reasons for instituting HRT. In some cases, there may be reason to continue HRT for more than 10 years.[13] It is unlikely that many women with severe hot flashes were randomized in the WHI (Women's Health Initiative) study. There is also little information on the ideal length of treatment in this type of situation. The SWAN study (Study of Women's Health Across the Nation) is now underway. It is acceptable for women to continue long-term HRT if symptom relief outweighs the associated risk.

Who should stop HRT?

It is obvious that continuous combined HRT should be stopped in asymptomatic patients. Estrogen/progestin therapy as primary prevention against cardiovascular disease is no longer recommended and, if HRT has been prescribed with this in mind, it should be terminated. We have no conclusive data to guide us with respect to women who want to stop the therapy. Even if HRT is withdrawn abruptly or gradually over a period of one to four months, for example, some patients will develop vasomotor symptoms and will have to start HRT once again.

How should HRT be stopped?

At present, there is little information in the literature relating to women who want to stop HRT. However, a patient with no hot flashes at the start of HRT can stop it immediately.[14] If she did present with hot flashes at the beginning, she has two options: to stop immediately or to reduce the dose

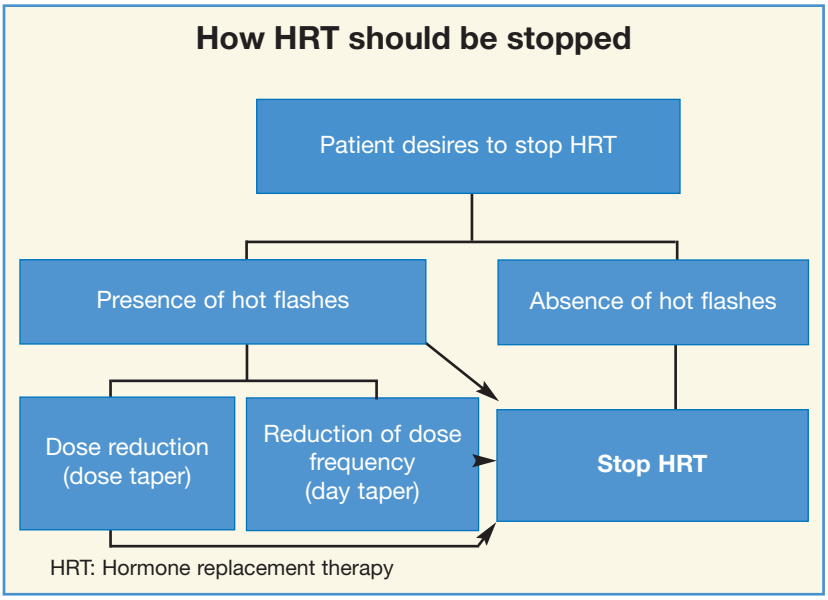

Figure 4.

(Figure 4). However, abrupt cessation may cause a worsening of symptoms for the patient and cause an increase in the number of medical visits.

We have two ways to reduce HRT dosage: decrease the dose (dose taper) or decrease frequency (day taper).[15] In many cases, reducing the dose seems more physiologically acceptable because there are no serum hormone peaks and it could potentially lead to improved tolerance for patients with respect to symptoms and a decrease in abnormal bleeding.

Take-home message

- Decisions concerning the use of HRT require an evaluation of the risks and benefits in each individual case.
- For women currently on HRT, it is important to assess the reasons for its use, together with the potential risks, benefits, and alternatives.
- There are no clear data on the significance of short-term use. An increase in breast cancer has been noted after four years, as well as the continuing effect of estrogen and progesterone, even after a year of treatment, because of the biology of breast cancer.
- Women taking HRT for vasomotor symptoms should be encouraged to stay on the treatment for a short period of time at the lowest possible effective dose.
- The use of continuous HRT should be stopped in asymptomatic women.
- Stopping progestins in women with an intact uterus is not recommended because of the risk of uterine cancer.
- Nevertheless, as long as no better treatments are available for moderate and severe hot flashes, HRT is not on the way out, but indications are becoming more strict and clinicians must adjust or change their prescription pattern for the good of our patients.

HRT and the elderly

There are few indications in elderly women.[16] However, HRT is a viable choice in women with persistent menopausal symptoms and/or low bone density, or who are unable to tolerate other treatment options. If treatment is continued, low doses must be used to minimize side-effects. HRT in such women will have little or no effect on incontinence or quality of life. Present or previous HRT lasting for more than 10 years has been associated with a decreased risk of Alzheimer's disease.[17] However, the WHI Memory Study (WHIMS), in 4,532 women over a four-year period, has shown that estrogen plus progestin increased the risk for probable dementia (mainly Alzheimer's) in post-menopausal women 65 and older (61 versus 40 cases). The RR was 2.05 with 95 confidence interval of 1.21-3.48 (23 additional cases of dementia per 10,000 person-years). Finally, treatment effects on mild cognitive impairment did not differ between groups.[18] CME

Web sites:

1. Canadian Task Force on Preventive Health Care: *www.ctphc.org*
2. U.S. Preventive Services Task Force: *www.preventiveservices.ahrq.gov*
3. SOGC: *www.sogc.org*
4. ACOG: *www.acog.org*
5. NAMS: *www.menopause.org*
6. Osteoporosis Society of Canada: *www.osteoporosis.ca*

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