

CONSENSUS OPINION

A Decision Tree for the Use of Estrogen Replacement Therapy or Hormone Replacement Therapy in Postmenopausal Women: Consensus Opinion of The North American Menopause Society

ABSTRACT

Objective: Menopause is associated with physiologic changes that may have negative effects on quality of life in some women and/or that may increase morbidity and mortality secondary to osteoporosis and/or coronary heart disease. Estrogen replacement therapy (ERT) and combined estrogen/progestogen therapy (hormone replacement therapy [HRT]) play an important role in reducing these negative effects. The North American Menopause Society (NAMS) sought to develop treatment algorithms that could assist the clinician in deciding whether to recommend ERT/HRT to postmenopausal women.

Design: NAMS held a closed conference of experts to develop a decision tree that outlined the rational use of ERT/HRT in postmenopausal women on the basis of risks versus benefits. The proceedings of the conference were used to assist the NAMS Board of Trustees in developing this consensus opinion of the Society.

Results: On the basis of the conference proceedings, NAMS developed three algorithms for the clinician to use as a tool in deciding whether to recommend ERT/HRT to a woman who is postmenopausal: (1) menopause-related symptoms, (2) cardiovascular risk, and (3) osteoporosis risk.

Conclusions: The goal of ERT/HRT is to enhance women's quality of life as well as to reduce the risks of death and disability associated with osteoporosis and coronary heart disease. The decision to initiate ERT/HRT must be individualized according to each woman's needs. This decision tree for ERT/HRT presents a rational approach to decision making on the basis of the principles of care; details of specific therapeutic interventions will change as data from clinical trials are presented. (*Menopause* 2000;7:76–86. © 2000, The North American Menopause Society.)

Key Words: Decision tree – Estrogen replacement therapy – Hormone replacement therapy – Menopause – NAMS consensus opinion.

The North American Menopause Society (NAMS) held a consensus conference to develop a decision tree for the use of estrogen replacement therapy or hormone replacement

therapy (ERT/HRT) in postmenopausal women. The proceedings of the conference were used to assist the NAMS Board of Trustees in developing a consensus opinion of the Society on a decision tree for recommending ERT/HRT. The NAMS consensus-building process has been described in a previous issue.¹

The purpose of this consensus opinion is to provide a decision tree that healthcare professionals can use to structure their decision of whether to recommend ERT/HRT for a postmenopausal woman. This article presents a basic decision tree for ERT/HRT use. It does not provide detailed therapeutic recommendations (e.g., type of hormone, mode of administration) because of the continuously increasing body of knowledge acquired from clinical trials.

Received October 29, 1999; accepted November 1, 1999.

The Board of Trustees of The North American Menopause Society (NAMS) developed this consensus opinion with assistance from the following participants in a closed conference held in Cleveland, Ohio, on July 10, 1998: Wulf H. Utian, MD, PhD; Margery L. S. Gass, MD; Jay M. Sullivan, MD; Glen D. Stettin, MD; and J. Christopher Gallagher, MD. Additional review was provided by Bruce Ettinger, MD, FACP, and Sandra Lewis, MD, FACC. Edited, modified, and subsequently approved by the NAMS Board of Trustees on October 11, 1999.

Address reprint requests to NAMS, P.O. Box 94527, Cleveland, OH 44101, USA.

Menopause is the permanent cessation of menses resulting from loss of ovarian follicular function. Clinically, menopause is important because the decline in estrogen often causes symptoms that adversely affect quality of life and that may increase the risk for coronary heart disease (CHD) and osteoporosis. The mean age for naturally occurring menopause in Western societies is 51 years; the majority of women live one third or more of their lives after menopause.²

Treatment for the adverse physiologic effects that may be associated with menopause can be achieved through lifestyle modifications, nonprescription remedies, and/or prescription therapies. Lifestyle modifications may include smoking cessation, exercise, weight control, stress reduction, and diet management. Among nonprescription products for menopause-related symptoms are those promoted as “natural therapy.” These products include vitamin E and soy products (foods and supplements) for the treatment of hot flashes as well as a variety of herbal products for providing an overall positive effect on quality of life. Scientific data supporting the use of these products, however, are limited.

Prescription therapies are predominantly hormonal, and they may involve the administration of unopposed estrogen replacement therapy (ERT) or estrogen plus progestogen therapy (as cyclic or continuous combination therapy), termed hormone replacement therapy (HRT). The goal of ERT/HRT is to enhance quality of life as well as to reduce death and disability from CHD and osteoporosis. Preventive ERT/HRT must be given on a long-term basis, perhaps lifelong, and the risks and benefits must be weighed carefully.

Clinicians should discuss ERT/HRT with all postmenopausal women, especially those who are experiencing premature menopause (before age 40) or induced menopause as a result of medical or surgical interventions. In the absence of contraindications, ERT/HRT can be recommended for the treatment of specific menopausal symptoms, for the possible reduction of the risk for CHD, and for the probable reduction of the risk for osteoporosis in all postmenopausal women in whom benefits are likely to outweigh risks. ERT/HRT should be accompanied by annual monitoring, including routine breast cancer surveillance, endometrial cancer surveillance when indicated, and recommendations for lifestyle changes that decrease the risk for CHD and osteoporosis.

Hormone therapy should include a progestogen when administered to a woman with a uterus to reduce the risk of adenocarcinoma of the endometrium, which is significantly increased in women who use unopposed ERT. When taken for more than 3 years, ERT is associated with a fivefold increased risk for endome-

trial cancer; ERT taken for more than 10 years is associated with approximately a 10-fold increase. Concurrent progestogen therapy greatly reduces the risk for endometrial cancer induced by estrogen, probably by reducing estrogen receptor activity.³ Data from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial⁴ showed a significantly increased risk for endometrial hyperplasia in women who were taking unopposed estrogen during the 3-year trial (34% vs. 1% for estrogen plus progestin).

Screening parameters for endometrial cancer for women who are using hormone therapy are as follows:

1. Women who are administered *cyclic* HRT should undergo a baseline pelvic examination. Endometrial evaluation should be considered if bleeding occurs at any time other than the expected time of withdrawal bleeding or when heavier or more prolonged withdrawal bleeding occurs.
2. Women who are administered *continuous* HRT should also undergo a baseline pelvic examination. Endometrial evaluation must be considered when irregular bleeding persists more than 6 months after beginning therapy. Early biopsy can be considered on the basis of individual circumstances.
3. Women with a uterus generally should not take unopposed ERT. When such a regimen is used despite this recommendation, women should undergo routine pelvic examinations and endometrial evaluations at baseline and annually thereafter. Endometrial evaluation should be performed after any episode of vaginal bleeding; reevaluation is necessary when bleeding is persistent.

DEVELOPMENT OF THE ALGORITHMS

Three algorithms in the decision tree for recommending ERT/HRT have been developed to help the clinician arrive at treatment decisions that are consistent with best medical practice. As always, clinical judgment regarding a specific patient must be exercised by the treating healthcare provider. These algorithms address ERT/HRT with regard to (1) menopause-related symptoms, (2) cardiovascular risk, and (3) osteoporosis risk. Consideration of all three algorithms is recommended to reach the best decision for a postmenopausal woman.

Standardized symbols are used in the algorithms to illustrate certain processes. A diamond denotes a decision-making process, a rectangle refers to an action process, a parallelogram denotes an input/output point, and an oblong refers to a terminator/endpoint.

**ALGORITHM 1:
ASSESS MENOPAUSE-RELATED SYMPTOMS**

The first step in the decision tree for recommending ERT/HRT to postmenopausal women is to assess menopause-related symptoms, as shown in Algorithm 1 (Fig. 1). The following section discusses the process presented in this algorithm.

Hormone therapy issues

Women often have concerns about menopause and ERT/HRT before they reach menopause. A discussion of the needs and concerns of the woman early in her premenopausal stage will help the healthcare provider identify the woman's health priorities. This discussion should cover all menopause-related symptoms and the role of ERT/HRT in CHD and osteoporosis, as well as potential risks associated with ERT/HRT, such as breast cancer. An early assessment of the woman's concerns and symptoms allows the clinician to modify a treatment plan to address the woman's individual needs.

ERT/HRT contraindications

Potential contraindications as well as factors that may require special considerations before initiation of ERT/HRT are listed in Table 1. As with all forms of drug therapy, the risks versus benefits must be evaluated.

Increased risk for breast cancer

The following factors are believed to correlate with an increased risk for breast cancer: familial predisposition, history of endometrial or ovarian carcinoma, history of breast cancer, hyperproliferative fibrocystic disease with atypia, early menarche, late menopause, or absence of an early pregnancy.⁵ Although great stress is sometimes placed on family history, most genetic breast cancers are estrogen-receptor negative.⁶⁻⁸

An increased risk for breast cancer is not considered to be an absolute contraindication for ERT/HRT use. Nevertheless, women who have an increased risk for breast cancer often reject ERT/HRT or their clinicians disqualify them from receiving this therapy. Conflicting findings have been reported regarding a possible link between ERT/HRT and breast cancer; however, the risk seems to be increased (30-40%) with long-term therapy (5-15 years). Moreover, although the risk for breast cancer was increased by ERT/HRT use in the Nurses' Health Study,⁹ epidemiologic studies also indicate reduced mortality in breast cancer patients who have undergone ERT/HRT.^{10,11} These findings emphasize the need for a careful evaluation of benefits versus risks associated with ERT/HRT before considering long-term therapy.

In women with breast cancer, ERT is widely considered to be contraindicated. However, in certain situations in which quality of life is a major issue, the clinician, in consultation with the patient's oncologist,

FIG. 1. Algorithm 1: Assessment of menopause-related symptoms.

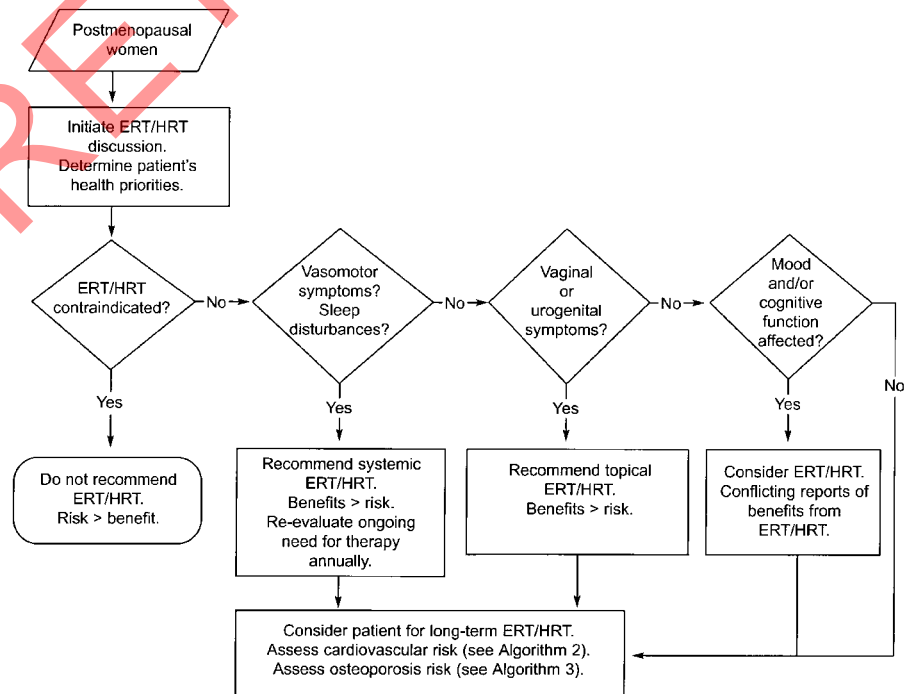


TABLE 1. Potential contraindications for ERT/HRT and factors requiring special consideration

Breast cancer	Therapy generally contraindicated unless decision to treat follows an informed discussion
Endometrial cancer within 5 y	For higher grades/stages, therapy generally contraindicated unless decision to treat follows an informed decision. For grade I, stage I, cautious use of therapy after hysterectomy.
Unexplained vaginal bleeding	Therapy contraindicated
Active liver disease	Therapy contraindicated
Chronic severe hepatic dysfunction (AST > twice normal)	Therapy contraindicated
Recent vascular thrombosis	Therapy contraindicated
Familial mixed hyperlipidemia or hypertriglyceridemia (TG > 300 mg/dL)	ERT may increase triglycerides in a few women. Consider nonoral route of administration.
History of endometriosis	ERT may exacerbate endometriosis
History of leiomyomas	ERT may exacerbate leiomyomas
Atraumatic thrombophlebitis or history of thromboembolic event disorder	Consider workup for coagulability disorder. Cautious use of therapy
History of gallbladder disease and no cholecystectomy	Cautious use of therapy
Seizure disorders	Cautious use of therapy
Migraine headaches	Cautious use of therapy

ERT, estrogen replacement therapy; HRT, hormone replacement therapy. Data from FDA-approved prescribing information for Estrace (Bristol-Myers Squibb), Estraderm (Novartis), Estratab (Solvay), Premarin (Wyeth-Ayerst), and Prempro (Wyeth-Ayerst).

may help the woman decide whether the benefits of such therapy outweigh its risks. The decision must be made with the full awareness that therapy might promote more rapid tumor growth.

Treatment of menopause-related symptoms

The goal of ERT/HRT in women with menopause-related signs and symptoms is to reverse the impact of lowered estrogen levels. Symptoms that are likely to respond to ERT/HRT include vasomotor effects such as hot flashes, night sweats, and sleep disturbances, as well as vaginal or urogenital symptoms such as vaginal dryness, dyspareunia, and recurrent urinary symptoms. The decision to initiate treatment for alleviating menopausal symptoms must be made separately from the decision to continue ERT/HRT for the purpose of decreasing the risk for CHD and/or osteoporotic fractures.

Vasomotor symptoms or sleep disturbances

Vasomotor symptoms (e.g., hot flashes, night sweats) affect up to 80% of menopausal women and may persist

for longer than 5 years in up to 25%.¹² Hot flashes result from a disruption of the thermoregulatory center within the hypothalamus, and they are believed to be attributable to the depletion of estrogen and the lack of ovarian hormonal feedback. When a woman experiences hot flashes at night, her sleep patterns are often disrupted, which can cause insomnia.¹³ If the benefits outweigh the risks, ERT/HRT can be recommended. The need for continued therapy should be reevaluated annually.

For women who need relief of vasomotor symptoms only, ERT/HRT may be administered for a few years and then discontinued. Gradual tapering of the dose may minimize recurrence of vasomotor symptoms. If symptoms recur, ERT/HRT may be reinstated along with annual reassessments.

Vaginal or urogenital symptoms

Vaginal and urogenital symptoms associated with menopause and/or aging include vaginal dryness, dyspareunia, urinary urgency, dysuria, frequency of urination, and recurrent urinary tract infections.^{14,15} Estrogen has been shown to relieve some of these symptoms. For a local response, unopposed topical estrogen (cream or ring) should be considered, although any form of ERT/HRT suited to the individual woman may be used.^{16,17} Although estrogen may alleviate dryness and urgency, there is no clinical trial evidence documenting that ERT is effective for urinary incontinence.^{18,19} Likewise, women with a mechanical or neurologic source of urinary incontinence will not be cured with estrogen.

Mood or cognitive function effect

Most studies show that clinical depression or panic attacks are not more common during postmenopause than at other times of life, and these should be diagnosed and treated with appropriate counseling and psychotropic medications, when needed.²⁰ Although mild forms of dysphoria associated with menopause may or may not improve with ERT/HRT, such therapy may provide a stabilizing effect during perimenopause, when hormone levels are more erratic. In the absence of contraindications, a trial of unopposed estrogen may be considered if the patient desires. One review of the literature suggests that progestogen may abrogate the beneficial effects of estrogen on mood.²¹

There are conflicting reports regarding the effects of ERT/HRT on cognitive function and Alzheimer's disease.²⁰⁻²³ Recent studies suggest an amelioration or delay in the onset of symptoms of Alzheimer's disease with long-term use of ERT/HRT.²⁴⁻²⁶ Long-term trials that are in progress may provide more reliable data on this subject.

Considerations for long-term ERT/HRT

Any discussion of long-term therapy should entail a consideration of potential long-term risks and benefits before moving on to Algorithms 2 and 3.

**ALGORITHM 2:
ASSESS CARDIOVASCULAR RISK**

CHD is the most common disease in women and the most common cause of death.²⁷ The median age of death resulting from CHD in women is 74 years.²⁷ Women, on average, die of CHD 10–15 years later than men; this delayed mortality is believed to be due, at least in part, to the protective effects of estrogen.²⁸

Although women who have CHD—or who are at increased risk for CHD—might benefit from ERT/HRT, the risks as well as the benefits must be discussed. The woman should be involved in deciding whether she should embark on long-term ERT or HRT, and the clinician should assess the woman’s perception of its value.

The decision tree for recommending ERT/HRT in women with cardiovascular risk is presented in Algorithm 2 (Fig. 2). The following section discusses the process presented in this algorithm.

Hormone therapy issues

Determining whether a woman is a candidate for ERT/HRT is not based solely on the presence of estab-

lished CHD but also on her likelihood of an increased risk for CHD. Risk factors for the development of cardiovascular disease are listed in Table 2. The risks associated with smoking, obesity, diabetes, hyperlipidemia, and hypertension add to the total cardiovascular risk.²⁹

Evidence from case-control studies demonstrates an overall cardiovascular risk reduction of approximately 35–50% in postmenopausal women who take ERT/HRT compared with those who do not.²⁸ The effect seems to be independent of age, type of menopause (surgical or natural), or presence or absence of cardiovascular disease. Grodstein et al.³⁰ observed a survival benefit in women with one or more cardiovascular risk factors; however, no significant benefit was observed among current users of estrogen who had no cardiovascular risk factors. In a study of women with CHD, Sullivan et al.³¹ also reported a risk reduction with ERT.

The CHD risk findings from the Heart and Estrogen/progestin Replacement Study (HERS)³² should be considered, as these data challenge previous recommendations from observational studies. After an average follow-up of 4.1 years, the investigators found no significant differences between the HRT treatment groups and the placebo recipients with respect to cardiovascular outcomes, although more myocardial infarctions occurred in the HRT-treated group during year 1. However, it should be noted that the conclusions drawn from these data have been challenged.

FIG. 2. Algorithm 2: Assessment of cardiovascular risk.

*For postmenopausal women who have coronary heart disease or have been receiving estrogen replacement therapy or hormone replacement therapy for more than 1 year, it may be appropriate to continue therapy until further clinical trial data are available. For postmenopausal women who have established coronary heart disease, use other appropriate treatments rather than initiate continuous-combined conjugated equine estrogens and medroxyprogesterone acetate.

†Attend to smoking, hypertension, lipids, angina, and left ventricular systolic dysfunction as indicated. See the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,³⁹ the National Cholesterol Education Program: Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults—Adult Treatment Panel II,⁴⁰ and the American Heart Association/American College of Cardiology Guide to Preventive Cardiology.⁴²

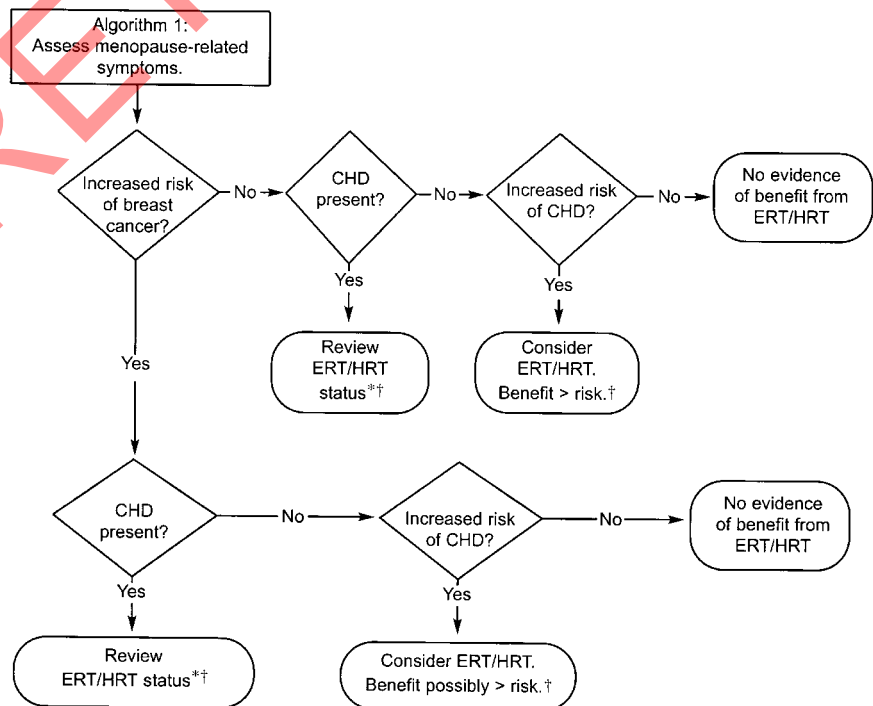


TABLE 2. Risk factors for cardiovascular disease in women²⁹

Alterable	Unalterable
Diabetes	Age >55 y
Hypertension	Premature menopause (age < 40 y)
High LDL cholesterol	Family history of CHD (<65 years in females)
Low HDL cholesterol (<35 mg/dL)	
Elevated triglycerides	
Physical inactivity	
Cigarette smoking (current)	
Obesity	

LDL, low-density lipoprotein; HDL, high-density lipoprotein; CHD, coronary heart disease.

For women with established CHD, it would be prudent to emphasize the cardiovascular risk reduction with established evidence-based treatments rather than initiate continuous-combined conjugated equine estrogens and medroxyprogesterone acetate. A discussion of these treatments, however, is beyond the scope of this article. For women who have CHD and have been receiving HRT for more than 1 year, it may be appropriate to continue treatment until further trial data are available.

The mechanisms by which ERT might reduce the risk for cardiovascular disease are believed to include beneficial effects on lipoprotein levels, vascular reactivity, and platelet adhesiveness. Estrogen alters the ratio of lipoproteins, increasing high-density lipoprotein concentrations and decreasing low-density lipoprotein concentrations.^{4,33} The serum levels of high-density lipoprotein, in particular, have been suggested to be the best predictor of CHD risk in some women.

The beneficial effect of estrogen on endothelial function may occur via the promotion of nitric oxide release, which results in vasodilation, reduced release of endothelin, inhibition of adhesion molecule expression, and increased endothelial proliferation and migration to repair areas of injury.^{34,35} The improved lipid profile and endothelial cell function are thought to contribute to stabilization of atherosclerotic plaques.³⁴ Estrogen increases the production of prostacyclin in the endothelium of blood vessels and decreases the production of thromboxane A2 by platelets, thus reducing platelet adhesiveness. These effects may contribute to a lowered risk for myocardial infarction and stroke in women who receive ERT.³⁵ Because oral estrogen can increase triglyceride levels, transdermal estrogen may be better suited for women who already have elevated triglyceride levels.

The administration of estrogen has been associated with an increased risk for deep-vein thrombosis and pulmonary embolism.^{33,36} Because these disorders are rare,

the increased absolute risk is slight. However, caution should be exercised when administering any form of ERT to women with a personal or family history of thromboembolism.

Oral ERT may be preferable when estrogen is used to reduce the risk for CHD, because the hepatic metabolism of estrogen seems to be responsible, at least in part, for the favorable effects that are exerted by ERT on total cholesterol and on high- and low-density lipoprotein.³⁷ Most of the data suggesting that estrogen reduces the risk for CHD are based on studies in which women took conjugated equine estrogens, although a similar benefit was observed in women who took estradiol valerate.³⁸

Other therapeutic approaches

Women with any potentially alterable risk factors for cardiovascular disease should be urged to initiate lifestyle changes that will decrease their overall risk. Counseling should focus on the long-term benefits of lifestyle issues, such as exercise and maintaining a healthy weight. In addition, women should be reminded that smoking cessation will lower not only their cardiovascular risk but also the risk for multiple types of cancer and for chronic pulmonary disease.

Finally, dietary and pharmacologic management of hypertension, hyperlipidemia, and diabetes mellitus should be initiated, when appropriate, according to established guidelines from The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,³⁹ the National Cholesterol Education Program: Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults—Adult Treatment Panel II,⁴⁰ the American Diabetes Association Clinical Practice Recommendations,⁴¹ and the American Heart Association/American College of Cardiology Guide to Preventive Cardiology.⁴²

ALGORITHM 3: ASSESS OSTEOPOROSIS RISK

Postmenopausal osteoporosis is a major health problem in Western countries, especially among thin, Caucasian women who are older than 70 years. An estimated 1.5 million bone fractures occur annually in women because of osteoporosis; the median age of first hip fracture in women is approximately 80 years. An estimated 4–6 million postmenopausal Caucasian women in the United States have osteoporosis. An additional 13–17 million have low bone density at the hip.⁴³ In women, the usual sites of osteoporotic fracture are the vertebrae, hip, distal forearm, pelvis, ribs, and other limb bones.

Menopause accelerates age-related bone loss, especially during the first decade after onset.⁴⁴ This event is of particular importance in women who have experienced early menopause (younger than 40 years), regardless of whether it occurred naturally or was medically induced.

Menopause is an appropriate time for a complete review of osteoporosis risk status and counseling on risk status reduction. Because a woman may decide to take ERT (or HRT) only if she knows that she is at risk for osteoporotic fractures, her clinician must be able to assess her individual risk and involve her in the decision-making process. The risk for breast cancer from ERT/HRT also must be balanced in the context of long-term therapy for the prevention or treatment of osteoporosis, particularly because effective alternative therapies for osteoporosis are available.

A decision tree for recommending ERT/HRT for the prevention of osteoporosis in postmenopausal women is presented in Algorithm 3 (Fig. 3). The following section discusses this algorithm.

Osteoporosis risk factors

A number of clinical risk factors have been linked to the development of postmenopausal osteoporosis. These include genetics, environment, menstrual status, medications, disease states, and advanced age (see Table 3). A positive history of fractures as an adult (either traumatic or nontraumatic) should raise the suspicion that a woman has decreased bone mineral density (BMD), warranting further assessment.⁴³ It is recommended that BMD be measured in all postmenopausal women, except for those who are at least 65 years old with an established osteoporotic fracture. These patients should be treated regardless of their BMD measurement.³⁹

BMD assessment

Clinicians have several available technologies to measure BMD, including radiation-based and radiation-free options. The choice of BMD testing method can be based on the available anatomic site, access to the technological

FIG. 3. Algorithm 3: Assessment of osteoporosis risk.

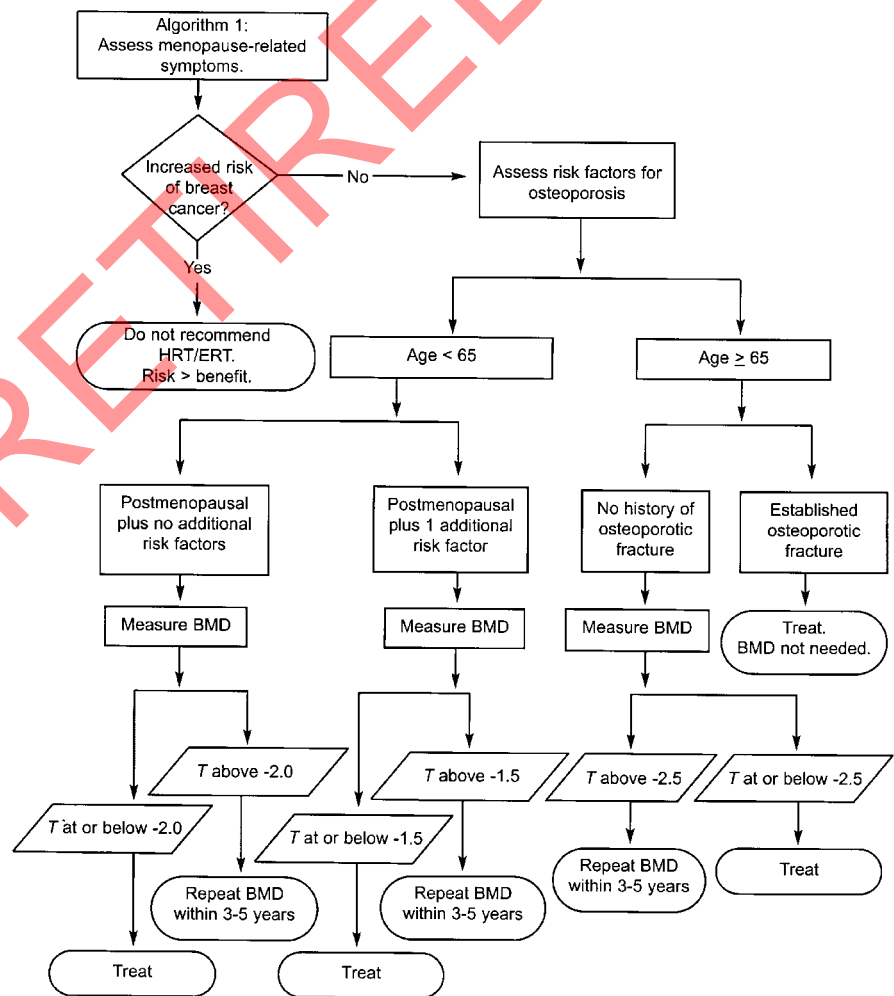


TABLE 3. Risk factors for postmenopausal osteoporosis

Genetic factors
First-degree relative with low-trauma fracture
Caucasian/Asian race
Slender physical frame
Environmental factors
Cigarette smoking
Excessive alcohol use (more than 7 drinks weekly, with one drink defined as one beer, 4 oz wine, or 1 oz liquor)
Sedentary lifestyle/prolonged immobilization
Diet low in calcium
Little exposure to sunlight and no vitamin D supplementation
Excessive use of caffeine
Menstrual status
Early menopause without ERT/HRT
Premenopausal hypogonadism
Previous amenorrhea (e.g., due to anorexia nervosa, hyperprolactinemia, or exercise-induced amenorrhea)
Disease states
Osteoporotic fracture as an adult
Primary hyperparathyroidism
Thyrotoxicosis
Cushing's syndrome
Multiple myeloma
Systemic mastocytosis
Rheumatoid arthritis
Malabsorption syndromes (e.g., celiac disease, Crohn's disease, surgery for peptic ulcer)
Chronic obstructive pulmonary disease
Anorexia nervosa
Chronic liver disease (e.g., primary biliary cirrhosis)
Chronic renal disease
Medications
Corticosteroids (7.5 mg/day or more of prednisone or equivalent for >6 mo)
Long-term use of certain anticonvulsants (e.g., phenytoin)
Anticoagulant agents (e.g., heparin, warfarin)
Immunosuppressive drugs (e.g., cyclosporine)
Levothyroxine
Intramuscular medroxyprogesterone in premenopausal women
Lithium
Heparin

equipment, and cost. The following presents information on an ultrasound-based test and the x-ray-based diagnostic standard.

Quantitative ultrasound

Quantitative ultrasound detects the transmission of high-frequency sound waves through or across bone, providing information on bone structure and strength. Ultrasound measurement sites include the heel, finger, tibia, and patella; of all ultrasound measurement sites, the best predictor is the heel (calcaneus). The advantages of ultrasound are its low cost, portability of equipment, ease of use, and lack of ionizing radiation. Disadvantages include nonuniform reporting and measurement of sites unresponsive to therapy.^{44,45}

Dual-energy x-ray absorptiometry

Dual-energy x-ray absorptiometry (DXA) is the “gold standard” for BMD measurement. DXA, the most thoroughly studied technology, uses a measurement of the absorption of two x-ray beams to calculate BMD. DXA can measure BMD at central or peripheral sites.

BMD scores

These measurements are expressed in terms of either a Z score or a T score. Z scores are obtained by comparing the individual's BMD measurement with the mean value in normal adults of the same age and gender. T scores are obtained by comparing the BMD measurement with the mean peak bone mass at age 20–30 of a “young and normal” adult of the same gender. A T score of zero represents the mean peak adult bone mass. In general, a change of 1 SD is equivalent to approximately a 12% change in BMD. Table 4 presents the osteoporosis definitions from the World Health Organization, based on bone mass measurement of any skeletal site in Caucasian women.⁴⁶ Recent data have shown that a T score of –2.5 varies from site to site at any age.⁴⁷ Thus, NAMS (as well as the National Osteoporosis Foundation⁴³) has based its recommendations on femur T scores only.

Interpretation and clinical application of these measures must be made after all other pertinent patient data are evaluated, particularly the age of the patient. A T score at or below –2.5 is clinically of more concern in a younger individual because more BMD will be lost during his or her lifespan. Nevertheless, age is an important risk factor—the risk of fractures is higher for a 75-year-old with a T score of –2.5 than for a 45-year-old with a T score of –2.5.

TABLE 4. World Health Organization's definition of osteoporosis in Caucasian women based on bone mineral density (BMD) of any* skeletal site⁴⁶

Normal	T score above –1	BMD within 1 SD of a “young normal” adult
Low bone mass	T score between –1 and –2.5	BMD between 1 and 2.5 SD below that of a “young normal” adult
Osteoporosis	T score at or below –2.5	BMD is 2.5 SD or more below that of a “young normal” adult

*Although the World Health Organization recommends any skeletal site, the NAMS and the National Osteoporosis Foundation recommendations are based on hip (i.e., proximal femur) BMD.

Treatment/prevention issues

Fortunately, bone loss can be slowed or reversed if alterable risk factors are identified and addressed appropriately.⁴⁴ Although many therapies are available for the prevention and/or treatment of osteoporosis, this article focuses on ERT/HRT.

As a general guide, treatment should be considered for the following populations:

- Postmenopausal women younger than 65 years with no additional osteoporosis risk factors and a femur *T* score at or below -2.0 .
- Postmenopausal women younger than 65 years with at least one additional osteoporosis risk factor and a femur *T* score at or below -1.5 .
- Postmenopausal women age 65 years and older with no history of an osteoporotic fracture and a femur *T* score at or below -2.5 .
- Postmenopausal women age 65 years and older with an established osteoporotic fracture (no BMD measurement is needed).

A repeat DXA test to measure BMD should be considered within 3–5 years for the following populations:

- Postmenopausal women younger than 65 years with no additional osteoporosis risk factors and a femur *T* score above -2.0 .
- Postmenopausal women younger than 65 years with at least one additional osteoporosis risk factor and a femur *T* score above -1.5 .
- Postmenopausal women age 65 years and older with no osteoporotic fracture and a femur *T* score above -2.5 .

Although ERT should be started as early as possible after menopause in women who are at risk for osteoporosis, several studies indicate that ERT can arrest bone loss, and retrospective studies suggest that estrogen reduces the incidence of fractures even when treatment is initiated later in life.²⁸ Studies suggest that adding progestogen to estrogen does not reduce the beneficial effects of estrogen on osteoporosis.⁴

For women with a contraindication to ERT/HRT and those who refuse or cannot tolerate any form of ERT/HRT, pharmacotherapeutic alternatives are available. Therapies that have been approved in the United States for the treatment and/or prevention of osteoporosis include raloxifene, alendronate, and salmon calcitonin. Fluoride is not approved in the United States for osteoporosis.⁴⁴

Raloxifene, a selective estrogen receptor modulator, has been shown to be effective in preventing and treat-

ing postmenopausal bone loss. Although its effect on BMD is small (1–2% increase), at least one study has demonstrated a significant reduction in vertebral, although not peripheral, fractures.⁴⁸ The influence of raloxifene on cardiovascular mortality is unknown. Hot flashes and leg cramps are the most commonly reported drug-related adverse effects. Raloxifene therapy also is associated with an increased risk for venous thromboembolism similar to that of estrogen.⁴⁹ Raloxifene does not seem to have an adverse effect on the risk for breast cancer.⁵⁰

As with other bisphosphonates, alendronate decreases bone turnover, inhibits osteoclast activity, and transiently shifts the balance between bone formation and resorption toward formation.^{51,52} For prevention of early postmenopausal bone loss, 5 mg daily of alendronate is the effective dose; for older women, a 10-mg daily dose may be required. When given in high doses, this nonhormonal drug has been associated with mild to moderate gastrointestinal symptoms, so it may be unwise to prescribe alendronate for patients with active upper gastrointestinal disease, such as gastroesophageal reflux disease, gastritis, or ulcer. Ulcerative esophagitis may develop in patients who have swallowing disorders or who do not remain upright after taking the drug.

Salmon calcitonin is a polypeptide hormone that interferes with osteoclasts and inhibits bone resorption. Recent studies have shown that 200 IU/day, but not 400 IU/day, significantly reduces vertebral fractures.⁵³ The effect on spinal BMD is small (1–2%), and no effect is seen on hip BMD. Bone turnover is reduced to a lesser degree than with other antiresorptive treatments. Salmon calcitonin has few adverse effects other than local nasal irritation with the nasal spray formulation.

All osteoporosis therapies should be used in conjunction with adequate calcium and vitamin D intake. Recommended total daily intake of elemental calcium for postmenopausal women is at least 1,200 mg/day.⁴³ Although calcium should ideally come from dietary sources, supplements in the form of calcium carbonate or calcium citrate may be used, taken with meals in divided doses. Because different calcium salts vary significantly in their content of elemental calcium, the actual supplemental dose required to provide the recommended dose also varies.

Vitamin D is essential for the intestinal absorption of calcium, and the recommended daily intake of vitamin D for postmenopausal women is 400–800 IU.⁴³ Some women in the United States obtain sufficient vitamin D in their diets, making supplementation unnecessary. However, women who consume less than 100 IU/day or who reside in northern climates (i.e.,

have decreased exposure to sunlight) may benefit from supplementation. Multivitamins usually contain at least 400 IU of vitamin D. Taking a single daily multivitamin is a convenient means of obtaining vitamin D, although some women may require additional vitamin D supplementation.

Bone markers

Biochemical markers of bone turnover have been used in clinical trials of antiresorptive therapies. However, bone markers have limited use in predicting or assessing the response to antiresorptive therapy in individual patients. Because these markers can vary from day to day by 25–30%, baseline measurements as well as several measurements during treatment are necessary. In general, the urine cross-links must be suppressed into the lower quartile of the normal range before an adequate antiresorptive effect can be confirmed.

CONCLUSION

The decision to initiate ERT or HRT in postmenopausal women is complex and involves consideration of multiple factors. The participation of the patient in the decision to initiate therapy is crucial for adherence over time. The treatment algorithms presented have been designed to assist the clinician in this decision process when individualizing a treatment plan.

Acknowledgments: NAMS appreciates the contributions of the following expert advisors: *Wulf H. Utian, MD, PhD* (Chair), Professor and Chairman, Department of Reproductive Biology, Case Western Reserve University, Director OB/GYN, University Hospitals of Cleveland, Cleveland, Ohio; *Bruce Ettinger, MD, FACP*, Senior Investigator, Division of Research, Kaiser Permanente Medical Care Program, Oakland, California; *Margery L. S. Gass, MD*, Associate Professor, Clinical OB/GYN, Director, University Hospital Menopause and Osteoporosis Center, University of Cincinnati College of Medicine, Cincinnati, Ohio; *Sandra Lewis, MD, FACC*, Clinical Associate Professor of Medicine, Portland Cardiovascular Institute, Oregon Health Sciences University, Portland, Oregon; *Jay M. Sullivan, MD*, Professor, Medicine, Chief, Division of Cardiovascular Diseases, University of Tennessee, Memphis, Tennessee (deceased); *Glen D. Stettin, MD*, Vice President, Utilization Management, Merck-Medco Managed Care, LLC, Montvale, New Jersey; and *J. Christopher Gallagher, MD*, Professor, Medicine, Creighton University School of Medicine, Omaha, Nebraska. The development of this manuscript was supported by an unrestricted educational grant from Wyeth-Ayerst Pharmaceuticals.

REFERENCES

1. Boggs PP, Utian WH. The North American Menopause Society development consensus opinions. *Menopause* 1998;5:67–8 (editorial).
2. McKinlay SM, Brambilla PJ, Posner JG. The normal menopause transition. *Maturitas* 1992;14:103–15.
3. Bresford SA, Weiss NS, Voigt LF, McKnight B. Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestin therapy in postmenopausal women. *Lancet* 1997;349:458–61.
4. The Writing Group for the PEPI Trial. Effects of estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995;273:199–208.
5. DeVita VT, Warrell RP Jr. Solid tumors. In: Kelly WN, ed. *Essentials of internal medicine*. Philadelphia: J.B. Lippincott, 1994:363–6.
6. Wagner TM, Moslinger RA, Muir D, et al. BRCA1-related breast cancer in Austrian breast and ovarian cancer families: specific BRCA1 mutations and pathological characteristics. *Int J Cancer* 1998;77:354–60.
7. Osin P, Gusterson BA, Philp E, et al. Predicted anti-oestrogen resistance in BRCA-associated familial breast cancers. *Eur J Cancer* 1998;34:1683–6.
8. Robson M, Gilewski T, Haas B, et al. BRCA-associated breast cancer in young women. *J Clin Oncol* 1998;16:1642–9.
9. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995;332:1589–93.
10. Sellers TA, Mink PJ, Cerhan JR, et al. The role of hormone replacement therapy in the risk for breast cancer and total mortality in women with a family history of breast cancer. *Ann Intern Med* 1997;127:973–80.
11. Schairer C, Byrne GM, Rosenberg PS, et al. Estrogen replacement therapy and breast cancer survival in a large screening study. *J Natl Cancer Inst* 1999;91:264–70.
12. Avis NE, Crawford SL, McKinlay SM. Psychosocial, behavioral, and health factors related to menopause symptomatology. *Women's Health* 1997;3:103–20.
13. Woodward S, Freedman RR. The thermoregulatory effects of menopausal hot flashes on sleep. *Sleep* 1994;17:497–501.
14. Barlow DH, Cardozo LD, Francis RM, et al. Urogenital ageing and its effect on sexual health in older British women. *Br J Obstet Gynaecol* 1997;104:87–91.
15. Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med* 1993;329:753–6.
16. Chetkowski RJ, Meldrum DR, Steingold KA, et al. Biologic effects of transdermal estradiol. *N Engl J Med* 1986;314:1615–20.
17. Nachtigall LE. Clinical trial of the estradiol vaginal ring in the U.S. *Maturitas* 1995;22:S43–7.
18. Fantl JA, Bump RC, Robinson D, McClish DK, Wyman J. Efficacy of estrogen supplementation in the treatment of urinary incontinence. *Obstet Gynecol* 1996;88:745–9.
19. Fantl JA, Cardozo L, McClish DK. Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis. First report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol* 1994;83:12–8.
20. Ballinger CB. Psychiatric aspects of menopause. *Br J Med* 1990;156:773–87.
21. Studd JWW, Smith RNJ. Estrogens and depression in women. *Menopause* 1994;1:33–7.
22. Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *JAMA* 1998;279:688–95.
23. Maoz B, Shiber A, Lazer S, Kopernick G. The prevalence of psychological distress among postmenopausal women attending a menopause clinic and the effect of hormone replacement therapy on their mental state. *Menopause* 1994;1:137–41.
24. Paganini-Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer's disease. *Arch Intern Med* 1996;156:2213–7.
25. Tang M-X, Jacobs D, Stern Y, et al. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet* 1996;348:429–32.
26. Baldereschi DM, DiCarlo A, Lepore V, et al. Estrogen-replacement therapy and Alzheimer's disease in the Italian Longitudinal Study on Aging. *Neurology* 1998;50:996–1002.
27. American Heart Association. *Heart and stroke statistical update*. Dallas: American Heart Association, 1999.

28. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;117:1016–37.
29. Kafonek SD. Postmenopausal hormone replacement therapy and cardiovascular risk reduction. *Drugs* 1994;47(Suppl. 2):16–24.
30. Grodstein F, Stampfer MJ, Colditz GA, et al. Postmenopausal hormone therapy and mortality. *N Engl J Med* 1997;336:1769–75.
31. Sullivan JM, Vander Zwaag R, Hughes JP, et al. Estrogen replacement and coronary artery disease: effect on survival in postmenopausal women. *Arch Intern Med* 1990;150:2557–62.
32. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;280:605–13.
33. Grodstein F, Stampfer MJ, Goldhaber SZ, et al. Prospective study of exogenous hormone and risk of pulmonary embolism in women. *Lancet* 1996;348:983–7.
34. Guetta V, Cannon RO III. Cardiovascular effects of estrogen and lipid-lowering therapies in postmenopausal women. *Circulation* 1996;93:1928–37.
35. Best PJM, Berger PB, Miller VM, Lerman A. The effects of estrogen replacement therapy on plasma nitric oxide and endothelin-1 levels in postmenopausal women. *Ann Intern Med* 1998;128:285–8.
36. Perez Gutthann S, Garcia Rodriguez LA, Gastellsague J, Duque Oliart A. Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. *BMJ* 1997;314:796–800.
37. Crook D, Cust MP, Gangar KF, et al. Comparison of transdermal and oral estrogen-progestin replacement therapy: effects on serum lipids and lipoproteins. *Am J Obstet Gynecol* 1992;166:950–5.
38. Falkeborn M, Persson I, Adami HO, et al. The risk of acute myocardial infarction after oestrogen and oestrogen-progestogen replacement. *Br J Obstet Gynaecol* 1992;99:821–8.
39. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997;157:2413–46.
40. National Cholesterol Education Program. Second report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel II). *Circulation* 1994;89:1329–445.
41. American Diabetes Association. Clinical practice recommendations. *Diabetes Care* 1999;22(Suppl. 1):S1–106.
42. Mosca L, Grundy SM, Judelson D, et al. Guide to preventive cardiology for women. AHA/ACC scientific statement: consensus panel statement. *Circulation* 1999;99:2480–4.
43. National Osteoporosis Foundation. *Osteoporosis: physician's guide to prevention and treatment of osteoporosis*. Belle Mead, NJ: Excerpta Medica, 1998.
44. Eastell R. Treatment of postmenopausal osteoporosis. *N Engl J Med* 1998;338:736–46.
45. Kleerekoper M. Detecting osteoporosis: beyond the history and physical examination. *Postgrad Med* 1998;103:45–68.
46. WHO Study Group. *Assessment of fracture risk and its application to screening for postmenopausal osteoporosis* (WHO Technical Report Series 843). Geneva, Switzerland: World Health Organization, 1994.
47. Faulkner KG, von Stetten E, Miller P. Discordance in patient classification using T-scores. *J Clin Densitom* 1999;2:343–50.
48. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. *JAMA* 1999;282:637–45.
49. Daly E, Vessey MP, Hawkins MM, et al. Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* 1996;348:977–80.
50. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial: Multiple Outcomes of Raloxifene Evaluation. *JAMA* 1999;281:2189–97.
51. McClung M, Clemmesen B, Daifotis A, et al. Alendronate prevents postmenopausal bone loss in women without osteoporosis: a double-blind, randomized, controlled trial. *Ann Intern Med* 1998;128:253–61.
52. Hosking D, Chilvers CED, Christiansen C, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. *N Engl J Med* 1998;338:485–92.
53. Silverman S, Chestnut C, Andriano K, et al. for the PROOF Study. Salmon calcitonin nasal spray (NS-CT) reduces risk of vertebral fracture(s) (VF) in established osteoporosis and has continuous efficacy with prolonged treatment: accrued 5 year worldwide data of the PROOF Study. *Bone* 1998;23(Suppl. 5):Abstract 1108.