Hormones and Healthy Bones
Joint Project of
National Osteoporosis Foundation and Association of Reproductive Health Professionals

Literature Review (January 2009)
Osteopenia/Low Bone Mass

Abstract: This statement summarizes the U.S. Preventive Services Task Force recommendations on hormone therapy for the prevention of chronic conditions in postmenopausal women and the supporting scientific evidence, and updates the Task Force's 2002 recommendations on hormone replacement therapy. The updated statement is based on the results of the Women's Health Initiative randomized, controlled trial, as well as the information in the 2002 summary of the evidence on this topic, which is available on the USPSTF Web site (http://www.preventiveservices.ahrq.gov).

Abstract: OBJECTIVE: The North American Menopause Society (NAMS) established a goal to create an evidence-based position statement regarding the management of postmenopausal osteoporosis. DESIGN: NAMS followed the general principles established for evidence-based guidelines to create this document. A MEDLINE search was conducted. Clinicians and researchers acknowledged to be experts in the field of osteoporosis were enlisted to review the evidence. The NAMS Board of Trustees reviewed and approved the final document. RESULTS: Osteoporosis, which has its highest rate of occurrence in postmenopausal women, increases the risk for fractures, including hip and spine fractures. These injuries are often associated with particularly high morbidity and mortality. Given the health implications of osteoporotic fractures, the primary goal of osteoporosis therapy is to prevent fractures by slowing or preventing bone loss, maintaining bone strength, and minimizing or eliminating factors that may contribute to falls. The evaluation of postmenopausal women for osteoporosis risk requires the recording of a medical history, a physical examination, and diagnostic tests. Major risk factors for osteoporosis are age, genetics, lifestyle (especially nutrition), and menopausal status. Management focuses first on nonpharmacologic measures, such as a balanced diet including adequate calcium and vitamin D intakes, appropriate exercise, smoking cessation, avoidance of excessive alcohol intake, and fall prevention. If pharmacologic therapy is indicated, FDA-approved options are estrogens (prevention only), bisphosphonates and selective estrogen-receptor modulators (prevention and treatment), and calcitonin (treatment only). CONCLUSIONS: Management of postmenopausal osteoporosis involves identifying the potential risk for osteoporosis and osteoporotic fracture, followed by measures that focus on reducing modifiable risk factors through lifestyle changes and, if indicated, pharmacologic therapy.

Abstract: OBJECTIVE: The objective of this NIH Consensus Statement is to inform the biomedical research and clinical practice communities of the results of the NIH Consensus Development Conference on Osteoporosis Prevention, Diagnosis, and Therapy. The statement provides state-of-the-art information and presents the conclusions and
recommendations of the consensus panel regarding these issues. In addition, the statement identifies those areas of study that deserve further investigation. The target audience of clinicians for this statement includes, but is not limited to, family practitioners, internists, gerontologists, orthopaedic surgeons, rheumatologists, obstetricians and gynecologists, and preventive medicine specialists. PARTICIPANTS: A nonfederal, nonadvocate, 13-member panel representing the fields of internal medicine, family and community medicine, endocrinology, epidemiology, orthopaedic surgery, gerontology, rheumatology, obstetrics and gynecology, preventive medicine, and cell biology. In addition, 32 experts from these same fields presented data to the panel and a conference audience of approximately 700. EVIDENCE: The literature was searched using MEDLINE and an extensive bibliography of references was provided to the panel. Experts prepared abstracts for their conference presentations with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience. CONSENSUS PROCESS: The panel, answering predefined questions, developed their conclusions based on the scientific evidence presented in open forum and the scientific literature. The panel composed a draft statement, which was read in its entirety and circulated to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement at the end of the conference. The panel finalized the revisions within a few weeks after the conference. The draft statement was made available on the World Wide Web immediately following its release at the conference and was updated with the panel's final revisions. CONCLUSIONS: Osteoporosis occurs in all populations and at all ages. Though more prevalent in white postmenopausal females, it often goes unrecognized in other populations. Osteoporosis is a devastating disorder with significant physical, psychosocial, and financial consequences. The risks for osteoporosis, as reflected by low bone density, and the risks for fracture overlap but are not identical. More attention should be paid to skeletal health in persons with conditions known to be associated with secondary osteoporosis. Clinical risk factors have an important, but as yet poorly validated, role in determining who should have BMD measurement, in assessing risk of fracture, and in determining who should be treated. Adequate calcium and vitamin D intake are crucial to develop optimal peak bone mass and to preserve bone mass throughout life. Supplementation of these two components in bioavailable forms may be necessary in individuals who do not achieve recommended intake from dietary sources. Gonadal steroids are important determinants of peak and lifetime bone mass in men, women, and children. Regular exercise, especially resistance and high-impact activities, contributes to development of high peak bone mass and may reduce the risk of falls in older individuals. Assessment of bone mass, identification of fracture risk, and determination of who should be treated are the optimal goals when evaluating patients for osteoporosis. Fracture prevention is the primary goal in the treatment of patients with osteoporosis. Several treatments have been shown to reduce the risk of osteoporotic fractures. These include therapies that enhance bone mass and reduce risk or consequences of falls. Adults with vertebral, rib, hip, or distal forearm fractures should be evaluated for the presence of osteoporosis and given appropriate therapy.


Abstract: The efficacy of estrogen with or without a progestogen as hormone replacement therapy (HRT) for menopausal symptoms is well-established. Recent large-scale randomized studies with combined estrogen/progestogen therapy (EPT) have raised a number of safety issues, specifically the potential risk for coronary heart disease. Subsequent analyses and other studies have indicated that HRT may be cardioprotective in younger postmenopausal women. A new continuous EPT combines natural 17beta-estradiol (E2) 1 mg with the novel progestin, drospirenone (DRSP) either 0.5 or 2 mg. DRSP has a physiological profile closer to that of natural progesterone than any other synthetic progestin. This paper reviews recent clinical trial data demonstrating the efficacy and safety of combined DRSP/E2 therapy as EPT in postmenopausal women. DRSP/E2 provides symptomatic relief of vasomotor symptoms and improvement in genitourinary atrophy. DRSP/E2 protects against endometrial hyperplasia and reduces the risk of osteoporosis. Combined DRSP/E2 therapy has a favorable impact on cholesterol and triglyceride levels, and decreases blood pressure in women with elevated blood pressure. The favorable efficacy and safety profile of DRSP/E2, and potential for long-term health benefits, represents a new option for the effective management of menopause and its clinical sequelae.


Abstract: Recent reports suggest that soy protein may reduce the risk of osteoporosis in peri- and postmenopausal women. The objective of this study was to examine whether soy supplementation exerts beneficial effects on serum and urinary biomarkers of bone metabolism in postmenopausal women, regardless of whether or not they are on hormone replacement therapy (HRT). A total of 71 women were randomly assigned to either soy protein (SP) or milk-based protein (MBP), 40 g daily for 3 months, in a double-blind parallel design. Forty-two women completed the study (20 on SP and 22 on MBP). Overall, both protein supplements positively influenced serum IGF-I, known to correlate with bone formation. However, SP had a more pronounced effect on IGF-I than MBP. Urinary deoxypyridinoline (Dpd) excretion, a specific biomarker of bone resorption, was significantly reduced by SP, but not by MBP when all women were included. Furthermore, women on MBP experienced a 33% increase in urinary calcium excretion, whereas SP did not have such an effect. To evaluate whether SP affects women differently on the basis of their HRT status, data from women on HRT (n = 22) and those not on HRT (n = 20) were analyzed separately. The subanalysis of the data indicated that SP had the greatest impact on serum IGF-I (an increase of 97%) in the women not on HRT. The changes in urinary Dpd due to SP were only observed in women not on HRT, indicating that the overall decrease in Dpd occurred with SP in the absence of HRT. These results indicate that soy protein may positively influence bone and calcium homeostasis in postmenopausal women, particularly those not on HRT.


Abstract: Millions of women are treated with hormone replacement therapy (HRT) for relief of menopausal symptoms, including vasomotor flushes and sweats for which oestrogen is uniquely and highly effective. Others may continue longer-term treatment in the hope that HRT will help to prevent chronic disease. The preservation of bone mass with continuing oestrogen therapy and reduction of subsequent risk of fracture is well
established. Observational studies of the metabolic and vascular effects of oestrogens have suggested a potential benefit in reducing the risk of vascular disease, but recently published randomized controlled trials demonstrate no evidence of benefit in women with established vascular disease or in apparently healthy women. The increased risks of breast cancer and thromboembolic disease have been confirmed in these trials, with evidence of increased risk of stroke. Observational data suggest there may be a small increased risk of ovarian cancer associated with longer-term use of HRT. The premature termination of one arm of the Women's Health Initiative randomized controlled trial caused concern among patients, doctors and pharmaceutical companies. There are difficulties in extrapolating the results from trials using a specific HRT product to advise women on the wide range of other hormone products, doses, combinations and routes of administration. However, in the absence of evidence that other products are safer, the data suggest that for many women the risks associated with long-term use of HRT outweigh the benefits. There are nonhormonal strategies for the prevention and treatment of osteoporosis. HRT is not, and has never been, licensed in the UK for the prevention or treatment of vascular disease, and the data suggesting potential benefit should now be regarded as biased. The absolute incidence of an adverse event is low, and the risk in an individual woman in a single year is very small, but the risks are cumulative over time with long-term use. The risk-benefit balance of each woman needs regular reappraisal with continued use.


Abstract: OBJECTIVE: To assess in post-menopausal women the efficacy and tolerability of a continuous oestradiol/intermittent norgestimate HRT regimen to prevent and to reverse post-menopausal loss of bone mineral density (BMD) and to determine the effects on serum bone turnover markers markers. METHODS: A 1-year, multicentre, international, placebo-controlled, randomised, double-blind clinical trial was conducted in 146 post-menopausal women with an intact uterus in order to assess the effect on bone loss of continuous oral 17beta-oestradiol (1 mg per day) combined with norgestimate (90 microg per day), for 3 consecutive days out of every 6-day treatment period (E2/iNGM). During a second year extension, all women agreeing to continue were on the E2/iNGM regimen. BMD was assessed prior to treatment and after 1 and 2 years or at the end of treatment in women stopping participation prematurely after at least 6 months of treatment. Serum bone turnover markers were determined prior to and at 1 year of treatment. Adverse events were collected at three-monthly intervals during clinic visits over the treatment period.

RESULTS: BMD in the lumbar spine, the primary endpoint, was evaluable in 117 subjects completing >6 months of treatment. BMD increased on average by 2.4% in women on the intermittent progestin regimen. It decreased by 1.4% in placebo treated women. The change from baseline and the difference between active and placebo treatment (Delta placebo) were highly significant (P < 0.0001). On E2/iNGM, also the BMD in the total hip increased (+1.49%, Delta placebo 3.73%, P < 0.0001). The serum markers for bone formation osteocalcin and type I collagen N-propeptide were significantly reduced compared to baseline by 31 and 44%, respectively and the bone resorption marker C-terminal crosslinked telopeptide of type I collagen by 59%. Minor increases (<10%) of markers in the placebo group were not significant. During a second year extension of the trial, all subjects were on active treatment. Subjects on placebo who lost (median+/-CI 95%) 0.66% (-2.3 to +0.5) of spine BMD during the first year now gained 4.41% (2.7-7.6). They also gained 1.6% (0.1-0.3.6) in the total hip. Subjects continuously on oestradiol/intermittent...
norgestimate (E2/iNGM) gained an additional 5.7% (2.3-13.5) in the lumbar spine and +0.1% (-0.6 to +2.2) at the total hip. Side effects reported by women on the intermittent progestin regimen significantly in excess over reports from the placebo group were uterine bleeding, abdominal and breast pain, but not headache. Back pain and weight gain was reported by significantly fewer women on active treatment compared to placebo.

CONCLUSION: The continuous oestradiol/intermittent norgestimate HRT regimen is well tolerated, reduces bone turnover and prevents post-menopausal bone loss in healthy post-menopausal women.

Abstract: OBJECTIVES: Results from the Women's Health Initiative showed that postmenopausal hormone replacement therapy (HRT) prevents fractures but has an overall unfavorable risk:benefit ratio, leading to the recommendation that HRT be used only for women with troublesome menopause symptoms, and for as short a time as possible. This recommendation has important implications for the timing and duration of HRT and the prevention of osteoporosis. The large number of women participating in the National Osteoporosis Risk Assessment (NORA) program provided the opportunity to evaluate bone mineral density (BMD) and 1-year fracture risk in analyses stratified by duration and recency of HRT. DESIGN: Participants were 170,852 postmenopausal women aged 50 to 104, without known osteoporosis, who were recruited from primary physicians offices across the US. BMD was measured at one of four peripheral sites, and the 1-year risk of osteoporotic fracture was assessed by questionnaire. RESULTS: At baseline, current HRT users had the highest T-scores at every age. Among current hormone users, women who had used HRT longest had the highest BMD levels. Women who had stopped HRT more than 5 years previously, regardless of duration of use, had T-scores similar to never-users. Current but not past hormone use at baseline was associated with a 25% to 29% lower risk of osteoporotic fracture (P < 0.0001) in 1 year, compared with nonusers. These findings were independent of age, ethnicity, body mass index, lifestyle, years postmenopausal, and site of BMD measurement. CONCLUSIONS: We conclude that postmenopausal BMD and fracture are closely associated with current, but not prior, HRT use. Use of HRT for 5 years or less, as proposed for treatment of symptomatic women during menopause transition, is unlikely to preserve bone or significantly reduce fracture risk in later years.


Abstract: BACKGROUND: Although estrogen has been clinically available for more than 6 decades, women have been confused by different opinions regarding the risks and benefits of menopausal hormone therapy (HT), estrogen therapy (ET), and estrogen-progestin therapy (EPT). The publication of recent randomized controlled trials (RCTs), notably, the Heart and Estrogen Replacement Study (HERS), Women's Health Initiative (WHI), and Women's Health Initiative Memory Study (WHIMS), has intensified the risk versus benefit controversy and prompted this review. OBJECTIVE: We provide a systematic, comprehensive, and critical review of selected literature that addresses the basic and clinical aspects of menopausal HT. RESULTS: Solid, consistent evidence based on observational, epidemiologic, and randomized controlled trials underpins the efficacy of menopausal HT for its regulatory agency-approved indications: vasomotor symptoms, vulvovaginal atrophy symptoms, and osteoporosis-related fracture prevention. ET and EPT increase the risk for venous thromboembolism, although the absolute number of events and the risk are both small. Though there is a small increase in the number of breast cancers in women who have used menopausal HT for more than 10 years, the biological meaning of this observation (cause versus unmasking versus chance) is unresolved. Most evidence shows that menopausal HT does not affect breast cancer recurrence and that overall longevity is higher in breast cancer survivors who select menopausal HT. Strong basic science and clinical observational evidence show a benefit of menopausal HT in the cardiovascular and central nervous systems. Data from recent RCTs that included predominantly overweight women aged between 63 and 71 years have been reported to
show more harm than benefit; the rush to generalize these studies to all women and all menopausal HT regimens is unjustified. CONCLUSION: Menopausal HT improves vasomotor symptoms and vulvovaginal atrophy symptoms and prevents osteoporosis-related fracture. Menopausal HT increases the likelihood of venous thromboembolism, but other harms such as breast cancer require further controlled studies. A clinical benefit of menopausal HT for cardiovascular or central nervous system disease prevention is unproven. RCTs of menopausal HT in newly menopausal women, or in women less than 3 years from menopause, are urgently needed to investigate the prevention of cardiovascular and central nervous system aging diseases.


Abstract: Over 24-25 February 2003 in Funchal, Madeira, Novo Nordisk gathered together 25 of the top international hormone replacement therapy (HRT) experts, in order to debate the results of the Women's Health Initiative (WHI) and interpret its possible implications for the future use of HRT. The meeting covered many interesting and controversial areas, addressing the complex and multifaceted issues with insight and realism. Some of the areas covered at the meeting were the use of HRT as a short- or long-term therapy for hot flushes, for general menopausal symptom relief and in osteoporosis prevention; the overall risk-benefit profile and specific breast cancer concerns were also discussed. The WHI data were reviewed and summarized, and, although it was generally agreed that the study was well designed and executed, its relevance to standard hormone therapy for clinical practice must be seriously called into question. The target population used in the WHI is not representative of the target population for whom menopausal HRT is normally considered. It is important to note that randomized controlled trials such as the WHI are really scientific tools for a group of research participants, not a form of individualized medical management. Since their publication, the relevance of the WHI study results for everyday clinical practice has been the subject of controversy. The WHI targeted a group of women who were much older than those normally treated and who had numerous other risk factors. These were not women for whom a practicing clinician would think about initiating hormone therapy with the regimen that was used. Putting a high-risk 70-year-old woman on 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate would not seem appropriate for any indication. With this in mind, we reviewed statements and guidance that followed the release of the WHI to the media, putting them in context with the actual results. Focusing on data taken out of context and without reference to subject profiles, the media created an emotive wave of uncertainty for patients and physicians, which needs to be addressed through realistic, factual communication. It is clear that hormone therapy is effective for postmenopausal symptoms and osteoporosis prevention. Timing is critical for the initiation of therapy and length of treatment. The individual's unique personal profile must be assessed. This leads to the paradox of osteoporosis prevention: therapy should be long-term, but it is long-term therapy that may increase breast cancer risk. The meeting reviewed the uncertain nature of the risks for breast cancer, although the evidence is becoming stronger that combinations of estrogen and progestogen cause a modest increase in risk after 5 years, while this seems not to be true for estrogen alone. Cardiovascular disease issues were also reviewed and discussed. This is perhaps the most misinterpreted result that came out of the WHI, given the population of women studied. Considering the vascular biology and effects of early interventions, the WHI finding that hormone therapy has no place in primary
cardiovascular protection is an unwarranted conclusion. Other issues regarding the risk-benefit profile of HRT for the individual patient were also discussed. Additionally, presenters explored the possibility of class effects against the potential risk factors associated with particular estrogen and progestogen types. It is quite clear that CEE and 17beta-estradiol differ with respect to their source and composition; pharmacokinetic and metabolic data indicate that they differ in their total estrogenic potency, with CEE possessing greater estrogenic potency. Using 17beta-estradiol at the lowest dosage level can provide safe and effective therapy for most indications. The evidence for progestogen differences is even more clear. Medroxyprogesterone acetate and norethisterone acetate have different pharmacokinetic profiles and different activities on steroid receptors. Evidence from preclinical and clinical studies supports the conclusion that these differences result in different pharmacological and clinical effects in favor of norethisterone acetate. Having comprehensively discussed and reviewed all available evidence, a consensus was achieved with regard to appropriate therapy: HRT should be given to women with menopausal complaints to meet their individual needs, taking into account their individual risk profile and the overall therapeutic objectives.

14. Canderelli R, Leccesse LA, Miller NL, Unruh Davidson J. Benefits of hormone replacement therapy in postmenopausal women. *J Am Acad Nurse Pract.* 2007;19:635-41. Abstract: PURPOSE: To provide an overview of current research regarding hormone replacement therapy (HRT) and to assist healthcare providers to better educate patients about potential benefits of this therapy. DATA SOURCES: A systematic review of healthcare literature was conducted with 602 articles selected from CINAHL, Medscape, Pubmed, and Medline databases. Keywords directing the search included hormone replacement therapy, benefits of hormone replacement therapy and trends, hormone replacement therapy and osteoporosis, hormone replacement, and menopause symptoms. CONCLUSIONS: According to the literature, HRT can assist women with postmenopausal symptoms. In addition, research shows that HRT can help some postmenopausal women with selected comorbid conditions such as osteoporosis, type II diabetes, certain cardiovascular pathologies, and colorectal cancer. The decision as to who should use any form of HRT needs to be based on the individual woman's needs, quality of life, and potential risks versus benefits. IMPLICATIONS FOR PRACTICE: HRT has been a benefit to many women in the treatment of postmenopausal symptoms. Recent studies have shown that HRT, whether it is combined estrogen and progestin therapy, or estrogen-only therapy, can help postmenopausal women with osteoporosis and some selected comorbid conditions. Recent research indicates that some women are dying from comorbid conditions rather than breast cancer. Although the research regarding HRT in some areas may be limited, further research adds to existing knowledge and offers new ideas and possibilities in the treatment of postmenopausal symptoms and selected comorbid conditions. Certainly HRT can improve quality of life and possibly longevity for selected women. Ongoing research is needed to further validate such benefits, as well as to further explore the risks and benefits of long-term HRT. Increased knowledge about HRT will help healthcare providers better educate patients about the potential benefits of HRT, while providing documentation about who should take selected types of HRT or whether alternative treatment is preferred.

Abstract: The age at which menopause occurs is a critical factor in the magnitude of its consequences. Most of the medium-to-long-term effects of oestrogen deprivation depend on their duration. The timing of the last menstruation is therefore important, but hypoestrogenic amenorrhoea during the reproductive age is also a relevant factor in the evaluation of individual risks. In recent years, moving post-menopausal women from the lowest point of ovarian hypofunction has been the most important motivation for developing guidelines for the hormonal management of menopause. However, recent data suggest that this may be associated with an unacceptable increase in morbidity in a number of women. Concerns about long-term hormone replacement therapy (HRT) at menopause have recently enhanced interest in a group of molecules that act on the oestrogen receptor with selective effects, known as selective oestrogen receptor modulators (SERMs). Of these, Raloxifene has been approved for the treatment and prevention of osteoporosis, and exhibits a pattern of actions particularly well matched to the needs and concerns of post-menopausal women. Further studies on SERMs may open up new vistas in patient-specific management of post-menopausal health. Finally, debates on the specific health consequences of menopause deal mainly with the risk of chronic disease. Gynaecologists and other health professionals would be advised to develop intervention strategies at menopause according to the continuum of a woman's life, beginning at the post-menarche and extending into later life.


Abstract: PURPOSE: To determine if estrogen plus progestin reduces the incidence of fractures or height loss in postmenopausal women with coronary disease. SUBJECTS AND METHODS: We enrolled 2,763 postmenopausal women with coronary disease and with an intact uterus into the Heart Estrogen/progestin Replacement Study, a randomized double-blind, placebo-controlled secondary prevention trial of cardiovascular disease. Radiographically documented clinical fractures were a prespecified secondary endpoint. Height loss was used as a surrogate for vertebral fractures. The average age of the women was 66.7 +/- 6.7 years, and fewer than 15% of the women had osteoporosis based on their bone density. Women were randomly assigned to either 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily (n = 1,380) or placebo (n = 1,383). Follow-up averaged 4.1 years; 82% of those assigned to hormone treatment were taking it at the end of 1 year, and 64% at the end of the study. RESULTS: During 10,554 person years of follow-up, 286 women experienced a fracture: 138 in the treatment group (26.3 per 1,000 person years) and 148 in the placebo group (28.0 per 1,000 person years); relative hazard, 0.94; 95% confidence interval 0.8 to 1.2, P = 0.61). These included 58 wrist fractures (1.01; 0.6 to 1.7); 27 hip fractures (1.09; 0.5 to 2.3); 32 spine fractures (0.69; 0.3 to 1.4), and 192 other fractures (0.91; 0.7 to 1.2). There was no difference in average height loss between the treatment and placebo groups or in the percent of women who lost more than 2 cm in height: 10.6% in the treatment group and 12.1% in the placebo group. CONCLUSIONS: There was no evidence of a reduction in the incidence of fractures or rate of height loss in older women not selected for osteoporosis. Randomized studies are needed to clarify the effect of hormone replacement therapy on fracture risk among women with and without osteoporosis.
Abstract: Research in animal models indicates that without estrogen, the effectiveness of exercise for increasing bone mineral in females is reduced. With decreased estrogen levels, there is an increase in the threshold at which strains are detected by bone, in turn reducing the transmission of mechanical to biochemical signals for bone formation. Studies combining estrogen replacement and exercise training in postmenopausal women have yielded mixed results but indicate that the combination of interventions may be more effective than either intervention alone for increasing bone mass. Given the continued debate over the risks and benefits of estrogen replacement, other compounds such as bisphosphonates or phytoestrogens may be preferred in combination with exercise training for optimally increasing bone mass and preventing osteoporotic fracture. Studies on animals show that the combination of bisphosphonate or phytoestrogen supplementation with exercise training is effective, but trials in humans are lacking.

Abstract: Bone mass is maintained when low-dose ethinylestradiol is used in combination with the new progestogen drospirenone as an oral contraceptive, making a regimen of drospirenone combined with 17beta-estradiol an attractive option for hormone replacement therapy (HRT) in postmenopausal women. Drospirenone is a novel progestogen, more closely related to endogenous progesterone in its pharmacological properties than other progestogens available; in combination with estrogen, drospirenone can closely mimic the premenopausal hormonal balance. In a phase II/III double-blind, placebo-controlled, randomized trial, three different doses of drospirenone plus low-dose 17beta-estradiol were compared with placebo, in order to determine their effects on bone density. Of 240 healthy postmenopausal women aged 45-65 years who enrolled, 180 completed the 2-year prospective study. Treatment groups received 1 mg 17beta-estradiol combined with 1, 2 or 3 mg drospirenone daily or placebo. Bone mineral densities at the lumbar spine, hip and total body and markers of bone turnover were measured at 1, 3, 6, 12, 18 and 24 months. In the pooled HRT groups, the bone mineral density at the lumbar spine, hip and total body increased by 7%, 4% and 3%, respectively, compared with placebo (all p < 0.001). Markers of bone turnover in HRT groups all decreased accordingly (serum osteocalcin 52%, serum bone-specific alkaline phosphatase 36%, serum CrossLaps 67% and urinary CrossLaps 75% from baseline; all p < 0.001). The combination of 17beta-estradiol with drospirenone offers a safe and effective medication for decreasing bone turnover and preventing postmenopausal bone loss in postmenopausal women.

Abstract: For many years hormone replacement therapy (HRT) was regarded as the gold standard for treatment of osteoporosis. In recent years this status has been challenged, because of the lack of a robust evidence base for anti-fracture efficacy, emerging evidence of adverse extraskeletal effects and the demonstrated efficacy of a number of alternative options in the prevention of osteoporotic fractures. The current consensus is that HRT is no longer regarded as a front-line option for prevention of osteoporotic fractures and that its use for this purpose should be restricted to women with osteoporosis who have menopausal symptoms and to older women who are intolerant of other therapies and/or express a strong
preference for HRT despite being informed about potential adverse effects. Nevertheless, the mechanisms by which estrogen exerts its beneficial skeletal effects remain a major area of research that has important implications for the development of novel therapies.

   Abstract: OBJECTIVE: To survey women's views on hormone replacement therapy (HRT), alternative therapies and sexual health using the Internet. Study design and main outcome measures. Three questionnaires were offered on a UK, patient-tailored, independent, clinician-led dedicated menopause website. They covered HRT, alternative therapies and sexual health. The anonymous responses of the users of the website were analysed. RESULTS: There were 1026, 1072 and 1002 responses for the HRT, alternative therapies and sexual health questionnaires, respectively. On the first, 75% of respondents were in favour of HRT; 36% felt media reports of the risks of HRT had been exaggerated and 73% of women did not know enough about HRT to make informed choices. In relation to alternative therapies, 85% of respondents felt they did not know enough to make informed choices, 71% received no advice before starting an alternative therapy and 69% were unaware of possible interactions. Ninety-five per cent would try alternative therapies before HRT in the belief that they were more natural and 68% were prepared to pay more than £10 a month for such therapies. On the questionnaire on sexual health, 88% of respondents indicated that they believed an active sex life was important. Fifty-three per cent recorded that they experienced dyspareunia, but 51% of women hid their symptoms and 31% made excuses to avoid intercourse; 54% felt their confidence had been adversely affected. Only 20% had discussed their symptoms with health professionals and only 12% were using prescribed treatment. CONCLUSIONS: Online questionnaires are a useful means to obtain data. Our surveys raised several issues, including the observations that the majority of women said they did not know enough about HRT and alternative therapies to make informed choices. There appeared to be many women with vaginal symptoms who had not spoken with a health professional and therefore were untreated.

   Abstract: Potential adverse effects limit the therapeutic envelope of hormone therapy as regards its effect on bone. This envelope can be enlarged considerably by targeting the younger patient at risk of fracture at the lowest dosage with an appropriate route of administration.

   Abstract: BACKGROUND: For decades, hormone replacement therapy (HRT), which includes both estrogen and progestin, has been administered to postmenopausal women to mainly treat the symptoms of menopause and help prevent osteoporosis, with the added benefit of preventing coronary heart disease (CHD). Recently released study results have left clinicians wondering if HRT should be used at all, and, if so, with whom and under what circumstances. OBJECTIVE: To provide readers with an example of the real-world operation of a pharmacy and therapeutics (P&T) committee in its use of a concise clinical monograph to guide its formulary decisions. METHODS: The most relevant information for this committee, interested in evidence, was an analysis of the most current pivotal trials
and observational studies that help define the place in therapy of HRT and provide information on product efficacy and safety. These included the Heart and Estrogen/progestin Replacement Study (HERS) and its extension trial, HERS II, in postmenopausal women with CHD and an average age of 67 years. The Women's Health Initiative (WHI) study, where the mean age of postmenopausal women was 63 years was also reviewed. The U.S. Food and Drug Administration (FDA) statements through January 8, 2003, on the appropriate use of these agents were also included in this clinical monograph for P&T committee review. RESULTS: HERS and HERS II provided evidence that HRT does not provide secondary prevention in women with CHD. Data from the WHI study concluded that HRT promotes CHD and breast cancer in this age group. The Women's Health, Osteoporosis, Progestin, Estrogen study concluded that lower doses of conjugated estrogens (0.3 mg) are just as effective in treating postmenopausal symptoms as higher doses (0.625 mg) and result in fewer side effects. CONCLUSION: The risk of breast cancer outweighs the benefits of osteoporosis prevention from HRT. According to labeling changes recommended by the FDA, HRT (or estrogen replacement therapy) should be limited to the shortest possible duration. Alternatives to HRT should be considered for the prevention of postmenopausal osteoporosis.

Abstract: During the perimenopause, both the quantity and quality of bone decline rapidly, resulting in a dramatic increase in the risk of fracture in postmenopausal women. Although many factors are known to be associated with osteoporotic fractures, measures to identify and treat women at risk are underused in clinical practice. Consequently, osteoporosis is frequently not detected until a fracture occurs. Identification of postmenopausal women at high risk of fracture therefore is a priority and is especially important for women in early postmenopause who can benefit from early intervention to maintain or to increase bone mass and, thus, reduce the risk of fracture. Most authorities recommend risk-factor assessment for all postmenopausal women, followed by bone mineral density measurements for women at highest risk (ie, all women aged >65 years, postmenopausal women aged <65 years with >1 additional risk factors for osteoporosis, and postmenopausal women with fragility fractures). All postmenopausal women can benefit from nonpharmacologic interventions to reduce the risk of fracture, including a balanced diet with adequate intake of calcium and vitamin D, regular exercise, measures to prevent falls or to minimize their impact, smoking cessation, and moderation of alcohol intake. Several pharmacologic agents, including the bisphosphonates (eg, alendronate, risedronate, and ibandronate) and the selective estrogen receptor modulator, raloxifene, have been shown to increase bone mass, to reduce fracture risk, and to have acceptable side-effect profiles. Women who have discontinued hormone therapy are in particular need of monitoring for fracture risk, in light of the accelerated bone loss and increased risk of fracture that occurs after withdrawal of estrogen treatment.

Abstract: BACKGROUND: Long-term post-menopausal hormone therapy (pHT) was often regarded as first-line therapy to prevent fractures in post-menopausal women, a recommendation under scrutiny given the benefit-risk profile of the Women's Health Initiative results of the estrogen-progestin combination. Apart from controlled clinical
studies providing data with fractures as an end point, measures of lumbar and hip bone mineral density (BMD) may be used to assess bone-related effects of pHT. The objective of this study was to conduct a systematic review of 2-year trials, published between 1990 and December 2002, and assessing changes in BMD by any estrogen including ethinyl estradiol, any estrogen plus any progestin, or tibolone. METHODS: We searched MEDLINE, EMBASE and systematic reviews. Thirty-nine randomized, prospective, controlled 2-year trials were analysed in pre-specified groups according to the profile of the compounds. RESULTS: Virtually all pHT regimens at least maintain BMD at the lumbar spine and the hip compared with baseline; there is no apparent difference between the various estrogenic compounds. Tibolone, a synthetic progestin, appears to be as effective as any estrogen. Most trials were conducted in early post-menopausal women, fewer in women with hysterectomy and/or bilateral oophorectomy. CONCLUSIONS: The size of impact on BMD does not appear to differ between tibolone and any estrogen compound studied.

   Abstract: HRT should not be used for the prevention or treatment of chronic disease (eg, heart disease, osteoporosis, dementia). HRT is effective in alleviating moderate to severe menopausal symptoms. Clinicians must be aware of the risks and benefits of HRT and discuss them thoroughly with their patients. As new forms and lower doses of hormones become available, additional studies will be needed to compare therapeutic strategies adequately. Studies of younger perimenopausal and menopausal women are needed. Whatever regimen is chosen, the lowest allowable estrogen dose to relieve symptoms for the shortest time is recommended. Alternatives to hormonal therapy are being examined and some may be considered. Table 1 provides an evidence-based summary of current recommendations.

   Abstract: Osteoporosis is a worldwide problem that results in fractures that lead to disability and high costs to society. Estrogen therapy is frequently utilized for postmenopausal symptoms, but also has proven protective effects on the skeleton. The main action of estrogen at the cellular level is to inhibit the osteoclast by increasing levels of osteoprotegerin (OPG). OPG binds to the receptor activator of NFkB and prevents osteoclast differentiation, activity and survival. Numerous trials have demonstrated the positive effect estrogen has on the improvement of bone mineral density, and lower doses have also proven efficacious with fewer side effects. Both observational and randomized clinical trials have demonstrated the ability of estrogen treatment to prevent fractures. Topics that remain controversial include the appropriate length of estrogen treatment for postmenopausal women and the appropriate follow-up after treatment discontinuation.

   Abstract: OBJECTIVES: The aim of the present study was to evaluate the effects of low doses of hormone replacement therapy (HRT) in normal young postmenopausal women. METHODS: In an open trial healthy, non-obese postmenopausal women received for 2 years a low-dose continuous combined HRT (LD-HRT) containing 1mg estradiol+0.5 mg norethisterone acetate each pill for 28 days, or 0.5 mg of 17beta-estradiol and 0.25 mg of
norethisterone acetate (Ultra low dose, Ultra-LD-HRT) along with 1000 mg of calcium per day. Control group consisted of women receiving only 1000 mg of calcium per day, for 2 years. Menopausal symptoms were evaluated by the Green climacteric scale for the first 12 weeks of the study while bleeding profiles, bone mineral density (BMD) and bone turnover were assessed for 24 months. RESULTS: LD-HRT and Ultra-LD-HRT were effective in reducing menopausal clinical symptoms. In the control group, BMD significantly (P<0.05) decreased at the spine (-2.8+/-.02%), and femoral neck (-2.8+/-.07%). In LD-HRT treated group BMD showed a significant (P<0.05) increase at the spine (5.2+/-.07%), and femoral neck (2.8+/-.04%) after 24 months. In the Ultra-LD-HRT treated women spine and femoral neck BMD showed a significant (P<0.05) increase (2.0+/-.03 and 1.8+/-.03%, respectively) after 24 months. In these women treated with LD-HRT and Ultra-LD-HRT the BMD values were significantly (P<0.05) different from those measured in calcium-treated women. CONCLUSIONS: LD-HRT and Ultra-LD-HRT can alleviate subjective symptoms providing an effective protection against the postmenopausal decrease of BMD.


Abstract: OBJECTIVE: The purpose of this report is not to provide descriptive data for practice recommendations but to point the way to more liberal thinking than the conservatism of today. The patients in this historical practice, where moderate dosages of estrogen are used, with androgens added when indicated, continue hormone replacement therapy (HRT) for many years. These women were audited to determine the reasons for continuance. DESIGN: During the 3 years from 1996 to 1999, 814 women have been followed prospectively, the date of this first visit recorded, as well as the date last seen, the years of hormone use, and their current hormone replacement, so that continuation rates could be determined. The records of the patients were reviewed in January 2005 to determine the impact of the Women's Health Initiative (WHI). RESULTS: Of the 814 patients, there were 573 surgically menopausal women with a mean age of 61.8+/-.3.25 years and 241 naturally menopausal women with a mean age of 58.6+/-.3.08 years. During the 3 years of observation, 692 women continued HRT while 122 discontinued their therapy. Of those continuing therapy, 606 were treated with the implantation of various combinations of estradiol and testosterone pellets, while 86 used injectables, patches or oral hormones. Continuation rates for pellet patients were 96.7% for 10 years, 88.8% for 20 years, and 21.9% for 40 or more years. Continuation rates for the other hormone users were 53.5% for 10 years and 20.9% for 20 years. Eighty-one percent of the patients were prescribed progestogens, and 18 different progestogens or dosages or regimens were used to individualize therapy and provide as side-effect-free a regimen as possible. Continuation rates in the 692 remaining patients declined to 66.7% during the next 5 years. CONCLUSIONS: Moderate dosages of estrogens, with androgens added when indicated, improve continuation rates. Therapy must be individualized so that not only are menopausal symptoms relieved but also side-effects are minimal and women continue to feel good. The implantation of estradiol and testosterone pellets is not necessary for even the majority of postmenopausal women. However, estrogen dosages must be adequate to provide a sense of well-being. After the WHI reports, continuation rates declined more rapidly.

Abstract: **OBJECTIVES:** To identify and describe current women's thoughts about the menopause, hormone treatment (HT) and perceptions about breast cancer. **METHODS:** Between December 2004 and January 2005, 4201 postmenopausal women in seven European countries were interviewed via a standardized computer-aided telephone interview protocol. **RESULTS:** Almost all women reported to have experienced climacteric symptoms, and 63% of the women rated them as being severe. Only 52% of women were aware of the benefits of HT for relief of climacteric symptoms. Although 84% felt that severe symptoms should be treated, only 40% had used HT at some point in time. Thirty-four percent of the women preferring treatment with natural products did so because of the risk of breast cancer associated with HT. HT was recognized by 59% of the women as one of the most important contributors to an increased breast cancer risk. Most women received their information about HT and breast cancer risk from the media. **CONCLUSIONS:** This European survey reveals that the majority of women experience climacteric symptoms but that their decision whether or not to use HT is highly dependent on their concern about breast cancer risk. An increase in knowledge of the benefits and risks of HT is required for women to make appropriate decisions about hormone use.


Abstract: Current guidelines recommend that postmenopausal hormone therapy (HT) be used primarily for treatment of vasomotor and urogenital symptoms associated with the menopausal transition and that women use the lowest effective dose for the shortest time necessary. Vasomotor symptoms improve or resolve spontaneously within a few months to a few years of onset in the majority of women, suggesting that most women should be able to discontinue HT within a few years of starting treatment. Approximately 75% of women who try to stop are able to stop HT without major difficulty. However, some women who would like to stop HT are unable to do so, mainly owing to the development of vasomotor symptoms. Troublesome symptoms associated with stopping HT appear to be more common among women who start HT for treatment of symptoms, but they also are reported by women who started HT for other reasons, such as prevention of osteoporosis. Unfortunately, little information is available to guide physicians in helping women who have difficulty stopping HT. Many clinicians recommend slowly tapering HT or adding another drug for treatment of hot flashes, but the effectiveness of these approaches has not been evaluated. For women who cannot tolerate even a slow taper, the value of symptom relief likely outweighs any increased risks due to HT use.


Abstract: This study examined the effect of hormone replacement, alendronate, or combination therapy on hip structural geometry in 373 postmenopausal women over 3 years. We found that antiresorptive agents alone or in combination result in improvement in parameters of hip structural geometry and BMD. These data provide additional information regarding potential mechanisms for fracture reduction with antiresorptive therapy. **INTRODUCTION:** Fracture reduction is only partially explained by increased BMD. The aim of this study was to examine changes in structural geometry of the hip,
MATERIALS AND METHODS: This was a double-blind, placebo-controlled, randomized clinical trial of 373 women over the age of 65 years, who were randomized to hormone replacement therapy, alendronate, combination therapy, or placebo for 3 years. The outcomes included the DXA-derived hip structure analysis program by Beck, which is an engineering interpretation of the DXA data. The indices included cross-sectional area, section modulus (a measure of bending strength), outer diameter, cortical thickness, and buckling ratio (an index of cortical bone stability). Properties were measured in cross-sectional regions traversing the femur at the narrowest point on the femoral neck, the intertrochanteric region, and the proximal shaft. RESULTS: In the femoral neck, improvement in the hip structure analysis indices were generally significantly greater with combination therapy than either monotherapy; increases were also greater at the intertrochanter compared with hormone replacement therapy. For example, the section modulus at the intertrochanter and narrow neck increased 10.6% and 10.3%, respectively, with combination therapy, 9.1% and 7.3% with alendronate, 5.8% and 6.9% with hormone replacement therapy, and 3.4% and 3.2% with placebo (p < 0.01 across the four groups). Buckling ratio increased, suggesting decreased stability in the placebo group, whereas there was either no change or significant improvements (p < 0.05) in each active treatment group. CONCLUSIONS: We conclude that changes in the distribution of bone mass underlying the improvements in density with antiresorptive agents in combination or alone have positive effects on structural strength and stability at the proximal femur. This study provides additional information on the potential mechanisms for fracture reduction with antiresorptive agents.


Abstract: OBJECTIVE: To establish the effect on bone mineral density (BMD) of long-term (nine years) continuous-combined hormone replacement therapy (ccHRT) with estradiol valerate/medroxyprogesterone acetate (E(2)V/MPA) and follow-up one year after discontinuation of ccHRT. STUDY DESIGN: A total of 279 women were treated with daily dosages of E(2)V + MPA: 1 mg + 2.5 mg (n = 69), 1 mg + 5 mg (n = 70) or 2 mg + 5 mg (n = 140) (Indivina), Orion Pharma, Espoo, Finland) for 8.5 years; all subjects received the lowest dosage for the next six months. BMD was measured at baseline, between 6 and 12 months, annually until the end of study and at one-year postdiscontinuation of ccHRT. Main outcome measure Change in BMD during nine years of treatment with ccHRT and at one-year postdiscontinuation of ccHRT. RESULTS: Progressive increase of vertebral BMD was observed with all dosage regimens throughout nine years, with corresponding reduction in the proportion of women fulfilling criteria for osteoporosis or osteopaenia. Femoral neck BMD reached a peak at about five to six years, whereas in the lumbar spine the BMD increase was sustained until the end of the study treatment. Mean BMD declined after cessation of ccHRT use but remained substantially above baseline levels. In a subset of women (n = 58) there was a rapid (> or =4%) loss of vertebral BMD in the year after termination of ccHRT use. These women had lower than average BMD at baseline but no other factor was identified that distinguished them from the overall study population. CONCLUSIONS: Low-dose ccHRT in postmenopausal women is associated with decreases in lumbar spine BMD for at least nine years. These gains are not sustained after cessation of therapy but the rate of BMD loss varies between individuals.
33. Hohenhaus MH, McGarry KA, Col NF. Hormone therapy for the prevention of bone loss in menopausal women with osteopenia: is it a viable option? Drugs. 2007;67:2311-21. Abstract: Osteopenia is a state of low bone mass, the appropriate clinical management of which is not always clear. The use of hormone therapy for postmenopausal bone loss has become controversial given recent data regarding the risks of therapy. Fragility fractures are common, and result in substantial morbidity and mortality. Although the fracture rate is higher among osteoporotic women, the substantially larger population of osteopenic women accounts for a higher absolute number of fractures. Osteopenia is defined solely according to the statistical properties of the distribution of bone mineral density (BMD) values, which limits its usefulness in clinical care. BMD, although inversely related to fracture risk, should not be used as the sole criterion for fracture risk. Limited data suggest that benefits of treatment seen in women with documented osteoporosis may not extend to osteopenic women. Although estrogen prevents postmenopausal bone loss, preservation of BMD does not necessarily translate into reduced fracture risk. In making decisions about whether to treat a woman with osteopenia, it is critical to estimate how treatments will affect the individual's risk of fracture. Treatment decisions should be based on whether the net benefits of treatment outweigh the anticipated risks, which will depend on the age of the patient and her risk profile. In our opinion, there is insufficient evidence to support treatment for women with a BMD in the osteopenic range in the absence of fragility fracture. For osteopenic women with higher risk, the availability of other treatments with a more favourable risk-benefit profile eliminates the role of hormone therapy for fracture prevention.

34. Jackson RD, Shidham S. The role of hormone therapy and calcium plus vitamin D for reduction of bone loss and risk for fractures: lessons learned from the Women's Health Initiative. Curr Osteoporos Rep. 2007;5:153-9. Abstract: Osteoporosis, a major public health problem, is characterized by increased risk for fracture. To reduce the morbidity and excess loss of life associated with this common disease, we need to understand the efficacy of treatment strategies for fracture reduction. The Women's Health Initiative Clinical Trials have extended our understanding of the effect of hormone therapy and calcium plus vitamin D supplements on risk for hip and total fractures. Although estrogen, with or without progestin, significantly decreases fracture risk at all skeletal sites-almost irrespective of underlying risk for osteoporosis-its risks outweigh its benefits, negating its general use for fracture reduction. For calcium-replete women, calcium plus vitamin D supplementation has a non-significant effect, hence the case for universal supplementation loses merit. But, that argument gains credibility for women over age 60-as a 21% reduction in hip fractures attests-showing that calcium plus vitamin D has a positive effect on bone health in older postmenopausal women.

35. Jackson RD, Wactawski-Wende J, LaCroix AZ, et al. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. J Bone Miner Res. 2006;21:817-28. Abstract: Further analyses from the Women's Health Initiative estrogen trial shows that CEE reduced fracture risk. The fracture reduction at the hip did not differ appreciably among risk strata. These data do not support overall benefit over risk, even in women at highest risk for fracture. INTRODUCTION: The Women's Health Initiative provided evidence that conjugated equine estrogen (CEE) can significantly reduce fracture risk in postmenopausal women. Additional analysis of the effects of CEE on BMD and fracture
are presented. MATERIALS AND METHODS: Postmenopausal women 50-79 years of age with hysterectomy were randomized to CEE 0.625 mg daily (n = 5310) or placebo (n = 5429) and followed for an average 7.1 years. Fracture incidence was assessed by semiannual questionnaire and verified by adjudication of radiology reports. BMD was measured in a subset of women (N = 938) at baseline and years 1, 3, and 6. A global index was used to examine whether the balance of risks and benefits differed by baseline fracture risk. RESULTS: CEE reduced the risk of hip (hazard ratio [HR], 0.65; 95% CI, 0.45-0.94), clinical vertebral (HR, 0.64; 95% CI, 0.44-0.93), wrist/lower arm (HR, 0.58; 95% CI, 0.47-0.72), and total fracture (HR, 0.71; 95% CI, 0.64-0.80). This effect did not differ among strata according to age, oophorectomy status, past hormone use, race/ethnicity, fall frequency, physical activity, or fracture history. Total fracture reduction was less in women at the lowest predicted fracture risk in both absolute and relative terms (HR, 0.86; 95% CI, 0.68-1.08). CEE also provided modest but consistent positive effects on BMD. The HRs of the global index for CEE were relatively balanced across tertiles of summary fracture risk (lowest risk: HR, 0.81; 95% CI, 0.62-1.05; mid risk: HR, 1.09; 95% CI, 0.92-1.30; highest risk: HR, 1.04; 95% CI, 0.88-1.23; interaction, p = 0.42). CONCLUSIONS: CEE reduces the risk of fracture and increases BMD in hysterectomized postmenopausal women. Even among the women with the highest risk for fractures, when considering the effects of estrogen on other important health outcomes, a summary of the burden of monitored effects does not indicate a significant net benefit.

Abstract: Since the introduction of hormone replacement therapy (HRT) in 1942, the availability of scientific information regarding the physiologic action of estrogen alone and in combination with progesterone has grown substantially. The specific physiology of changes in endogenous estrogen as a causal factor in bone loss that occurs as the result of menopause is now better understood. Accumulating evidence regarding the benefit of estrogen in protecting against bone loss at the time of menopause made it the first choice for prevention and treatment of osteoporosis, until the findings of the Women's Health Initiative (WHI) were announced in 2002. Fortunately, the availability of multiple alternative agents for prevention and treatment of osteoporosis in menopausal women has provided clinicians with other options. There remain a small number of patients who cannot tolerate or afford these alternative therapies. Recent publications resulting from the WHI should be understood by practicing physicians who are faced with this dilemma and may need to consider HRT in treating patients with osteoporosis.

Abstract: OBJECTIVE: The purpose of the study was to assess the cost effectiveness of hormone therapy (HT) for postmenopausal women without menopausal symptoms at an increased risk of fracture in Sweden, the UK and the US. METHODS: Using a state-transition model, the cost effectiveness of 50 year old women was assessed based on a societal perspective and the medical evidence found in the Women Health Initiative (WHI) trials. The model had a lifetime horizon divided into cycle lengths of 1 year and comprised the following disease states: hip fracture, vertebral fracture, wrist fracture, breast cancer, colorectal cancer, coronary heart disease, stroke and venous thromboembolic events. An intervention was modelled by its impact on the disease risks during and after the cessation
of treatment. The model required data on clinical effects, risks, mortality rates, quality of life weights and costs valid for Sweden, the UK and the US. The main outcome of the model was cost per QALY gained of HT compared to no treatment. RESULTS: The results indicated that HT compared to no treatment was cost-effective for most sub-groups of hysterectomised women, whereas for women with an intact uterus without a previous fracture, HT was commonly dominated by no treatment. Fracture risks were the single most important determinant of the cost effectiveness results. CONCLUSIONS: HT is cost-effective in women with a hysterectomy irrespective of prior fracture status. In women with an intact uterus, opposed HT was cost-effective in those with a prior vertebral fracture, but cost-ineffective in women without a prior vertebral fracture. Even though HT is found cost-effective for a selection of osteoporotic women, it is unlikely to be considered for first-line therapy for osteoporosis because bisphosphonates have shown a similar reduction in fracture risks but without an increased risk of adverse events.

Abstract: BACKGROUND: Hormone replacement therapy (HRT) could benefit women who have reached the natural menopause, have had a hysterectomy or have a family history of osteoporosis. OBJECTIVE: Our aim was to monitor changes in women's knowledge of, and attitudes towards, HRT since 1991. METHODS: The study was a repeat of a postal survey conducted in 1991 in the Grampian region in the North East of Scotland. Six hundred women, aged 20-69 years, were selected randomly from the eight Local Health Care Co-operatives in Grampian, Scotland. The main outcome measures were women's knowledge of HRT, their attitudes towards it and the percentage of users, past users and never users within the sample. RESULTS: A 79% response rate was achieved. Overall, 17% of post-menopausal women were current takers (increased from 9% in 1991), 22% were previous takers (increased from 7%) and 61% were never takers (decreased from 84%). This increase in ever use of HRT was more pronounced in the less educated women (increase of 24% since 1991) compared with the more educated (increase of 13%). Almost half (48%) of post-menopausal women had considered taking HRT (25% increase). However, of never users, the majority (86%) had never considered HRT and had not discussed it with a doctor. Attitudes towards the menopause remained positive, although knowledge of the effects of HRT and of risk factors for osteoporosis had decreased. Forty-two per cent of never users would be persuaded to take HRT if they knew it would not cause any problems, and 52% would be persuaded to take HRT on the recommendation of a doctor. CONCLUSIONS: Since 1991, HRT use increased overall; this increase was greater in the less educated women. However, the majority of post-menopausal women remain never users, and many were unaware of HRT. Conflicting research evidence since 1991 on the risks and benefits of HRT may account for the decrease in the women's knowledge of the effects of HRT.

Abstract: Lower doses of conjugated estrogens (CE) alone or combined with lower doses of medroxyprogesterone acetate (MPA) increase mean bone mineral density (BMD) from baseline at the spine and hip in early postmenopausal women. However, not all women on therapy gain BMD. The incidence of continued bone loss (defined as a loss of BMD of >2% from baseline) among women using lower doses of CE and CE/MPA is unknown. This
randomized, double-blind, placebo-controlled, multicenter substudy of the Women's Health, Osteoporosis, Progestin, Estrogen (Women's HOPE) trial investigated the incidence of continued bone loss with lower-dose CE and CE/MPA. Eight hundred twenty-two healthy postmenopausal women with intact uteri received CE 0.625, CE 0.625/MPA 2.5, CE 0.45, CE 0.45/MPA 2.5, CE 0.45/MPA 1.5, CE 0.3, CE 0.3/MPA 1.5 (all doses in mg/day), or placebo for 2 years along with 600 mg/day of calcium. Changes from baseline in spine and total hip BMD were compared among treatment groups in an intent-to-treat analysis. At 12 months, < 10% of women on active treatment lost > 2% of spinal BMD (except CE 0.3/MPA 1.5 [15.6%]), compared with 41.2% of women on placebo. At 24 months, the percentages of women on active treatment who lost > 2% of spine BMD ranged from 4.5% with CE 0.45/MPA 1.5-15.6% with CE 0.3/MPA 1.5, compared with 55.2% of women taking placebo. More than 85% of women on active treatment did not experience continued BMD loss at the hip at 12 months and 24 months, in contrast to 30.6% of women on placebo at 12 months and 36.5% at 24 months. Women receiving active treatment who lost > 2% of spine or hip BMD also had a lesser reduction in biochemical markers of bone turnover. In summary, continued bone loss among early postmenopausal women treated with lower doses of CE or CE/MPA is uncommon.

40. Lukes A. Evolving issues in the clinical and managed care settings on the management of menopause following the women's health initiative. J Manag Care Pharm. 2008;14:7-13. Abstract: BACKGROUND: Publication of the Women's Health Initiative (WHI) trial results in 2002 significantly reduced physician and patient confidence in and acceptance of hormone replacement therapy (HRT) as an appropriate treatment option for menopause-associated vasomotor symptoms (VMS). This was true despite the fact that the WHI trial was a primary prevention study conducted in postmenopausal women and was not designed to evaluate the efficacy of HRT in the treatment of VMS. OBJECTIVE: To review data from the WHI, including recent analyses, demonstrating the risks and benefits of HRT in postmenopausal women, to describe changes in menopause treatment guidelines and HRT use since publication of early WHI results nearly 6 years ago, and to identify opportunities for improving the quality of care in perimenopausal women. SUMMARY: Early results from the WHI demonstrated that the risks of longterm HRT in postmenopausal women outweighed the benefits, leading study investigators to conclude that HRT should not be initiated or continued for the primary prevention of coronary heart disease (CHD) in postmenopausal women. Treatment guidelines published by several professional and managed care organizations continue to advocate the use of HRT for treatment of moderate-to-severe VMS. Nevertheless, physician and patient confidence in HRT has declined, as evidenced by a decrease in new HRT prescriptions and an increase in the discontinuation rate of HRT immediately following publication of the preliminary WHI results. Recent analyses demonstrate that the risk for CHD in postmenopausal women is largely dependent upon the age of the woman and the number of years since menopause, with a lower risk for CHD in women aged 50 to 59 years and in women who experienced menopause within the previous 10 years. The highest risk for CHD was evident in women aged 70 to 79 years and in women who experienced menopause 20 or more years ago. Although these data do not support the use of HRT as a primary prevention strategy in postmenopausal women, they do suggest the need to further evaluate the benefits and risks of HRT in perimenopausal women based on patient-specific characteristics, including age and time since menopause. CONCLUSION: Menopausal women present a unique opportunity for health care providers to improve the quality of care among women, not only as it relates to the treatment of VMS, but also as it relates to osteoporosis and
cardiovascular disease, 2 common comorbidities in perimenopausal and postmenopausal women.

Abstract: BACKGROUND: Although several agents are available to treat osteoporosis, the relative efficacy and toxicity of these agents when used to prevent fractures has not been well described. PURPOSE: To compare the benefits in fracture reduction and the harms from adverse events of various therapies for osteoporosis. DATA SOURCES: MEDLINE (1966 to November 2007) and other selected databases were searched for English-language studies. STUDY SELECTION: For the efficacy analysis, investigators selected studies that reported the rate of or risk for fractures. For the adverse event analysis, they selected studies that reported the relationship between an agent and cardiovascular, thromboembolic, or upper gastrointestinal events; malignant conditions; and osteonecrosis. DATA EXTRACTION: Using a standardized protocol, investigators abstracted data on fractures and adverse events, agents and comparators, study design, and variables of methodological quality. DATA SYNTHESIS: Good evidence suggests that alendronate, etidronate, ibandronate, risedronate, zoledronic acid, estrogen, parathyroid hormone (1-34), and raloxifene prevent vertebral fractures more than placebo; the evidence for calcitonin was fair. Good evidence suggests that alendronate, risedronate, and estrogen prevent hip fractures more than placebo; the evidence for zoledronic acid was fair. The effects of vitamin D varied with dose, analogue, and study population for both vertebral and hip fractures. Raloxifene, estrogen, and estrogen-progestin increased the risk for thromboembolic events, and etidronate increased the risk for esophageal ulcerations and gastrointestinal perforations, ulcerations, and bleeding. LIMITATION: Few studies have directly compared different agents or classes of agents used to treat osteoporosis. CONCLUSION: Although good evidence suggests that many agents are effective in preventing osteoporotic fractures, the data are insufficient to determine the relative efficacy or safety of these agents.

Abstract: This study evaluated the additive effects of hormone replacement therapy (HRT) and a 1-year site-specific resistance-training (RT) program involving two free weight exercises (i.e., squat and deadlift) 2 days/week as a strategy to reverse or attenuate bone loss at the lumbar spine in early postmenopausal women. Participants from a group of self-selected HRT or non-HRT (N=141) users were randomly assigned to RT (exercise) or no training, creating four groups: 1) non-HRT plus RT [NHRT plus exercise (n=35)]; 2) HRT plus RT [HRT plus exercise (n=37)]; 3) HRT no resistance training [HRT no exercise (n=35)]; or 4) control [non-HRT no resistance training group (n=34)]. Mean age and months past menopause did not differ between groups (52.1+/−3.0 years and 52.8+/−9.9 months, respectively). Post-menopausal status was confirmed by follicle-stimulating hormone levels > or =40 mIU/mL. Bone mineral density (BMD) of the spine was assessed by Dual Energy X-ray Absorptiometry (Hologic), at baseline and month 12. Data were analyzed using a 4 (experimental condition) x 2 (time) repeated measures multivariate analysis of variance to determine the effects of RT on HRT and non-HRT in early postmenopausal women. The main effects for group (P<0.007), time (P<0.001), and the
group by time interaction (P<0.001) were each significant. Control participants experienced an average of -3.6% reduction of BMD at the spine. HRT treatment with no exercise showed bone loss of -0.66%. One year of RT produced increases in spine BMD of +0.43% and +0.70%, respectively for the NHRT plus exercise, and HRT plus exercise groups with no differences between the NHRT and HRT exercise groups. In conclusion, RT alone was as effective as HRT in preventing bone loss at the spine and was more effective than HRT alone in attenuating bone loss at the spine. Moreover, there was no additional benefit in combining HRT with RT for preventing bone loss at the spine in this group of early postmenopausal women.

Abstract: INTRODUCTION: Short-term hormone replacement therapy (HRT) relieves menopausal symptoms and increases bone mineral density (BMD), but bone loss reoccurs upon discontinuation. This study assesses whether short-term HRT provides long-term BMD benefits. METHOD: This was a prospective study of women aged 50-54 years followed up for 9 years. Women were categorized into three groups according to the treatment they received: No-HRT (n = 340), Short-term HRT (2-4 years, n = 60), and Long-term HRT (9 years, n = 187). RESULTS: BMD increased significantly at the hip (2.4%, p < 0.001) and spine (8.0%, p < 0.001) over 9 years in the Long-term HRT group. Women without treatment lost BMD at the hip (-4.2%, p < 0.001) and spine (-3.5%, p < 0.001). Women in the Short-term HRT group had no significant loss of BMD at the hip (-1.6%, p = 0.08) or spine (-1.4%, p = 0.18) over 9 years. BMD in the Short-term HRT group was significantly higher at 9 years than in the No-HRT group at both spine (difference 0.023 g/cm(2), p = 0.048) and hip (difference 0.016 g/cm(2), p = 0.042). CONCLUSION: After 9 years, women who had taken short-term HRT had no significant loss of BMD and were better off in terms of BMD than those left untreated. Short-term HRT in the early postmenopausal period provides long-term BMD benefits.

Abstract: The natural isoflavone phytoestrogen genistein has been shown to stimulate osteoblastic bone formation, inhibit osteoclastic bone resorption, and prevent bone loss in ovariectomized rats. However, no controlled clinical trial has been performed so far to evaluate the effects of the phytoestrogen on bone loss in postmenopausal women. We performed a randomized double-blind placebo-controlled study to evaluate and compare with hormone-replacement therapy (HRT) the effect of the phytoestrogen genistein on bone metabolism and bone mineral density (BMD) in postmenopausal women. Participants were 90 healthy ambulatory women who were 47-57 years of age, with a BMD at the femoral neck of <0.795 g/cm2. After a 4-week stabilization on a standard fat-reduced diet, participants of the study were randomly assigned to receive continuous HRT for 1 year (n = 30; 1 mg of 17beta-estradiol [E2] combined with 0.5 mg of norethisterone acetate), the phytoestrogen genistein (n = 30; 54 mg/day), or placebo (n = 30). Urinary excretion of pyridinoline (PYR) and deoxypyridinoline (DPYR) was not significantly modified by placebo administration either at 6 months or at 12 months. Genistein treatment significantly reduced the excretion of pyridinium cross-links at 6 months (PYR = -54 +/- 10%; DPYR = -55 +/- 13%; p < 0.001) and 12 months (PYR = -42 +/- 12%; DPYR = -44 +/- 16%; p < 0.001). A similar and not statistically different decrease in excretion of pyridinium cross-
links was also observed in the postmenopausal women randomized to receive HRT. Placebo administration did not change the serum levels of the bone-specific ALP (B-ALP) and osteocalcin (bone Gla protein [BGP]). In contrast, administration of genistein markedly increased serum B-ALP and BGP either at 6 months (B-ALP = 23 +/- 4%; BGP = 29 +/- 11%; p < 0.005) or at 12 months (B-ALP = 25 +/- 7%; BGP = 37 +/- 16%; p < 0.05). Postmenopausal women treated with HRT had, in contrast, decreased serum B-ALP and BGP levels either at 6 months (B-ALP = -17 +/- 6%; BGP = -20 +/- 9%; p < 0.001) or 12 months (B-ALP = -20 +/- 5%; BGP = -22 +/- 10%; p < 0.001). Furthermore, at the end of the experimental period, genistein and HRT significantly increased BMD in the femur (femoral neck: genistein = 3.6 +/- 3%, HRT = 2.4 +/- 2%, placebo = -0.65 +/- 0.1%, and p < 0.001) and lumbar spine (genistein = 3 +/- 2%, HRT = 3.8 +/- 2.7%, placebo = -1.6 +/- 0.3%, and p < 0.001). This study confirms the genistein-positive effects on bone loss already observed in the experimental models of osteoporosis and indicates that the phytoestrogen reduces bone resorption and increases bone formation in postmenopausal women.


Abstract: Menopausal women should not consider that hormonal treatment is an obligatory long-term commitment. Estrogen-based treatments are extremely effective for vasomotor symptom relief and for vaginal atrophy. HRT also is one of several effective methods for the primary prevention of osteoporosis. If trials were done early after the menopause when the endothelium is likely still to be intact, estrogen-based treatment might be shown to prevent coronary heart disease. However, greater efficacy is to be expected from smoking cessation, proper nutrition, exercise, moderate alcohol consumption, statins, beta-blockers and angiotensin-converting enzyme inhibitors. The treatment options for a menopausal woman should include non-drug-related strategies, non-hormonal pharmaceutical therapies as well as hormonal treatments. The first objective of this contribution is to call to the attention of practising physicians the fact that the Women's Health Initiative (WHI) and Heart and Estrogen/Progestin Replacement Study (HERS) studies involved women much older than the early postmenopausal age groups for whom HRT is prescribed because of symptoms. The second objective is to emphasize that the attending physicians must not only treat the symptomatic women but also prevent the occurrence of diseases more prevalent after 60 years of age. Hormones can safely be used for the former, when not contraindicated, whereas for the latter non-pharmacological interventions and non-hormonal medications are preferable.


Abstract: OBJECTIVE: Postmenopausal bone loss and osteoporotic fractures can be prevented by hormone replacement therapy (HRT). However, opposed HRT may increase the risk of breast cancer above that associated with estrogen alone and in non-hysterectomized women estrogen substitution alone increases the risk of uterine cancer, which triggered renewed interest in long-cycle HRT regimens (estrogen replacement therapy with progesterone-free intervals up to 6 months). The effects on bone of such long-cycle HRT regimens are unknown. The objective of the present study was to compare the effects on bone and the endometrium of long-cycle HRT and conventional HRT.

METHODS: Seventy-three healthy non-hysterectomized postmenopausal women were randomized to either conventional HRT (estradiol (E2) 2 mg/d during 12 days, E2 2 mg/d
plus 1 mg/d of norethisterone acetate (NETA) during 10 days, E2 1 mg/d for 6 days) or long-cycle HRT treatment (two cycles with E2 2 mg/d during 28 days, followed by one cycle of conventional HRT and repeated every 3 months). Primary endpoint was the change in bone mineral density (BMD) at the lumbar spine (LS) over 24 months.

RESULTS: BMD at LS increased significantly versus baseline in both treatment groups (conventional HRT +3.8 +/- 0.6%, long-cycle HRT +3.3 +/- 0.5%, p < 0.0001 for both) with no significant difference between treatment groups over 24 months. Similar significant BMD increases versus baseline were observed at the femoral neck, while biochemical markers of bone turnover (osteocalcin and deoxypyridinoline) were significantly decreased over 24 months. There were no endometrial or breast related adverse events reported. CONCLUSION: Long-cycle HRT may be a valid alternative to conventional HRT with regard to protection against postmenopausal bone loss.


Abstract: CONTEXT: Estrogen therapy is known to prevent osteoporosis, but studies have shown that conventional doses increase adverse events. Whether lower doses, one quarter of standard treatment, prevent bone loss is not known. OBJECTIVE: To examine the effect of 3 years of treatment with 0.25 mg/d of micronized 17beta-estradiol on bone mineral density (BMD) and bone turnover in healthy older postmenopausal women. DESIGN, SETTING, AND PARTICIPANTS: Randomized, double-blind, placebo-controlled trial conducted from July 24, 1998, through June 14, 2002, at a university general clinical research center in the United States. Healthy, community-dwelling women (N = 167) who were older than 65 years at enrollment. INTERVENTION: Dosage of 0.25 mg/d of micronized 17beta-estradiol (n = 83) or placebo (n = 84); all women who had not had a hysterectomy received 100 mg/d of oral micronized progesterone for 2-week periods every 6 months. MAIN OUTCOME MEASURES: The BMD of the hip, spine, wrist, and total body measured annually for 3 years. Serum and urine biochemical markers of bone resorption and formation and sex hormones were measured at baseline, 3 months, and during years 1 and 3 of treatment. RESULTS: Mean BMD increased at all sites for participants taking low-dose estrogen (17beta-estradiol) compared with placebo (P<.001). Compared with participants receiving placebo, participants taking low-dose estrogen had BMD increases of 2.6% for the femoral neck; 3.6%, total hip; 2.8%, spine; and 1.2%, total body. Markers of bone turnover, N-telopeptides of type 1 collagen, and bone alkaline phosphatase decreased significantly (P<.001) in participants taking low-dose estrogen compared with placebo. Estradiol, estrone, and sex hormone-binding globulin levels increased in the estrogen-treated group compared with placebo. The adverse effect profile was similar; specifically, there were no statistically significant differences in breast tenderness, changes in endometrial thickness or pathological effects, or annual mammographic results between the 2 groups. The number of abnormal mammograms over 3 years was 15 for the low-dose estrogen group and 10 for the placebo group (8 occurred at baseline) (P =.26). There were no reports of breast cancer during the study. CONCLUSIONS: In older women, a dosage of 0.25 mg/d of 17beta-estradiol increased bone density of the hip, spine, and total body, and reduced bone turnover, with minimal adverse effects. Future studies evaluating the effect of low-dose estrogen on fractures are indicated.

Abstract: A total of 489 elderly women aged 65-75 yr who participated in a 3-yr, randomized, blinded osteoporosis trial underwent measurements of serum estradiol, bioavailable estradiol, and SHBG. At baseline, bone mineral density (BMD) was lower at the femoral sites (7-19%, P < 0.05), total body (6-8%, P < 0.05), and spine (5-9%, P = 0.2) in women in the lowest tertile for serum total estradiol [<9 pg/ml (33 pmol/liter)], serum bioavailable estradiol [<2.4 pg/ml (8.8 pmol/liter)], or highest tertile for serum SHBG (>165 nmol/liter), compared with women in the highest tertiles of total estradiol [>13.3 pg/ml (49 pmol/liter)] and bioavailable estradiol [>4 pg/ml (14 pmol/liter)] or lowest tertile for SHBG (<113 nmol/liter). Bone markers were increased in women in the lowest tertile for serum total estradiol (not significant) and bioavailable estradiol (P < 0.05) and highest tertile for SHBG (P < 0.05). In the longitudinal study, the rate of bone loss in the placebo group was significantly higher in total body (P < 0.05) and spine (P < 0.05) in women in the lowest tertile, compared with the highest tertile of serum bioavailable estradiol. After treatment with conjugated equine estrogens 0.625 mg/d, the increase in BMD was 4-6% higher at the femoral sites (P < 0.05), total body (P < 0.05), and spine (not significant), in the lowest tertile, compared with the highest tertile of serum bioavailable estradiol or highest tertile, compared with the lowest tertile of serum SHBG. In summary, small variations in endogenous serum estradiol and high serum SHBG determine differences in BMD and rate of bone loss in elderly women and also affect the response to treatment with estrogen. Women with a serum estradiol level of less than 9 pg/ml (33 pmol/liter) are optimal candidates for estrogen therapy for osteoporosis prevention.


Abstract: The risks of low bone mineral density, osteoporosis and fractures, are major concerns in postmenopausal women. Although postmenopausal hormone therapy is effective for reducing these risks, safety issues have been raised by the results of studies such as the Women's Health Initiative. Although there are scientifically valid reasons to be wary of the general applicability of the Women's Health Initiative findings, the study has underscored the continuing need for research into new forms of menopausal hormone therapy. Low-dose transdermal estrogen monotherapy can preserve bone density while relieving vasomotor symptoms. Transdermal administration may offer advantages, including lack of first-pass liver metabolism, which permits the use of lower doses and avoids a negative impact on the lipid profile. Moreover, a recently published 2-year study of ultra-low-dose transdermal estrogen monotherapy in an older population similar to that of the WHI reported significant increases in bone mineral density, accompanied by significant reductions in markers of bone turnover, with no increased risk of endometrial hyperplasia or other side effects. Additional studies are warranted to shed further light on the possible benefits of low-dose estrogen monotherapy for the prevention of bone loss in postmenopausal women.

Abstract: BACKGROUND: Based on the potential risks of post-menopausal hormone therapy (HT) found by the Women's Health Initiative, guidelines for HT now recommend use of the lowest effective dose and shortest treatment duration consistent with individual treatment goals. Current (2003) guidance established by the US Food and Drug Administration (FDA) recommends that clinical assessments of HT include women with more frequent and more intense vasomotor symptoms than previously studied. Therefore, this analysis was conducted to further assess the efficacy of a low-dose combination of norethindrone acetate and ethinyl estradiol (NA/EE) previously assessed in dose-ranging studies, while meeting conservative FDA trial design and analysis criteria. OBJECTIVES: The aim of this post hoc analysis and overview was to present data on the efficacy and tolerability of a low-dose combination—NA/EE 0.5 mg/2.5 microg—in the treatment of postmenopausal symptoms, based on data from previously published studies of NA/EE. In addition, the effects of low-dose NA/EE on bone and endometrium are briefly reviewed. METHODS: Data from 3 previously published randomized, placebo-controlled trials were analyzed using current FDA guidance for the assessment of HT in postmenopausal women. Studies 1 and 2 assessed the efficacy of NA/EE at various doses, including 0.5 mg/2.5 microg, in vasomotor symptom (hot-flush [HF]) relief over 16 and 12 weeks, respectively, using self-reporting of symptom frequency and intensity (scores: 0=none; 1=mild; 2=moderate; and 3=severe) in daily diaries. Study 3 assessed the effects of NA/EE at various doses, including 0.5 mg/2.5 microg, on bone and endometrium, using quantitative computed tomography of the lumbar spine at 12 and 24 months and endometrial biopsy at 6, 12, 18, and 24 months of treatment. In all 3 studies, women were asked to record vaginal bleeding and spotting in diaries. Any adverse events were recorded in diaries and/or at clinic visits. Physical and gynecologic examinations and standard clinical laboratory testing were conducted at baseline and at appropriate follow-up visits in all 3 studies. RESULTS: Studies 1, 2, and 3 enrolled 219, 266, and 1265 women, respectively. Overall, in studies 1 and 2, 91% of women were white, the mean age was approximately 52 years, and mean time since last menstrual period was approximately 24 months. In study 1, NA/EE 0.5 mg/2.5 microg was associated with significant reductions from baseline in mean weekly total HF frequency from week 4 (63.6%) through week 16 (73.7%) (all, P<0.05). In study 2, the frequency of moderate or severe HFs was decreased by 61.1% at week 4 (P<0.05) and by 82.2% at week 12 (P<0.001) with NA/EE 0.5 mg/2.5 microg, and the mean intensity score was significantly lower than that with placebo at weeks 8 and 12 (both, P=0.001). In study 3, cumulative amenorrhea rates were approximately 90% in the NA/EE 0.5-mg/2.5-microg and placebo groups at 12 months. Lumbar spine bone mineral density (BMD) was maintained at 24 months with NA/EE 0.5 mg/2.5 microg but was significantly decreased from baseline, by 7.4%, in the placebo group (P<0.001). Endometrial hyperplasia was not observed in the group receiving NA/EE 0.5 mg/2.5 microg over 24 months. The tolerability of NA/EE was similar to that of placebo. The most common adverse events experienced with NA/EE were headache (15.2%), abdominal pain (10.2%), and breast pain (9.0%). CONCLUSIONS: The results from this post hoc analysis and overview of 3 previously published studies suggest that NA/EE 0.5 mg/2.5 microg was associated with decreased frequency and intensity of vasomotor symptoms. This dose of NA/EE was also associated with maintenance of BMD over 24 months, a significant positive effect on BMD compared with placebo. Low-dose NA/EE was also associated with cumulative amenorrhea rates comparable to those of placebo and was not associated with endometrial hyperplasia. This dose was well tolerated, with rates of adverse events generally similar to those of placebo.
Abstract: This presentation, developed from a symposium lecture at the 40th Annual Convention of the American College of Osteopathic Family Physicians on March 22, 2003, in Nashville, Tenn, highlights three pivotal studies that have altered the preferred option for the treatment and prevention of osteoporosis in post-menopausal women. The Heart Estrogen/progestin Replacement Study (HERS), the HERS II, and the Women's Health Initiative provide evidence that the benefits (fewer colorectal cancers and hip fractures) of using hormone replacement therapy--conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d) specifically--did not outweigh the risks (more CHD-related deaths, strokes, venous thromboembolisms, and invasive breast cancer). Treatment and prevention options for osteoporosis now include modification of risk factors, calcium and vitamin D supplementation, third-generation bisphosphonates (alendronate sodium and risedronate sodium), selective estrogen receptor modulators, and synthetic parathyroid hormone.

Abstract: The clinical aftermath of the reporting of the initial findings of the Women's Health Initiative (WHI) in 2002 was a profound reduction in the use of hormone therapies by menopausal women. This reduction led to a well documented increase in vasomotor symptoms and vaginal atrophy among those women who discontinued their hormone regimens. However, another adverse impact among these women, as well as many other menopausal women, is the well recognized increased likelihood of osteoporosis resulting from the decline in circulating estradiol levels associated with natural and surgical menopause. Although the use of non-hormonal drugs such as bisphosphonates has been shown to reduce the risk of fracture in women with osteoporosis, bisphosphonates have not been shown to reduce the risk of fracture in non-osteoporotic women. Indeed, only oral estrogen (as demonstrated in the WHI studies) has been shown to reduce the risk of fracture in osteoporotic and non-osteoporotic women. As non-oral hormone therapies have been shown to be as effective in treating vasomotor symptoms and vulvovaginal atrophy and to have a different (and perhaps more beneficial) physiological effect than oral regimens, it behooves us to assess the impact of non-oral hormone regimens on bone mineral density and fracture risk. Although there are no clinical trials that primarily assess the impact of non-oral regimens on fracture risk in menopausal women, numerous studies are consistent in demonstrating the positive impact of non-oral regimens in maintaining and increasing bone mineral density among users, even for those women using estrogen doses that are considered to be "too low" to have a beneficial impact on other menopausal symptoms.

Abstract: The US Food and Drug Administration (FDA) approved marketing of diethylstilbestrol in 1941 and conjugated equine estrogens (CEE) in 1942 for treatment of menopausal symptoms. Estrogen sales doubled and tripled in the mid-1960s to mid-1970s, until 1975, when reports of increased endometrial cancer in estrogen users resulted in a dramatic decline. Estrogen use increased again, with evidence of protective effects of progestins on estrogen-induced endometrial changes, combined with a 1982 report that Premarin (conjugated estrogen tablets; Wyeth Pharmaceuticals, Philadelphia, PA) retained
bone mass and a 1984 National Institutes of Health (NIH) Consensus Conference on Osteoporosis statement that estrogens were the most effective means for preventing bone loss. Despite conflicting reports in 1985 regarding the relation between estrogens and coronary heart disease (CHD), many published observations of reduced CHD risk in estrogen users—reinforced by clinical trial findings in 1995 of favorable lipoprotein changes in women assigned to CEE with or without a progestin—promoted increased use through the 1990s. By 2001, approximately 15 million US women were using estrogen therapy, with or without progestins. The 2002 Women’s Health Initiative (WHI) report of greater harm than benefit of combined CEE plus a progestin resulted in a precipitous decrease in estrogen and progestin use and a serious reevaluation of menopausal hormone therapy, as well as increased interest in alternative approaches to managing menopausal symptoms, including use of "bioidentical" hormones. FDA guidelines regarding treatment indications for vasomotor symptoms, vaginal atrophy, and osteoporosis prevention have resulted in approval of several estrogen (and progestin) formulations, doses, and routes of administration, thereby providing many options for women who seek conventional therapy.

Abstract: The Women's Health Initiative study worked on the assumption that one dose would fit all asymptomatic postmenopausal women. The investigators therefore often used the wrong dose, of the wrong hormones, on the wrong patients and therefore came to many wrong conclusions. Different combinations of different hormones are necessary for different symptoms and different age groups. Hormone replacement therapy may be commenced in the perimenopausal phase, the early postmenopause, the late postmenopause or after hysterectomy and bilateral salpingo-oophorectomy or a premature menopause. These all require different treatments. Similarly, various indications such as vasomotor symptoms, sexual problems, depression or the treatment/prevention of osteoporosis all need different combinations of estradiol and possibly progestogen and testosterone, according to the specific requirements of the patient.

Abstract: In view of the fact that fractures are the clinically relevant events, risk factors for fractures are discussed first. Bone mineral density (BMD) appears to be a much less important risk factor for the most severe hip fractures than the risk of falling. No results of experimental studies on hormones and fractures at advanced age are available. An overview of the effects of progestins on bone is given. Effects of progestins on bone have been studied by in vitro experiments using cell lines and by more relevant clinical observations. Prospective studies have been conducted following the use of progestins contained in oral contraceptives, alone or in combination with oestrogens; long-term contraception by injection of depot preparations; so-called "add-back" hormonal therapy attempting to reverse the adverse effects of gonadotropin releasing hormone agonists on bone and after different regimens of hormone replacement therapy (HRT) in postmenopausal women. From the data there are no indications that the various progestins, used in clinical practice, have either a bone-protective or an oestrogen antagonistic activity. Progestins do not add or subtract much of the protective action of oestrogens on the bones.

Abstract: OBJECTIVE: The objective of the study was to determine the effects of several doses of conjugated estrogens (CE) and CE plus medroxyprogesterone acetate (MPA) on body composition (BC). STUDY DESIGN: This was a randomized, double-blind, placebo-controlled substudy of the Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) trial. Healthy women (n = 822, 1-4 years after menopause) were randomly assigned to receive the following treatments daily for 2 years: CE, 0.625 mg; CE, 0.625 mg, and MPA, 2.5 mg; CE, 0.45 mg, and MPA, 2.5 mg; CE, 0.45 mg, and MPA, 1.5 mg; CE, 0.3 mg, and MPA, 1.5 mg; or placebo. Body weight (BW) was assessed every 3-4 cycles and fat body mass (FBM), lean body mass (LBM), and percent body fat (PBF) at cycles 6, 13, 19, and 26. RESULTS: In the placebo group, BW, FBM, and PBF increased at each visit during the study. Changes in these parameters were smaller in the active groups. These effects were independent of CE dose and the presence of MPA. Changes in LBM were small and comparable across groups. CONCLUSION: Treatment with CE or CE and MPA for up to 2 years does not affect BC.


Abstract: In industrialized countries, coronary heart disease (CHD) is not only the leading cause of death in women but of disability as well. Menopause, regardless of age at onset, is associated with a marked increase in CHD risk. Based on epidemiologic studies demonstrating mainly positive biologic effects of hormone replacement therapy (HRT) on CHD risk factors and outcomes, earlier recommendations decreed that most, if not all, postmenopausal women should be treated with long-term HRT. Recent randomized controlled trials with clinical CHD endpoints have shown that previously held dicta may not be accurate. Selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene are alternatives to HRT. SERMs represent a growing class of compounds that act as either estrogen receptor agonists or antagonists in a tissue-selective manner. This pharmacologic profile may offer the opportunity to dissociate favorable cardiovascular effects of estrogen from unfavorable stimulatory effects on the breast and endometrium. The only data available regarding the effects of tamoxifen on cardiovascular events in postmenopausal women are from breast cancer trials. They showed fewer fatal myocardial events in women randomly assigned to tamoxifen compared with women assigned to placebo. Raloxifene is a so-called second-generation SERM. It seems clear that raloxifene increases bone mineral density, has no effect on the endometrium, and holds high promise for the prevention of breast cancer. The effect of raloxifene on cardiovascular disease is uncertain. On the basis of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, raloxifene may offer some protection to women with cardiovascular disease or to those who are at high risk. Proof that raloxifene reduces the risk of CHD requires a clinical trial with hard clinical endpoints. Such a study is currently underway. Clinical trials have demonstrated that the synthetic 19-nortestosterone derivative tibolone reduces climacteric complaints and prevent osteoporosis without causing menstrual bleeding. Tibolone lowers lipoprotein(a), fibrinogen, and plasminogen activator inhibitor-1 levels and improves glucose tolerance, insulin sensitivity, and endothelial function; however, it also lowers
high-density lipoprotein cholesterol by >20%. The long-term impact of tibolone on the risk of CHD is not known and needs to be studied.


Abstract: OBJECTIVE: Since the findings from the Women's Health Initiative became available in July 2002, millions of women have discontinued postmenopausal hormone therapy (HT). The objective of this study was to evaluate the association between HT cessation and hip fracture risk. METHODS: Women who participated in the National Osteoporosis Risk Assessment and completed the 12-month follow-up survey were studied. All participants were aged at least 50 years, were postmenopausal, and had no previous diagnosis of osteoporosis. Baseline and 12-month follow-up questionnaires assessed use of HT and incident fractures. Of the 140,584 women in this study, 269 reported an incident hip fracture. A logistic regression model was used to assess association between HT use and incident hip fracture, controlling for potential confounders. RESULTS: Consistent with the Women's Health Initiative, women in National Osteoporosis Risk Assessment who were currently on HT had a 40% lower incidence of hip fractures compared with those who never used HT. Women who stopped using HT more than 5 years earlier had similar hip fracture risk to never users, as expected. However,Surprisingly, women who had discontinued HT within the previous 5 years had an increased hip fracture odds ratio of 1.65 (95% confidence interval 1.05, 2.59) relative to never users of HT. CONCLUSION: Postmenopausal women who have discontinued HT within the past 5 years have a risk for hip fracture that is at least as high as that in women who have never used HT. LEVEL OF EVIDENCE: II-2