Osteoporos Int (2008) 19:1363–1368
DOI 10.1007/s00198-008-0661-8

SPECIAL FEATURE

Assessing response to osteoporosis therapy

E. M. Lewiecki · N. B. Watts

Received: 17 April 2008 / Accepted: 12 May 2008 / Published online: 11 June 2008

Abstract Patients treated with pharmacological agents to improve bone strength and reduce fracture risk may not achieve optimal skeletal benefit for reasons that include poor compliance and persistence, inadequate calcium and vitamin D intake, malabsorption, and medications or co-morbidities with adverse skeletal effects. Monitoring the effects of therapy can inform the patient and physician that the drug is having its expected skeletal response. Treatment is often monitored with serial bone mineral density (BMD) measurements using dual-energy X-ray absorptiometry or bone turnover markers (BTMs). Stable or increasing BMD is associated with reduced fracture risk in clinical trials, and is considered an indication of good response to therapy in individual patients outside of clinical trials. There are many differences between subjects in clinical trials and patients being treated in clinical practice. Thus, although defining a clinical practice patient as a "nonresponder" or "suboptimal responder" to treatment is problematic, a pragmatic approach would be to consider evaluation for contributing factors and possible changes in therapy in patients who have a statistically significant decrease in BMD, do not have the expected change in BTMs, or have a fracture.

Keywords Bone mineral density · Bone turnover marker · Dual-energy X-ray absorptiometry · Fracture · Nonresponder · Osteoporosis · Responder · Treatment

E. M. Lewiecki (✉)
New Mexico Clinical Research & Osteoporosis Center,
300 Oak St. NE,
Albuquerque, NM 87106, USA
e-mail: LEWIECKI@aol.com

N. B. Watts
University of Cincinnati Bone Health and Osteoporosis Center,
Cincinnati, OH, USA

Introduction

Osteoporosis is a common skeletal disease that is characterized by low bone strength resulting in increased risk of fractures. It has serious clinical consequences and is costly to individuals and to society [1]. Osteoporosis can be diagnosed in one of two ways—clinically, in the presence of a fragility fracture, or densitometrically, according to the T-score, which represents the standard deviation (SD) difference between the BMD of the patient and that of a young-adult reference population. Operationally, BMD is assessed by dual-energy X-ray absorptiometry (DXA), the most widely validated technology for assessment of skeletal health. DXA of central skeletal sites (spine and hip) is considered the "gold-standard" method for the diagnosis of osteoporosis and monitoring changes in BMD because: (a) biomechanical studies have shown a strong correlation between mechanical strength and BMD measured by DXA [2]; (b) large epidemiological studies have established a strong relationship between fracture risk and BMD measured by DXA [3]; (c) the World Health Organization (WHO) classification of BMD for the diagnosis of osteoporosis and osteopenia [4] is largely based on reference data obtained by DXA; (d) most randomized clinical trials showing a benefit with pharmacologic intervention have selected subjects based on low BMD measured by DXA [5]; (e) there is a relationship between reduction in fracture risk with pharmacologic therapy and BMD increase measured by DXA [6]; and (f) DXA accuracy and precision are excellent [7]. A T-score of -2.5 or less at the femoral neck, total hip, lumbar spine, or one-third (33%) radius is consistent with a diagnosis of osteoporosis [4, 8]. It is now recognized that a combination of BMD and clinical risk factors predicts fracture better than BMD or clinical risk factors alone. The WHO methodology for quantitative estimation of 10-year

probability of fracture (FRAX™) can be used with country-specific cost-effectiveness analyses to identify patients in whom pharmacological therapy to reduce fracture risk is likely to be cost-effective [1]. Many drugs have been shown to reduce the risk of fracture in prospective randomized clinical trials [9].

Despite general recognition that osteoporosis is a major public health concern and the availability of clinical diagnostic tools and effective therapeutic agents, it remains underdiagnosed and undertreated, even in patients at very high risk of fracture [10]. Patients being considered for treatment may not be thoroughly evaluated for factors contributing to skeletal fragility and fracture risk. When treatment is started, it is often not taken correctly or not taken long enough to have a full therapeutic effect [11]. Some treated patients may develop other medical problems that alter the benefit/risk ratio of treatment, start medications that have adverse skeletal effects, or fail to have an adequate intake of calcium and vitamin D. For reasons such as these, it is generally the standard of practice to monitor patients for treatment effect, as is done for other chronic asymptomatic medical disorders, such as hypertension and hyperlipidemia. However, given the limited methods available for monitoring and some controversy over how to implement them, there is confusion regarding monitoring therapy and assessing therapeutic effect. Diez-Perez and Gonzalez-Macias, in an article in this issue of *Osteoporosis International*, propose classifying patient response to therapy as inadequate, possibly adequate, or appropriate according to BMD and fracture status [12]. We applaud their effort to bring order to such an important aspect of osteoporosis care, and offer our thoughts on the necessity and the methods of monitoring patients being treated with pharmacological agents in clinical practice.

Goals of osteoporosis therapy

The conventional wisdom is that patients who are at high risk for fracture should be identified by means of BMD testing and consideration of clinical risk factors. Those who are at sufficiently high risk of fracture should receive pharmacological therapy to reduce the risk of fractures. This is the most cost-effective strategy to reduce the huge personal and economic burden of osteoporosis, and is endorsed by organizations that include the WHO, the International Society for Clinical Densitometry (ISCD), the International Osteoporosis Foundation (IOF) and the National Osteoporosis Foundation (NOF). The 10-year probability at which it is cost-effective to treat varies by country according to factors such as the cost of treatment, cost of fracture care and societal willingness to pay. Pharmacological therapy reduces fracture risk by improving bone strength, while other interventions, such as muscle strengthening and balance training, may reduce fracture risk by reducing the risk of falling.

Some patients who have not crossed the threshold for cost-effectiveness may also be treated, particularly in the United States, where prevention of disease is often felt to have a value of its own. These are often patients who are felt to be at risk for bone loss who are treated in order to maintain or increase bone mass, prevent irreversible deterioration of trabecular microarchitecture, and stabilize other non-BMD determinants of bone strength. This, in essence, is treatment to prevent osteoporosis, and thereby reduce long-term (lifetime) fracture risk, rather than treatment to reduce fracture risk over a shorter time period (e.g., 5–10 years).

Should patients on prescription medications for osteoporosis be monitored?

The initiation of treatment of osteoporosis is the beginning of a continuing relationship between the patient and healthcare provider to assure that the patient benefits from the treatment without experiencing undue harm. When a decision to treat is made, it is not likely to be fully effective unless a number of requirements are met: (a) the prescription must be filled and refilled for self-administered medication, or in the case of injectable bisphosphonate therapy, the patient must appear for the scheduled injection and return when the next dose is scheduled; (b) the medication must be taken regularly and correctly; (c) it must be absorbed in sufficient quantity and be delivered to its target organ (bone); (d) the patient must continue to take the medication long enough for it to have a significant therapeutic effect; (e) the patient must have lifestyle that is consistent with good bone health, including regular physical activity, if possible, and adequate intake of calcium and vitamin D; and (f) there must be no other diseases, conditions, or medications that impair the drug effect or adversely affect skeletal health. Given the complex nature of this process, it cannot be assumed that the drug will achieve its therapeutic goals without verification. Failure to comply with any of the above requirements, which may result in poor treatment effect, may not be immediately apparent to the patient or physician. By monitoring treatment effect in some fashion and observing for factors associated with poor treatment effect, optimal healthcare can be delivered.

Assessing success or failure in achieving treatment goals

When the goal of therapy is preventing fractures, the ultimate indicator of success is the absence of fractures. In clinical trials, statistical analysis is used to compare fracture rates in patients receiving intervention with a control group,

something that cannot be done in individual patients. A fracture is a stochastic event (i.e., subject to randomness) that may or may not occur, regardless of fracture probability. Having a fracture does not prove drug failure, just as the absence of a fracture does not prove drug benefit. For example, even with a remarkable 70% reduction of vertebral fracture risk in patients treated with intravenous zoledronate [13], 3.3% of treated patients still experienced new vertebral fractures. These were not necessarily treatment failures; it is possible that had they not been taking the drug, fracture severity would have been worse or the number of fractures greater. It is, in fact, a common observation in clinical trials that treatment reduces the risk of multiple fractures to a far greater magnitude than the risk of a first incident fracture.

Since the beneficial effects of pharmacological agents are mediated through improvement of bone strength, a direct measurement of bone strength would be ideal. This can be done with cadaver bone specimens by applying a load to bone and measuring the force necessary for ultimate failure, or fracture. In living patients, there is no way to directly measure bone strength; therefore, surrogates of bone strength must be used. BMD testing is the most widely available surrogate measurement of bone strength. The measurement of bone turnover markers (BTMs), which are independent predictors of fracture risk [14], has been used extensively in clinical trials and is emerging as a potential clinical tool in selected patients. Others methods, such as finite element analysis and "virtual bone biopsy" with high resolution imaging techniques are measures of bone strength that are under investigation in the research setting but not yet applicable in clinical practice.

Monitoring treated patients

If every patient treated for osteoporosis in clinical practice responded the same as the average patient in the treatment group of the pivotal fracture trial of an approved drug, there would be little or no need to monitor for effectiveness of treatment. However, there are differences between patients in clinical practice and subjects in clinical trials [15], suggesting that many or most clinical practice patients treated for osteoporosis would not qualify for participation in the clinical trials that provided the data for drug approval. These differences include variable levels of understanding of osteoporosis and well as differences in age, sex, concomitant medications, and comorbidities. For these reasons, patients in clinical practice may not respond as expected and monitoring to assess treatment benefit is appropriate. BMD measurement is an imperfect surrogate for response to therapy (i.e., improvement in bone strength, reduction in fracture risk), but remains the best available clinical tool. Greater increases in BMD are generally associated with greater fracture risk reduction [6], although fracture reduction has been demonstrated in treated patients with stability [16], and in some studies with loss of BMD [17], presumably due to alterations in bone turnover. An analysis of data in the alendronate Fracture Intervention Trial showed that in patients who took at least 70% of the study drug, those who had bone "loss" (0–4% BMD decrease) on treatment had a reduced fracture risk compared to those in the control group with the same level of bone "loss" [18]. The application of these data to clinical practice is limited, since "loss" of 0–4% in an individual patient may not be a loss at all, but instead could be within the range of measurement error. In the same study, treated patients who had a BMD decrease of more than 4% had a lower rate of fracture than control group patients with the same level of BMD decrease, although the difference was not statistically significant, probably because of the small number of "losers" in the treated group. For patients in clinical practice, a decrease in BMD that meets or exceeds the least significant change (LSC), as calculated according to standardized methods [19], should be cause for clinical concern, further evaluation, and reconsideration of the treatment regimen [20]. Stability or an increase in BMD is an acceptable response to therapy. Measurement of BTMs may provide helpful information in the evaluation for factors contributing to bone loss, and BTM changes in response to therapy have been associated with reduction in fracture risk [21]. A fracture while on treatment is an undesirable event, but does not necessarily represent poor response to therapy.

Defining response to therapy

Considering the great variability of clinical scenarios in patients treated for osteoporosis, it is unlikely that any definition of response to therapy will cover all situations physicians encounter. Diez-Perez and Gonzalez-Macias have identified some of the previously published definitions of poor response to therapy [22–29] and proposed their own operational classification of response: "inadequate" (incident fracture and significant BMD decrease), "possible inadequate" (incident fracture or significant BMD decrease) or "appropriate" (no fracture and stability or increase in BMD), with the requirement that patients are compliant to therapy, have an adequate calcium and vitamin D intake, and have been treated for at least one year. We suggest a somewhat different approach. A significant loss of BMD (meeting or exceeding the calculated LSC) may represent suboptimal response to therapy and should initiate further investigation to determine contributing factors. This includes assessment of adherence (compliance + persistence) to

therapy, adequacy of calcium and vitamin D intake, drug absorption and metabolism, and possibly a search for other co-morbidities with adverse skeletal effects. If BTMs are used to assess treatment effects, a change that is less than expected for the therapeutic agent (or an absolute value above the premenopausal reference range or possibly above the median for premenopausal women) should trigger consideration of further evaluation of contributing factors. Fractures, unfortunately, are not a reliable clinical endpoint for evaluating effectiveness in individual patients. While any fracture is disturbing for the patient and the physician, the stochastic nature of this event renders it an unreliable marker of poor treatment effect in individual patients. We recommend that fractures be carefully considered in the evaluation of all patients with osteoporosis or low bone mass, but that they not be used in classifying response to therapy. Also, fractures will elevate BTMs, so a recent fracture would invalidate the use of BTMs for monitoring.

Clinical approach to patients who are losing BMD on therapy

Although the care of patients should be based on the best available medical evidence, many or most clinical decisions involve patients or circumstances that are not the same as those in published clinical trials. An analysis of 120 consecutive patients with osteoporosis seen at an academic medical center showed that most would not have qualified for clinical trials of the type used to register the same drugs that are used for treatment [15]. A common clinical practice dilemma, and a frequent cause for referral to an osteoporosis expert, occurs when a treated patient is found to be a "bone loser." It is therefore helpful for clinicians to have a systematic method for evaluating these patients. The extent of the evaluation will vary according to the individual clinical situation and available healthcare resources. We offer our approach to managing a patient with apparent bone loss by addressing the following clinical questions.

Is there a genuine bone loss? Many patients with reported "bone loss" are victims of poor quality bone densitometry rather than poor responders to therapy. The first step in evaluating a patient who is reported to have lost bone is to validate that the test has been done and interpreted correctly. This may be an intimidating process for a physician not familiar with the nuances of bone densitometry, but there are some principles that can be understood by all. Among the conditions that must be met in order to have a valid comparison of BMD tests are: (a) measurements must be done on the same instrument or different instruments that have been cross-calibrated (vary rarely done); (b) the DXA facility must have completed a precision assessment in patients typically seen at the facility to determine the precision error and least significant change (LSC)—the smallest BMD change that that is statistically significant with a specified level of confidence (the ISCD recommends a 95% level of confidence); (c) the instrument used must be correctly calibrated and have routine quality control measures to assure that there has no shift or drift in BMD measurements over time; (d) patient positioning must be correct and similar with the measurements being compared; (e) the same skeletal site must be measured using the same scan mode in compared tests (e.g., a left total hip cannot be compared to a right total hip, different vertebral bodies cannot be compared, and a measurement with one scan mode cannot be compared with another); (f) BMD must be compared, not T-scores or Z-scores, since the reference databases used to derive these calculated values may have changed over time, even when BMD has not; (g) there must be no confounding local structural change or artifact, such as a large change in body weight, recent contrast study, or insertion of surgical hardware in an area of measurement; and (h) a thorough medical history to assess possible medications with adverse skeletal effects (e.g., glucocorticoids, anticonvulsants, aromatase inhibitor therapy, or androgen deprivation therapy) or intervening medical disorders or diseases, such as limited weight-bearing due to stroke or severe osteoarthritis. It is helpful for DXA technologists and clinicians who supervise and interpret DXA studies to have training in bone densitometry.

How should bone loss be evaluated? Once it is confirmed that there is a genuine loss of BMD that is at least as great as the LSC in a treated patient, then a search for factors contributing to bone loss is indicated. It should be determined, as best as is possible, whether the patient is taking the prescribed medicine in the correct dose, regularly and correctly. Once this is ascertained, the possibility of malabsorption of an oral agent should be considered—an especially important aspect of treatment with a bisphosphonate. Causes of malabsorption include obvious ones, such as known inflammatory bowel disease or intestinal resection, or unapparent ones, such as asymptomatic celiac disease or gastroparesis. The patient should be assessed for adequacy of calcium and vitamin D intake. Laboratory testing should be customized according to the clinical situation, but may include a complete blood count; serum calcium, phosphorus, 25-hydroxyvitamin D level, alkaline phosphatase, creatinine, thyroid stimulating hormone level (especially in patients on thyroid hormone therapy or with symptoms of a thyroid disorder), celiac antibodies, serum and/or protein electrophoresis, BTMs and a 24-hour urine for calcium, creatinine, and sodium.

Should patient management be changed in a bone loser? If a patient is found to have a correctable medical problem, it should be treated. This may be simple, such as

maintaining an adequate calcium and vitamin D intake, when that was not previously the case, or more complex, such as a lifelong gluten-free diet in a patient found to have celiac disease. Referral to an oncologist may be indicated if malignancy is suspected, such as when an M-component is identified on serum protein electrophoresis. An injectable bisphosphonate should be considered in a patient not responding to an oral bisphosphonate due to malabsorption or poor adherence to therapy. An anabolic agent should be considered in a patient at high risk for fracture who is not responding to an antiresorptive medication. In patients who lose bone while on teriparatide or PTH(1–84), options for a "step-up" in therapy are limited, since those are the only currently approved anabolic agents and there is no proven anti-fracture benefit to combining an anabolic and anti-resorptive drug. Clinicians may take comfort in knowing that BMD loss on teriparatide may in part be due to an increase in measured bone area rather than loss of bone mineral content. A recent analysis of the teriparatide pivotal fracture trial showed that femoral neck bone-losers (loss greater than 4% at one year) showed a significant reduction in vertebral fracture risk [17]. In many or most patients diagnosed as bone losers, one or more contributing factors of clinical significance can be identified and treated [20].

Summary

Patients treated for osteoporosis are a heterogeneous population with variable understanding of osteoporosis, uncertainties in compliance and persistence to therapy, and numerous co-morbidities that may influence response to therapy. Monitoring for treatment effect is an important component of patient management. Although BMD testing is an imperfect clinical tool for monitoring response to therapy, it is the best available option for doing so at this time. BTMs may provide helpful information on the metabolic effects of therapy. Fractures are undesirable, but do not necessarily represent poor response to therapy. Patients with a significant loss of BMD, unexpected values for BTMs, or fractures should be considered for evaluation to determine previously unrecognized contributing factors. Treatment plans should be reassessed according to the results of the medical evaluation.

Conflicts of interest None.

References

1. Kanis JA, on behalf of the World Health Organization Scientific Group (2007) (2007) Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK: Printed by the University of Sheffield.
2. Lotz JC, Cheal EJ, Hayes WC (1991) Fracture prediction for the proximal femur using finite element models: Part I–Linear analysis. J Biomechan Eng 113:353–360
3. Marshall D, Johnell O, Wedel H (1996) Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 312:1254–1259
4. Kanis JA, the WHO Study Group (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Osteoporos Int 4:368–381
5. Cranney A, Tugwell P, Wells G, Guyatt G (2002) Systematic reviews of randomized trials in osteoporosis: Introduction and methodology. Endocr Rev 23:497–507
6. Wasnich RD, Miller PD (2000) Antifracture efficacy of antiresorptive agents are related to changes in bone density. J Clin Endocrinol Metab 85:231–236
7. Mazess R, Chesnut CH III, McClung M, Genant H (1992) Enhanced precision with dual-energy X-ray absorptiometry. Calcif Tissue Int 51:14–17
8. Binkley N, Bilezikian JP, Kendler DL, Leib ES, Lewiecki EM, Petak SM (2006) Official Positions of the International Society for Clinical Densitometry and Executive Summary of the 2005 Position Development Conference. J Clin Densitom 9:4–14
9. MacLean C, Newberry S, Maglione M, McMahon M, Ranganath V, Suttorp M, Mojica W, Timmer M, Alexander A, McNamara M, Desai SB, Zhou A, Chen S, Carter J, Tringale C, Valentine D, Johnsen B, Grossman J (2008) Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. Ann Intern Med 148:197–213
10. US Department of Health and Human Services (2004) Bone Health and Osteoporosis: A Report of the Surgeon General. US Department of Health and Human Services, Office of the Surgeon General.
11. Cramer JA, Gold DT, Silverman SL, Lewiecki EM (2007) A systematic review of persistence and compliance with bisphosphonates for osteoporosis. Osteoporos Int 18:1023–1031
12. Diez-Perez A, Gonzalez-Macias J (2008) Inadequate responders to osteoporosis treatment: proposal for an operational definition. Osteoporos Int DOI 10.1007/s00198-008-0659-2
13. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR (2007) Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 356:1809–1822
14. Garnero P, Hausherr E, Chapuy M-C, Marcelli C, Grandjean H, Muller C, Cormier C, Breart G, Meunier PJ, Delmas PD (1996) Markers of bone resorption predict hip fracture in elderly women: The EPIDOS prospective study. J Bone Miner Res 11:1531–1538
15. Dowd R, Recker RR, Heaney RP (2000) Study subjects and ordinary patients. Osteoporos Int 11:533–536
16. Chesnut CH III, Silverman S, Andriano K, Genant H, Gimona A, Harris S, Kiel D, LeBoff M, Maricic M, Miller P, Moniz C, Peacock M, Richardson P, Watts N, Baylink D, PROOF Study Group (2000) A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. Am J Med 109:267–276
17. Watts NB, Miller PMR, Chen P, Arsenault J, Krohn K (2008) Vertebral fracture risk is reduced for women who lose femoral neck bone mineral density during teriparatide therapy [abstract]. J Clin Densitom 11:In press
18. Chapurlat RD, Palermo L, Ramsay P, Cummings SR, The Fracture Intervention Trial (2005) Risk of fracture among women who lose bone density during treatment with alendronate. Osteoporos Int 16:842–848
19. Baim S, Binkley N, Bilezikian JP, Kendler DL, Hans DB, Lewiecki EM, Silverman S (2008) Official positions of the

International Society for Clinical Densitometry and executive summary of the 2007 position development conference. J Clin Densitom 11:75–91
20. Lewiecki EM, Rudolph LA (2002) How common is loss of bone mineral density in elderly clinical practice patients receiving oral bisphosphonate therapy for osteoporosis? J Bone Miner Res 17 (Suppl 2):S367
21. Bauer DC, Black DM, Garnero P, Hochberg M, Ott S, Orloff J, Thompson DE, Ewing SK, Delmas PD (2004) Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the fracture intervention trial. J Bone Miner Res 19:1250–1258
22. Lewiecki EM (2003) Nonresponders to osteoporosis therapy. J Clin Densitom 6:307–314
23. Del Puente A, Scognamiglio A, Itto E, Ferrara G, Oriente P (2000) Intramuscular clodronate in nonresponders to oral alendronate therapy for osteoporosis. J Rheumatol 27:1980–1983
24. Adami S, Isaia G, Luisetto G, Minisola S, Sinigaglia L, Gentilella R, Agnusdei D, Iori N, Nuti R (2006) Fracture incidence and characterization in patients on osteoporosis treatment: the ICARO study. J Bone Miner Res 21:1565–1570
25. Heckman GA, Papaioannou A, Sebaldt RJ, Ioannidis G, Petrie A, Goldsmith C, Adachi JD (2002) Effect of vitamin D on bone mineral density of elderly patients with osteoporosis responding poorly to bisphosphonates. BMC Musculoskelet Disord 3:6
26. Sawka AM, Adachi JD, Ioannidis G, Olszynski WP, Brown JP, Hanley DA, Murray T, Josse R, Sebaldt RJ, Petrie A, Tenenhouse A, Papaioannou A, Goldsmith CH (2003) What predicts early fracture or bone loss on bisphosphonate therapy? J Clin Densitom 6:315–322
27. Jakob F, Marin F, Martin-Mola E, Torgerson D, Fardellone P, Adami S, Thalassinos NC, Sykes D, Melo-Gomes J, Chinn C, Nicholson T, Cooper C (2006) Characterization of patients with an inadequate clinical outcome from osteoporosis therapy: the Observational Study of Severe Osteoporosis (OSSO). QJM 99:531–543
28. Obermayer-Pietsch B, Nickelsen T, Marin F, Barker C, Hadji P, Farrerons J, Audran M, Boonen S, Anastasilakis A, McCloskey E (2006) Response of BMD to 24 months of teriparatide (rhPTH 1–34) in patients with and without prior antiresorptive treatment: final results from the EUROFORS study. J Bone Miner Res 21 (Suppl 1):S43
29. NICE (National Institute for Clinical Excellence) (2004) Final appraisal determination- secondary prevention of osteoporotic fragility fractures in postmenopausal women. NICE: