

## Treatment of patients with postmenopausal osteoporosis is worthwhile. The position of the International Osteoporosis Foundation

Pierre D. Delmas · René Rizzoli · Cyrus Cooper  
Jean-Yves Reginster

Received: 27 October 2004 / Accepted: 8 November 2004 / Published online: 23 November 2004  
© International Osteoporosis Foundation and National Osteoporosis Foundation 2004

Although many agents have been used in the treatment of osteoporosis, only in the past 10 years have large, double-blind placebo-controlled trials been published on postmenopausal women with the condition of using incident fractures as the primary endpoint. Several agents have been proven to significantly decrease the risk of vertebral and, in some instances, long bone fractures [1]. Tables 1 and 2 show the anti-fracture efficacy of the most commonly used agents for which large fracture trials are available, i.e., the bisphosphonates alendronate and risedronate, the selective estrogen receptor modulator (SERM) raloxifene, the 1–34 fragment of recombinant human parathyroid hormone (teriparatide), and to some extent nasal calcitonin. These agents have consistently shown a substantial reduction of the risk of vertebral fracture ranging from 30–65% according to agent and patient populations. A significant reduction of the risk of nonvertebral fractures has been shown with alendronate and risedronate, ranging from 16–36% according to studies, and with teriparatide (53%

reduction). Table 2 shows the effect of treatments on hip fracture risk in populations of decreasing risk from top to bottom. Indeed, hip fracture risk is highly dependent on age, and most studies performed in osteoporotic women younger than 75 years do not have the statistical power to demonstrate an effect of any agent on hip fracture incidence. A decrease in the risk of nonvertebral fractures, including hip, has been shown in the elderly, especially among institutionalized men and women treated with calcium and vitamin D supplementation [1]. That supplementation, however, cannot be considered a sufficient treatment of established osteoporosis, as it is included in the active treatment and placebo groups of most trials. Etidronate has been shown to decrease vertebral—but not nonvertebral—fracture risk, and it has been superseded by newer more potent bisphosphonates. Vitamin D metabolites and the vitamin K menatetrenone have been shown in some small studies to decrease the risk of fragility fractures, but the evidence is still limited [1]. Finally, anti-fracture efficacy has been recently shown with a new bisphosphonate, ibandronate [2] and with strontium ranelate [3], but these agents are not yet widely available. Despite these significant advances in the field of osteoporosis there is still uncertainty over the question of whom to treat. Healthcare agencies differ markedly in the indications for treatment so that authoritative guidance is needed.

Following the operational definition of osteoporosis on the basis of bone mineral density measurements in 1994 [4], the International Osteoporosis Foundation (then the European Foundation for Osteoporosis) was one of the first organizations to give guidance on whom to treat [5]. The approach taken was that of a case-finding strategy, where prospective patients were identified on the basis of strong clinical risk factors for fracture. The risk factors included prolonged estrogen deficiency, exposure to glucocorticoids and a prior fragility fracture, as well as some other risk factors associated with a marked increase in fracture risk independent of bone mineral density (BMD). It was proposed that patients with such risk factors be referred

---

P.D. Delmas is president of the International Osteoporosis Foundation (IOF); R. Rizzoli is chairman of the IOF Committee of Scientific Advisors; C. Cooper and J.-Y. Reginster are members of the IOF Committee of Scientific Advisors

---

P. D. Delmas  
Claude Bernard University of Lyon  
and INSERM Research Unit 403, Lyon, France

R. Rizzoli  
University of Geneva, Geneva, Switzerland

C. Cooper  
University of Southampton, Southampton, UK

J.-Y. Reginster  
University of Liège, Belgium

P. D. Delmas (✉)  
Pavillon F, Hôpital E. Herriot, 5 Place d'Arsonval,  
69437 Lyon Cedex 03, France  
E-mail: delmas@lyon.inserm.fr  
Tel.: +33-4-72117484  
Fax: +33-4-72117483

**Table 1** Vertebral fracture (VF) incidence over 3 years (% of patients) and relative risk (*RR*) with 95% confidence interval (CI) in pivotal trials performed with alendronate, nasal calcitonin, raloxifene, risedronate, and the recombinant 1–34 fragment of human parathyroid hormone (PTH), given at the approved dose in

the treatment of postmenopausal osteoporosis. Groups of patients receiving other doses in these trials have been deleted from the table. The 3-year incidence was extrapolated from 4.2 years in FIT-2, and 5 years in PROOF. Adapted from references [1,20]

Agent	Trial [ref]	Risk profile	Mean age (years)	VF incidence			<i>RR</i> (95% CI)
				No. of patients randomized	Placebo	Active agent	
Alendronate (5/10 mg)	FIT-1 [21]	High (prevalent VF)	71	2,027	15%	8%	0.53 (0.41–0.68)
Calcitonin (200 IU)	PROOF [22]		69	557	15.6%	10.8%	0.67 (0.47–0.97)
Raloxifene (60 mg)	MORE-2 [23]	Low (without prevalent VF)	68	1,539	21.2%	14.7%	0.70 (0.6–0.9)
Risedronate (5 mg)	VERT-US [24]		69	1,628	16.3%	11.3%	0.51 (0.36–0.73)
Risedronate (5 mg)	VERT-MN [25]		71	815	29%	18.1%	0.59 (0.43–0.82)
Teriparatide (20 µg)	Neer et al. [26]		69	892	14%*	5%*	0.35 (0.22–0.55)*
Alendronate (5/10 mg)	FIT-2 [27]		68	4,432	2.7% <sup>†</sup>	2.1% <sup>†</sup>	0.56 (0.39–0.8)
Raloxifene (60 mg)	MORE-1 [23]		65	3,012	4.5%	2.3%	0.50 (0.31–0.82)**

\*Incidence and *RR* at 21 months

\*\*In the subgroup of women with a *T*-score < –2.5

for bone densitometry, and that treatment be offered to patients in whom bone mineral density lay at or below the threshold for osteoporosis (a *T*-score of –2.5 SD). This strategy has been widely adopted in many European countries [6]. The approach is, however, conservative in that patients must have the risk factor in addition to the diagnostic criterion for osteoporosis. For this reason effective treatments are withheld from many individuals at high risk.

In 1998 the National Osteoporosis Foundation (NOF) of the US published its physician guidance [7], based on a detailed health economic analysis of interventions [8]. Although based also on a case-finding

strategy, the approach differs from that of the International Osteoporosis Foundation in three important respects. The first is that the BMD threshold at which intervention is recommended is less stringent. Secondly, a variable BMD threshold is used, depending on the presence or absence of clinical risk factors. For example, in women aged 65 years or more, treatment is recommended in women with a *T*-score of –2.0 SD in the absence of clinical risk factors, but with a *T*-score of –1.5 SD in the presence of clinical risk factors. It was acknowledged, therefore, that the presence of independent risk factors should influence the intervention threshold. A third difference of the NOF approach is the

**Table 2** Hip fracture incidence over 3 years (% of patients) and relative risk (*RR*) with 95% confidence interval (CI) in pivotal trials performed with alendronate, nasal calcitonin, parathyroid hormone (PTH), raloxifene and risedronate in the treatment of

postmenopausal osteoporosis. Groups of patients receiving other doses in these trials have been deleted from the table. The 3-year incidence was extrapolated from 4.2 years in FIT-2, and 5 years in PROOF. Adapted from references [1, 20]

Agent	Trial [ref]	Risk profile	Mean age (years)	Hip fracture incidence			<i>RR</i> (95% CI)
				No. of patients randomized	Placebo	Active agent	
Risedronate (2.5 mg and 5 mg)	HIP [28]	70–80 years with osteoporosis	74	5,445	3.2%	1.9%	0.6 (0.4–0.9)
		> 80 years with/without osteoporosis	83	3,886	5.7%*	2.3%*	0.4 (0.2–0.8)
Alendronate (5/10 mg)	FIT-1 [21]	Patients with vertebral fractures	71	2,027	2.2%	1.1%	0.49 (0.23–0.99)
Calcitonin (200 IU)	PROOF [22]		69	557	1.8%	1.2%	0.5 (0.2–1.6)
Risedronate (5 mg)	VERT-US [24]		69	1,628	1.8%	1.4%	n.a.
Risedronate (5 mg)	VERT-MN [25]		71	815	2.7%	2.2%	n.a.
Teriparatide (20 µg)	Neer et al. [26]		69	892	0.74%**	0.037%**	n.a.
Raloxifene (60mg and 120 mg)	MORE [23]		67	7,705	0.7%	0.8%	1.1 (0.6–1.9)
Alendronate (5/10 mg)	FIT-2 [27]	<i>T</i> -score < –2.5	n.a.	1,631	1.6%	0.72%	0.44 (0.18–0.97)
		<i>T</i> -score < –1.6	68	4,432	0.8%	0.65%	0.79 (0.43–1.44)

\*In the subgroup with prevalent vertebral fractures

\*\*Incidence at 21 months

n.a. not available

view that bone mineral density tests should be offered to all women aged 65 years or more, a recommendation endorsed by other organizations in the US [9,10]. This view is not shared outside the US, largely because the screening test (BMD) has low sensitivity and positive predictive value over most reasonable assumptions. Indeed, the vast majority of fractures will occur in individuals designated to be at low risk [4,11].

In recent years, a number of risk factors for fracture have been identified that are independent of BMD. These include age, a family history of fracture, a prior fragility fracture, exposure to long-term glucocorticoids, smoking tobacco, and elevated biochemical indices of bone turnover [12–14]. The evaluation risk using all these independent risk factors adds information to that provided by BMD. The consequences are that sensitivity (detection rate) of the assessment can be improved, without sacrificing specificity [11]. The integration of these risk factors with BMD poses challenges for expressing risk that can readily inform clinicians and patients. For this reason there is a growing opinion that intervention thresholds for osteoporosis should be based on absolute risk (probability) of fracture, rather than solely on diagnostic thresholds provided by the *T*-score [14,15]. A consequence is that guidance needs to be given concerning the level of risk that is sufficiently high to merit an intervention. These issues are particularly important for health care purchasers who must ensure an equitable distribution of resources across many disease categories. In this context, cost-utility analysis to evaluate treatment strategies takes into account not only fractures avoided, but also change in attendant morbidity and mortality. In addition, comparisons can be made between different diseases. The unit of measurement is the quality adjusted life years gained, where each year of life is valued according to its utility—ranging from zero, the least desirable health state, to 1, or perfect health. This is balanced against the cost of intervention and the cost of fractures avoided.

In this issue, Kanis and colleagues have undertaken a cost-effectiveness analysis to determine intervention thresholds in Sweden [16]. Concurrently, intervention thresholds have been determined for the UK by the same authors [17]. The effects of treatment, based on a meta-analysis of bisphosphonate trials, assumed a relative risk reduction of 35%, treatment for 5 years and an offset of effect thereafter that dissipated over a further 5 years. The threshold at which treatment was considered to be cost-effective was £30,000 per quality adjusted life year gained as recommended by NICE [18]. The 10-year probability of hip fracture and of the four major clinical fractures at which intervention became cost-effective is shown for women in Table 3. The thresholds for hip fracture are rather similar between Sweden and the UK, despite different costs and fracture risks. An important finding is that the threshold of fracture probability at which treatment becomes cost-effective is lower with decreasing age. For example, in women from the UK, intervention at the age of 50 years is cost-effective with a

**Table 3** Ten-year probability (%) of hip fracture and of the four major clinical fractures (spine, hip, humerus, forearm) at which treatment becomes cost-effective (from references [16, 17, 29, 30])

Age (years)	UK	Sweden		
	Hip	Hip	Major 4	Hip/Total*
50	1.10	1.17	9.2	3.8
55	1.81	1.80	11.0	7.3
60	2.64	2.73	13.6	11.4
65	3.70	3.98	16.2	14.5
70	5.24	5.11	17.6	21.0
75	6.87	6.08	19.4	26.3
80	8.52	7.40	22.0	38.8
85	8.99	7.23	20.2	35.6

\*Proportion of osteoporotic fractures accounted for by hip fracture according to age (5-year age intervals, i.e., 50–54, 55–59, etc.) in women from Sweden

10-year probability of hip fractures that exceeds 1.1%. By contrast, treatment becomes cost-effective at the age of 70 years with a 10-year hip fracture probability of 8.5%. This appears to be paradoxical, but it arises because intervention decreases the risk of all osteoporotic fractures. In younger women, proportionately more fractures occur at sites other than the hip. In addition, survival is longer in younger women. It is interesting to note that the 10-year probability of hip fracture at which treatment is cost-effective is actually lower than the average risk of Swedish women 65 years old and over, and of British women over the age of 75 years [16,17].

The important question is what the clinical scenarios are for which treatment can be considered to favorably compete with other chronic diseases. Several clinical scenarios are covered in the analysis undertaken in the setting of the UK. For patients with established osteoporosis (a prior fragility fracture and a BMD of  $-2.5$  SD), treatment is always cost effective, irrespective of age. Indeed, cost-effective scenarios are found for individuals with a history of a prior fracture, even without the measurement of BMD. In such patients it is cost-effective to intervene from the age of 65 years in the absence of information on BMD. There is also good news for strategies aimed at preventing the first fracture. It is cost-effective to intervene in women from the UK at the threshold of osteoporosis from the age of 60 years. From a population perspective, women rarely have a *T*-score of exactly  $-2.5$  SD at the hip, thus, in women with osteoporosis it is cost-effective to intervene irrespective of age.

Some caution must be exercised in applying these recommendations widely. Firstly, the setting of intervention thresholds will depend critically upon fracture costs and willingness of different countries to pay for treatment. In addition, the estimates of efficacy and intervention cost are based on the use of bisphosphonates; the costs of other interventions will vary. In addition, hormone replacement treatment and the selective estrogen receptor modulators have extra-skeletal benefits and risks that will affect intervention thresholds for these particular agents. Indeed, as shown

in this issue, raloxifene is also cost-effective in these clinical scenarios due to its favorable effects on breast cancer, in addition to decreasing vertebral fracture risk, despite limited effects on nonvertebral fracture [19]. The model used is, however, conservative in its assumption about the offset time, the length of treatment, and the exclusion of morphometric fractures. In addition, the increase in risk of fracture associated with a prior fracture may be underestimated for patients with a prior vertebral fracture, in whom the risk of a subsequent vertebral fracture is particularly high [13]. Within these limitations the treatment of established osteoporosis can now be justified. There is also good news for the prevention of the first fracture. Favorable health economic scenarios can be devised once the interrelationship of clinical risk factors and BMD are established.

## References

- Delmas PD (2002) Treatment of postmenopausal osteoporosis. *Lancet* 359:2018–2026
- Recker R, Stakkestad JA, Chesnut CH 3rd, Christiansen C, Skag A, Hoiseth A, Ettinger M, Mahoney P, Schimmer RC, Delmas PD (2004) Insufficiently dosed intravenous ibandronate injections are associated with suboptimal antifracture efficacy in postmenopausal osteoporosis. *Bone* 34:890–899
- Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, Cannata J, Balogh A, Lemmel EM, Pors-Nielsen S, Rizzoli R, Genant HK, Reginster JY (2004) The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 350:459–468
- World Health Organization (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO Technical Report Series 843, WHO, Geneva
- Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D (1997) Guidelines for diagnosis and management of osteoporosis. The European Foundation for Osteoporosis and Bone Disease. *Osteoporos Int* 7:390–406
- Compston JE, Papapoulos SE, Blanchard F (1998) Report on osteoporosis in the European Community: current status and recommendations for the future. Working Party from European Union Member States. *Osteoporos Int* 8:531–534
- National Osteoporosis Foundation (1998) Physicians guide to prevention and treatment of osteoporosis, Washington, DC
- National Osteoporosis Foundation (1998) Osteoporosis: review of the evidence for prevention, diagnosis and treatment and cost-effectiveness analysis. *Osteoporos Int* 8 [Suppl 4]:S7–80
- U.S. Preventive Services Task Force (2002) Screening for osteoporosis in postmenopausal women: recommendations and rationale. *Ann Intern Med* 137:526–528
- Lewiecki EM, Watts NB, McClung MR, Petak SM, Bachrach LK, Shepherd JA, Downs RW Jr (2004) Official positions of the international society for clinical densitometry. *J Clin Endocrinol Metab* 89:3651–3655
- Kanis JA, Johnell O, Oden A, De Laet C, Jonsson B, Dawson A (2002) Ten-year risk of osteoporotic fracture and the effect of risk factors on screening strategies. *Bone* 30:251–258
- Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J (2000) The use of biochemical markers of bone turnover in osteoporosis. Committee of Scientific Advisors of the International Osteoporosis Foundation. *Osteoporos Int* 11 [Suppl 6]:S2–17
- Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA 3rd, Berger M (2000) Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res* 15:721–739
- Kanis JA (2002) Diagnosis of osteoporosis and assessment of fracture risk. *Lancet* 359:1929–1936
- Kanis JA, Gluer CC (2000) An update on the diagnosis and assessment of osteoporosis with densitometry. Committee of Scientific Advisors, International Osteoporosis Foundation. *Osteoporos Int* 11:192–202
- Kanis JA, Johnell O, Oden A, Borgstrom F, Johansson H, De Laet C, Jonsson B (2004) Intervention thresholds for osteoporosis in men and women: a study based on data from Sweden. *Osteoporos Int* (DOI 10.1007/s00198-004-1623-4; this issue)
- Kanis JA, Borgstrom F, Zethraeus N, Johnell O, Oden A, Jonsson B (2004) Intervention thresholds for osteoporosis in men and women. *Bone* (in press)
- Raftery J (2001) NICE: faster access to modern treatments? Analysis of guidance on health technologies. *Bmj* 323:1300–1303
- Kanis JA, Borgstrom F, Johnell O, Oden A, Sykes D, Jonsson B (2004) Cost-effectiveness of raloxifene in the UK—An economic evaluation based on the MORE-study. *Osteoporos Int* (DOI 10.1007/s00198-004-1688-0; this issue)
- Delmas PD, Calvo G, Boers M, Abadie E, Avouac B, Kahan A, Kaufman JM, Laslop A, Lekkerkerker JF, Nilsson P, Van Zwieten-Boot B, Kreutz G, Reginster JY (2002) The use of placebo-controlled and non-inferiority trials for the evaluation of new drugs in the treatment of postmenopausal osteoporosis. *Osteoporos Int* 13:1–5
- Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE (1996) Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet* 348:1535–1541
- Chesnut CH, 3rd, 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 (2000) A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. *Am J Med* 109:267–276
- Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, Christiansen C, Delmas PD, Zanchetta JR, Stakkestad J, Gluer CC, Krueger K, Cohen FJ, Eckert S, Ensrud KE, Avioli LV, Lips P, Cummings SR (1999) Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 282:637–645
- Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, Chesnut CH 3rd, Brown J, Eriksen EF, Hoeseyni MS, Axelrod DW, Miller PD (1999) Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA* 282:1344–1352
- Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, Lund B, Ethgen D, Pack S, Roumagnac I, Eastell R (2000) Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporos Int* 11:83–91
- Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH (2001) Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 344:1434–1441
- Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ (1998) Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 280:2077–2082

28. McClung M, Clemmesen B, Daifotis A, Gilchrist NL, Eisman J, Weinstein RS, Fuleihan Ge-H, Reda C, Yates AJ, Ravn P (1998) Alendronate prevents postmenopausal bone loss in women without osteoporosis. A double-blind, randomized, controlled trial. Alendronate Osteoporosis Prevention Study Group. *Ann Intern Med* 128:253–261
29. Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B (2001) Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporos Int* 12:989–995
30. Kanis JA, Oden A, Johnell O, Jonsson B, De Laet C, Dawson A (2001) The burden of osteoporotic fractures: a method of setting intervention threshold. *Osteoporos Int* 12:417–427