falling for professional environmental assessment—for example, to occupational therapy.[34] People who have difficulty in performing a simple sit to stand test or taking over 13 seconds to complete a simple timed "up and go test"[35] should be referred to a geriatrician or falls clinic for a more comprehensive evaluation.

The physiological profile assessment instrument is a useful, inexpensive tool for evaluating risk of falling.[36] Among older people living in the community, this well validated instrument has a 75% positive predictive accuracy for distinguishing multiple fallers in the next year from those who will fall once or less.[36]

Another question is whether general practitioners should prescribe hip protectors to prevent hip fractures related to falls. Hip protectors are designed to shunt the force and energy of impact away from the greater trochanter, thus preventing fracture.[37] The first randomised clinical trials of hip protectors showed good efficacy, but later, more inconsistent, study results have been attributed to differences in study designs, variation in the devices' capacity to attenuate biomechanical forces, and widely varying user compliance.[20 37] Like antiresorptive drugs, hip protectors seem to have poor long term compliance.[20 37]

SUMMARY POINTS

Falling, not osteoporosis, is the strongest single risk factor for fractures in elderly people

Bone mineral density is a poor predictor of an individual's fracture risk

Drug treatment is expensive and will not prevent most fractures in elderly people

Randomised controlled trials show that falls in older people can be reduced by up to 50%

General practitioners should shift the focus in fracture prevention by systematically assessing risk of falling and providing appropriate interventions to reduce the risk

Nevertheless, current meta-analyses and systematic reviews suggest that in institutions with high rates of hip fracture, the use of hip protectors may reduce hip fractures by 23-60%.[23 37-39] However, there is no evidence of benefit from hip protectors for lower risk people living in the community.[38]

In summary, it is time to shift the focus in fracture prevention from osteoporosis to falls. Falling is an under-recognised risk factor for fracture, it is preventable, and prevention provides additional health benefits beyond avoiding fractures.

Contributors and sources: The authors have a long experience and research interest in methodological issues of bone densitometry, epidemiology, and prevention of osteoporosis, falls, and fractures in elderly people. This article arose out of discussions at several meetings on osteoporosis and hip fracture prevention including, most recently, the Paulo symposium on preventing bone fragility and fractures in Tampere, Finland, May 2006.
TLNJ conceived the paper and wrote the first draft with KMK. All authors contributed to the initial critical review of the literature, planned the rationale for the article, contributed to the serial drafts and agreed the final submission. TLNJ is guarantor.

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Drugs for pre-osteoporosis: prevention or disease mongering?

After looking at data used to support treatment of women with slightly lowered bone mineral density, **Pablo Alonso-Coello and colleagues** argue that proponents have overstated the benefits and underplayed the harms

Osteoporosis is a controversial condition. An informal global alliance of drug companies, doctors, and sponsored advocacy groups portray and promote osteoporosis as a silent but deadly epidemic bringing misery to tens of millions of postmenopausal women.[1] For others, less entwined with the drug industry, that promotion represents a classic case of disease mongering—a risk factor has been transformed into a medical disease in order to sell tests and drugs to relatively healthy women.[2] Now the size of the osteoporosis market seems set to greatly expand, as the push begins to treat women with pre-osteoporosis. These are women who are apparently at risk of being at risk, a condition known as osteopenia that is claimed to affect more than half of all white postmenopausal women in the United States.[3] We examine the evidence from four post-hoc analyses of trials of osteoporosis drugs that is claimed to support this move.

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Expanding an already controversial condition

In 1994 a small study group associated with the World Health Organization defined "normal" bone mineral density as that of young adult women, instantly categorising many older women as having abnormal bones.[4] The working group proposed osteoporosis should be diagnosed when bone mineral density is 2.5 standard deviations below the mean for healthy young adult women and osteopenia be diagnosed when bone density was 1.0 to 2.5 standard deviations below the mean (table 1). The authors of the definition stated these cut-off values were "somewhat arbitrary," and as others have subsequently observed, these criteria were intended for epidemiological studies and not as the clinical treatment thresholds they are being used for today.[6]

As disclosed in the report, the drug industry contributed to the funding of the World Health Organization's study group.[4] The disclosure reads: "This meeting was organized by the WHO Collaborating Centre for Metabolic Bone Disease, Sheffield, England, the World Health Organization and the European Foundation for Osteoporosis and Bone Disease, with financial support from the Rorer

Table 1 | WHO classification of osteoporosis

	Bone mineral density*	T score	Prevalence (%)†
Normal	‹1 SD	›–1	20
Osteopenia (or low bone mass)	1-2.5 SD	–1 to –2.5	52
Osteoporosis	≥2.5 SD	≤–2.5	28

*Below the young adult mean.
†In white women older than 50 years.[5]

Foundation, Sandoz Pharmaceuticals and Smith Kline Beecham."

Notwithstanding ongoing debate about the definition of this condition, there is currently widespread agreement that well designed and well conducted randomised trials have shown that most of the drugs now approved for the treatment of women with postmenopausal osteoporosis reduce the risk of important fractures. Furthermore, in women with moderate or especially high risk, these treatments are cost effective, although this is not necessarily the case in osteopenic women.[7]

What remains uncertain is the risk of fracture that warrants treatment and, given its limited predictive power in establishing women's fracture risk, the appropriate role of bone mineral density in guiding prevention.[8] Since the mid-1990s, drug marketing in the United States and elsewhere has encouraged treatment of younger postmenopausal women at relatively low risk of fracture. As part of that strategy, measurement of bone mineral density has been widely promoted—sometimes aggressively—as the key way to diagnose osteoporosis.[1] Against the backdrop of controversy and uncertainty, current attempts to promote drug therapies to people with osteopenia warrant scepticism.

Treating those at risk of being at risk?

In recent years several scientific publications have reanalysed data from the original trials of osteoporosis drugs, including alendronate, raloxifene, risedronate, and strontium ranelate (table 2).[9-12] The key aim has been to present subgroup analyses to investigate the benefits of these drugs for women with pre-osteoporosis or osteopenia, which is said to affect around half of all older women. In Europe, drug companies have already begun to market their drugs to women with osteopenia. In Spain, after complaints from two of the authors, regional drug authorities have required two companies (Lilly and Procter and Gamble) to modify their promotional materials.[13] As with other attempts to define and treat new categories

Table 2 | Studies reanalysing data of patients with osteopenia

	Raloxifene[10]	Alendronate[9]	Risedronate[11]	Strontium ranelate[12]
Original trials	MORE trial (7705 women)	FIT I and FIT II trials (6457 women)	Four trials: BMD and VERT trials	SOTI (1649 women) and TROPOS (5091 women)
Dose	60 mg/day	5 mg/day for 2 years and 10 mg/day afterwards	5 mg/day	2 g/day
Inclusion criteria	Osteoporosis or radiographically apparent vertebral fractures	FIT I: T score ‹–1.6 with at least one vertebral fracture at baseline	BMD trials: T score ‹–2	SOTI: osteoporosis and at least one vertebral fracture
		FIT II: no vertebral fracture at baseline	VERT: ≥2 radiographically identified vertebral fractures or 1 vertebral fracture and low lumbar spine BMD (T score ‹–2)	TROPOS: osteoporosis
No of women in reanalysis	2557	3737 without vertebral fracture	620 women	1166 women
		3737 overall		
Mean age	65 years	68 years	64 years	75 years
Follow up	3 years	3-4.5 years	1.5-3 years	3 years
Subgroup inclusion criteria	Osteoporotic and osteopenic women without previous vertebral fracture.	T score ‹–1.6 and ›2.5 with or without vertebral fracture	Baseline femoral neck T score between –1 and –2.5 and no prevalent vertebral fracture	Lumbar spine osteopenia with any bone mineral density at femoral neck without vertebral fracture
Risk of vertebral fracture in osteopenic women without baseline vertebral fracture	Clinical vertebral fracture	Clinical vertebral fracture (2797 women)	Morphometric vertebral fracture	Morphometric vertebral fracture (4447 women)
	Control event rate: 1.2%	Control event rate: 0.9%	Cumulative incidence: 4.2% for placebo, 1.8% for risedronate	Control event rate: 8.6%
	RR=0.25; 95% CI 0.04 to 0.63 (20 events). ARR=0.9%	RR=0.46; 95% CI 0.16 to 1.17 (19 events). ARR=0.5%	HR=0.44; 95% CI 0.11 to 1.78	RR=0.41; 95% CI 0.17 to 0.99 (23 events). ARR=5.1%
Results in original trials for osteoporotic women	RR=0.7; 95% CI 0.5 to 0.8	FIT I : HR=0.45; 95% CI 0.27 to 0.72	VERT: RR=0.59; 95% CI 0.43 to 0.82	TROPOS: RR=0.61; 95%CI 0.51 to 0.73
		FIT II (any clinical fracture): RR=0.86; 95% CI 0.73 to 1.01		SOTIS: RR=0.59; 95% CI 0.48 to 0.73
Risk of non-vertebral fracture in osteopenic women	—	—	Cumulative incidence: 5.4% for placebo 0.4% for risedronate	—
			HR=0.09; 95% CI 0.01 to 0.71†	
Limitations acknowledged by authors	Yes*	Yes*	Yes*	Yes
Potential conflicts of interest‡	Yes	Yes	Yes	Yes
Years since original trial	4	7	7-10	2-3

RR=relative risk; ARR=absolute risk reduction; HR=hazard ratio.
*Not in abstract or conclusions.
†Risedronate was found to reduce the risk of combined morphometric vertebral and non-vertebral fractures (HR=0.27; 0.09 to 0.83). Nevertheless, when women with baseline lumbar spine T scores below –2.5 were excluded this effect did not reach significance (HR=0.22; 0.03 to 2.02).
‡ See text for details.

of pre-disease, such as pre-hypertension,[14] and pre-diabetes,[15] this move to treat pre-osteoporosis raises serious questions about the benefit-risk ratio for low risk individuals, and about the costs of medicalising and potentially medicating an enormous group of healthy people.

Reanalysis: science in the service of marketing?

In broad terms the key finding of all four reanalyses is that the benefit of anti-osteoporosis drugs remains, in relative terms, roughly the same in the low risk women with osteopenia as in women with densitometric osteoporosis and those who have had fractures. That is no surprise—a substantial body of evidence shows that relative risk reductions are usually more or less constant across patients with varying baseline risk.[16] Even so, the post-hoc criteria for choosing the osteopenic subgroups are questionable. Particularly problematic is the inclusion of women with vertebral fractures, a subgroup whose high risk of subsequent fracture is well documented (table 2). Furthermore, in the unlikely event that reductions in relative risk differ substantially, the reanalyses are underpowered to show this (range of number of events 19-23). Thus, if the goal of these reanalyses is to prove that relative effects are similar across risk groups, the evidence is necessarily weak.

Exaggerating benefits

In general, the reanalyses tend to focus more heavily, although not exclusively, on describing the reduction in fracture risk in relative rather than absolute terms. This is especially apparent in the abstract and the conclusions. When absolute baseline risk of fracture is low, as it is for women without existing fractures or other major risk factors, the absolute benefits of any treatment will similarly be low, and the numbers needed to treat will be high. Impressive sounding reductions in relative risk can mask much smaller reductions in absolute risk. What is relevant to people is that much lower baseline risk means much smaller absolute benefits from potentially long term drug treatment and therefore much higher risk to benefit and cost to benefit ratios.

The authors of the raloxifene reanalysis cite a 75% reduction in relative risk in the first line of their discussion, although this translates into only a 0.9% reduction in absolute risk.[10] But what baseline risk should we use to estimate the absolute effect of prophylaxis in osteopenic women? The four studies show widely disparate absolute risks in control patients: from 0.9% to 8.6% over three to five years. Few events and the likelihood of idiosyncratically selected populations make this variability unsurprising. Data from large community cohorts are more appropriate for estimating baseline risk. These suggest that incidence is unlikely to be greater than 1% a year.[17 18] Even if we use the largest relative risk reduction from the four studies,[10] this incidence implies that we need to treat 133 (95% confidence interval 104 to 270) women for three years to prevent a single vertebral fracture. In other words, up to 270 women with pre-osteoporosis might need to be treated with drugs for three years so that one of them could avoid a single vertebral fracture.

Aside from the tendency to emphasise the relative over the absolute risk reduction, the authors of three of the four reanalyses focus exclusively on vertebral fractures, rather than long bone and hip fractures, which are more relevant to patients.[9 10 12] In addition, two reanalyses use morphometric rather than clinical vertebral fractures as their outcome of interest.[11 12] Two thirds of vertebral fractures are subclinical or asymptomatic and may not affect quality of life. As a consequence showing that drugs reduce vertebral fractures may not be as important to patients as it seems.

Playing down side effects

The flip side of exaggerating benefits is playing down harms, and most of the reanalyses have this problem. The analysis of strontium ranelate does not mention side effects.[12] Yet the drug is known to cause diarrhoea, and there is concern over an increased risk of vascular, neurological, and laboratory abnormalities.[19 20] Only recently the European Medicines Agency recommended changes in the product information because of the risk of severe hypersensitivity reactions.[21]

Similarly the reanalysis of raloxifene data focuses solely on the potential benefits, with no mention of

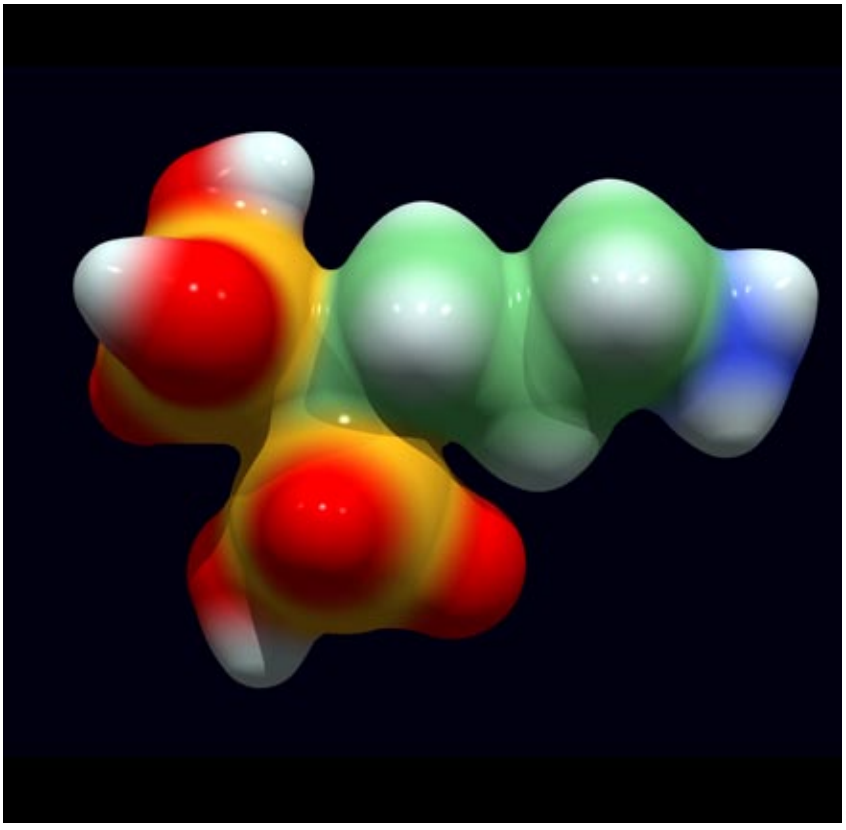
SUMMARY POINTS

Drug treatments reduce the risk of fracture in women with osteoporosis

Drug marketing is being directed at women with osteopenia with a low risk of fracture

The rationale for this strategy comes from questionable post-hoc reanalyses that understate side effects and overstate potential benefits

Treatment decisions should be based on the assessment of the absolute risk of fracture



SPL

Alendronate: who needs it?

an increased risk of venous thromboembolism[22] or, as recently observed, an increased risk of stroke.[23] Alendronate has well established side effects, including potentially serious gastrointestinal side effects and rare but catastrophic osteonecrosis of the jaw, which again are not discussed.[24] Although the risedronate analysis briefly mentions side effects, perhaps not coincidentally, the authors state the drug is as safe as placebo.[11]

Potential conflicts of interest

Like much of the published literature on osteoporosis, these analyses have potential conflicts of interest. All of the original drug trials being reanalysed were funded by industry. In three of four cases, drug company employees were part of the team conducting the reanalyses.[9-11] In the other case, the reanalysis was conducted by a group that included investigators with financial ties to industry.[12] In the reanalysis of raloxifene, three of the eight investigators were employees of Eli Lilly, the drug's manufacturer.[10] The reanalysis of Merck's alendronate was funded by Merck, and three of the five main authors have potential conflicts of interest: one is a Merck employee, one is a consultant to Merck, and the other is on Merck's speakers bureau.[9] For the reanalysis of data on risedronate two of the five authors are employees of Procter and Gamble, the company that markets the drug in Spain.[11] In the case of the strontium ranelate paper, three out of eight authors serve as consultants, advisory board members, and speakers for Servier, the manufacturer of this drug. The Institute de Recherches Internationales Servier sponsored the study.[12]

Where to from here?

The World Health Organization is currently developing an absolute fracture risk algorithm that will provide guidance on how to deal with women categorised as having osteopenia.[25] Whether this advice will stop industry efforts to encourage treatment in low risk women is, however, questionable. The drug industry has already begun marketing its osteoporosis drugs to the large group of women defined as having osteopenia: potentially half of the world's postmenopausal women. Notwithstanding the genuine value of these drugs in reducing fracture risk for some women, we need to ask whether the coming wave of marketing targeting those women with pre-osteoporosis will result in the sound effective prevention of fractures or the unnecessary and wasteful treatment of millions more healthy women.

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Contributors and sources: PA-C and ALG-F, are both active members of the Spanish Society of Family and Community Medicine, working there on women's health issues. GG is a clinical trialist and methodologist who has published a number of systematic reviews of osteoporosis therapies. RM is a health writer, researcher, and author who has written previously about osteoporosis and disease mongering. PA-C and ALG-F developed the concept of the paper and produced the first draft. RM drafted a revised document. GG contributed to the discussion of the content of the paper, in particular the methodological limitations of the studies and responding to reviewer comments. All authors revised the paper, made relevant contributions, and approved its content. PA-C is the guarantor.

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