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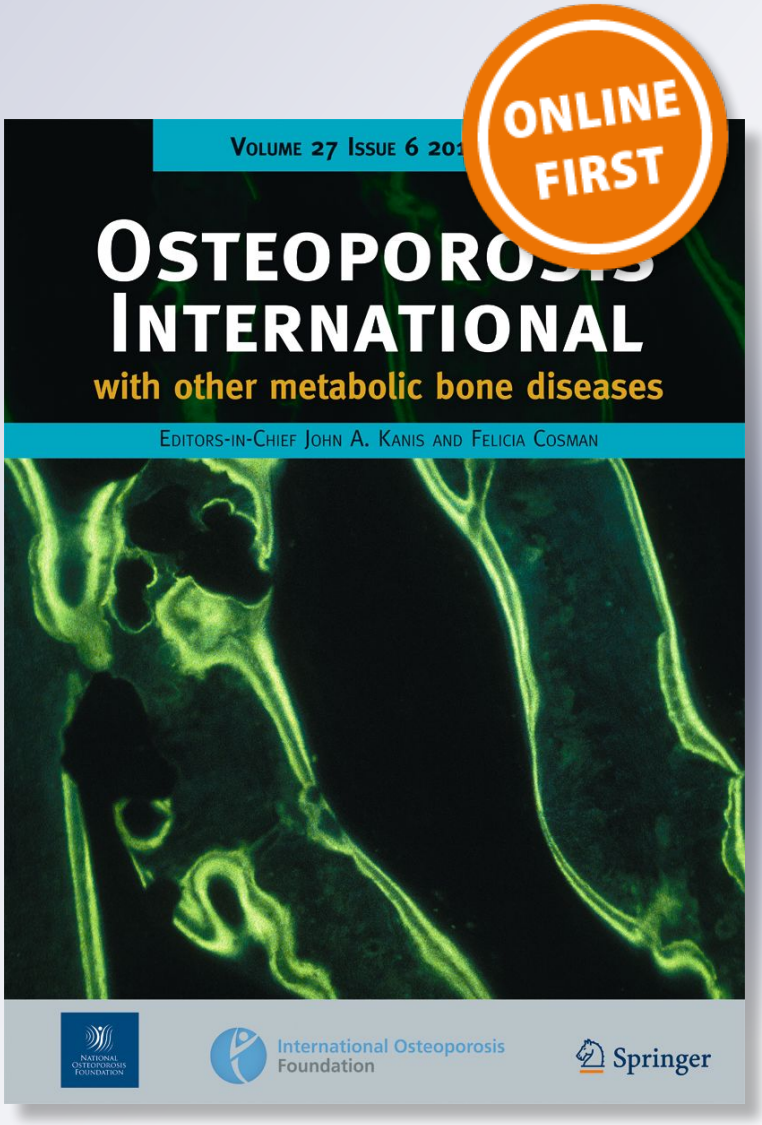

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Review of the guideline of the American College of Physicians on the treatment of osteoporosis

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Abstract

Summary This review, endorsed by the International Osteoporosis Foundation and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, summarizes several failings of the recent guidelines of the American College of Physicians (ACP) on the treatment of low bone density or osteoporosis to prevent fractures.

Introduction The ACP recently issued guidelines for the treatment of low bone density or osteoporosis to prevent fractures.

Methods Literature review and critical review of the ACP guidelines.

Results The guideline is lacking in scope due to the endorsement of treatment based on T-scores rather than fracture risk assessment and in failure to adequately consider anabolic therapies.

Conclusions The ACP guideline appears outdated.

Keywords Bone mineral density · Fracture risk · FRAX · Intervention thresholds · Treatment guidelines

The American College of Physicians (ACP) recently issued guidelines for the treatment of low bone density or osteoporosis to prevent fractures [1]. ACP recommends that clinicians offer pharmacological treatment to reduce spine and hip fracture risk in women with osteoporosis, and consider treatment in women at high risk. More specifically, ACP strongly recommends "that clinicians offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis."

The recommendations are largely based on a systematic review of randomized controlled trials. Whereas a review of such evidence is to be commended, the guideline largely ignores other important evidence that might modulate the way guidelines are formulated [2–5]. The areas of concern discussed below include the scope of guidelines, the position on FRAX, the limited duration of therapy, and the use of anabolic interventions.

Scope

The restricted scope of the ACP guidelines is exemplified in the title that refers to treatment in men and women with osteoporosis. Two definitions of osteoporosis are provided; one, the WHO definition based on the T-score for bone mineral density and the other an individual with a prior fragility fracture. Except for teriparatide and raloxifene (not recommended as first-line treatments), the ACP guideline considers that the evidence is insufficient to recommend treatment of patients with prior fracture with other interventions. Thus, the gateway to treatment is a BMD diagnosis of osteoporosis though no recommendations are provided on who should have a BMD measurement in the first place. The guideline fails in the sense that there is no indication to whom they apply and no reference to any relevant literature.

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The use of BMD as the exclusive gateway to assessment is problematic for many reasons. Problems include the low sensitivity of BMD for fracture prediction [6, 7], the different significance of a given T-score according to age [8], and risks that differ according to latitude [9] socioeconomic prosperity [10] and country [11]. In many countries, intervention thresholds, historically based on the T-score for BMD, have been replaced in recent years by more complete risk assessment tools that take account of the added weight of the risk factors on fracture risk [12–16]. For example, 20 years ago, the European Foundation for Osteoporosis (now the International Osteoporosis Foundation) issued guidelines for the diagnosis and management of osteoporosis [17], shortly followed by those of the Royal College of Physicians in the UK [18]. Both organizations recommended treatment in patients with osteoporosis based on bone mineral density measurements. Prospective patients to be referred for bone densitometry were identified by the presence of clinical risk factors associated with osteoporosis. The guidance utilized risk factors for fracture as an initial step for assessment, but recommended treatment only in individuals with a T-score of − 2.5. Guidelines in the UK [19, 20] and Europe [21, 22] and many other countries [23] now accommodate FRAX as the primary gateway to risk assessment. Others, including the US National Osteoporosis Foundation and American Association of Clinical Endocrinologists include thresholds of fracture risk [24, 25]. Against this shift, the ACP updated guidance, firmly entrenching a T-score treatment threshold of − 2.5 SD, is reminiscent of European and UK guidance some 20 years ago [17, 18].

Review of FRAX

The ACP guidance eschews the use of FRAX and states that there is no evidence from randomized control trials demonstrating a benefit of fracture reduction when FRAX scores are used for treatment decision-making. The argument implies that the beneficial effects of treatment on fracture risk are restricted to patients with osteoporosis. Irrespective of the veracity of the statement, the argument presupposes that high FRAX scores with or without BMD do not identify individuals with low bone mineral density—a supposition that has for several years been shown to be ill-founded [26–28]. An example of the application of the guidelines used by the National Osteoporosis Guideline Group (NOGG) in the UK is given in Table 1, which shows that the case-finding strategy (the use of age-specific intervention thresholds) identifies women with low BMD. Moreover, the conclusion that these drugs only act in BMD-proven osteoporosis is a flawed one, driven by subgroup analyses, most of which are post hoc [29]. Indeed, the relevant question in a more statistically appropriate manner is as follows: is there an interaction between the effect of treatment and baseline BMD? All studies that have examined this for the outcome of vertebral fractures have not shown any impact of baseline BMD on risk reduction during therapy.

The ACP acknowledges that moderate-quality evidence from post hoc analysis of 1 RCT showed no significant interaction between fracture risk as assessed by FRAX and the efficacy of raloxifene for reducing the relative risk for vertebral fractures in women older than 75 years. It neglected to indicate that similar findings for a majority of interventions used in osteoporosis including strontium ranelate [30], raloxifene [31, 32], bazedoxifene [31], clodronate [33], daily and weekly teriparatide [34, 35], abaloparatide [36], denosumab [37] alendronate [38] as well as a basket of interventions used by general practitioners in the UK [39]. Most of these were post hoc but, in the case of denosumab, was a pre-planned analysis. In addition, the "screening for prevention of fractures in older women" (SCOOP) study was a prospective randomized study that demonstrated efficacy for hip fracture in women selected on the basis of hip fracture probability assessed using FRAX [39].

It is axiomatic that different intervention thresholds will identify different patients at different risk. Some examples are given in Table 2 based on the National Health and Nutrition Examination Survey (NHANES) 2005–2008 [40,

Table 1 NOGG strategy applied to women without prior fracture, by age (/1000) [26] with kind permission from Springer Science+Business Media B.V

Age (years)	Number scanned	Number selected	Expected hip fractures	Expected MOF	Mean FN T-score
50	63	22	2	52	− 1.78
55	48	16	2	27	− 2.28
60	59	14	2	17	− 2.67
65	131	38	7	48	− 2.58
70	140	29	8	38	− 2.91
75	89	18	6	23	− 3.35
80	69	15	6	16	− 3.60
85	50	15	7	20	− 3.66
			40	241	

FN femoral neck, *MOF* major osteoporotic fracture (hip, clinical spine, forearm, and proximal humerus), *NOGG* National Osteoporosis Guideline Group

Table 2 Number selected as being above the intervention threshold and the proportion who will fracture over 10 years (mean 10-year fracture probability of major osteoporotic fracture (MOP) and hip fracture) in men and women aged 50 years or more from the NHANES cohort according to different intervention thresholds [41], with kind permission of John Wiley and Sons

Selection	Men			Women		
		% who fracture			% who fracture	
	N	MOF	Hip	*N*	MOF	Hip
None	1959	6.0	1.5	1649	10.2	2.4
FRAX fixed thresholds[a]	266	13.5	6.3	387	21.2	7.9
FRAX at fracture threshold[b]	54	16.3	4.0	144	26.0	9.7
FRAX fixed thresholds + prior fracture[c]	326	12.3	5.3	414	20.5	7.5
FRAX at fracture threshold + prior fracture[c]	121	11.9	2.9	179	23.4	8.2
NOF[d]	330	11.7	4.9	511	17.7	6.2
Prior fracture[c]	71	8.9	2.1	57	19.0	6.1
T-score ≤ -2.5[e]	79	11.2	5.4	298	17.3	6.7
Prior fracture and T-score ≤ -2.5[e]	148	9.9	3.6	335	17.0	6.4

[a] FRAX with 20 and 3% probability thresholds for major fracture and hip fracture respectively

[b] FRAX with age-specific thresholds equivalent to a woman with prior fracture

[c] Prior hip or spine fracture

[d] National Osteoporosis Foundation Guidelines [24]

[e] T-score at proximal femur or lumbar spine

41]. It is of interest that the ACP guideline selects the greater number of patients eligible for treatment than an age-specific FRAX threshold, but the latter identifies a population at much higher risk.

Limited duration of therapy

A serious deficit in the ACP guideline is that it recommends that clinicians treat osteoporotic women with pharmacologic therapy only for 5 years. Such a statement, based on low-quality evidence, has very negative and potential dangerous effects. The recommendation is based on an inadequate interpretation of the long-term studies with bisphosphonates which demonstrate that the incidence of non-vertebral fracture does not differ between patients who continue or discontinue alendronate or zoledronic acid after 5 and 3 years of therapy, respectively [42, 43] The interpretation overlooks the fact that, in the Fracture Intervention Trials with alendronate, there was no significant effect of therapy on non-vertebral fracture risk compared to placebo [44, 45] except in a subgroup of patients with previous vertebral fractures or with hip BMD T-score values ≤ -2.5 [46]. Thus, if alendronate therapy does not reduce non-vertebral fracture risk in the overall set of patients, it is hardly surprising that stopping treatment had no adverse effect on non-vertebral fracture risk. In the case of zoledronic acid after 3 years, the study was hopelessly underpowered to elicit an effect of stopping treatment on this outcome. For both alendronate and zoledronic acid, stopping treatment increases the risk of vertebral fracture [42, 43], a finding that the ACP guideline chose to ignore. The dangers of stopping treatment are obfuscated by the long offset of action of the bisphosphonates but more readily demonstrated with denosumab. Cessation of treatment results in a rapid decrease in bone mineral density and an increase in fracture rate [47–49], whereas continuation of treatment has a progressive benefit for

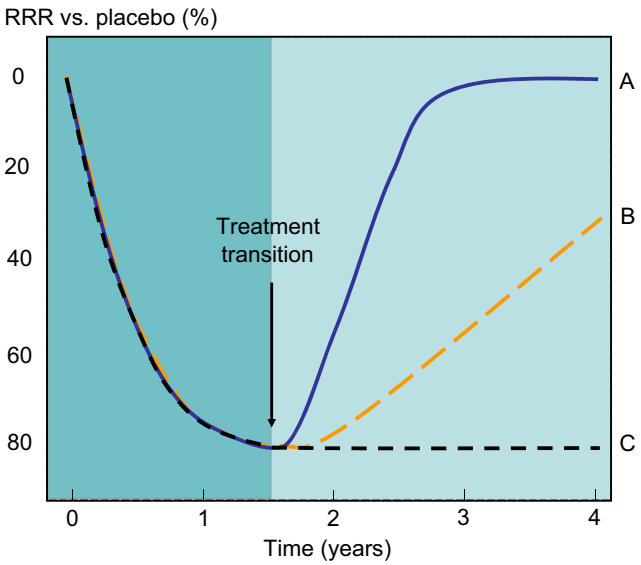

Fig. 1 The effects of a bone-forming agent on the relative fracture risk reduction (RRR) compared with placebo. In scenario A, treatment with a bone-forming agent induces a marked effect on fracture risk over an 18-month exposure compared with placebo. On stopping the bone-forming agent, the effect on fracture wanes off over a similar time interval of 18 months. In scenario C, placebo group remains untreated, whereas the group treated with a bone-forming agent is transitioned to an inhibitor of bone turnover which maintains the efficacy up to 4 years. In scenario B, both the treatment and the placebo groups are treated after the exposure with an inhibitor of bone turnover [adapted from 57]

at least 10 years [50, 51]. In short, the prescription of a fixed treatment interval is inappropriate in osteoporosis [52] as in many other chronic disorders. Ironically, the ACP do not make the same oversight in type 2 diabetes and hyperlipidemia [53].

Missed opportunity for anabolic treatment

The ACP guideline recommends that clinicians offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis. These drugs strengthen trabecular bone by reducing bone turnover but do not rebuild the damaged trabecular architecture. They have less or even no effect on strengthening cortical bone. Perhaps the greatest deficit of the ACP guideline is the dismissive attitude to anabolic treatment such as teriparatide, parathyroid hormone, and abaloparatide. The guideline acknowledges that treatment with teriparatide reduces radiographic vertebral and non-vertebral fractures compared with placebo in postmenopausal osteoporotic women. The position is predicated by the view of the ACP that there are no differences in efficacy between available interventions.

Gains in BMD following treatment with teriparatide and abaloparatide are very substantial compared with the bisphosphonates, SERMs, and denosumab and are expected to be translated in terms of fracture risk reduction. Indeed, in a head-to-head comparative trial, teriparatide has been shown to have superior efficacy than risedronate on vertebral and clinical fractures [54]. The relative risk reduction for clinical vertebral fractures was 56% (95% CI = 32–71%) and that for all clinical fractures 52% (26–68%). In a head-to-head comparison, abaloparatide increased BMD and reduced the risk of non-vertebral fractures more than teriparatide and, indeed, more rapidly [55]. Romosozumab (still an investigational agent) followed after 12 months by alendronate for a further year showed superior efficacy on fracture outcomes compared with alendronate alone, albeit with some concerns over adverse cardiovascular effects [56]. These observations indicate the emergence of a rank order of the efficacy of interventions unappreciated by the ACP.

Given that treatments with anabolic agents are limited to 18–24 months and given that efficacy will wane once treatment is stopped, the real potential of the anabolic treatments is whether their greater effect on BMD and fracture can be maintained with the inhibitors of bone turnover once treatment is stopped (Fig. 1) [57]. In the case of abaloparatide, efficacy was shown in an 18-month placebo control study with significant reductions in risk of vertebral, non-vertebral, clinical, and major osteoporotic fractures compared with placebo [55]. Efficacy was maintained with a subsequent 24-month treatment with alendronate (70 mg weekly) given to patients previously taking or abaloparatide or placebo (scenarios A and B in Fig. 1). The relative risk reduction for vertebral fracture seen in the placebo control phase of the study (RRR = 86%) was maintained in the extension phase of the trial (RRR = 84%). A sustained effect was also seen for non-vertebral fracture, major osteoporotic fracture, and hip fracture risk reduction [58].

The advent of anabolic therapy that can be sustained past the duration of exposure opens a new era in the management of osteoporosis, particularly those patients at imminent risk [59].

Conclusion

We recognize that several papers cited in this editorial postdate the review of the ACP though the opinions were well rehearsed. Notwithstanding, the ACP guideline appears outdated even at its time of publication, lacking in scope due to the endorsement of treatment based upon T-scores, rather than fracture risk assessment and in failure to adequately consider anabolic therapies.

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Compliance with ethical standards

Conflicts of interest JAK reports grants from Amgen, Eli Lilly, and Radius Health; non-financial support from Medimaps and Asahi; and other support from AgNovos. JAK is the architect of FRAX but has no financial interest. Professor Cooper reports personal fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda, and UCB. RR has received consulting fees or advisory board fees from Radius Health, Labatec, Danone, and Nestlé. J-YR has received advisory board or speaker fees from Asahi-Kasei, Eli Lilly, IBSA-Genévrier, Nycomed-Takeda, PharmEvo, Radius Health, Roche, Servier, UCB, Will Pharma, and Zodiac.

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