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6

Secondary fracture prevention: Drug treatment, fall prevention and nutrition requirements

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A B S T R A C T

In view of the high imminent risk for subsequent fractures, evaluation as early as possible after the fracture will result in early decisions about drug treatment, fall prevention and nutritional supplements.

Drug treatment includes anti-resorptive and bone forming agents. Anti-resorptive therapy with broad spectrum fracture prevention and early anti-fracture effects are the first choice. In patients with multiple or severe VFs, the bone forming agent teriparatide should be considered.

Adequate calcium and vitamin D are needed in all patients, together with appropriate nutrition, including adequate protein intake.

Introduction: the concept and level of imminent fracture risk

A recent fracture in postmenopausal women and in men older than 50 years is a clinically very important warning signal for an increased risk of subsequent fractures [1], and even for increased

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mortality [2]. Fracture risk in women and men with a prior fracture is double the risk of those without prior fracture [1], but this increased risk is not constant over time. The increase is up to 3–12 times higher immediately following any fracture [3], waning off thereafter, with a persisting increased risk up to 10 years later [4].

The short-term high risk of subsequent fracture has been labelled as an "imminent" fracture risk [4–6]. Imminent fracture risk refers to both the timing of this risk (at short term, i.e. within one to two years) and the higher level of the imminent risk compared to long-term risk. The imminent fracture risk is reported as absolute risk (AR) (or incidence rate). This was initially reported for the risk of any fracture after hospitalisation for vertebral fractures (VFs) (Table 1) [7].

The AR was higher at short term than at long term, indicating the imminence of fracture risk. The imminent fracture risk increased with age and was higher in women than in men.

High imminent fracture risk has also been shown for recurrent morphometric VFs [8] and for recurrent non-vertebral fractures [9–11].

Based on these epidemiologic data on imminent subsequent fracture risk, it has been recommended that secondary fracture prevention should be started as early as possible after a fracture has occurred in high-risk patients [5,6]. The fracture liaison service (FLS) and ortho-geriatric care after hip fracture are considered the most effective organisational approaches for secondary fracture prevention [5,12] and is further discussed elsewhere in this issue of the journal.

Drug treatment to reduce subsequent fracture risk

Fracture risk reduction in randomised controlled trials (RCTs) in patients with a prior fracture

The inclusion criteria in the pivotal placebo-controlled RCTs with fracture reduction as primary endpoint varied between studies [13–23]. It is important to realize that no RCTs are available with a recent fracture as an inclusion-criterion, with the exception of one study with zoledronate (versus placebo) that included only patients with a recent hip fracture [22] and one with teriparatide (versus risedronate) that included patients with a recent clinical vertebral fracture [24]. Interestingly, the majority of pivotal phase 3 RCTs (7 out of 10) have enrolled individuals with as inclusion criterion a prevalent VF (of unknown date) and/or a low BMD, of which five also included patients with a VF and osteopenia. Other RCTs included a minority of patients with a fracture history. All anti-resorptive treatments decreased the risk of VFs. Reductions of non-vertebral, clinical and hip fractures have only been demonstrated with alendronate, risedronate, zoledronate and denosumab.

Based on the results of pivotal RCTs and its inclusion criteria, the following patient categories with a recent fracture are candidate for anti-resorptive drugs: those with a recent hip fracture, a prevalent VF, or a T-score ≤ -2.5, which represent around 50% of FLS patients [25]. As patients with a recent fracture have an increased risk of subsequent VFs and NVFs, the first choice of drug treatment are drugs that have been shown to prevent a broad spectrum of fractures, including VF, NVF and hip fractures (alendronate, risedronate, zoledronate and denosumab).

In postmenopausal women with severe osteoporosis (two moderate or one severe VF) in combination with any T-score −1.5 [24], and comped to daily risedronate, teriparatide reduced the risk of VFs

Table 1
Incidence rates of subsequent fracture at 6 months and at 4 years after hospitalisation for VF [7].

Subjects	Population	After fracture	
		at 6 months	at 4 year
Women			
60 yrs	0.5%	9.5%	4.5%
85 yrs	5.5%	21.5%	10.2%
Men			
60 yrs	0.3%	8.1%	2.0%
85 yrs	2.9%	16.0%	4.0%

and clinical fractures, also in the prespecified subgroups of patients with a history of a recent clinical VF, history of NVF, previous treatment with bisphosphonates, and in all age tertiles [26]. Therefore, teriparatide may be considered as a first-choice agent in such patients with a recent fracture. The strategy to build up new bone with a bone forming agent in patients with multiple or severe VFs and low BMD, is much more attractive than the use of bisphosphonates, who stabilize or have a limited effect on BMD. Since the cost of teriparatide is higher than that of anti-resorptives, some worries arise about the economic consequences. In patients visiting the FLS, around 5% shown to be candidates for teriparatide [25].

In a review of guidelines for treatment in 35 countries worldwide, a prior fracture was considered an indication for treatment (without any other risk evaluation) after any fracture in 13 guidelines, after a VF (in 20 countries), after a hip fracture (in 18), or after other fractures (in 12). In some guidelines, and depending on the sentinel fracture location, additional age (in 18), BMD (in 15) and/or FRAX (in 5) criteria were included. In 15 guidelines men were also included [27].

In view of the high imminent fracture risk, drug treatment should be started as early as possible after fracture in high risk patients and should also have an early effect on subsequent fractures. Early fracture reduction has been shown for VFs and NVFs depending on the drug (Table 2).

Correction of secondary osteoporosis and other metabolic bone diseases

Up to 50% of FLS patients have secondary osteoporosis and other metabolic bone diseases, of which 27% are newly diagnosed. Treatment of underlying diseases that are associated with fracture risk has been shown to reduce the risk of fractures, such as in patients with primary hyperparathyroidism, secondary hyperparathyroidism due to vitamin D deficiency, idiopathic hypercalciuria, hyperthyroidism and hypercortisolism [34]. These underlying diseases should therefore be evaluated and treated adequately.

Cohort studies on drug treatment initiation at the FLS

Despite the strengths of RCTs, they also have limitations, as their results do not reflect the true effects of anti-osteoporosis treatments in real-world patients and actual practice settings [35,36]. On the other hand, observational studies, can give information using large data sets to study the effectiveness (under real-world conditions) and with longer follow-up, with inclusion of more complex and older patients, and larger patient numbers. Observational studies have challenges, including patient selection and immortality bias, and the conditions of collecting data during follow up [35,36].

Several cohort studies evaluated the effect of FLS on subsequent fracture and mortality risk. In an earlier review of 22 FLS studies, only three studies reported a lower subsequent fracture rate related to FLS care [37]. The results on fracture incidence were variable, showing a reduction of fractures after hip fracture [38] and after clinical fractures [39], questionable results [40,41], no fracture reduction [42], or

Table 2
Earliest reported fracture reduction (within 24 months) during drug treatment in pivotal RCTs or post-hoc analyses of RCTs and in observational studies (in months) [24,28–33].

RCT	radiographic VF	NVF	clinical fracture
Versus placebo			
Zoledronate	12		12
Risedronate	6	6	
Alendronate	24	24	
Teriparatide	7	6	
Denosumab	12		
Abaloparatide	19	18	18
Romosozumab	12		12
Head-to-head comparisons			
Romosozumab vs alendronate	12		12
Teriparatide vs risedronate	12		24

even an increased fracture risk [43]. The reasons for these discrepancies are unclear but could be related to differences in adherence to therapy, longer survival, immortal time bias, confounding by indication or other unknown confounders.

Effect of drug treatment on mortality

In the pivotal RCTs with BPs, only zoledronate after hip fracture demonstrated reduced mortality [22,44]. This could reflect the strong effectivity of zoledronate, but also that the hip fracture cohort had a higher mortality risk at baseline compared to other studies. In addition, several observational studies indicate that patients treated with nitrogen-containing bisphosphonates could have a longer survival [12,39,43–47].

New treatments

Abaloparatide is a modified 1–34 amino terminal fragment of PTH-related peptide has not been studied after a recent fracture and is not reviewed because it has only been approved by FDA in the US, but not by EMA in Europe.

Romosozumab is a unique monoclonal antibody that binds sclerostin, increases bone formation and decreases bone resorption [32,33,48]. The superiority of romosozumab during one year, followed by two years alendronate as compared to three years alendronate in patients with VF and low BMD or a recent hip fracture opens another way to start bone forming therapy in such high-risk patients with a recent fracture.

Remarkably, while in FRAME no cardiovascular risk signals were found, during the first year of ARCH, significantly more ischemic coronary events were reported (0.8% with romosozumab versus 0.3% with alendronate, RR: 2.6), but during the 2.7 years of the whole study the differences were not significant (1.5% vs 1.0%, respectively). The reasons of this imbalance are unclear, but it should be noted that substantially more participants had one or more cardiovascular risk factors at baseline in ARCH than in FRAME. Romosozumab has currently been approved by the Food and Drug Administration (FDA in the US) and in Japan, and currently submitted to the European Medicines Agency (EMA) in Europe.

Fall prevention programs after a recent fracture

Falls and fractures following a fall

Similar to the finding that a recent fracture is a warning signal for an imminent fracture risk, a recent fall in elderly is a warning signal for an imminent fall and fracture risk.

There are potentially over 400 risk factors for falling [49]. In the medical history, a fall during the last year is the strongest predictor of subsequent falls, thus for imminent risk of subsequent falls [50].

A previous fall of any date after 50 years is incorporated as a risk factor in Garvan and qFracture algorithm, but not in FRAX [51–54]. Therefore, in subjects with a prior fall the calculated fracture risk is higher by using Garvan than FRAX [55].

In the MrOs study, past falls in men predicted incident fractures independently of FRAX probability, confirming the value of fall history in fracture risk assessment [56]. In addition to FRAX, fall history and BMD, measures of physical performance and muscle strength were independent predictors of fracture risk [57].

The high imminent risk of NVF after a recent fracture and of repeat hip fractures indicates that falls are the most frequent provocative factor for subsequent fractures, as found after a distal radius or hip fracture [58–60].

Behavioral and environmental fall prevention strategies that prevent falls

Many fall prevention programs have been developed. These were recently reviewed in several meta-analyses (Table 3) [61–69]. They varied in population selection (community dwelling, institutionalized or

both combined, subacute hospital setting, older than 60 or 65 years) and the selected fall prevention strategies (behavioral and environmental strategies and calcium and vitamin D supplementation). The evaluated behavioral and environmental fall prevention strategies that have been shown to reduce the risk of falls in these analyses according to community-based or institutionalized subjects are shown in Table 3. The effects of these interventions varied between strategies, between their effect on fracture rate or fracture risk, and whether they were studied in the community or in care facilities.

In another study in 173 patients with a recent hip fracture, extended physiotherapy was successful in reducing falls compared to usual care [70]. The effects of calcium and vitamin D supplements will be discussed in depth the next part of this chapter.

Prevention of fall-related fractures have been only rarely reported in the above-mentioned fall prevention meta-analyses that included between 4000 [67] and 160,000 subjects [64]. In trials of behavioral and environmental fall prevention reporting fracture outcomes, they were only successful in reducing fall rate, but not for the number of fractures or the number of patients with fractures when analyzing multifactorial strategies. In two meta-analyses of studies (including less than 1000 community living subjects), exercise reduced the risk of fractures in older people [69] and subjects younger than 75 years old [67]. In the Cochrane review it was concluded that multifactorial interventions may reduce the rate of falls compared with usual care or attention control, however with little or no effect on other fall-related outcomes [66].

Need of nutritional supplements after fracture

The calcium and vitamin D tandem

The total dietary calcium content of average diet in most societies is between 500 and 800 mg/day and vitamin D deficiency is endemic worldwide [71]. It is therefore not surprising that also patients presenting at the FLS report insufficient calcium intake and have low serum levels of 25(OH)D. In a review of 33 FLS centers, the reported total mean daily calcium intake at entry of the FLS was 759–912 mg/day and less than 1200 mg/day in >85% of patients [72], regardless of age, sex, BMD or sentinel fracture [73]. Mean serum vitamin D ranged between 44 and 68 nmol/L and serum vitamin D levels <50 nmol/L were found in 42%–72% of patients. Mean serum vitamin D was lower in patients with a hip than in non-hip fractures (35 vs. 48 nmol/L, respectively, $p = .019$). The prevalence of vitamin D < 50 nmol/L was similar for men and women, for patients aged <75 years and those aged ≥75 years, and for patients with osteoporosis, osteopenia and a normal BMD [73,74]. Thus, in patients attending the FLS, low calcium intake and low serum 25(OH)D levels are highly prevalent. This proportion could be even higher in patients not attending the FLS, especially in the elderly, of whom many even when invited do not attend the FLS [75].

Nutritional supplement studies differ from drug studies in several ways [76]. First, once an adequate concentration has been achieved, additional intake has no effect.

Second, nutrition components often act in concert [76]. In the context of bone physiology, calcium intake and vitamin D should be considered as an unavoidable tandem [77].

The effect of calcium and vitamin D supplements on fall and fracture risk is a complicated issue. The many meta-analyses included different doses and combinations of calcium and vitamin D monotherapy, combinations or pooling studies of vitamin D with and without calcium), different populations (community living, institutionalized or remaining in nursing homes, malnourished subjects), different outcomes (number of falls and/or fractures, repeated falls, number of subjects with falls and/or fractures, number of falls per subject) and exclusion of high risk groups (e.g. institutionalized subjects, or "not knowing to have osteoporosis or vitamin D deficiency"). In addition, evaluating calcium intake with a standardized short calcium intake list is not very reliable [78,79] and calcium absorption not only depends on its amount, but also varies according to being ingested as food or as a salt (carbonate, citrate), other food components and the location of absorption [80].

Mono-supplements with calcium have no effect on fall or fracture risk [81]. Mono-supplementation with vitamin D reduced the risk of falls and fractures in subjects with a high risk of vitamin D deficiency, but its effect in community-living subjects remains inconclusive [82].

Table 3
Effect of behavioral and environmental fall prevention strategies on falls and fractures in community dwelling subjects and in care and hospital settings.

	Fall rate (falls/person-years)		Fall risk (number of fallers)	Fracture risk
	Any fall	Injurious fall		
Multifactorial interventions	−24% [69], −23% [66], −21% [63], −36% [62]		NS [63,66,69]	NS [66]
Multi-component intervention, including exercise	−26% [66]		−18% [66]	very low quality of evidence [66]
Multiple-component group exercise	−29% [69]		−15% [69]	
Multiple-component home-based exercise	−32% [69]		−22% [69]	
Tai Chi	NS [69]		−29% [69]	
Exercise	NS [63]	−30% [67], −49% [64]	−11%, injurious fall risk: 19% [63]	−66% [69], −61% [67]
Exercise + vision		−83% [64]		
Exercise + vision + environment		−70% [64]		
Education + exercise	NS [62]			
Exercise + hazard modification	NS [62]			
Home safety	−19% [69]		−12% [69]	
Care facilities				
Exercise				
Care	NS [61]		NS [61]	
Multifactorial interventions				
Care	NS [61]		NS [61]	
Hospital	−31% [61]		Inconclusive [61]	

The effect of supplementation with the combination of 800 IU vitamin D/day with calcium on falls has been shown in subjects with vitamin D deficiency [69], but not in meta-analyses on supplements of vitamin D with and without calcium supplements [63,83].

The effect of supplementation with the combination of 800 IU vitamin D/day with calcium on fractures is considered significant for hip, NVF and any fracture, depending on the meta-analysis. In all RCTs calcium and vitamin D supplements were provided, and adequate intake of calcium and vitamin D is indicated in all patients receiving anti-resorptive or bone forming drugs. Such supplements are also necessary to prevent hypocalcemia after starting zoledronate or denosumab, especially in patients with malnutrition, malabsorption (including after gastric bypass) and chronic kidney disease.

Harvey et al. concluded that for fracture prevention, calcium and vitamin D supplements should target individuals at high risk of deficiencies, and patients receiving anti-osteoporosis drugs [84]. In Table 4, suggestions for adequate calcium and vitamin D supplementation for all patients with a recent fracture are indicated.

Trials reporting compliance rates of >80% showed a greater treatment effect on reducing all types of fracture [85]. Compliance for calcium and vitamin D are indeed a problem. In a prospective study at the FLS with 800IU D/day, 27% of patients did not reach a serum 25(OH)D $\geq$ 50 nmol/L after 11 months. Possible explanations could be a low compliance, but also malabsorption such as in celiac disease, or genetic variability in vitamin D receptor polymorphisms or vitamin D binding protein [86].

Table 4
Suggestions for optimizing calcium and vitamin D intake in all patients at the after a recent fracture [89].

- Optimizing of total calcium intake towards 1000–1200 mg/day	
no diary products[a]	+4 diary products or 1000 mg calcium supplement
1–2 diary products/day	+2 diary products/day or +500 mg calcium supplement
3–4 diary products/day	no supplementation necessary
- Vitamin D supplement of 800 IU/day	

[a] Dairy product = 200 ml of milk or yoghurt or 1 slice of cheese.

Several side effects have been reported with calcium and/or vitamin D supplementation. The safety of calcium with vitamin D supplements (in terms of gastrointestinal tolerance, kidney stones and potential cardiovascular side effects) is still a matter of debate [83]. However, in several of the included studies of Bolland et al., calcium supplements resulted in a total calcium intake largely exceeding the daily dose of 1000–1200 mg/day [87,88]. On the other hand, Abrahamson concluded that the combination of calcium and vitamin D has shown the strongest anti-fracture benefits but also the strongest suspicion of renal and cardiovascular potential for harm and that further studies are needed to resolve this controversy [81].

Other nutritional supplements

Several studies have identified protein as a key nutrient for elderly adults [90]. Low protein intake is frequently found in elderly [91]. In a recent consensus paper, Rizzoli et al. concluded that there is no adverse effect of higher protein intakes on bone, with even benefits in attenuating age-related bone loss and reducing hip fracture risk [90,92,93].

After a recent hip fracture, there is limited evidence that oral multi-nutrient supplements started before or soon after surgery prevent complications within the first 12 months after hip fracture and very low-quality evidence that oral supplements reduce unfavorable outcome [94].

Neelemaat et al. reported that a combination of protein and vitamin D reduced the risk of falls in malnourished older adults [95].

The acid load accompanying modern diets may have adverse effects on bone and muscle metabolism that can be reversed with alkaline salts [96]. No direct evidence was found of acid load from a balanced diet on osteoporosis progression, fragility fractures or altered bone strength [97].

In a post-hoc analysis of the WHI study, higher adherence to a Mediterranean diet was associated with a lower risk for hip fractures [98].

Milk and its derivates cheese and yogurt provide a complex source of essential nutrients, including protein, calcium, phosphorus, potassium, and magnesium and are regularly fortified with vitamin D, thus contributing to bone health [90]. In the Framingham Original Cohort, greater intakes of milk and milk plus yogurt were associated with a non-significant 40% lower risk for hip fracture in older adults [99].

No data on the effect of these and other nutritional supplements (such as phosphorus, potassium, and other macro- and micro-nutrients that are important for bone health) on falls and fractures were found in patients with a recent fracture.

Summary

In view of the high imminent risk for subsequent fractures, early evaluation and treatment decisions are indicated in women and men older than 50 years with a recent fracture.

Treatment decisions include starting anti-resorptive drug treatment as a first choice in high-risk patients. In patients with multiple or severe VFs, the bone forming agent teriparatide should be considered. All patients with a recent fracture need adequate calcium and vitamin D intake, appropriate nutrition advices and fall prevention in patients at high risk of falls.

Practice points

- In women and men older than 50 years, the imminent fracture risk is highest after a recent vertebral and non-vertebral fracture, and is also high after a vertebral or non-vertebral fracture of unknown date.
- Secondary fracture prevention should start early after a fracture has occurred.
- It includes drug treatment in high-risk patients, fall prevention in those with a high fall risk, adequate calcium and vitamin D intake and adequate nutrition.
- From an organisational perspective, the fracture liaison service (FLS) and ortho-geriatric care after hip fracture are considered the most effective approaches for secondary fracture prevention.

Research agenda

Uncertainties about reducing the imminent fracture risk that need to be resolved in patients 50 years and older with a recent fracture include:

- What is the effect on imminent fracture, mortality and quality of life of:
  - o sequential therapy with bone-forming and anti-resorptive agents?
  - o immediate fall prevention
  - o nutritional supplements
- What is the cost/effectiveness of immediate versus delayed secondary fracture prevention in real-world circumstances?
- What is the supplementary cost/effectiveness of secondary fracture prevention in the fracture liaison service in real-world circumstances?

Conflicts of interest

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