Secondary fracture prevention

Citation for published version (APA):

Geusens, P., Lems, W. F., Bours, S., & Bergh, J. P. V. (2019). Secondary fracture prevention: Drug treatment, fall prevention and nutrition requirements. *Best Practice & Research in Clinical Rheumatology*, 33(2), 290-300. <https://doi.org/10.1016/j.berh.2019.04.005>

Document status and date:

Published: 01/04/2019

DOI:

[10.1016/j.berh.2019.04.005](https://doi.org/10.1016/j.berh.2019.04.005)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

6

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

P. Geusens^{a, b, *}, W.F. Lems^c, S. Bours^a, J.P. vd Bergh^{b, d, e}

^a Department of Internal Medicine, Subdivision Rheumatology, CAPHRI Care and Public Health Research Institute, Maastricht University Medical Centre +, P.O. Box 5800, AZ Maastricht, 6202, the Netherlands

^b Biomedical Research Centre, Hasselt University, Agoralaan, Gebouw D, Diepenbeek, 3590, Belgium

^c Amsterdam Rheumatology & Immunology Center, Amsterdam, the Netherlands

^d Department of Internal Medicine, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre +, P.O. Box 5800, AZ Maastricht, 6202, the Netherlands

^e Department of Internal Medicine, VieCuri Medical Centre, Tegelseweg 210, BL Venlo, 5912, the Netherlands

A B S T R A C T

Keywords:

Imminent fracture risk
Drug treatment
Fall prevention
Nutrition

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.

© 2019 Elsevier Ltd. All rights reserved.

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

* Corresponding author. Department of Internal Medicine, Subdivision Rheumatology, CAPHRI Care and Public Health Research Institute, Maastricht University Medical Centre +, P.O. Box 5800, AZ Maastricht, 6202, the Netherlands.

E-mail addresses: piet.geusens@scarlet.be (P. Geusens), WF.Lems@vumc.nl (W.F. Lems), s.bours@mumc.nl (S. Bours), jvdbergh@viecuri.nl (J.P. vd Bergh).

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
Romozosumab	12		12
Head-to-head comparisons			
Romozosumab 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] –83% [64] –70% [64]	–11%, injurious fall risk: 19% [63]	–66% [69], –61% [67]
Exercise + vision				
Exercise + vision + environment				
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 dairy products ^a	+4 dairy products or 1000 mg calcium supplement
1–2 dairy products/day	+2 dairy products/day or +500 mg calcium supplement
3–4 dairy 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 derivatives 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:
 - sequential therapy with bone-forming and anti-resorptive agents?
 - immediate fall prevention
 - 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

None.

Funding

None.

References

- [1] Klotzbuecher CM, Ross PD, Landsman PB, Abbott 3rd TA, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res* 2000;15(4):721–39.
- [2] Tran T, Bliuc D, Hansen L, Abrahamsen B, van den Bergh J, Eisman JA, et al. Persistence of excess mortality following individual non-hip fractures: a relative survival analysis. *J Clin Endocrinol Metab* 2018 Sep 1;103(9):3205–14.
- [3] van Geel TA, van Helden S, Geusens PP, Winkens B, Dinant GJ. Clinical subsequent fractures cluster in time after first fractures. *Ann Rheum Dis* 2009;68(1):99–102.
- [4] Kanis JA, Johansson H, Oden A, Harvey NC, Gudnason V, Sanders KM, et al. Characteristics of recurrent fractures. *Osteoporos Int* 2018;29(8):1747–57.
- [5] Roux C, Briot K. Imminent fracture risk. *Osteoporos Int* 2017;28(6):1765–9.
- [6] Ferrari S, Reginster JY, Brandi ML, Kanis JA, Devogelaer JP, Kaufman JM, et al. Unmet needs and current and future approaches for osteoporotic patients at high risk of hip fracture. *Arch Osteoporos* 2016;11(1):37.
- [7] Johnell O, Oden A, Caullin F, Kanis JA. Acute and long-term increase in fracture risk after hospitalization for vertebral fracture. *Osteoporos Int* 2001;12(3):207–14.
- [8] Siris ES, Genant HK, Laster AJ, Chen P, Misurski DA, Kregge JH. Enhanced prediction of fracture risk combining vertebral fracture status and BMD. *Osteoporos Int* 2007;18(6):761–70.
- [9] Balasubramanian A, Zhang J, Chen L, Wenkert D, Daigle SG, Grauer A, et al. Risk of subsequent fracture after prior fracture among older women. *Osteoporos Int* 2019;30(1):79–92.
- [10] Gehlbach S, Saag KG, Adachi JD, Hooven FH, Flahive J, Boonen S, et al. Previous fractures at multiple sites increase the risk for subsequent fractures: the Global Longitudinal Study of Osteoporosis in Women. *J Bone Miner Res* 2012;27(3):645–53.
- [11] Banefelt J, Akesson KE, Spangeus A, Ljunggren O, Karlsson L, Strom O, et al. Risk of imminent fracture following a previous fracture in a Swedish database study. *Osteoporos Int* 2019 Mar;30(3):601–9.
- [12] Hawley S, Javaid MK, Prieto-Alhambra D, Lippett J, Sheard S, Arden NK, et al. Clinical effectiveness of orthogeriatric and fracture liaison service models of care for hip fracture patients: population-based longitudinal study. *Age Ageing* 2016; 45(2):236–42.
- [13] Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet* (London, Engl) 1996;348(9041):1535–41.
- [14] Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998;280(24):2077–82.
- [15] Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. 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* 1999;282(14):1344–52.
- [16] Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. 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* 2000;11(1):83–91.

- [17] McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med* 2001;344(5):333–40.
- [18] Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. 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* 1999;282(7):637–45.
- [19] Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344(19):1434–41.
- [20] Chesnut 3rd CH, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 2004;19(8):1241–9.
- [21] Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356(18):1809–22.
- [22] Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007;357(18):1799–809.
- [23] Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361(8):756–65.
- [24] Kendler DL, Marin F, Zerbini CAF, Russo LA, Greenspan SL, Zikan V, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet (London, Engl)* 2017.
- [25] van der Velde RY, Bours SPG, Wyers CE, Lems WF, Geusens P, van den Bergh JPW. Effect of implementation of guidelines on assessment and diagnosis of vertebral fractures in patients older than 50 years with a recent non-vertebral fracture. *Osteoporos Int* 2017;28(10):3017–22.
- [26] Geusens P, Marin F, Kendler DL, Russo LA, Zerbini CA, Minisola S, et al. Effects of teriparatide compared with risedronate on the risk of fractures in subgroups of postmenopausal women with severe osteoporosis: the VERO trial. *J Bone Miner Res* 2018;33(5):783–94.
- [27] El-Hajj Fuleihan G, Chakhtoura M, Cauley JA, Chamoun N. Worldwide fracture prediction. *J Clin Densitom* 2017;20(3):397–424.
- [28] Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int* 2008;19(6):733–59.
- [29] Vestergaard P, Mosekilde L, Langdahl B. Fracture prevention in postmenopausal women. *BMJ Clin Evid* 2011;2011.
- [30] Lindsay R, Krege JH, Marin F, Jin L, Stepan JJ. Teriparatide for osteoporosis: importance of the full course. *Osteoporos Int* 2016;27(8):2395–410.
- [31] Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. *JAMA* 2016;316(7):722–33.
- [32] Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med* 2016;375(16):1532–43.
- [33] Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med* 2017;377(15):1417–27.
- [34] Bours SP, van den Bergh JP, van Geel TA, Geusens PP. Secondary osteoporosis and metabolic bone disease in patients 50 years and older with osteoporosis or with a recent clinical fracture: a clinical perspective. *Curr Opin Rheumatol* 2014;26(4):430–9.
- [35] Fahms J, Geusens P, van den Bergh JP. The emperor's new clothes: “what randomized controlled trials don't cover”. *J Bone Miner Res* 2018 Aug;33(8):1394–6.
- [36] Alarkawi DA S, Bliuc D, Center J, Prieto-Alhambra D. The challenges and opportunities of pharmacoepidemiology in bone diseases. *JBMR Plus* 2018;2(4):187–94.
- [37] de Bruin IJA, Wyers CE, van den Bergh JPW, Geusens P. Fracture liaison services: do they reduce fracture rates? *Ther Adv Musculoskel Dis* 2017;9(7):157–64.
- [38] Hawley S, Leal J, Delmestri A, Prieto-Alhambra D, Arden NK, Cooper C, et al. Anti-osteoporosis medication prescriptions and incidence of subsequent fracture among primary hip fracture patients in England and Wales: an interrupted time-series analysis. *J Bone Miner Res* 2016;31(11):2008–15.
- [39] van Geel T, Bliuc D, Geusens PPM, Center JR, Dinant GJ, Tran T, et al. Reduced mortality and subsequent fracture risk associated with oral bisphosphonate recommendation in a fracture liaison service setting: a prospective cohort study. *PLoS One* 2018;13(6):e0198006.
- [40] Bawa HS, Weick J, Dirschl DR. Anti-Osteoporotic therapy after fragility fracture lowers rate of subsequent fracture: analysis of a large population sample. *J Bone Jt Surg Am* 2015;97(19):1555–62.
- [41] Ong KL. Can't Catch a Break: try Using Anti-Osteoporotic Therapy: commentary on an article by Harpreet S. Bawa, MD, et al.: “Anti-osteoporotic therapy after fragility fracture lowers rate of subsequent fracture: analysis of a large population sample”. *J Bone Jt Surg Am* 2015;97(19):e65.
- [42] Nakayama A, Major G, Holliday E, Attia J, Bogduk N. Evidence of effectiveness of a fracture liaison service to reduce the re-fracture rate. *Osteoporos Int* 2016;27(3):873–9.
- [43] Brozek W, Reichardt B, Zwerina J, Dimai HP, Klaushofer K, Zwettler E. Antiresorptive therapy and risk of mortality and refracture in osteoporosis-related hip fracture: a nationwide study. *Osteoporos Int* 2016;27(1):387–96.
- [44] Sattui SE, Saag KG. Fracture mortality: associations with epidemiology and osteoporosis treatment. *Nat Rev Endocrinol* 2014;10(10):592–602.
- [45] Bolland MJ, Grey AB, Gamble GD, Reid IR. Effect of osteoporosis treatment on mortality: a meta-analysis. *J Clin Endocrinol Metab* 2010;95(3):1174–81.
- [46] Leal J, Gray AM, Hawley S, Prieto-Alhambra D, Delmestri A, Arden NK, et al. Cost-effectiveness of orthogeriatric and fracture liaison service models of care for hip fracture patients: a population-based study. *J Bone Miner Res* 2017;32(2):203–11.
- [47] Beaupre LA, Morrish DW, Hanley DA, Maksymowych WP, Bell NR, Juby AG, et al. Oral bisphosphonates are associated with reduced mortality after hip fracture. *Osteoporos Int* 2011;22(3):983–91.

- [48] Canalis E. Management of endocrine disease: novel anabolic treatments for osteoporosis. *Eur J Endocrinol* 2018;178(2): R33–44.
- [49] Masud T, Morris RO. Epidemiology of falls. *Age Ageing* 2001;30(Suppl. 4):3–7.
- [50] Lusardi MM, Fritz S, Middleton A, Allison L, Wingood M, Phillips E, et al. Determining risk of falls in community dwelling older adults: a systematic review and meta-analysis using posttest probability. *2001 J Geriatr Phys Ther* 2017;40(1):1–36.
- [51] Kanis JA, Harvey NC, Johansson H, Oden A, Leslie WD, McCloskey EV. FRAX update. *J Clin Densitom – Off J Int Soc Clin Densitom* 2017;20(3):360–7.
- [52] Leslie WD, Lix LM. Comparison between various fracture risk assessment tools. *Osteoporos Int* 2014;25(1):1–21.
- [53] Kanis JA, Harvey NC, Johansson H, Oden A, McCloskey EV, Leslie WD. Overview of fracture prediction tools. *J Clin Densitom – Off J Int Soc Clin Densitom* 2017;20(3):444–50.
- [54] Edwards BJ. Osteoporosis risk calculators. *J Clin Densitom – Off J Int Soc Clin Densitom* 2017;20(3):379–88.
- [55] van Geel TA, Huntjens KM, van den Bergh JP, Dinant GJ, Geusens PP. Timing of subsequent fractures after an initial fracture. *Curr Osteoporos Rep* 2010;8(3):118–22.
- [56] Harvey NC, Oden A, Orwoll E, Lapidus J, Kwok T, Karlsson MK, et al. Falls predict fractures independently of FRAX probability: a meta-analysis of the osteoporotic fractures in men (MrOS) study. *J Bone Miner Res* 2018;33(3):510–6.
- [57] Harvey NC, Oden A, Orwoll E, Lapidus J, Kwok T, Karlsson MK, et al. Measures of physical performance and muscle strength as predictors of fracture risk independent of FRAX, falls and BMD: a meta-analysis of the Osteoporotic Fractures in Men (MrOS) Study. *J Bone Miner Res* 2018 Dec;33(12):2150–7.
- [58] Dewan N, MacDermid JC, Grewal R, Beattie K. Risk factors predicting subsequent falls and osteoporotic fractures at 4 years after distal radius fracture—a prospective cohort study. *Arch Osteoporos* 2018;13(1):32.
- [59] Stenvall M, Olofsson B, Lundstrom M, Svensson O, Nyberg L, Gustafson Y. Inpatient falls and injuries in older patients treated for femoral neck fracture. *Arch Gerontol Geriatr* 2006;43(3):389–99.
- [60] Harwood RH, Sahota O, Gaynor K, Masud T, Hosking DJ. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: the Nottingham Neck of Femur (NONOF) Study. *Age Ageing* 2004;33(1):45–51.
- [61] Cameron ID, Gillespie LD, Robertson MC, Murray GR, Hill KD, Cumming RG, et al. Interventions for preventing falls in older people in care facilities and hospitals. *Cochrane Database Syst Rev* 2012;12:Cd005465.
- [62] Cheng P, Tan L, Ning P, Li L, Gao Y, Wu Y, et al. Comparative effectiveness of published interventions for elderly fall prevention: a systematic review and network meta-analysis. *Int J Environ Res Publ Health* 2018;15(3).
- [63] Guirguis-Blake JM, Michael YL, Perdue LA, Coppola EL, Beil TL. Interventions to prevent falls in older adults: updated evidence report and systematic review for the US preventive services task force. *JAMA* 2018;319(16):1705–16.
- [64] Tricco AC, Thomas SM, Veroniki AA, Hamid JS, Cogo E, Striffler L, et al. Comparisons of interventions for preventing falls in older adults: a systematic review and meta-analysis. *JAMA* 2017;318(17):1687–99.
- [65] Grossman DC, Curry SJ, Owens DK, Barry MJ, Caughey AB, Davidson KW, et al. Interventions to prevent falls in community-dwelling older adults: US preventive services task force recommendation statement. *JAMA* 2018;319(16):1696–704.
- [66] Hopewell S, Adedire O, Copsey BJ, Boniface GJ, Sherrington C, Clemson L, et al. Multifactorial and multiple component interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev* 2018;7:Cd012221.
- [67] El-Khoury F, Cassou B, Charles MA, Dargent-Molina P. The effect of fall prevention exercise programmes on fall induced injuries in community dwelling older adults: systematic review and meta-analysis of randomised controlled trials. *BMJ (Clin Res Ed)* 2013;347:f6234.
- [68] Vlaeyen E, Coussement J, Leysens G, Van der Elst E, Delbaere K, Cambier D, et al. Characteristics and effectiveness of fall prevention programs in nursing homes: a systematic review and meta-analysis of randomized controlled trials. *J Am Geriatr Soc* 2015;63(2):211–21.
- [69] Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev* 2012;9:Cd007146.
- [70] Bischoff-Ferrari HA, Dawson-Hughes B, Platz A, Orav EJ, Stahelin HB, Willett WC, et al. Effect of high-dosage cholecalciferol and extended physiotherapy on complications after hip fracture: a randomized controlled trial. *Arch Intern Med* 2010;170(9):813–20.
- [71] Wimalawansa SJ, Razzaque MS, Al-Daghri NM. Calcium and vitamin D in human health: hype or real? *J Steroid Biochem Mol Biol* 2018;180:4–14.
- [72] Vranken L, Wyers CE, van den Bergh JPW, Geusens P. The phenotype of patients with a recent fracture: a literature survey of the fracture liaison service. *Calcif Tissue Int* 2017;101(3):248–58.
- [73] Bours SP, van Geel TA, Geusens PP, Janssen MJ, Janzing HM, Hoffland GA, et al. Contributors to secondary osteoporosis and metabolic bone diseases in patients presenting with a clinical fracture. *J Clin Endocrinol Metab* 2011;96(5):1360–7.
- [74] Malgo F, Appelman-Dijkstra NM, Teraat MF, van der Heide HJ, Schipper IB, Rabelink TJ, et al. High prevalence of secondary factors for bone fragility in patients with a recent fracture independently of BMD. *Arch Osteoporos* 2016;11:12.
- [75] Sanli I, van Helden SH, Ten Broeke RHM, Geusens P, Van den Bergh JPW, Brink PRG, et al. The role of the Fracture Liaison Service (FLS) in subsequent fracture prevention in the extreme elderly. *Aging Clin Exp Res* 2018 Oct 11. <https://doi.org/10.1007/s40520-018-1054-2> [Epub ahead of print].
- [76] Heaney RP. Vitamin D and calcium interactions: functional outcomes. *Am J Clin Nutr* 2008;88(2):541s–4s.
- [77] Heaney RP. The Vitamin D requirement in health and disease. *J Steroid Biochem Mol Biol* 2005;97(1–2):13–9.
- [78] Rasch LA, de van der Schueren MA, van Tuyl LH, Bultink IE, de Vries JH, Lems WF. Content validity of a short calcium intake list to estimate daily dietary calcium intake of patients with osteoporosis. *Calcif Tissue Int* 2017;100(3):271–7.
- [79] Magarey A, Baulderstone L, Yaxley A, Markow K, Miller M. Evaluation of tools used to measure calcium and/or dairy consumption in adults. *Publ Health Nutr* 2015;18(7):1225–36.
- [80] van der Velde RY, Brouwers JR, Geusens PP, Lems WF, van den Bergh JP. Calcium and vitamin D supplementation: state of the art for daily practice. *Food Nutr Res* 2014;58.
- [81] Abrahamsen B. The calcium and vitamin D controversy. *Ther Adv Musculoskel Dis* 2017;9(5):107–14.
- [82] Bischoff-Ferrari HA, Bhasin S, Manson JE. Preventing fractures and falls: a limited role for calcium and vitamin D supplements? *JAMA* 2018;319(15):1552–3.

- [83] Bolland MJ, Grey A, Reid IR. Should we prescribe calcium or vitamin D supplements to treat or prevent osteoporosis? *Climacteric – J Int Menopause Soc* 2015;18(Suppl. 2):22–31.
- [84] Harvey NC, Biver E, Kaufman JM, Bauer J, Branco J, Brandi ML, et al. The role of calcium supplementation in healthy musculoskeletal ageing : an expert consensus meeting of the european society for clinical and economic aspects of osteoporosis, osteoarthritis and musculoskeletal diseases (ESCEO) and the international foundation for osteoporosis (IOF). *Osteoporos Int* 2017;28(2):447–62.
- [85] Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet (London, Engl)* 2007;370(9588):657–66.
- [86] Shab-Bidar S, Bours SP, Geusens PP, van der Velde RY, Janssen MJ, van den Bergh JP. Suboptimal effect of different vitamin D3 supplementations and doses adapted to baseline serum 25(OH)D on achieved 25(OH)D levels in patients with a recent fracture: a prospective observational study. *Eur J Endocrinol* 2013;169(5):597–604.
- [87] Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ (Clin Res Ed)* 2010;341:c3691.
- [88] Bolland MJ, Leung W, Tai V, Bastin S, Gamble GD, Grey A, et al. Calcium intake and risk of fracture: systematic review. *BMJ (Clin Res Ed)* 2015;351:h4580.
- [89] Geusens PP, van den Bergh JP. Bone: new guidelines for multistep fracture prevention in men. *Nat Rev Rheumatol* 2012;8(10):568–70.
- [90] Rizzoli R. Dairy products, yogurts, and bone health. *Am J Clin Nutr* 2014;99(Suppl. 5):1256s–62s.
- [91] Baum JI, Kim IY, Wolfe RR. Protein consumption and the elderly: what is the optimal level of intake? *Nutrients* 2016;8(6).
- [92] Munger RG, Cerhan JR, Chiu BC. Prospective study of dietary protein intake and risk of hip fracture in postmenopausal women. *Am J Clin Nutr* 1999;69(1):147–52.
- [93] Wengreen HJ, Munger RG, West NA, Cutler DR, Corcoran CD, Zhang J, et al. Dietary protein intake and risk of osteoporotic hip fracture in elderly residents of Utah. *J Bone Miner Res* 2004;19(4):537–45.
- [94] Avenell A, Smith TO, Curtain JP, Mak JC, Myint PK. Nutritional supplementation for hip fracture aftercare in older people. *Cochrane Database Syst Rev* 2016;11:Cd001880.
- [95] Neelemaat F, Lips P, Bosmans JE, Thijs A, Seidell JC, van Bokhorst-de van der Schueren MA. Short-term oral nutritional intervention with protein and vitamin D decreases falls in malnourished older adults. *J Am Geriatr Soc* 2012;60(4):691–9.
- [96] Dawson-Hughes B, Harris SS, Palermo NJ, Gilhooly CH, Shea MK, Fielding RA, et al. Potassium bicarbonate supplementation lowers bone turnover and calcium excretion in older men and women: a randomized dose-finding trial. *J Bone Miner Res* 2015;30(11):2103–11.
- [97] Rizzoli R, Biver E, Bonjour JP, Coxam V, Goltzman D, Kanis JA, et al. Benefits and safety of dietary protein for bone health—an expert consensus paper endorsed by the european society for clinical and economical aspects of osteoporosis, osteoarthritis, and musculoskeletal diseases and by the international osteoporosis foundation. *Osteoporos Int* 2018 Sep;29(9):1933–48.
- [98] Haring B, Crandall CJ, Wu C, LeBlanc ES, Shikany JM, Carbone L, et al. Dietary patterns and fractures in postmenopausal women: results from the women's health initiative. *JAMA Int Med* 2016;176(5):645–52.
- [99] Sahni S, Mangano KM, Tucker KL, Kiel DP, Casey VA, Hannan MT. Protective association of milk intake on the risk of hip fracture: results from the Framingham Original Cohort. *J Bone Miner Res* 2014;29(8):1756–62.