

## 2020 recommendations for osteoporosis treatment according to fracture risk from the Swiss Association against Osteoporosis (SVGO)

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### Summary

Current guidelines from the Swiss Association against Osteoporosis (SVGO) dating from 2015 recommend therapy for men and women at increased fracture risk, specifically those with a vertebral or hip fracture; those with bone mineral density T-score  $<-2.5$  at spine or hip; and those with a high 10-year probability of a major osteoporotic fracture as calculated by using FRAX. However no specific treatment recommendations have been made so far in our country to guide therapy according to the baseline level of risk. We now define four risk subgroup categories (imminent and very high, high, moderate, low) and propose an algorithm for osteoporosis therapy according to the level of fracture risk.

**Keywords:** osteoporosis, fragility fractures, bone mineral density, SERMs, bisphosphonates, teriparatide, denosumab, romosozumab

### Introduction

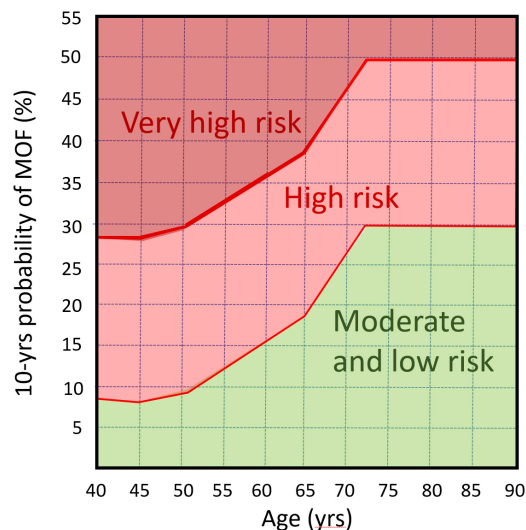
In Switzerland, one woman in two and one man in five will sustain a fragility fracture after the age of 50. Hence the number of incident fragility fractures is at least 75,000 per year; 140,000 subjects have prevalent hip or vertebral fractures and 450,000 have osteoporosis (in 2010) [1]. In turn, the acute complications of osteoporosis are a major cause of hospitalisations and the chronic complications, such as the loss of mobility and independence in daily living activities, increase the needs for secondary care and nursing homes. Yet primary and secondary prevention of fragility fractures remains insufficient, as it is estimated that less than 10% of subjects with osteoporosis and only 20% of subjects with low-trauma fractures receive anti-osteoporotic medications [2]. Hence identification and treatment of subjects at high risk of fragility fractures remains critical.

Current guidelines from the Swiss Association against Osteoporosis (SVGO) dating from 2015 recommend therapy for men and women at increased fracture risk, specifically those with a vertebral or hip fracture; those with bone mineral density (BMD) T-score  $<-2.5$  at spine or hip; and

those with a high 10-year probability of major osteoporotic fractures calculated by using the fracture risk assessment tool FRAX. By high risk we mean at least equivalent to the 10-year risk of an individual of the same age and sex with a prevalent vertebral fracture, which in Switzerland corresponds to about 10% by age 50 years and 30% by age 72 years (fig. 1). In addition, patients receiving chronic glucocorticoid therapy, anti-aromatase therapy or androgen suppression therapy are also considered at high risk and recommended for osteoporosis treatment. More recently, SVGO also made recommendations regarding the duration and the sequence of osteoporosis therapy [3]. In particular, it was recommended that high risk patients, including those older than 65 yrs and fallers remain treated until reaching a bone mineral density (BMD) at hip better than  $-2.0$  T-score.

There are multiple classes of drugs available for the treatment of osteoporosis and fracture prevention, including:

**Figure 1:** Intervention thresholds for osteoporosis therapy based on the 10-year risk of a major osteoporotic fracture in Switzerland.



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antiresorptives, namely, selective oestrogen receptor modulators (SERMs: raloxifene, bazedoxifene), bisphosphonates (alendronate, risedronate, ibandronate, zoledronate) and monoclonal antibodies (denosumab); bone forming agents (teriparatide); and, very recently approved in Switzerland, a new monoclonal antibody, romosozumab, with dual antiresorptive and anabolic effects. As stated in the 2015 SVGO guidelines: “In general an anti-resorptive (AR) is recommended as first line (without specifying whether and when it should be SERMs, bisphosphonates or denosumab), whereas teriparatide (TPT) could be recommended as first line in case of severe osteoporosis (i.e., BMD  $<-2.5$  + vertebral fracture).”

However, no specific treatment recommendations have been made so far in our country to guide therapy according to the baseline level of risk. Here we provide new guidance to categorise patients at various levels of risk based on their probability of a major osteoporotic fracture (rather than hip fracture only, which accounts for only a fraction of the former) and to choose the most appropriate first-line therapy for each risk category.

### New evidence regarding patients at very high and/or imminent risk

Recent publications have provided new evidence regarding the identification of very high risk patients and the efficacy of certain treatments in this population. First, patients with a *recent* major osteoporotic fracture (spine, hip, pelvis, humerus or radius) are increasingly recognised as being at “imminent risk”, since the relative risk of a second fracture is increased several fold within the first 2 years after the index fracture but declines thereafter, and 40% to 60% of all recurrent fractures will occur within those 2 years [4]. According to some very recent Medicare data from the US, after 65 years of age, 25% of patients with a vertebral fracture and 15% or more of those with a hip or pelvis fracture will refracture within 2 years, whereas 10% or more of those with humerus or distal radius fractures will refracture within 2 years [5].

An important consequence of identifying subjects with recent fractures is the positive impact it has on the cost-benefits of therapy. Indeed, by taking into account the imminent risk of refracturing in these subjects, the number of secondary fractures potentially prevented by treatment would be doubled compared with subjects with similar fractures but in whom the recentness of the fracture has not been taken into account [6]. Moreover, it has been estimated that in these imminent-risk patients, parenteral therapy with denosumab, teriparatide or romosozumab would prevent more fractures than using an oral bisphosphonate [6].

Two recent major head-to-head trials have demonstrated the greater anti-fracture efficacy of teriparatide and romosozumab compared with oral bisphosphonates (risedronate and alendronate) in high-risk subjects defined by severe and/or multiple vertebral fractures (VERO [7] and ARCH [8], respectively). Notably, romosozumab also substantially increased BMD at spine and hip within 1 year and significantly more so than bisphosphonates or teriparatide [8, 9]. However, its benefits and risks should be evaluated carefully in patients at higher cardiovascular risk, since romosozumab was associated with more car-

diovascular serious adverse events than alendronate in one study [8].

Accordingly, the International Osteoporosis Foundation (IOF) jointly with the European Society for the Clinical and Economic Aspects of Osteoporosis (ESCEO) have recently proposed an algorithm for the management of patients at low, high and very high risk of osteoporotic fractures, in which they still recommend a potent anti-resorptive (bisphosphonate or denosumab) in high-risk patients, but consideration of an anabolic agent (teriparatide, romosozumab) first in very high-risk patients [10]. In women with a recent major osteoporotic fracture, use of an anabolic drug for a short period (12–18 months) followed by an anti-resorptive over a total duration of therapy of 10 years would result in more fractures saved than use of an anti-resorptive followed by an anabolic drug over the same period [10].

Based on these new developments, we now delineate the various risk categories and recommended treatments for each level of risk in order to facilitate the management of osteoporosis in Switzerland, notwithstanding the current limitations for reimbursement of some drugs in our country.

### Risk stratification

- Risk stratification should take into consideration previous fragility fractures, BMD, age and other clinical risk factors as encompassed in FRAX (table 1). Moreover, the risk of falls should be taken into consideration, as subjects with risk factors for falls (such as >1 fall in past year, Parkinson’s disease, urinary incontinence, etc.) may have a fracture risk that is nearly double that of individuals with similar bone risk profiles but without falls [11].
- In patients at risk, BMD should be evaluated at spine and hip using dual energy X-ray absorptiometry (DXA). When possible, a vertebral fracture assessment and trabecular bone score by DXA could also be performed to further refine the risk evaluation.
- Bone turnover markers, particularly carboxy terminal crosslinked telopeptides of type 1 collagen (CTX) and procollagen type 1 N-terminal propeptide (PINP), are not recommended for risk stratification. However they may be useful to guide treatment decisions in some risk categories (below) and to monitor treatment efficacy in all categories.
- Subjects should be considered at *imminent risk* (i.e., >10% fracture risk within 2 years) if they have suffered

**Table 1:** Clinical risk factors for fractures in FRAX.

Age
Sex
Body mass index
Previous fracture
Parental hip fracture
Current smoking
Alcohol >3 units/d
Glucocorticoids
Rheumatoid arthritis
Secondary osteoporosis (type 1 diabetes, malabsorption, chronic liver disease, hypogonadism, untreated hyperthyroidism, adult osteogenesis imperfecta)

- a recent (<2 years) clinical vertebral or low-trauma hip fracture, or any recent major osteoporotic fracture (including humerus, radius, pelvis) after the age of 65.
- Subjects should be considered at *very high risk* when their 10-year probability of major osteoporotic fracture according to FRAX is at least 20% absolute risk above the intervention threshold at any age (fig. 1). This would correspond to a 10-year FRAX probability of about 50% after the age of 70, equivalent to an imminent risk of 10% within 2 years (above).
- For instance, a 55-year-old woman with a previous wrist fracture, body mass index (BMI) 20 kg/m<sup>2</sup>, who smokes, whose mother had a hip fracture, and whose hip BMD is -2.7 T-score would reach the very high risk threshold for her age (FRAX probability 34%). Another example would be a 70-year-old woman with a previous vertebral fracture, on 5 mg/d prednisone for a chronic inflammatory disorder, hip BMD -3.1 T-score (FRAX probability 46%).
- Subjects with previous major osteoporotic fractures (>2 years) and/or FRAX probabilities above the intervention threshold but less than 20% above that limit (fig. 1) should be considered *high risk*, irrespective of their BMD level (since more than 50% of fragility fractures occur in subjects with BMD levels  $\geq -2.5$  T-score).
- Subjects receiving chronic glucocorticoid, aromatase inhibitor or androgen suppression therapy should also be considered *high risk* if their BMD is <1.5 T-score and/or FRAX probability above the intervention threshold (fig. 1).
- Subjects with BMD <-2.5 T-score but no previous fracture and a FRAX probability below the intervention threshold should be considered at *moderate risk*.
- Subjects with osteopenia (T-score >-2.5 and <-1.0) and no other risk factors should be considered at *low risk*.

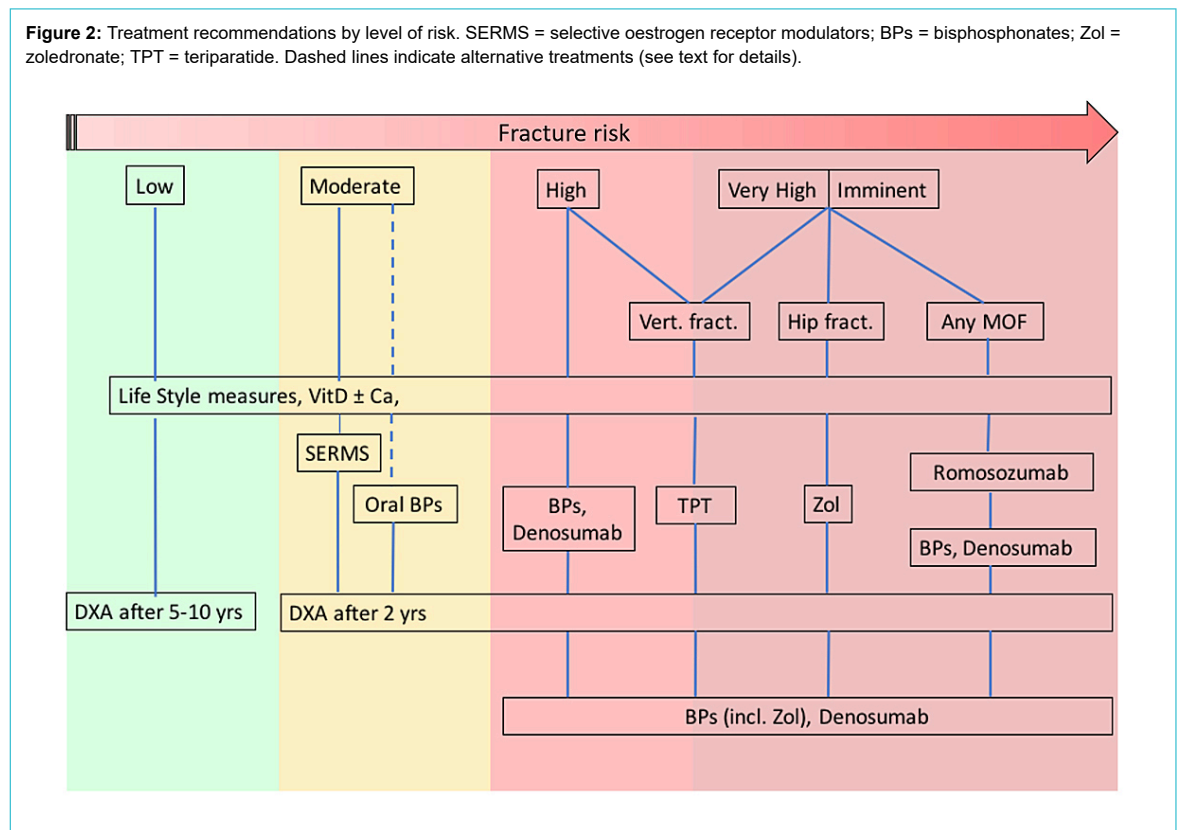
**Treatment by risk category**

Despite numerous studies comparing the effects of various treatments on BMD changes, only a few trials, including the VERO and ARCH trials mentioned above, directly compared the anti-fracture efficacy of osteoporosis drugs in high-risk patients [7, 8, 12], and none has compared anabolics with the most potent anti-resorptives (zoledronate and denosumab). Moreover, a single trial specifically recruited patients with a recent hip fracture, hence at imminent risk, and demonstrated that a yearly infusion of zoledronate initiated within 3 months after the fracture reduced secondary clinical fractures by 32% and mortality by 25% compared with placebo (median follow-up 1.9 years) [13]. *Post-hoc* analyses of the FREEDOM trial also reported that denosumab significantly reduced vertebral and hip fractures in high risk subjects (>75 yrs, hip T-score <-3.0, previous fracture) [14]. Denosumab has also been shown to reduce fracture risk in other high-risk categories, namely in postmenopausal women with early breast cancer receiving an aromatase inhibitor [15], as well as in men with non-metastatic prostate cancer receiving androgen suppression therapy [16].

Treatment recommendations for the various risk categories are shown in figure 2 and explained below.

- In patients at *imminent / very high risk with a vertebral fracture*, teriparatide for 18–24 months is recommended (in absence of formal contraindications such as re-

**Figure 2:** Treatment recommendations by level of risk. SERMS = selective oestrogen receptor modulators; BPs = bisphosphonates; Zol = zoledronate; TPT = teriparatide. Dashed lines indicate alternative treatments (see text for details).



cent cancer / radiation therapy to the skeleton), followed by an anti-resorptive (bisphosphonate or denosumab)

- In patients at *imminent / very high risk with a hip fracture*, zoledronate once yearly is recommended when renal function is not compromised (creatinine clearance >35 ml/min). Alternatively, consider denosumab.
- — In all patients at *imminent / very high risk*, romosozumab is also recommended as first-line therapy for 1 year, followed by an anti-resorptive (bisphosphonate or denosumab), potentially excluding patients with recent cardiovascular events and/or at high cardiovascular risk
- In *high-risk* patients, including those on glucocorticoids, aromatase inhibitors or androgen suppression therapy, a potent anti-resorptive is recommended (note that denosumab is not approved for glucocorticoid-induced osteoporosis). Alternatively, consider teriparatide if there is a vertebral fracture or spine BMD <−3.5 T-score [17], but taking into consideration the contraindications to teriparatide in some cancer patients.
- In *moderate-risk subjects* who do not receive oestrogen replacement therapy, consider SERMS, eventually oral bisphosphonates if bone turnover markers such as CTx and P1NP are above the premenopausal threshold.
- In *all the above categories*, repeat DXA after 2 years and reevaluate fracture risk before deciding on pursuing treatment
- In *low-risk* subjects, recommend life style measures, vitamin D supplements (800–1000 IU/d) ± calcium (500–1000 mg/d) if necessary, and repeat DXA after 5–10 years or if clinical risk increases.

## Discussion

These new recommendations on osteoporosis treatment differ from the previous SVGO guidelines (2015) by further defining four risk categories, including a new one – imminent and very high risk. Furthermore, among the armamentarium of osteoporosis drugs available, newly enriched by a potent anabolic agent with dual anti-resorptive properties, romosozumab, we now delineate which drugs should be used to initiate therapy according to the fracture risk category. In defined patients at imminent / very high risk in particular, a more aggressive approach with bone forming agents or anabolics is now recommended as first-line therapy, although some reimbursement issues may still be present. By recommending specific classes of drugs according to the level of fracture risk, we hope to facilitate the decision making of all doctors involved in the management of osteoporosis and thereby to narrow the treatment gap for this common disease. Nevertheless, we acknowledge that the threshold for “very high risk” as defined here is somewhat arbitrary. We intentionally chose a threshold for very high risk that is quite elevated in order to keep the size of the targeted population relatively limited, in consideration of the potential risks and/or higher costs of anabolic agents. The recent development of teriparatide biosimilars may actually favour its use among imminent / very high risk subjects. To note that, using a lower “very high

risk” threshold in the UK population, it has been estimated that only about 15% of post-menopausal women will fall into that category at any age [10]. We therefore expect that only 10% or less of post-menopausal women in Switzerland will fall into that category. Further studies are needed in Switzerland and elsewhere to evaluate whether such threshold captures a sufficient proportion of subjects effectively at very high risk, or on the contrary is too restrictive, which would call for adapting our guidelines in the future.

## Potential competing interests

KL has received a research grant from Amgen and was principal investigator in several multicentre clinical trials of Amgen UCB and MSD. SF has received research and/or consulting grants from Amgen, UCB, Agnunos, Alixiun, Gedeon Rühle and Galapájus.

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