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How to implement guidelines and models of care

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A B S T R A C T

In subjects older than 50 years, the presence of clinical risk factors (CRFs) for fractures or a recent fracture is the cornerstone for case finding. In patients who are clinically at high short- and long-term risk of fractures (those with a recent clinical fracture or with multiple CRFs), further assessment with bone mineral density (BMD) measurement using dual-energy absorptiometry (DXA), imaging of the spine, fall risk evaluation and laboratory examination contributes to treatment decisions according to the height and modifiability of fracture risk. Treatment is available with anti-resorptive and anabolic drugs, and from the start of treatment a lifelong strategy is needed to decide about continuous, intermittent, and sequential therapy. Implementation of guidelines requires further initiatives for improving case finding, public

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awareness about osteoporosis and national policies on reimbursement of assessment and therapy.

Who to target in women and men older than 50 years?

In subjects older than 50 years, case finding based on the presence of clinical risk factors (CRFs) for fractures is the cornerstone to identify on clinical grounds patients at high risk for fractures who, in a second step, need evaluation by bone densitometry using dual-energy absorptiometry (DXA), imaging of the spine with vertebral fracture assessment (VFA) using DXA or X-rays, fall risk evaluation and laboratory investigations. Treatment decisions can then be made according to the height and modifiability of the fracture risk [1-3]. CRFs include age, gender, body mass index (BMI), ethnicity, parenteral and personal fracture history, lifestyle (smoking and alcohol intake) and the risk of falls, and more than 85 conditions, diseases and medications contribute to fracture risk [4].

Clinical case finding and further evaluation can be initiated at different moments during lifetime, before or after a fracture, and with different strategies [1].

First, a general population is screened to identify individuals with one or more CRFs [5].

Second, in daily clinical practice, by a high-risk approach in two specific clinical situations: patients identified at the time they present with a recent clinical fracture [6] and individuals without a recent clinical fracture with CRFs [2,3].

Third, a relatively new approach is by opportunistic screening, which is most obvious for prevalent vertebral fractures (VFs) that can be detected by thoracic and abdominal imaging that was initially performed for other diagnostic purposes [7-9].

A recent clinical fracture is on itself an indication for further assessment because it offers a window of opportunity to identify the underlying causes and then to decide about the treatment [6]. The same holds for an opportunistically diagnosed VFs [10]. In individuals without a recent clinical fracture, fracture risk calculators such as FRAX (fracture risk assessment tool), GARVAN (Garvan fracture risk calculator), qFracture (qFracture risk calculator) and many others are available to refine the long-term absolute fracture risk on clinical grounds and decide on further assessment [3].

General population screening

The use of DXA for population screening has limited value because it has low sensitivity for predicting fracture risk on its own [11]. In most studies on population screening, the screening strategy starts with the calculation of fracture risk based on CRFs to decide whether to proceed with DXA, imaging of the spine, fall risk evaluation and laboratory investigations.

Three population screening studies (SCOOP (screening for prevention of fractures in older women trial) and SOS (Stichting ArtsenLaboratorium and Trombosedienst (SALT) osteoporosis study) in primary care populations and ROSE (Risk-Stratified Osteoporosis Strategy Evaluation study) in a random population) have been recently published (Fig. 1) [12-15] and were included in a meta-analysis [5].

The differences in approach regarding the first step (the presence of at least one CRF or CRFs with FRAX calculation) and the second step (DXA alone, or combined with VFA by DXA, fall risk and laboratory investigation) reflect the differences in local guidelines that were used in these studies [3]. The ages of the participants ranged from 65 to 90 years old. No such screening studies are available in younger subjects.

High-risk approach in daily practice

In daily practice, a high-risk approach starts in subjects who have one or more CRFs with full evaluation of the presence of all CRFs and then to decide about further assessment. In principle, any risk factor that alerts the physician to the possibility of osteoporosis and, more specifically, a high fracture

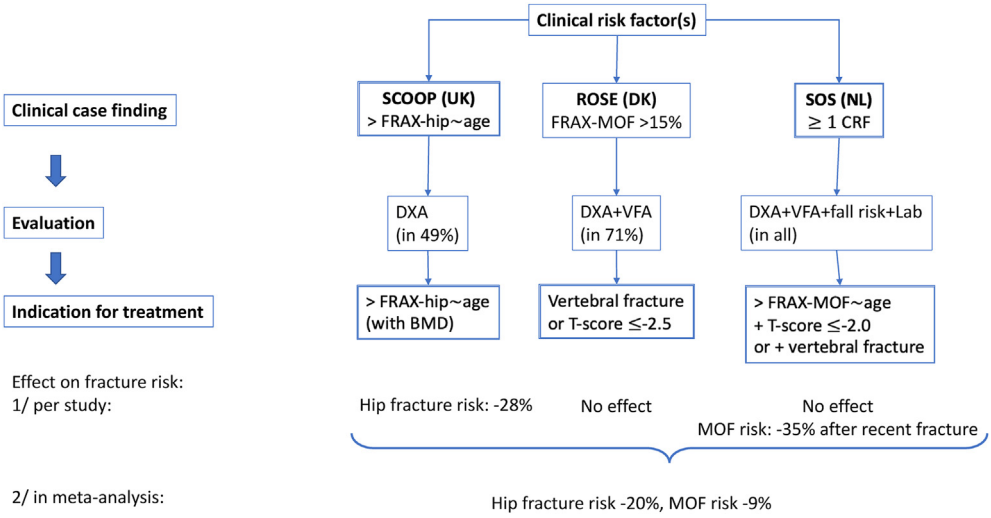

Fig. 1. Clinical case finding, evaluation and indication for treatment in three population screening studies using local guidelines.

risk, is a candidate for further evaluation [16]. Such subjects present in two specific and very different clinical situations: patients with a recent fracture and those with CRFs but no recent fracture [17].

At the time of a clinical fracture

In the perspective of lifetime bone health after the age of 50 years, the fracture history is the central component. A recent fracture after the age of 50 years is a single and prominent CRF for subsequent fractures that requires immediate clinical attention, as the risk of subsequent fracture and mortality is increased at the short- and long-term.

A prior fracture at any time after the age of 50 years doubles the risk of a subsequent fracture. After including a prior fracture in FRAX, a 10-year risk of 10% would increase to 20%. The long-term risk of 20% suggests that fracture risk is linear over time, at a rate of 2% per year. However, this is an over-simplification, as fracture risk is not constant over lifetime [18], but specifically increased, *e.g.* after a recent fracture, and in patients starting glucocorticoids (see elsewhere in this journal).

This time dependency of subsequent fracture risk is important to consider and may be related to the presence and appearance of risk factors over time, such as temporarily increased post-fracture bone loss or incident falls and is presented in Fig. 2. Special attention is needed for situations that result in a

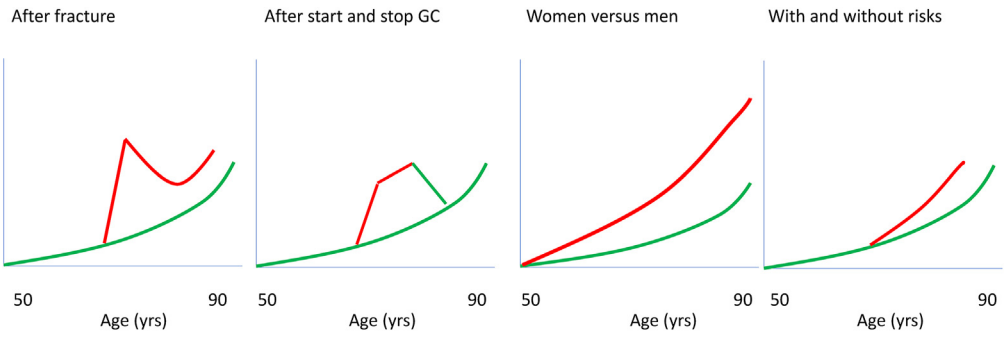

Fig. 2. Schematic examples of patterns of time-dependency of fracture risk.GC: glucocorticoids.

high short-term risk, often referred as imminent risk. The imminent fracture risk indicates that the fracture risk is expected to be higher at short (near) term than at long term [19].

Earlier findings of the imminence of subsequent clinical and morphometric VFs, hip fractures, and other non-VFs after a sentinel fracture have been confirmed and extended in many recent observational studies [20-24].

Within 2 years, 12–18% of any clinical fracture recurred and 31% recurred within 5 years, the level of which depended on the location of the sentinel fracture and the subsequent fracture [21,25]. Of the recurrent MOF (major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture)) fractures occurring within 10 years, 34% occurred within the first 2 years after a fracture. Compared to the population, the risk was 2.7 times higher for recurrent MOFs within the first year and remained 1.4 times higher after 10 years [25].

As a result, there is a growing international consensus that a patient over the age of 50 with a recent fracture deserves high priority for evaluation and treatment immediately following a fracture. The fracture liaison service (FLS) is considered the best organizational approach for secondary fracture prevention [6,26-28]. A meta-analysis of five studies found that structural interventions with FLS increased the prescription of bone mineral density (BMD) measurement significantly (OR:9.99) [29]. In one FLS study in patients with a recent clinical non-VF, the implementation of VFA with DXA increased diagnosis of subclinical VFs from 2.2% to 26.6% [30].

One of the major challenges in FLS care is non-attendance. In a recent study in patients who did not respond to FLS invitation found that male gender, frailty, living alone, having low general education, or having a low interest in bone health and subsequent fracture risk were independently associated with FLS non-attendance, whereas adequately perceived advice (to have a bone densitometry and attend the FLS) was strongly associated with FLS attendance [31]. Even among the non-attenders, a quarter of patients consented with a home visit, mainly older women with a major fracture, of whom the majority believing the fracture was caused by a fall and only a minority by the underlying osteoporosis [32].

The focus in studies on patients with a recent fracture has enlarged our insights in their phenotype and the risk factors for subsequent fracture (Fig. 3) [33].

Most patients with a recent fracture have no osteoporosis [30]. This reflects the prevention paradox of patients attending the FLS with a clinical non-VF, of which only 32% had osteoporosis, but 49% had osteopenia and 19% had normal BMD. Still, respectively, 27%, 28% and 21% had subclinical morphometric VF on VFA using DXA, many had comorbidities, and 2/3 had a combination of bone- and fall-related risks [34]. In a review of 33 FLSs, all FLSs performed a DXA, but imaging of the spine only 27%, laboratory examination 64%, fall risk evaluation 24% and FRAX 12% [33].

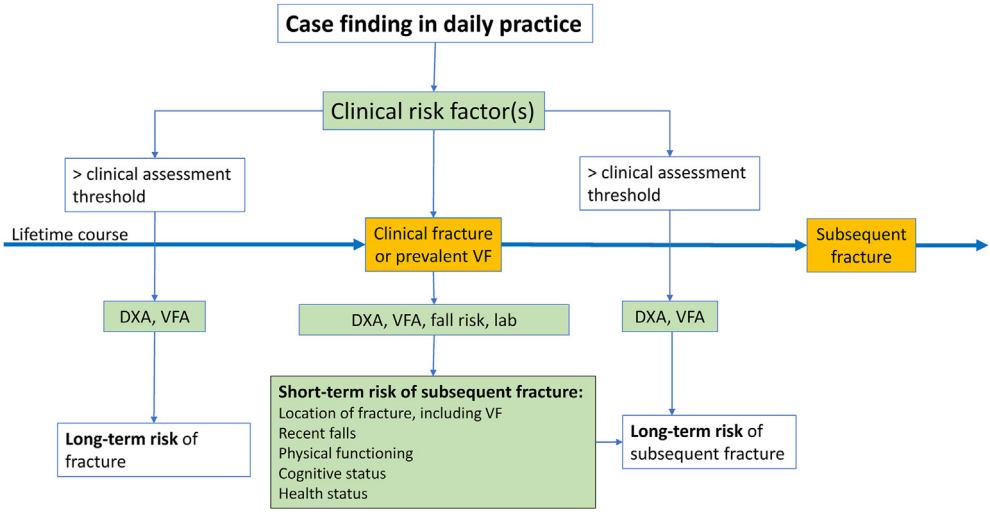

Fig. 3. Examples of timing of CRF evaluation and further assessment in relation to prevalence and incidence of fractures over time.

In addition to the classical risk factors for long-term risk (such as age, gender, and BMD), risk factors for the absolute imminent subsequent fracture risk include accelerated generalized bone loss following a fracture [35], the location of sentinel and subsequent fracture (including the presence of subclinical morphometric VFs, their number and degree of deformity) [8,36], beginning GC, fall risks (including medications that increase the risk of falls), recent fall(s), physical function, cognitive status, and general health [20,37-41]. The risk of subsequent fracture is increased whether the sentinel fracture occurred after a low- or high-energy trauma [42].

A previous fracture is included in most algorithms for risk calculation of subsequent fracture [3,43], but the recency of fracture is not yet included [44]. FRAX can be adapted for the recency of fracture (depending on age, gender, and risk for subsequent fracture with multipliers up to >7) and for recent falls (multiplier of 1.3 for every recent fall, up to $\geq$ 5 falls). In case of recent falls, other fracture algorithms can be used that include the number of recent falls, such as Garvan and qFracture [44].

These findings redirect the communication with a patient who has recently had a clinical fracture away from confusion (about the role of falls, degree of injury, lack of awareness or interest for bone and subsequent fracture risk) towards communication about the immediate need for evaluating the presence, degree, reasons for underlying decreased bone strength and fall risk, the presence or absence of subclinical VFs, the height of risk of subsequent fracture and the high risk of mortality after major fractures. Many patients at high risk of subsequent fracture who do not respond to an invitation at the FLS are still approachable for secondary fracture prevention, despite their belief that a fall rather osteoporosis was considered the cause of a fracture [32].

Recognising the causes and triggers that contribute to the imminence of subsequent fracture risk will help rheumatologists and patients to timely start interventions that quickly and substantially increase bone strength, prevent bone loss, prevent falls and minimize triggers related to the imminence of fracture risk [6].

In view of these findings, a recent fracture is on itself an indication for further evaluation with a full medical history, including comorbidities, DXA, VFA, fall risk assessment and laboratory investigation [6,10,45].

In individuals without a recent fracture

In the absence of a recent fracture, case finding starts with identifying the presence of one or more other CRFs as a trigger for full clinical risk assessment, including non-recent prior fractures.

Various clinical algorithms are available to calculate the yearly, 5-year and 10-year fracture risk, with and without BMD and without including the recency of fracture [43,44]. With the clinical calculation of fracture risk (without BMD), the area under the curve (AUC) for calculating these fracture risks was low (AUC <0.70) [43]. In a prospective population-based study in Denmark for three years, none were found to be superior, even when compared to simpler algorithms with fewer risk factors [44,46].

FRAX is the most validated and calibrated algorithm for fracture prediction. FRAX is incorporated in various ways in more than 100 guidelines [11]. Adjustments for FRAX have been proposed for 10 specific additional risk factors, of which seven are CRFs, but the accuracy of using multiple adjustments is not available [17]. For the rheumatologists, it is important to note that RA (rheumatoid arthritis) is included in FRAX, but not considering the severity of RA. Adjustments for the dose but not the duration of GC use are available.

In regions without access to DXA, the IOF (International osteoporosis foundation)/ESCEO (European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis) recommends FRAX based on CRFs for treatment decisions [11]. Where DXA is available, recommendations about the level of clinical fracture risk at which DXA should be performed vary between guidelines [1,3,47,48], with thresholds based on age, or with a fixed value at any age, or a hybrid by combining both (Fig. 4).

The IOF/ESCEO recommends DXA only in a subgroup of individuals with intermediate fracture risk to refine FRAX [11]. This leaves very high-risk patients without results of baseline BMD. By the rapid progress of insights about case finding and further assessment, it is not unexpected that, in the new recent guideline of the UK, DXA is also recommended in high and very high-risk patients to guide drug choice and provide a baseline for BMD monitoring [17].

VFs are the most frequent fractures, but 2/3 occur subclinical [49]. Imaging of the thoracic and lumbar spine is the only way to detect a subclinical VF. BMD and prevalent VF are independent risk

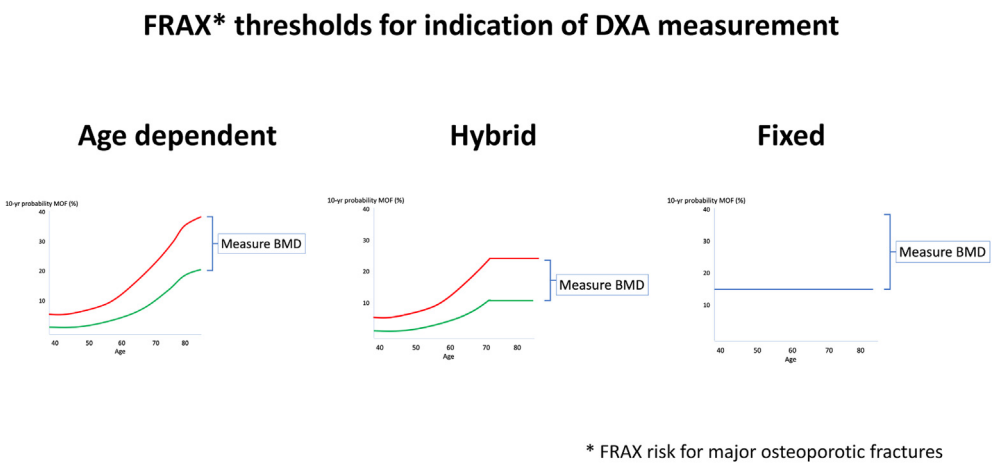

Fig. 4. Examples of thresholds for measuring DXA based on FRAX.

factors for future fractures and their combination is a better predictor for fractures than either alone [8,50,51]. In the recent UK guideline, spine imaging is recommended, be it only in case of clinical suspicion of a VF or in the presence of osteoporosis [17]. In view of the high prevalence of VFs in patients with a non-VF fracture and osteopenia, VFA will also identify high-risk patients in that group [30]. The use of FRAX without DXA and without a full fracture history (including subclinical VFs) in defining very high risk remains therefore to some extent arbitrary [10,52-54]. In addition, before beginning the treatment, clinical and laboratory examinations allow to evaluate the presence of underlying diseases that influence treatment decisions [45].

In conclusion, in daily rheumatology practice, in patients with a high fracture risk based on the presence of CRFs, DXA combined with VFA will contribute to refining fracture prediction and identification of modifiable risks. DXA provides baseline values at the spine and hip for follow up and treatment decisions based on BMD, as changes in total hip BMD have emerged as a major predictor of future risk of both non-VFs and VFs [55]. VFA provides baseline data about the full fracture history and about the incidence of first or new VFs during follow up. This is underlined by the recent IOF position paper that advises to perform a VFA in each patient with an indication for DXA [10].

Opportunistic screening on chest or abdominal CT-scans

One strategy to improve VF detection is to employ computed tomography (CT) scans obtained as a part of routine patient care to opportunistically screen for the presence of VFs.

Routine CT scans of the thorax and abdomen are performed for diagnosis and monitoring of various medical conditions, but the skeleton is often overlooked as radiologists will concentrate on the primary reason for having a CT [7]. Diagnosing VFs on routine CT scans could be of specific interest when CT scans are performed in patients with comorbidities that attribute to osteoporosis and fracture risk such as chronic obstructive pulmonary disease (COPD), inflammatory bowel disease (IBD), etc. For instance, in the ECLIPSE (Evaluation of Chronic obstructive pulmonary disease (COPD) Longitudinally to Identify Predictive Surrogate End-points study) study, in women and men with COPD, chest CT scans were analyzed in more than 1200 patients at baseline and after one and three years follow up. At baseline, one in five had a prevalent VF. Within one year, 29.2% of the patients with a prevalent VF had a new incident VF, and 58.5% within three years. The incidence of VF was higher with increasing number and severity of prevalent VFs [8,9].

Only 26% of VF visualized incidentally on CT were reported by the radiologist [7]. Therefore, software-based services are now emerging that (semi)automate the process of identifying VFs [56,57].

There will be a need of imaging of all thoracic and lumbar vertebral levels as the prevalence of VFs is highest in the most loaded mid-thoracic and the thoraco-lumbar regions [58].

The presence of an opportunistically found VF should be interpreted in the clinical context in which the CT was performed [7]. It is yet to be determined how opportunistic CT imaging could be clinically integrated with current diagnostic methods. Outside an oncology indication for CT (in which malignant bone disease should be considered), a grade 2 or 3 VF should trigger evaluation of the presence of CRFs for fractures and consideration of DXA. Further data will be required to develop the pathway after an opportunistically found VF.

In conclusion, both in population screening and in a case finding high-risk approach, the presence of one or more CRFs is the driver to decide about assessment with DXA, VFA, laboratory investigations and fall risk (Fig. 3). The central component is the presence of a recent fracture and/or a prevalent morphometric VF, which are on itself indications for further assessment. Over lifetime, the identification of patients at high risk therefore requires a detailed fracture history. This includes the recency and site of a fracture, including the presence, number, and severity of VFs. In patients without a recent clinical fracture, there is a need for a uniform fracture risk approach, but heterogeneity will remain in view of the differences in fracture risk between countries and in case finding strategies between guidelines [1]. Whatever method is used for fracture risk assessment in whatever context, the goal is to identify patients at high fracture risk. The higher the imminent subsequent fracture risk, the more urgent is the need for prompt decisions for highly effective treatment with rapid action [53]. The higher the long-term fracture risk, the higher is the need immediate decisions about long-term strategies with continuous, intermittent, or sequential treatments [55].

What interventions for what populations?

Population screening

In the above-mentioned systematic review, not only clinical case finding and further assessment differed between population screening studies but also the treatment thresholds, using only FRAX, or FRAX + BMD, or FRAX + VF, or only BMD, or VF without FRAX (Fig. 1) [5]. Treatment advice for bisphosphonates was given in 13%–25% of patients in the screening group.

None of the studies found a significant effect regarding the primary endpoint (osteoporotic fracture in SCOOP, major osteoporotic fractures (hip, wrist, humerus and clinical VFs) (MOF) in ROSE, total fractures in SOS). In SCOOP, a significant reduction was found for the risk of hip fracture as a pre-specified secondary endpoint in the subgroup at high risk (HR:0.72), with no impact of screening on falls in women informed to be at high risk of hip fracture [15]. In SOS, a post-hoc subgroup analysis in patients with a recent (<2 years) clinical fracture showed a significant lower incidence of MOF (HR:0.65) and hip fractures (HR:0.38).

In the meta-analysis, the risk of MOFs was significantly lower in the screened group compared to patients in the usual care group (HR:0.91), as was the risk of hip fractures (HR:0.80), although this was mainly driven by the SCOOP study.

The SCOOP approach with a number-to-screen of 111 to prevent one hip fracture and with 15% on treatment after one year (55% in the high risk group) was considered cost effective in the UK, with a cost of £7594 per prevented hip fracture, despite of having no effect on any fracture [59].

These outcomes show that, using various ways of a 2-step screening and assessment strategy in community dwelling elderly women between the age of 65 and 95, treatment was found to be beneficial in the subgroup at high risk for hip fracture. The reason for the disappointing effect on fracture risk reduction in the meta-analysis is unclear. One reason could be the prevention paradox [60]. As the high-risk group in SCOOP constitutes only 14% of the studied population, reducing the incidence of fractures in that group alone will not be sufficient to adequately prevent all fractures in the total population. Low uptake of osteoporosis medication, small differences in uptake between the screening and control group and low adherence after one year may also have contributed to these results [61,62].

High-risk approaches

Fracture prevention has been documented in RCTs (randomized controlled trial) in patients >50 years of age with, most often, a combination of prevalent morphometric VF with various BMD thresholds, two studies with fracture history without BMD criterium (after multiple prevalent morphometric VFs of unknown date or after a recent hip fracture), one study with a subgroup of only CRFs and studies with osteoporosis or osteopenia without fracture history as criterium. Therefore, the numbers needed to treat (NNT) and relative risk ratios (RRR) and absolute risk ratios (ARR) are different as per study, even with the same drug.

For details of RCTs in fracture prevention, we refer the reader to a network meta-analysis of 107 RCTs in postmenopausal women [63], a meta-analysis of 28 RCTs in men [64] and a recent review in postmenopausal women [65]. Patients with secondary osteoporosis or other bone diseases were excluded from these studies and are discussed elsewhere in this journal.

The RCTs evaluated the near-term fracture risk during two to three years. The absolute risk of non-VFs in the placebo group was 11% during two years after a recent hip fracture and, during three years, was 16% in patients with baseline multiple VFs, 14% with baseline osteopenia plus a VF, 9% with baseline osteopenia without VF and 8% with baseline T-score < -2.5 [66-69].

In most RCTs, a variable proportion of participants had a history of non-VFs. No RCTs have been performed with a recent non-vertebral non-hip (NVNH) fracture as the only inclusion criterium.

Therefore, when applying the evidence of RCTs, baseline assessment includes medical history, DXA, VFA and laboratory investigation [17,52,55].

Treatment strategy at start

As fracture prevention includes decisions at long-term, a lifelong strategy should be considered from the start of a first treatment. The decision about the first treatment (anti-resorptive or anabolic treatment) will influence the strategy at long-term [63,64]. Most studies were performed in women and osteoporotic fractures are less common in men. However, in both genders, the same risk factors for fractures apply, and thus the same advice can be given in women and men with similar thresholds.

Depending on the clinical presentation (recent fracture or not) and the fracture risk, different first treatment approaches can be considered when taking into account the inclusion criteria of RCTs.

Treatment approach after a recent fracture. One RCT was specifically designed to evaluate the effect of zoledronate versus placebo on fracture risk in patients with a recent hip fracture, irrespective of BMD, with a mean age of 74 years and a life expectancy of >6 months [66]. These were treated within 90 days with zoledronate every year for three years. This reduced the risk of morphometric VFs (HR:0.54) and of non-VFs fractures (HR:0.73) and an unexplained significant reduction in mortality (HR:0.72).

In the ARCH (Active-controlled fracture Study in Postmenopausal Women with Osteoporosis at High Risk of Fracture trial) trial (comparing romosozumab to alendronate for one year, followed by alendronate in both groups), patients with a recent hip fracture were also included (9% of the study population (N = 354) [70]. Unfortunately, no separate analyses on the specific efficacy of romosozumab in patients with a recent hip fracture have been published.

Treatment approach in FLS patients. No RCTs have been performed with as only inclusion criterium a NVNH without BMD criteria.

In a meta-analysis of seven FLS studies, FLS significantly increased treatment prescription (OR:3.82) [29]. In a meta-analysis of implementation of FLS, 3/16 clearly described care, 40%–80% performed a DXA and treatment was initiated in 20–80% [71]. Still, and considering methodological issues, the risk of subsequent fractures and mortality was significantly lower when comparing hospitals with and without a FLS (OR:0.70 and 0.73, respectively), or when comparing in the same hospital before and after the introduction of a FLS (OR:0.62 and 0.65, respectively).

As most patients with a recent NVNH clinical fracture at the FLS have osteoporosis or osteopenia and >20% have a subclinical morphometric VF, treatment can be based on results of BMD and VFA. In

very high-risk patients with low BMD and prevalent VFs or other multiple previous fractures, anabolic treatment should be considered as first treatment and anti-resorptive treatment in osteoporosis or osteopenia without VF.

In view of the heterogeneity of FLSs, studies on fracture and mortality risk with a more uniform approach, stricter methodology and with higher treatment uptake and adherence at a long-term treatment will be needed [6,71].

After fracture of unknown date. Risedronate treatment in patients with >1 VF without BMD criterium decreased the risk of VFs (RR:0.51) but without effect on non-VFs [67].

In postmenopausal women with a prevalent morphometric VF and variable degrees of a low BMD among studies, including osteopenia or osteoporosis, all treatments resulted in significant reduction of VF risk [65]. Hip fracture reduction was observed with alendronate (RR:0.61), risedronate (RR:0.73), zoledronate (RR:0.60), denosumab (RR:0.56) and romosozumab (RR:0.44) [65]. Non-VF risk reduction was observed with romosozumab (RR:0.67), alendronate (RR:0.84), risedronate (RR:0.78), zoledronate (RR:0.79), denosumab (RR:0.80), teriparatide (RR:0.62), lasofoxifene (RR:0.84), hormone therapy (RR:0.78) and tibolone (RR:0.73). Abaloparatide also reduced fracture risk (RR:0.51) but is not available in Europe [65].

Low BMD without a history of fractures. In patients with osteoporosis but without a clinical fracture history and without a prevalent VF, age, level of osteoporosis and presence of musculoskeletal diseases can be taken into consideration for clinical judgment about the treatment by the rheumatologist. In women between the age of 60 and 70, shared decision making is recommended and in women, in the late 60s and beyond, bisphosphonates are recommended, and denosumab that results in higher increases of BMD [4].

In a study in New Zeeland in women older than 70 years with osteopenia as only inclusion criterium, zoledronate every 18 months for 6 years reduced the risk of VFs (HR:0.45) and non-VFs (HR:0.66) compared to placebo [68]. The cumulative risk of clinical fractures was already >20% after 6 years, much higher than the median predicted 10-year risk of 12% at baseline. Thus, in New Zeeland fracture risk might be higher than in some other countries. Meanwhile, this study provides background to consider treatment in the context of a broader strategy for fracture prevention [61].

Only CRFs. Risedronate reduced the risk of hip fractures in women older than 70 years with very low BMD and/or CRFs (RR:0.70). Hip fracture reduction was shown in the subgroup of 70–79 years with osteoporosis (RR:0.60) or a prevalent VF (RR:0.40), but not in the subgroup of 80+ of which the majority was recruited solely on the basis of CRFs, again indicating that BMD and a prevalent VF contribute to treatment decisions [72].

Comparison between drugs: anabolic versus anti-resorptive treatment. In two RCTs with fracture prevention as primary endpoint, anabolic treatment was compared to anti-resorptive treatment.

In the VERO (Vertebral Fracture Treatment Comparisons in Osteoporotic Women trial) trial in postmenopausal women with at least two grade-2 or one grade-3 VFs and a T-score of ≤ -1.5, teriparatide during two years reduced the risk of new morphometric VFs (RR:0.44) and of first clinical fractures (RR:0.48) as compared to risedronate [73]. Similar results were found in a wide range of prespecified subgroup settings such as the presence or absence of prevalent VFs or of prior NVFs and in subgroups according to age and baseline BMD [74].

In the ARCH trial, postmenopausal women with at least one grade-2 or grade-3 VF in combination with a T score ≤ -2.0 at the total hip or femoral neck, or with a recent hip fracture (9% of all participants), were randomized to romosozumab versus alendronate for one year, followed by alendronate in both groups [70]. Over a period of two years, romosozumab during one year followed by alendronate significantly reduced the risk of new morphometric VFs (HR:0.52), non-VFs (HR:0.81) and hip fractures (HR:0.62) and new clinical fractures (HR:0.73) as compared to alendronate alone. In view of potential side effects, a history of stroke or myocardial infarction is a contra-indication for starting romosozumab.

Choice of first treatment. When the costs of the various drugs are considered, bisphosphonates will remain first choice in most countries and denosumab as a second choice. Anabolic treatments, albeit being more expensive, are more effective in reducing fractures compared to anti-resorptives especially in high-risk populations, such as those with a low BMD together with prevalent VFs, or after recent or multiple fractures with a very high risk. Romosozumab treatment is more effective in raising BMD in treatment naive patients and thus it seems more rational to start high risk patients upfront with romosozumab. No interaction in fracture prevention was found with teriparatide based on the presence or absence of a history of recent (suboptimal dosed) bisphosphonate use [74].

Long-term strategy

Once medical treatment is started, a life-long treatment strategy is needed [75]. Many different strategies are possible at long-term: continuous, sequential or intermittent treatment with temporarily stopping with a so called "drug holiday".

Continuing alendronate for 10 years instead of stopping after 5 years decreased the risk of non-VF in women without a prevalent VF when they had a femoral neck T-score of ≤ -2.5 [76].

During ten years treatment with denosumab, there was a continuous gain in bone density. Despite aging of the study population, non-VF rates upon 4–10 years of treatment were lower than initially observed with 3 years of therapy [77].

For anabolic therapies treatment duration is based on the pharmacodynamic properties and temporarily changes in markers of bone formation and resorption of both romosozumab and teriparatide, for which treatment is advocated for 12 months, respectively, 24 months and should always be followed by anti-resorptive treatment. In addition, while anti-resorptives can be re-started, this is not advocated for anabolic treatments. Teriparatide is only approved for 24 months use due to the black box warning of the small increased risk of osteosarcoma in rats, but not in humans [55]. Romosozumab is approved for one-year treatment but does not have this restriction and has been shown to be effective when re-started after a break [78]. However, there are data on BMD and bone markers, but not on fracture prevention or on the safety of such a strategy. Therefore, for designing a long-term strategy, one must decide on the duration of therapy and the sequential order of anti-resorptive and anabolic therapy (Fig. 5) [62,75].

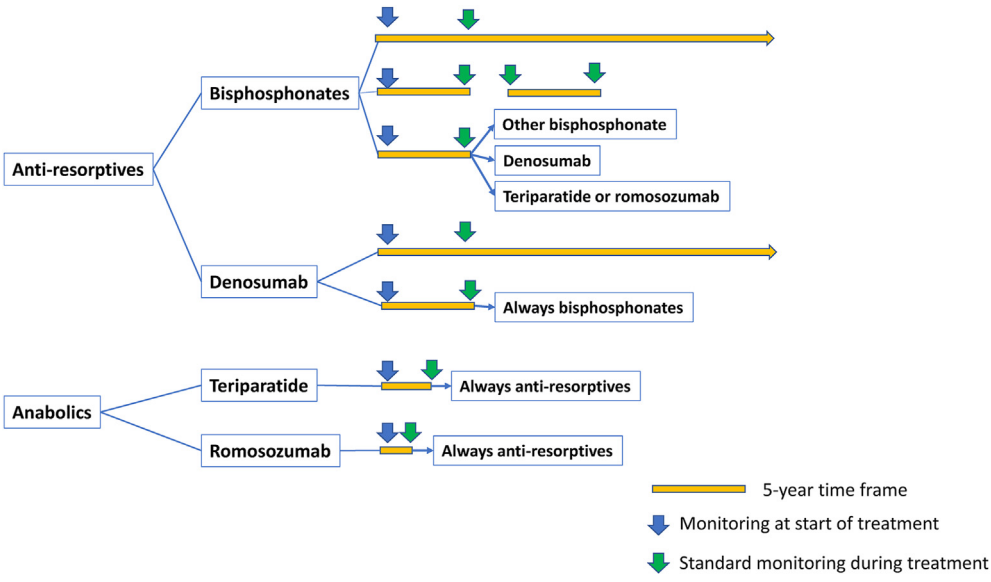

Fig. 5. Examples of long-term strategies for fracture prevention (see text for explanation).

After anabolic treatment. Anabolic treatment should always be followed by anti-resorpitve treatment.

This has been shown after teriparatide, abaloparatide and romosozumab [79]. In the DATA (Denosumab and teriparatide transitions in postmenopausal osteoporosis study) switch trial, a clear ongoing increase in BMD was observed if teriparatide was followed with denosumab [80]. In an observational study, the incidence of VFs was lower in patients treated with teriparatide and anti-resorptive treatment than in patients only treated with anti-resorptives [81].

In the ARCH trial, patients were switched to alendronate after 12 months of treatment with romosozumab and after this switch, the clinical fracture rate was lower than that of patients treated with alendronate from the beginning [82]. There are no studies comparing romosozumab and teriparatide on a fracture endpoint, but a head-to-head study showed that in patients who were recently treated with adequately dosed bisphosphonates, romosozumab increased the BMD and calculated bone strength at the hip while teriparatide showed a small temporarily decrease [57]. In the FRAME (Fracture study in postmenopausal women with osteoporosis trial) study, romosozumab treatment was followed by 2 years of denosumab treatment and showed a higher increase in BMD than in the alendronate treated patients in the ARCH trial [82,83].

After anti-resorptive treatment. For anti-resorptive drugs, there is a very important difference in the mechanism of action between bisphosphonates, which are incorporated into the bone matrix, and denosumab which remains in the circulation. This difference became clear after the first reports on the so-called rebound phenomenon on bone turnover, immediate and accelerated bone loss, and an associated rebound in VF risk after discontinuing denosumab [84]. This phenomenon has been linked to the occurrence of newly discovered bone cells, the osteomorphs. In a study of murine osteoclasts *in vitro*, these cells split-off from osteoclasts during RANKL (receptor activator of nuclear factor kappa beta (NFkB) ligand) inhibition and can rapidly fuse to many new osteoclasts when RANKL inhibition is stopped [85]. Therefore, from the start of denosumab an exit strategy should be designed and discussed with the patients to minimize the risk for this rebound phenomenon when stopping therapy. Recent studies have shown that the longer denosumab treatment is given, the higher is the risk for a more severe rebound phenomenon after stopping and that bisphosphonates can dampen this [84]. On the contrary, safety data on denosumab for >10 years have become available showing a favorable safety profile and ongoing anti-fracture effect [77]. Treatment strategies in patients started on denosumab might be intentional long-term use up to 10 years that is especially potentially attractive in more fragile elderly patients or deliberately short-term use of three years or when a T-score target is achieved [86], followed by a course of bisphosphonates. It is not advocated after denosumab to start directly with an anabolic drugs because the rebound phenomenon will still occur, and in the case of teriparatide has been associated with a temporarily decrease in BMD at the spine and hip and a continuous decrease at the radius [80].

Bisphosphonates are incorporated into the bone matrix and do not result in a rebound phenomenon when stopped [87]. A drug holiday is recommended after 5 years alendronate or 3 years of zoledronate in low-risk patients but continuation if risk is still high. After discontinuing bisphosphonates, follow up after 2–3 years is needed to re-evaluate fracture risk and decide whether to restart switch treatment. In women who discontinued alendronate after 4–5 years, there was still a gradual decline in BMD and progressive increase in bone markers. In women who continued alendronate for 10 years ongoing treatment efficacy was observed. In the case of risedronate data are limited, with only one report of an ongoing lower risk of VFs when medication was continued after five years during two additional years.

In the HORIZON (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly trial) trial with yearly zoledronate, after 3 years, the risk for morphometric VFs and non-VFs was low in patients with a total hip T-score > −2.5, without new fractures, and with no more than one CRF [88]. In addition, the benefit of prolonged treatment after the first period should be weighed against the small risk for rare side effects (atypical femur fractures and osteonecrosis of the jaw) that are time and dose dependent. After bisphosphonates treatment can be switched to any other anti-osteoporotic drugs. Both romosozumab and teriparatide can be initiated although the effect on BMD increase might be less pronounced, albeit still being significant [89]. Fracture data in patients who received such sequential therapy are lacking.

For deciding about a long-term strategy for osteoporosis treatment, one should consider patient's life expectancy, previous VFs and risk profile. It might be beneficial to treat high risk patient's first with

anabolic treatment, followed by a short course of denosumab to increase BMD even more and to consolidate treatment with bisphosphonates, whereas in others it might be more beneficial to subsequently treat with a bisphosphonate [55].

In conclusion, the different mechanism of action of the different available compounds allows tailored treatment and long-term strategies.

Patients with a very high risk, such as a combination of low BMD and VF, multiple prior fractures, a recent fracture, a very low BMD, or a very high FRAX with low BMD and VFs, deserve special attention of the rheumatologist to consider anabolic treatment over anti-resorptive treatment [17].

Standard monitoring during therapy includes a regular clinical review of patient's tolerance and adherence after starting treatment, with after 2–5 years during treatment a medical history including new risk factors, DXA, VFA, fall risk, laboratory examinations and eventual the use of bone markers (Fig. 5) [17,53,87].

Standard monitoring allows decisions about successful treatment (no new risk factors, no new fractures, including morphometric VFs, BMD T-score > -2.5) versus treatment failure (new or worsening risk factors, new fractures, including new morphometric VFs, T-score < -2.5, bone loss >5%).

Adherence and compliance should be checked at regular intervals because of high risk of non-compliance [90,91]. In this context, there is increasing interest in the role communication at the FLS [92], of shared decision making and patient preferences should be considered [91].

How to implement?

The example of the development of a FLS guideline in the Netherlands

One of the most difficult steps in modern medicine is the implementation of recommendations and guidelines in daily practice [93]. Not only facilitators but also several (different) barriers play a role. In 120 different surveys, Cabana found lack of awareness (n = 46), lack of familiarity (n = 31), lack of agreement (n = 33), lack of self-efficacy (n = 19), lack of outcome expectancy (n = 8) and external barriers to perform recommendations (n = 34) [94]. Some of the barriers are within doctors' control, but others are related to organizational culture.

Guideline adherence is, like in other diseases, also in osteoporosis and fracture prevention a huge problem [2]. It concerned the process of case finding of patients, the need for public awareness about osteoporosis and the national policies on reimbursement of assessment and therapy. Examples are organizational short-comings, low disease-perception and complexity of guidelines [95-97].

However, the set-up and running a FLS is a complex process, which needs a leader, and in which a rheumatologist, together with other specialties (endocrinologists, geriatricians, physiotherapists, nurses, *etc.*) can play a central role. FLSs increase evaluation and treatment initiation and reduce the risk of subsequent fracture and mortality [71].

In a recent review of the countries of the EU (+UK and Switzerland), there was a high variability of policy framework, service provision and service uptake between countries [48]. Only three countries reported a FLS density of >50%. In 20 countries, rheumatologists were involved [98]. The mean treatment gap in six EU countries increased from 56% in 2010 to 73% in 2017.

We describe as an example the situation in the Netherlands, because the newly developed guideline was based on and aligned with a recent in-depth analysis and investigation of osteoporosis' care by the Dutch Healthcare Institute in the Netherlands, and it will be followed by a broadly driven multidisciplinary implementation plan.

The previous multidisciplinary guideline (since 2011) clearly described the role of the FLS in evaluation, treatment initiation and follow up. Despite all efforts DXA and VFA were performed in only 26% of all patients aged 50 and older after a recent fracture [14].

For developing the new guideline on osteoporosis and fracture prevention, all stakeholders (medical specialists, general practitioners, FLS nurses and the patient organization) participated and could give comments to officially approve the guideline.

Meanwhile, the Dutch Healthcare Institute report (in 2020) recognized 3 main themes regarding the low treatment rate, namely, underdiagnosis of patients at risk for subsequent fracture,

Table 1
Implementation of guideline topics for secondary fracture prevention at the FLS.

Topic	Implementation problem	Recommendation in (new) guideline on the topic, yes/no	Recommendation in (new) guideline	Extra solutions: examples of other forms of recommendations
Prevent underdiagnosis of high fracture risk	Improve the organization of health care after fracture in patients 50 years and older	Yes	Multidisciplinary fracture prevention team in every hospital with active role to track patients after fracture. The electronic patient chart should automatically deliver an appointment at the FLS outpatient clinic directly after presenting with a fracture on the ED, if the patient is over 50 years of age.	Responsibility to form this multidisciplinary fracture prevention team by the board of the hospital.
	Measure BMD in patients on glucocorticoids and high risk of secondary osteoporosis	yes	Recommendation with flowchart when DXA has to be performed, and when the treatment is necessary.	Flowchart
	Perform more often VFA to diagnose vertebral fractures	yes	Always perform additional imaging of the spine (VFA or X-ray) when a DXA is indicated.	
	Improve reporting on vertebral fractures	yes	Recommendation aligned with radiologists on standardization of reports on which vertebrae are visible, on rating vertebrae with the method of Genant, and on using the term vertebral fracture when height loss is 20% or more.	
	Coordinate guidelines to simplify recommendations and alignment of recommendations for primary care and for various medical specialists.	no		Guideline was developed with all medical specialties together to stimulate the alignment.
	Perform fall risk assessments in patients after a fall or fracture	Yes, partly	Recommendation for patients 50 −65 years old: how to recognize reversible fall risk factors and how to treat them.	A guideline on fall risk prevention existed already for patients 65 years and older.
Improve treatment of high fracture risk and osteoporosis	Start drug therapy in patients after fracture with treatment indication	yes	Recommendation of preferred treatment in various situations and patient groups with an extensive flowchart.	Flowchart
	Start bisphosphonates in patients on glucocorticoids	yes	Recommendation with a flowchart for different age groups.	Flowchart

(*continued on next page*)

Table 1 (*continued*)

Topic	Implementation problem	Recommendation in (new) guideline on the topic, yes/no	Recommendation in (new) guideline	Extra solutions: examples of other forms of recommendations
	Coordinate medication monitoring for patients on glucocorticoids	no		Recommendation on follow up and treatment adherence of patients on medication in general, not specific of patients on glucocorticoids.
	Coordinate maintaining osteoporosis therapy such as bisphosphonates	yes	Recommendation on follow up and treatment adherence. Recommendation on responsibility of medical specialists and the role of the general practitioner.	
	Do not stop denosumab without a follow up treatment plan	yes	Recommendation with flow chart, when to stop and how to stop or to continue in selected patient groups.	Flowchart
	Advise on the prevention of falls	yes	Recommendation on exercise and fall risk prevention.	
Improve information for public and patients	Improve description of risk factors for fractures in patient information	Yes	All items are addressed as recommendations in the guideline, in an extension on the organization of health care for fracture prevention. 'Improve and standardize information on fracture risk, osteoporosis vertebral fractures, fall risk and underlying diseases. Give this information at the time of the fracture (at the ED) and give information on the diagnostic trajectory. Refer to DOA. Improve and standardize information on treatment options for osteoporosis and high fracture risk. Underline the importance of compliance to therapy. Use a decision aid. '	
	Describe the four factors of diagnostic process better	Yes		
	Improve information on fall risk prevention and lifestyle	Yes		
	Improve information of various therapies such as bisphosphonates, denosumab and other medication	yes		
	Describe information on follow up of treatments	yes		
	Refer patients for more information to Osteoporosis association in the Netherlands	yes		
	Use a decision aid, connect it to the guidelines and coordinate its accessibility for patients	yes		
Extra identified barriers formulated by expert group,	Financial conditions to organize care in general practices	yes	Recommendation for the organization of healthcare, health care insurers should pay extra for FLS care performed by GP's.	
		yes	Recommendation to redefine financial incentive: one financial	

Improving financial conditions within the hospitals to avoid low value care		compensation for all medical specialties in the hospital	
Role of pharmacies in treatment adherence	yes	Recommendation for pharmacists in their responsibility in alarming when compliance of treatment fails.	
Improve the awareness of people for fractures and underlying diseases.	no		Recommendation: 'Organize a national campaign to create awareness for the impact of fractures and the importance of diagnostic trajectory for underlying causes and or treatment for fracture risk'. Responsibility was assigned to DOA.

BMD: Bone Mineral Density by DXA, VFA: Vertebral fracture assessment by DXA.
FLS: Fracture Liaison Service, ED: Emergency Department.
GP: General Practitioner.
DOA: the Dutch Osteoporosis Association.

undertreatment of various patient groups at high fracture risk and a low quality of patient information on osteoporosis and fracture prevention.

A major barrier for implementation is that so many medical specialties are involved and recommended that a fracture prevention team of combined specialties should be responsible to track patients after fracture.

Finally, the guideline expert group recommended a national awareness campaign on the impact of fracture and the importance of a diagnostic trajectory.

In Table 1, the implementation problems, recommendations in the guideline and extra solutions are tabulated. We list here the main findings.

Improve underdiagnosis. Every hospital is recommended to have a multidisciplinary fracture prevention team under supervision by a bone expert with an active administrative system to track patients systematically and automatically with a recent fracture.

In all patients, DXA should be accompanied by also imaging of the spine and radiologists were instructed to use a relatively simple scheme to report the results.

Improve treatment. Flowcharts were constructed to simplify the start of anti-osteoporotic drug treatment, the follow up, and addressing the question of continuous, intermittent or sequential therapy over lifetime.

Fall prevention recommendations in patients who have recently fractured or fallen.

One recommendation was on the coordination of monitoring treatment for patients on adherence of treatment for all patients on treatment and recommendations on the responsibility of medical specialist and the role of GP and pharmacies in maintaining treatment adherence.

Improve information for public and patients. The focus was on the improvement of information for public and patients by recommending standardizing information directly at the emergency unit at the time of a fracture, verbally and written.

Extra solutions. Financial incentives are major drivers for change and should take into account general practice support and financial incentive to improve the quality of care in the hospital.

Future initiatives. Audit and feedback (A&F) on a personal level for physicians could help change behavior and improve the delivered care [17,99]. A&F can overcome the lack of self-efficacy and lack of outcome expectancy. In the Netherlands, A&F in FLS care is poorly implemented, which leaves room for improvement.

Finally, the guideline expert group recommended a national awareness campaign to address the impact of fracture and the importance of a diagnostic trajectory for underlying causes.

In conclusion, these recommendations on implementation will help rheumatologists to be involved in the process of guideline development and to maximally implement the case finding, assessment, treatment and follow up of patients at high risk of fracture.

Practice Points

- Case finding based on the presence of one or more CRFs is the essential initial step to trigger clinical risk evaluation for deciding about further assessment with DXA and imaging of the spine.
- Identifying patients with a recent clinical fracture or with a subclinical VF is the cornerstone for assessment with DXA, VFA, laboratory examination and fall risk evaluation and to consider secondary fracture prevention.
- Since osteoporosis is a chronic and progressive metabolic bone disorder, sequential strategies for lifelong fracture prevention are developed based on anti-resorptive and anabolic treatment.
- In high-risk patients, starting treatment with anabolic drugs is superior to starting with anti-resorptives and should be considered especially in those with fractures.
- Implementation of guidelines requires special attention to treatment initiation, adherence, structural changes in health care organization and public awareness.

Research agenda

- For clinical case finding, fracture risk algorithms need further refinement and simplification.
- Further long-term studies are needed on secondary fracture prevention with early and higher implementation of assessment and treatment.
- Implementation of long-term therapy needs further studies including the role of shared decision making, patient preferences and monitoring of therapy.

Declaration of Competing interest

Piet Geusens.

Clinical studies, advisory boards, speaker fees from Abbott, Amgen, BMS, Celgene, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, UCB, Fresenius, Mylan, Sandoz, Merck.

Natasha M. Appelman-Dijkstra. Clinical studies/speaker fees from Amgen, UCB, Kyowa Kirin,

M. Carola Zillikens.

Hanna Willems. Clinical studies/advisory boards/speaker fees from Amgen, UCB.

Willem F. Lems. Advisory boards/speaker fees Amgen, UCB, Pfizer, Galapagos.

Joop van den Bergh. Advisory boards/speaker fees from Amgen, UCB.

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