Expert opinion on the management of patients with osteoporosis with anabolic drugs in Italy

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SUMMARY

Objective. Fragility fractures (FF) resulting from osteoporosis pose a significant public health challenge in Italy, with considerable socio-health and economic implications. Despite the availability of safe and effective drugs, osteoporosis remains underdiagnosed and undertreated, leaving over 2 million high-risk Italian women without treatment. This paper aims to identify and propose key improvements in the management of osteoporosis, focusing particularly on the critical issues related to the use of anabolic drugs in secondary prevention, according to the current Italian Medicines Agency (AIFA) Note 79.

Methods. The Expert Panel, composed of nine recognized Italian experts in rheumatology, analyzed current practices, prescribing criteria, and the most recent literature. Three main reasons for revising the indications on pharmacological treatment of osteoporosis were identified: inadequate treatment of osteoporosis, new evidence regarding frontline placement of anabolics in high-risk conditions, and emerging sequential or combined strategies.

Results. The proposed improvements include the adoption of the Derived Fracture Risk Assessment algorithm for accurate fracture risk assessment, revision of AIFA Note 79 to reflect current evidence, improved prescribing appropriateness, broader access to anabolic agents, and the provision of sequential therapies with antiresorptives for teriparatide. These changes aim to enhance patient outcomes, streamline healthcare processes, and address the high percentage of undertreated individuals.

Conclusions. This expert opinion emphasizes the importance of the appropriate use of anabolic drugs to reduce FF and associated costs while ensuring the sustainability of the National Health Service. The proposed recommendations are in line with the latest scientific evidence, providing a comprehensive strategy to optimize the management of osteoporosis in Italy.

***Key words**: Osteoporosis, fragility fractures, AIFA Note 79, anabolic drug, teriparatide.*

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INTRODUCTION

Fragility fractures (FF) resulting from osteoporosis are a major public health challenge in Italy, representing a significant and growing burden from both a socio-health and economic perspective. Despite the magnitude of the problem, osteoporosis remains largely underdiagnosed and undertreated. Currently, more than 2 million Italian women at high risk of fracture receive no treatment for osteoporosis, despite the existence of safe and effective drugs (1).

The main goal of osteoporosis therapy is to reduce the risk of fracture. Therefore, an accurate assessment of fracture risk is the first step in the treatment decision-making process to optimally determine who, when, and

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how to treat. This includes the more general concept of therapeutic appropriateness, which stems from the convergence of patient interests and the sustainability of the National Health Service (NHS).

Indeed, it is important to emphasize that while the main goal is to protect the patient's health, resources are limited and must be used properly. In Italy, prescriptive appropriateness in the field of osteoporosis has been regulated for several years by the Italian Medicines Agency (AIFA) Note 79, which establishes the criteria by which drugs identified as effective can be prescribed at the expense of the NHS. The Note was updated in August 2022 and again in February 2023, including a new anabolic drug (romosozumab) among those reimbursable by the NHS and providing for the prescribability of anabolics by all interested specialists.

A panel of nine recognized Italian rheumatologists met to draft an expert opinion on the critical issues of the current use of anabolic drugs in Italy and the possibilities for improving their use. The panel addressed and discussed various aspects related to the current management of patients with osteoporosis, with particular reference to the use of anabolic drugs in secondary prevention according to the current Note 79. Specifically, the discussion among the experts developed by answering a series of questions on three main topics: management of the patient with osteoporosis according to the current AIFA Note 79 and proposed revisions of the Note; risk stratification and risk assessment tools; and therapeutic strategies and sequential treatment, considering the pros and cons of teriparatide, romosozumab, and denosumab. The manuscript was drafted and revised following an in-depth review of current literature using the PubMed/MEDLINE database and based on current prescribing criteria according to AIFA, information from AIFA's OSMed reports, and the clinical experiences of the participants. The aim was to provide a critical review and suggest proposals that would contribute to better use of anabolic drugs in the secondary prevention of FF, in line with the latest scientific evidence and guidelines.

Definition, epidemiology, and clinical, economical, and social impact of osteoporosis and subsequent fragility fractures in Italy

Osteoporosis is a systemic skeletal disease characterized by decreased bone mineral density (BMD) and impaired bone structure, leading to increased fragility and fracture risk (2). The diagnostic criteria are densitometric and/or clinical. According to the World Health Organization, osteoporosis is defined as a BMD, as measured by dual-energy X-ray absorptiometry, less than 2.5 standard deviations (SD) from the mean reference value for healthy young adults (T-score ≤-2.5 SD) at the skeletal site considered, usually the femur or spine (3). It is defined as severe if already complicated by a FF, that is, a fracture not due to efficient trauma. The latter occurrence, especially in the femur, vertebra, or wrist, may suffice as a clinical criterion for the diagnosis of osteoporosis once other pathologies have been excluded (4). It is referred to as "silent disease" because it is often asymptomatic until a FF occurs, most commonly of the wrist, vertebrae, or proximal femur (5).

Osteoporosis can be divided into primary, which includes forms that appear after menopause (postmenopausal), or due to advancing age for both sexes (senile), or secondary to other diseases, medications, or lifestyle risk factors (5). One of the main processes involved in the pathophysiology of osteoporosis is the imbalance between bone formation and bone resorption. The regulation of bone homeostasis involves a complex interaction between osteoblastic (responsible for bone formation) and osteoclastic (involved in bone resorption) cells, which work synergistically to maintain bone integrity and strength. Alterations in this balance can lead to loss of bone mass and increased risk of fractures, hence the rationale for antiresorptive (bisphosphonates or denosumab) or anabolic (teriparatide or romosozumab) therapeutic approaches.

In Italy, osteoporosis is estimated to affect about 5 million people, more than 80% of whom are postmenopausal women (6). According to ISTAT data for the year 2022, 7.9% of the Italian population (13.2% of

females and 2.1% of males) reported having osteoporosis, with prevalence progressively increasing with advancing age, particularly in women after age 55 years, reaching 30.8% over age 74 years (44.9% of females and 9.2% of males) (7). Since its incidence increases with age, affecting most of the population after the eighth decade of life, the number of osteoporotic patients is likely to increase due to increased life expectancy (1). FF are the most important clinical manifestation of osteoporosis and have a significant impact in terms of both disability and mortality (1).

The considerable clinical impact of osteoporosis is reflected, also from an economic point of view, in the high healthcare costs, especially those related to hospitalizations and indirect costs due to disability (1, 6). The economic significance is, moreover, determined by the fact that bone fractures are one of the most common causes of disability affecting health care costs in Western countries (1). In 2019, in Italy, considering only FF afferent to an emergency department, about 570,000 new bone FF occurred, with an expenditure of € 9.5 billion by the Italian NHS. Of this, only half a billion is due to costs for pharmacological management. With an aging population and a lack of adequate intervention policies, the number of FF is expected to increase by 25% in the next 15 years (1). Therefore, reducing the health and social impact of bone fragility means not only preserving patients' autonomy and quality of life but also realizing significant health economies.

Is there a need to update the reimbursability criteria for the pharmacological treatment of osteoporosis, especially in secondary prevention with anabolic drugs?

The Expert Panel believes there are basically three reasons for revising the indications on pharmacological treatment of osteoporosis, especially in secondary prevention with anabolic drugs:

1) evidence of inadequate treatment of osteoporosis, especially the use of anabolic drugs, even under conditions of safe opportunity such as after FF;
2) new evidence regarding frontline placement of anabolics in conditions with very high or imminent risk of fracture;
3) recent evidence for new sequential or combined strategies in the use of antiresorptive and anabolic drugs and novel therapeutic targets now possible.

Evidence of inadequate treatment of osteoporosis

The osteoporosis patients still appear to be "children of a lesser God" (8). Osteoporosis is not currently recognized by the NHS as a chronic disease, even if already manifested by FF, and there are no exemptions for related diagnostic tests. The percentage of patients who are entitled to treatment but do not receive it or receive it inadequately is still very high, exceeding 70%, particularly in women (1). In fact, if lifestyle modifications and correction of any calcium and/or vitamin D deficits are not sufficient, the physician may indeed recommend targeted drug therapy under conditions of FF risk (5).

There are numerous anti-fracture drugs available today, of which both efficacy and an acceptable safety profile have been amply demonstrated. Consequently, they are considered useful in terms of cost-benefit balance and therefore reimbursable by the NHS according to the AIFA Note, especially in specific conditions with a high risk of fracture (9). Secondary prevention of osteoporosis focuses on reducing the risk of future fractures in patients who have already suffered from them. Numerous scientific studies have shown its importance because patients with previous FF have an increased risk of new FF (10). More recently, it has been observed that when a vertebral FF is unrecognized, the risk of both vertebral and nonvertebral new fractures increases in the next 2 years after the previous fracture (11).

Prevention of FF has long been one of the priorities identified by the Ministry of Health. In 2010, in the Ministry of Health's Notebook *Diagnostic and Therapeutic Appropriateness in the Prevention of Frailty Fractures* precise goals for primary and secondary prevention of FF were set:

1) place more than 80% of subjects hospitalized for FF on anti-fracture therapy;

2) keep more than 70% of patients started on anti-fracture treatment at one year;
3) reduce femoral FFs by 20%.

These goals have not been met. Less than 20% of patients with major FF (at the level of the vertebra, proximal femur, humerus, and forearm) now enter secondary prevention programs for refracture within one year of the fracture episode, less than 50% of those on therapy are adherent to antifracture therapy one year after initiation (12). Notably, OsMed Reports continue to show very low use of teripatide (Figure 1) (12), which has been available for years, even in patients with prior FF and in conditions in which AIFA recommends its use.

New evidence regarding frontline placement of anabolics in conditions with very high or imminent risk of fracture

Previous FF, especially if recent or multiple, represents a very high-risk condition, also called imminent. Recent international and national guidelines recommend the first-line use of anabolic drugs in these conditions (13-16). This is based on the following evidence:

1) with anabolic drugs, compared with antiresorptive drugs, the greatest densitometric increases can be achieved, for which a close correlation with fracture risk reduction has been demonstrated (17);
2) head-to-head and network meta-analysis studies have demonstrated the greater and faster (within 1 year) ability of anabolics compared with antiresorptives to reduce fracture risk (18-21);
3) the use of antiresorptives such as bisphosphonates require at least 1 year of treatment before they have a substantial impact in reducing fracture risk (22, 23);
4) prior treatment with antiresorptives attenuates the densitometric gains achievable with anabolics (24, 25);
5) a close correlation between T-score and fracture risk, both vertebral and nonvertebral, is confirmed (26); for achieving the densitometric target of a T-score >-2.5, *i.e.*, to return from a condition of osteoporosis to one of osteopenia (27), it is preferable to use a sequential strategy involving the first-line use of an anabolic followed by an antiresorptive (28).

Based on this evidence, the first-line use of anabolics in conditions characterized by severe quantitative and qualitative impairment of bone mass, or conditions characterized by a very high risk of fracture, such as following previous FF, especially multiple and recent FF, seems appropriate. This has been recognized by AIFA in its Note 79 for years already, placing teriparatide in the first-line in patients with very high fracture risk conditions such as those of patients with three vertebral or femur fractures or with combined high-risk factors such as a previous vertebral fracture and chronic corticosteroid use. However, the significant reduction in the cost of the drug due to the arrival of biosimilars and recent reassuring evidence in terms of safety justify less restrictive access criteria than in the past.

Recent evidence for new sequential or combined strategies in the use of antiresorptive and anabolic drugs and novel possible therapeutic targets

The increase in available pharmacological options with different and innovative mechanisms of action now facilitates planning more appropriate combinations or sequential therapeutic strategies over the long term. Anabolic drugs that, when adminis-

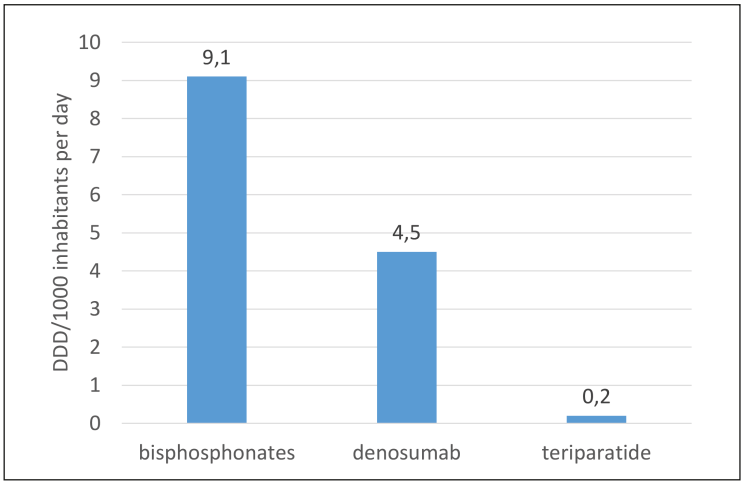

Figure 1 - OsMed Report 2022. Osteoporosis drugs: consumption (DDD/1000 inhabitants per day).

tered intermittently, act through the parathyroid hormone receptor by stimulating osteoblastic activity and thus promoting bone neoformation include teriparatide and, proximally, abaloparatide. Recently approved and introduced is romosozumab, which, by blocking the action of sclerostin, an inhibitor of the Wnt pathway, allows for a combined effect of stimulating neoformation and inhibiting bone resorption.

The availability of therapeutic approaches with different mechanisms of action now makes it imperative to identify not only which molecule is most appropriate for each clinical condition but also which may be the ideal (medium- to long-term) pharmacological strategy through sequential approaches. Moreover, drug therapies with anabolics, such as teriparatide and romosozumab, can only be carried out for a limited period of time, involving a 24- and 12-month course of treatment, respectively. With the exception of bisphosphonates, discontinuation of pharmacological treatment for osteoporosis is known to be accompanied by an undesirable resumption of bone loss that can nullify much of the densitometric effect achieved and be associated with a rapid increase in fracture risk. Therefore, it is essential in these cases to always provide appropriate sequential therapy.

The densitometric effects of anabolic-acting therapies are somewhat consolidated and amplified by subsequent antiresorptive therapy (18, 29, 30). On the other hand, it is well known that certain sequential approaches may produce negative effects: in patients who fracture under antiresorptive treatment with denosumab, the shift to teriparatide may even be counterproductive and dangerous in terms of fracture risk. In this case, the initiation of combination therapy of denosumab with teriparatide may be appropriate (31). In recent years, in fact, combination studies, *i.e.*, simultaneous administration of an anabolic drug and an antiresorptive agent, have become available, which have shown the possible synergistic effect of some drugs administered in combination, at least in terms of bone turnover markers (32) and densitometric results (33); however, there is a lack of documentation in terms of antifracture efficacy. In particular, combination therapy of teriparatide with zoledronate results in faster densitometric gains than treatment with teriparatide alone, especially in predominantly cortical bone such as that of the femur (34). The DATA-study showed that combination therapy of teriparatide and denosumab in women with postmenopausal osteoporosis results in greater densitometric increases at the lumbar and femoral levels than those obtained with monotherapy (35).

Proposals for improving the use of anabolics in the management of osteoporosis

Use of the Derived Fracture Risk Assessment algorithm

FF risk assessment is a crucial element in identifying patients who might benefit from preventive and therapeutic interventions. In particular, recognizing a condition of high FF risk appears crucial in judging the appropriateness of pharmacological treatment, perhaps through tools for accurate yet feasible and rapid assessment. The assessment of FF risk in the individual patient results from the complex interaction and integration of multiple factors, densitometric, anamnestic, and clinical. For the integrated assessment of multiple risk factors, computerized mathematical algorithms have been created to estimate the risk of FF over the next 10 years by integrating information from BMD measurement with information from the presence of multiple other anamnestic and clinical risk factors independent of BMD. The recent Superior Institute of Health (ISS, *Istituto Superiore di Sanità*) guidelines on *Diagnosis, Risk Stratification and Continuity of Care of Fragility Fractures* recommend the use of algorithms for FF risk assessment (15). One of the earliest and most widely internationally used algorithms is the Fracture Risk Assessment Tool (FRAX®), a fracture risk assessment tool (https://frax.shef.ac.uk/FRAX/) developed by the University of Sheffield (36, 37).

To calculate risk, the system uses an algorithm based on risk factors such as age, gender, body mass index, family history of fractures, previous fractures, tobacco and

alcohol use, corticosteroid use, and BMD value (if available). To overcome some of the limitations of FRAX®, mainly due to the use of limited and only dichotomous variables, the "Derived Fracture Risk Assessment" (DeFRA) (https://defra-osteoporosi.it/) has been developed in Italy, with the contribution in particular of the Section of Rheumatology of the Department of Medicine of the University of Verona. The DeFRA stratifies in more detail some of the variables already present in FRAX® and considers others to improve the predictivity of fracture risk (38).

The DeFRA has the auspices of the Italian Society of Osteoporosis, Mineral Metabolism, and Skeletal Diseases (*Società Italiana dell'Osteoporosi, del Metabolismo Minerale e delle Malattie dello Scheletro*), the Italian Society of Rheumatology (*Società Italiana di Reumatologia*), and the Italian Bone Interdisciplinary Specialists Group. Available free online, it is currently used in Italy by more than 12,000 physicians, both general practitioners (GPs) and specialists of different backgrounds, distributed throughout the country. The ISS Guidelines on *"Diagnosis, Risk Stratification and Continuity of Care of Fragility Fractures"* have rated it at least equivalent to FRAX® and recommend its use (11, 15). DeFRA has been found to be more accurate than FRAX®, particularly in postmenopausal women with certain forms of secondary osteoporosis, such as those associated with diabetes (39, 40), or systemic lupus erythematosus (41).

The use of DeFRA has also been recommended by a Commission of the Superior Council of Health on Orthopedic Pathology in fragile conditions (42) and by the Diagnostic Therapeutic Care Pathways for the prevention of FF in several regions, including Campania, Veneto, and Lombardy. DeFRA allows physicians to know in a few seconds the degree of their patient's risk of suffering a fracture in the next decade, whether pharmacological treatment is recommended and with which drug, and whether or not a specialist evaluation is indicated. The potential of using DeFRA in the appropriate management of the pharmacological treatment of osteoporosis is manifold. Consider the possibility of contributing to counseling for the patient and improving the GP/specialist interaction, clarifying their respective competencies, and rationalizing the criteria for access to specialist outpatient clinics, resulting in shorter waiting lists. DeFRA also enables the collection of clinical data to help verify and improve prescriptive appropriateness. Finally, using DeFRA can facilitate the implementation of AIFA recommendations on the appropriate use of drugs, according to Note 79. DeFRA was recently updated based on the risk factors considered by AIFA in Note 79 and new ones identified in the NIH guidelines (15).

Revision of Note 79

AIFA's Note 79 regulates the criteria for prescribing drugs for the treatment of osteoporosis paid for by the NHS and, at the same time, is a guide for prescriptive appropriateness. In fact, it guides the choice of drugs, using a classification based on their efficacy in the various forms of osteoporosis, safety, and cost, and aims to treat those who really need to prevent FF, both in primary and secondary prevention. This involves careful assessment of the patient's fracture risk and consideration of the balance between drug efficacy, potential side effects, and the cost of treatment. Currently, note 79 indicates the use of anabolics (teriparatide or romosozumab) only in secondary prevention, that is, in patients with previous vertebral or femoral fractures or subjects with other fractures with demonstrated BMD reduction (Table I) (9).

The Expert Panel highlighted several critical issues in the current AIFA Note 79 and hypothesized some proposals for changes to the note to improve the prescription of osteoporosis drugs, particularly anabolic ones. Experts agree that the current note does not provide all the opportunities to adequately manage secondary prevention, and this is also why many patients who would benefit from treatment continue to be undertreated, resulting in personal and social costs for recurrences of FF that could actually be prevented.

Table I - Secondary prevention in subjects with previous osteoporotic fractures. Reproduced and translated from: AIFA, 2022 (9).

Vertebral or femoral fractures			
Condition	**Treatment I choice**	**II choice**	**III choice**
1-2 fractures	Alendronate (±vit. D), Risedronate, Zoledronate	Denosumab, Ibandronate, Raloxifene, Bazedoxifene	
≥3 fractures	Teriparatide	Denosumab Zoledronate	Alendronate (± vit.D) Risedronate, Ibandronate
≥1 fracture + T-score column or femur ≤-4			
≥1 fracture + treatment >12 months with prednisone or equivalent ≥5 mg/day			
New vertebral or femoral fracture despite treatment in Note 79 for at least 1 year			
Female patients with column or femur T-score <-2.5 (<-2.0 if ≥2 moderate or severe vertebral fractures or if femoral fracture in previous 2 years) + medical history ≥1 moderate or severe vertebral fracture or ≥2 mild vertebral fractures or femoral fracture + 10-year fracture risk (determined with validated calculator) high ≥20% + inability to follow other effective treatments (intolerance, ineffectiveness, or expiration of the authorized period of use)	Romosozumab for up to 12 months, followed by antiresorptive drugs (bisphosphonates or denosumab)		
Non-vertebral and non-femoral fractures			
+ T-score column or femur ≤-3			
Female patients with column or femur T-score <-2.5 + history of ≥2 nonvertebral fractures + 10-year fracture risk (determined with validated calculator) high ≥20% + inability to follow other effective treatments (intolerance, ineffectiveness, or expiration of approved period of use)	Romosozumab for up to 12 months, followed by antiresorptive drugs (bisphosphonates or denosumab)		

The following are possible changes proposed for Note 79 to be made by AIFA.

1) The criteria for patient access to teriparatide are still those established 10 years ago by AIFA in the first version of the current Note 79, when the drug costed more than twice as much, efficacy demonstrations were limited, and there were still uncertainties about safety. Today, thanks to the arrival of biosimilars, the cost/benefit balance has definitely changed; there are demonstrations of greater and faster efficacy in comparison with antiresorptives; and, thanks to the long experience with their use, of reassuring data in terms of safety (43-46). Therefore, we believe that the current restriction of teriparatide prescription to particularly severe, if not dramatic, conditions of osteoporosis is no longer justified. Currently, teriparatide use in Italy is reserved for patients with an average 10-year risk of major fractures of 80% (Figure 2) (47), when AIFA itself already considers a risk greater than 20% to be significant, enough to justify the use of other anabolic such as romosozumab. It is believed that the same risk conditions can be proposed today for teriparatide as for romosozumab.
2) Incorporating DeFRA into the note review could allow to easily identify patients who fall into the very high fracture risk range for which first-line use of anabolics and not an antiresorptive is indicated (Figure 3). This would also resolve some of the inconsistencies in the supplementation of Note 79 made for romosozumab, which is sometimes inconsistent with the rest of the note. For

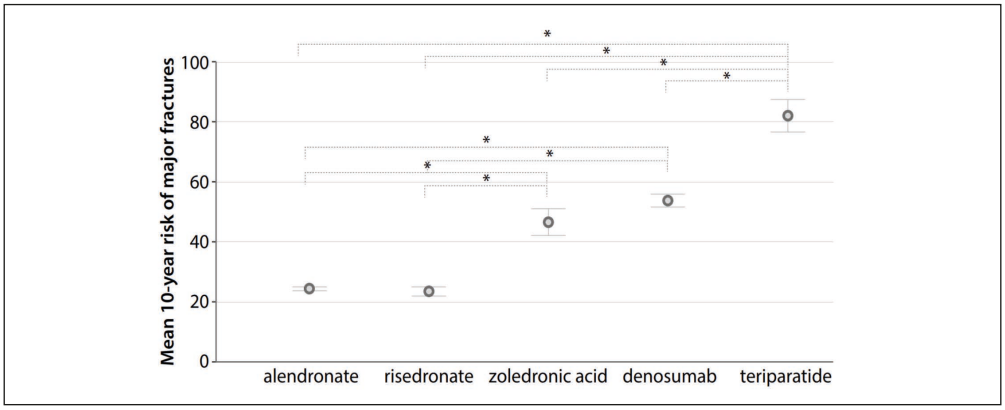

Figure 2 - Different fracture risk profiles of patients treated with osteoporosis drugs in Italy. Modified from Adami et al., 2020 (47).

example, the case of a patient with two nonvertebral fractures and a T-score of less than -2.5 who might be treatable with romososumab but not with other drugs at NHS charge. The incorporation of DeFRA could allow to use of age-adjusted risk thresholds, such as those in DeFRA. This would correct the discrimination resulting from the fixed threshold of 20% major fracture risk at 10 years indicated in note 79 as a condition of significantly increased risk, which does not take into account the different age-related life expectancy and paradoxically penalizes younger patients compared with older ones. Moreover, DeFRA incorporation could supplement the current complicated text of the note, which cannot even be summarized with a flowchart as done in the previous version, facilitating and encouraging its application in clinical practice; it could also integrate treatment plans, and provide AIFA with clinical information on the profile of patients being treated with osteoporosis drugs, which is still missing from OsMed Reports and useful for monitoring the appropriateness of treatments.

3) The provision of sequential therapies with antiresorptives also for teriparatide, as done for romosozumab, and the provision, under particular conditions of very high fracture risk, of the possible combination of teriparatide with zoledronate or denosumab. This would enable physicians to use drugs with complementary mechanisms of action more appropriately to maximize treatment outcomes for the benefit of patients.

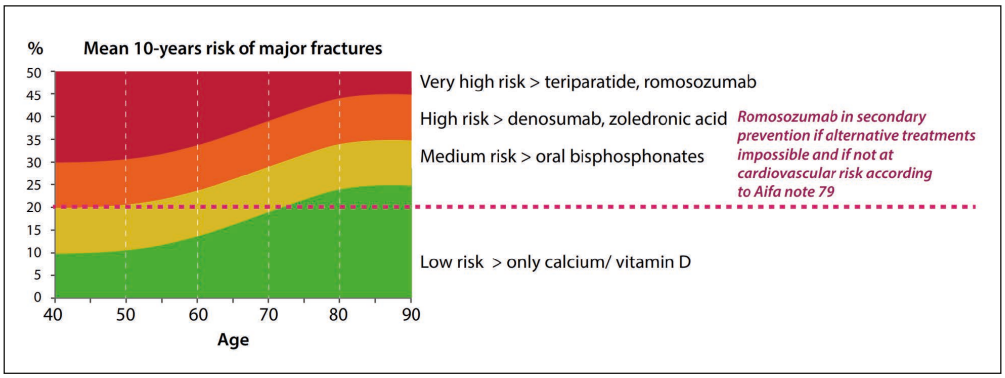

Figure 3 - Fracture risk bands and proposed treatment thresholds according to the Derived Fracture Risk Assessment.

CONCLUSIONS

This expert opinion is the result of a discussion among experts. It stems from the intent to address current gaps and critical issues in the management of osteoporosis, particularly with regard to the current use of anabolic agents. The goal achieved was to provide a critical review and suggest proposals that could contribute to better management of anabolic drugs in the secondary prevention of FF, in line with the latest scientific evidence and guidelines. It is believed that the more appropriate use of anabolic drugs, according to new criteria and strategies, can contribute to a significant reduction in FF and related costs, safeguarding the sustainability of the NHS.

Contributions
MR, contributed to the conception and design of the manuscript, which was discussed and approved at the expert meeting by all the other authors. All authors contributed to the revision of the manuscript and have read and approved the submitted version.

Conflict of interest
The authors certify that there is no actual or potential conflict of interest in relation to this article.

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Availability of data and materials
Data available from the corresponding author upon request.

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