Current Treatment of Osteoporosis and Future Prospects

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Keywords

Osteoporosis · Fracture · Bisphosphonates · Denosumab · Teriparatide · Abaloparatide · Romosozumab · Screening · Under-treatment

1 Introduction

The past two decades have seen substantial advances in the availability of pharmacological options to reduce the risk of fragility fractures in the older population. These treatments vary in their mechanism of action, their efficacy and their safety profile and offer the opportunity to provide a personalized approach to the management of individuals at increased risk of fracture [1]. This chapter reviews the available therapeutic options and the evidence that supports their use in clinical practice. While much progress has been made, challenges remain, including low treatment rates in high-risk individuals, poor treatment adherence, and uncertainties about the optimal duration of therapy.

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2 Overview of Existing Treatments

2.1 Anti-Resorptive Agents

2.1.1 Bisphosphonates

The bisphosphonates are the most widely used pharmacological intervention worldwide, and in nearly all guidelines are considered the first-line treatment option to reduce fracture risk, a recommendation based mainly on their low cost and superior cost-effectiveness when compared to other treatments. A variety of dosing regimens is available: alendronate and risedronate are given orally and are most frequently administered once weekly, ibandronate can be given by mouth once monthly or by intravenous injection once every 3 months, and zoledronate is given as a short intravenous infusion once yearly. Alendronate, risedronate, and zoledronate have all been shown to reduce vertebral, non-vertebral, and hip fractures in post-menopausal women with osteoporosis, whereas for ibandronate, evidence for reduction in non-vertebral and hip fractures is lacking [2–8]. Gastrointestinal effects are common with oral bisphosphonates, and acute phase reaction occurs in approximately one-third of patients receiving their first infusion or injection of intravenous bisphosphonate. Osteonecrosis of the jaw and atypical femoral fractures occur very rarely with oral or intravenous bisphosphonates at the doses used to treat osteoporosis.

All of the pivotal clinical trials of bisphosphonates were conducted in post-menopausal women with osteoporosis. However, the majority of fractures occur in individuals with osteopenia, not osteoporosis, and there has been some uncertainty as to whether evidence of efficacy can be extrapolated to the osteopenic population. A recent prospective randomized study of the effects of zoledronate in post-menopausal women with osteopenia indicates that, at least for this bisphosphonate, significant reductions in vertebral, non-vertebral, and clinical fractures can be achieved during a follow-up period of 6 years [9]. It should be noted that in this study, zoledronate, 5 mg, was given at 18 months intervals.

As a result of their unique pharmacokinetic properties, beneficial effects on BMD persist for some time following withdrawal of therapy; there are differences between bisphosphonates in the longevity of persistence, although how these translate into fracture reduction is not well established. After cessation of alendronate, ibandronate, or risedronate therapy, bone loss recommences after 1–3 years, whereas BMD is maintained for longer periods after withdrawal of zoledronate [10, 11]. Two recent studies have provided evidence for sustained effects of zoledronate on BMD beyond the 3 years noted in the HORIZON extension study [12, 13]. In a 3-year open-label extension of a multidose randomized controlled trial in osteopenic post-menopausal women, increased BMD was maintained over 5 years following a single intravenous infusion of 5 mg zoledronate, while in HIV-positive men, BMD remained elevated for up to 12 years following two annual doses of 4 mg.

Given the greater potency of zoledronate, its low dosing frequency and prolonged action, a case can be made for greater use of this drug as a first-line option in individuals at increased risk of fracture. Adherence to zoledronate, although not optimal, is better than that seen with oral bisphosphonates [14]. Furthermore, the

results of the study by Reid et al. suggest that there may be a benefit in treating older women (age > 75 years) at a lower level of fracture risk than that usually required for treatment in guidelines [15]. Finally, there is some evidence to suggest that dosing frequencies of longer than one year may be effective, although this is based almost exclusively on BMD changes.

2.1.2 Denosumab

Denosumab was the first biologic to be approved for the prevention of fracture. It is a potent anti-resorptive that acts by inhibiting RANKL and has been shown to reduce the risk of hip, vertebral and non-vertebral fractures in post-menopausal women with osteoporosis [16]. Prolonged treatment, for up to 10 years, results in continued increases in BMD in the spine and hip, and although placebo control data for fracture only extend to 3 years of treatment, fracture incidence with long-term treatment is consistent with continued anti-fracture efficacy [17]. It is administered as a subcutaneous injection once every 6 months. The safety profile is generally good; in the extension of the phase 3 study, atypical femoral fractures occurred in only 2 women during the 10-year period, and osteonecrosis of the jaw occurred in 13 women, with a possible association between risk and duration of therapy [18].

In most national guidelines, denosumab is regarded as a second-line option on the basis of its higher cost when compared to bisphosphonates. There have been no direct head-to-head comparator studies of denosumab versus bisphosphonates with fracture outcomes. Rapid reversal of its effects on biochemical markers of bone turnover and BMD are seen after cessation of therapy, and increased risk of vertebral fractures, sometimes multiple has been reported [19]. It is therefore essential that if treatment is stopped, alternative anti-resorptive therapy is considered. This is discussed in more detail later in this chapter in the section on sequential therapy.

2.1.3 Selective Oestrogen Receptor Modulators (SERMS)

Raloxifene and bazedoxifene are anti-resorptive agents that have been shown to reduce the risk of vertebral but not non-vertebral fractures [20, 21]. They are administered orally once daily and are generally regarded as second-line options because of the lack of proven efficacy against non-vertebral and hip fractures. Raloxifene reduces the risk of breast cancer and may therefore be preferred in women with risk factors for this disease who are also at increased risk of fracture. However, it can cause vasomotor and other menopausal symptoms and is associated with an increased risk of venous thromboembolism. In addition, an increased risk of death from stroke was reported in the MORE study [22]. Because of its limited spectrum of anti-fracture efficacy, its use is mainly restricted to the treatment of post-menopausal women at increased risk of vertebral fracture who are intolerant to other anti-osteoporosis medications.

Bazedoxifene, in a combined formulation with conjugated equine oestrogens, has similar effects on BMD to those of raloxifene but is also effective in relieving menopausal symptoms. Although no fracture data are available for this combined preparation, reductions in vertebral fracture were demonstrated with bazedoxifene alone. Other than its effects on menopausal symptoms, its safety profile is generally similar to that of raloxifene.

2.1.4 Hormone Replacement Therapy

A range of oral and transdermal formulations of unopposed oestrogen or combined oestrogen and progestogen are approved for the prevention of osteoporosis. Because of the adverse risk/benefit profile of long-term hormone replacement therapy in older post-menopausal women, most guidelines recommend that the use of hormone replacement therapy to prevent fractures should be limited to early post-menopausal women (age < 60 years) who also have troublesome menopausal symptoms [23]. Oestrogen and progestogen combinations are associated with increased risk of breast cancer, coronary heart disease, stroke, and venous thromboembolism; the safety profile of unopposed oestrogen differs in that the risks of breast cancer and coronary heart disease are not increased, although there is an increase in the risk of endometrial hyperplasia/neoplasia in non-hysterectomized women.

2.2 Anabolic Agents

2.2.1 Teriparatide and Abaloparatide

Teriparatide (human recombinant PTH 1–34) has been shown to reduce vertebral and non-vertebral fractures in post-menopausal women with osteoporosis [24]. Abaloparatide, an analogue of the 1–34 fragment of PTHrP, also reduces vertebral and clinical fractures in post-menopausal women with osteoporosis [25]. There is no direct evidence that either teriparatide or abaloparatide reduces hip fractures.

Transient decreases in hip BMD in the first 12–18 months of teriparatide treatment have been reported, although longer-term studies show increases in hip BMD and maintenance of or increase in hip bone strength [26–28]. An increase in cortical thickness in the hip, particularly in areas loaded during walking, has also been reported after 18–24 months of treatment with teriparatide [29]. Because of the early adverse effects on cortical bone BMD and structure noted in some studies, it may be advisable to combine teriparatide with an anti-resorptive drug for the first year or so of treatment in individuals at high risk of hip fracture. In the phase 3 study of abaloparatide, BMD increases in the spine and hip were significantly greater with abaloparatide when compared with teriparatide, although this did not translate into a significantly greater reduction in vertebral or non-vertebral fracture reduction [25]. Side effects of teriparatide and abaloparatide include hypercalcaemia and postural hypotension. Both are administered by daily subcutaneous injection.

The duration of teriparatide and abaloparatide is restricted by regulatory agencies to 18–24 months. Withdrawal of either drug is followed by bone loss, and subsequent anti-resorptive therapy is required to maintain BMD at or above its post-treatment level. In the ACTIVE Extend study, significant reductions in vertebral and non-vertebral fractures were seen when 18 months of treatment with abaloparatide was followed by 24 months of alendronate when compared to the placebo/alendronate group [30].

In the VERO study, a comparator study powered for fracture outcomes, teriparatide was shown to be significantly more effective than risedronate 35 mg once weekly in reducing vertebral and all clinical fractures [31]. The higher cost of teriparatide compared to anti-resorptive has limited its use in many countries, although

this may change as cheaper biosimilars become available. In addition, the demonstration of its superiority to risedronate in reducing fractures has led to recommendations that anabolic therapy should be considered as a first-line treatment option for individuals at high risk of fracture.

2.2.2 Romosozumab

Romosozumab is a monoclonal antibody that binds and inhibits sclerostin and has both anabolic and anti-resorptive effects. In post-menopausal women with severe osteoporosis vertebral and clinical fractures were significantly reduced compared to placebo after one year of treatment [32]. Subsequent treatment with denosumab for 24 months in both groups resulted in a significantly greater reduction in vertebral, non-vertebral, and clinical fractures in the group who had been treated with romosozumab for the first year [33]. Romosozumab is given once monthly by subcutaneous injection. Injection-site reactions may occur, and osteonecrosis of the jaw and atypical femoral fractures have been very rarely reported. It may also be associated with an increased risk of cardiovascular disease [34]. This increase in risk was not seen in placebo-controlled studies, and might reflect a protective effect of alendronate rather than an adverse effect of romosozumab; nevertheless, the FDA approval includes a boxed warning stating that romosozumab may increase the risk of heart attack, stroke and cardiovascular death and should not be used in patients who have had a heart attack or stroke within the previous year.

The effects of romosozumab on biochemical markers of bone turnover are transient, with the return to baseline values within 1 year, although BMD continues to increase over 2 years of treatment. Following the withdrawal of treatment, bone turnover increases, and bone loss occurs. The duration of romosozumab therapy is limited to 12 months, and following its cessation anti-resorptive therapy should be given to maintain beneficial effects.

In a comparator study, in which 1 year of treatment with romosozumab followed by 1 year of alendronate was compared with 24 months alendronate therapy (ARCH), significantly greater reduction in vertebral, non-vertebral, and hip fractures at 24 months was shown in the former group [35]. A significant reduction in vertebral fracture was also observed at 12 months in the romosozumab treated women when compared to those treated with alendronate.

3 Duration of Therapy

Osteoporosis is a chronic disorder that often requires life-long treatment. Pivotal clinical trials rarely extend beyond 3 years, and extension studies, although valuable in some respects, suffer from decreasing sample sizes and inevitable sources of bias. Robust evidence for anti-fracture efficacy beyond 3–5 years at most is therefore lacking, and long-term safety data are largely reliant on observational studies.

The concept of drug holidays applies only to the bisphosphonates and is based on the rationale that treatment effects persist for some time following withdrawal of therapy, and also that the risk of rare but serious side effects such as osteonecrosis of the jaw and atypical femoral fractures might be reduced by such an approach. For all other pharmacological interventions, bone loss in the first 6–12 months occurs

after cessation of therapy and maintenance of beneficial effects requires sequential treatment with an alternative agent, as discussed below.

Most guidelines recommend that the need for continued treatment is assessed after 5 or 3 years of oral or intravenous bisphosphonates, respectively, based on limited evidence from extension studies [10, 11]. Post hoc analyses indicate that women with a low hip BMD T-score, prevalent vertebral fracture, or incident fracture during therapy are most likely to benefit from the continuation of treatment [36, 37]. In addition, a previous history of hip or vertebral fracture, older age and current glucocorticoid therapy are widely regarded as indications for continued treatment. In other individuals, fracture risk can be assessed 2–3 years after the withdrawal of treatment to evaluate whether therapy should be restarted. At present, there is no evidence to guide decisions about the continuation of treatment after 10 years of therapy.

4 Sequential Therapy

Generally, the sequence of anti-resorptive followed by anti-resorptive, or anabolic followed by anti-resorptive is recommended, since blunting of the response to teriparatide has been reported in people previously treated with bisphosphonates [38, 39] and transition from denosumab to teriparatide is accompanied by increased bone turnover and bone loss at the hip and spine [40]. However, transitioning from bisphosphonates to romosozumab is associated with gains in both spine and hip BMD, albeit smaller than those seen in bisphosphonate naïve patients, and gains in estimated hip bone strength [41].

The timing and choice of agent following the withdrawal of denosumab therapy is currently an active topic of investigation. A recent study indicates that a single infusion of zoledronate 5 mg, 6 months following denosumab withdrawal, maintains BMD for 1–2 years, [42], but this finding has not been universal, and further studies are needed.

5 Glucocorticoid-Induced Osteoporosis

Glucocorticoid-induced osteoporosis is the most common secondary cause of fragility fractures. Defining characteristics are the rapidity with which bone loss and increased fracture risk occur following initiation of therapy and the predilection for vertebral fractures [43, 44]. Adverse skeletal effects are seen most commonly with continuous oral glucocorticoid therapy and are dose related. The increase in fracture rate is seen within 3–6 months of starting therapy but declines with a longer duration or discontinuation of glucocorticoids [45, 46].

The speed of onset of adverse effects on bone has important implications for management. Fracture risk assessment should be performed as soon as possible after initiation of glucocorticoid therapy, and bone protective therapy should be started promptly in individuals with increased fracture risk. Bisphosphonates,

denosumab, and teriparatide are widely approved in glucocorticoid-treated individuals at increased risk of fracture; although bisphosphonates are generally regarded as the first-line option on the grounds of cost-effectiveness, teriparatide has been demonstrated to be superior to alendronate in its effects on BMD and vertebral fracture and should be considered as the preferred option in individuals at very high risk [47].

6 Osteoporosis in Men

Treatment options for osteoporosis in men are similar to those in women and are based on BMD bridging studies in which similar BMD changes are seen to those associated with fracture reduction in post-menopausal women. Approved options include alendronate, risedronate, zoledronate, denosumab, and teriparatide. Selective oestrogen receptor modulators and ibandronate are not approved for the treatment of osteoporosis in men.

7 Positioning of Treatments

The range of therapeutic options currently available, with their different mechanisms of action and varying spectrum of anti-fracture efficacy, offers the opportunity to personalize treatment according to individual profiles of disease severity, risk of adverse effects, and patient preference. Cost-effectiveness is an important underlying consideration that has to embrace the comparative efficacy of interventions, their adverse effects and adherence. In addition, the rapidity of action is a particularly relevant issue in individuals at high imminent fracture risk [48].

7.1 Comparative Efficacy

An important consideration in making treatment decisions is the spectrum of anti-fracture efficacy, i.e. whether fracture reduction has been demonstrated at vertebral and non-vertebral sites, including the hip (Table 1). All available interventions reduce vertebral fracture risk, whereas not all have been shown to reduce non-vertebral and/or hip fracture. Interventions with a broad spectrum of efficacy are generally preferred, although, for people at high risk of vertebral fracture, anabolic therapies may be the first-line option because of their greater efficacy (see below). Of the three anabolic therapies, only romosozumab has been shown to reduce hip fracture and hence may be preferred in patients at high risk of vertebral fracture who also have low hip BMD.

Head-to-head comparisons with fracture outcomes are not available for anti-resorptive drugs. However, based on BMD outcomes, superiority has been demonstrated for zoledronate over risedronate in glucocorticoid-induced osteoporosis and for zoledronate over alendronate in patients with solid organ transplantation

Table 1 Summary of anti-fracture efficacy of approved pharmacological interventions, based on the results of randomized placebo or comparator-controlled trials in post-menopausal women

Intervention	Vertebral fracture	Non-vertebral fracture	Hip fracture
Alendronate	A	A	A
Ibandronate	A	A*	NAE
Risedronate	A	A	A
Zoledronate	A	A	A
Denosumab	A	A	A
HRT	A	A	A
Bazedoxifene	A	NAE	NAE
Abaloparatide	A	A	NAE
Romosozumab	A	A**	A**
Teriparatide	A	A	NAE

A Grade A recommendation; *NAE* not adequately evaluated; *HRT* hormone replacement therapy.
*post hoc analysis
**demonstrated in comparator trial versus alendronate

[49, 50]. Currently, alendronate, and to a lesser extent risedronate, are the most commonly used bisphosphonates, but given its prolonged duration of action, better treatment adherence and likely greater potency, a case can be made for wider use of zoledronate.

The VERO and ARCH studies have established that, in people with severe osteoporosis, anabolic therapy is superior to oral bisphosphonate therapy in reducing fracture [31, 35]. An important caveat to this is that anabolics have not been compared to the most potent anti-resorptives, namely denosumab and zoledronate. Nevertheless, on the basis of current evidence, anabolic therapy should be considered for initial therapy in individuals at very high risk of fracture. Although more expensive than anti-resorptive drugs, anabolic therapy is restricted to 1 year for romosozumab and 18–24 months for abaloparatide and teriparatide and is then followed by less costly anti-resorptive drugs. Health economic analyses to establish the cost-effectiveness of these regimens are currently in progress.

Comparative data on different anabolic therapies exist, although mainly for non-fracture outcomes. In the ACTIVE study, abaloparatide therapy resulted in significantly greater increases in hip and spine BMD compared to teriparatide and a significantly greater reduction in major osteoporotic fractures (a pre-specified secondary end-point), although not in vertebral, non-vertebral, or clinical fractures [25]. In the Phase 2 study of romosozumab, BMD increases at the hip and spine were significantly greater for romosozumab than teriparatide. In addition, using QCT and finite element analysis, changes in volumetric BMD and bone strength were shown to be significantly greater with romosozumab, this difference being particularly marked in the hip [51, 52]. Taken together with the available data on anti-fracture efficacy, these findings suggest that in individuals at very high risk of hip fracture, romosozumab may be the preferred anabolic option.

7.2 Comparative Safety

All drugs have adverse effects, the absolute risk of which may be influenced by individual patient characteristics. For example ongoing significant dental disease is an important risk factor for ONJ, and hence bisphosphonates and denosumab should generally be avoided in this situation. Similarly, HRT should be avoided in people at increased risk of breast cancer and both HRT and SERMs in people with a history of or predisposition to stroke or thromboembolism. Because of the possible increase in the risk of cardiovascular disease associated with romosozumab, this drug should not be used in people with a history of myocardial infarction or stroke.

Atypical femoral fractures and osteonecrosis of the jaw are well documented rare but serious adverse effects of bisphosphonates and denosumab [53, 54]. However, in the doses used to treat osteoporosis, there is no evidence that the risk of these events varies between different bisphosphonates, and there are no data directly comparing denosumab and the bisphosphonates with respect to their incidence. Gastrointestinal side effects, particularly dyspepsia and oesophagitis, are common with oral bisphosphonates but can be mitigated to some extent by ensuring compliance with the dosing instructions and avoiding their use in people with the gastro-oesophageal disease. Acute phase reaction occurs in approximately one-third of individuals receiving their first dose of intravenous bisphosphonate but can be prevented or reduced by concomitant administration of paracetamol and occurs only very rarely with subsequent infusions.

The anabolic drugs are generally well tolerated, although the need for daily subcutaneous injection is a barrier to treatment in some individuals. Teriparatide and abaloparatide therapy are associated with a small increase in the risk of hypercalcaemia, which appears to be higher for the former drug at the approved doses for osteoporosis [25]. Direct comparison between anabolics and anti-resorptives of adverse events in VERO and ARCH did not reveal any significant difference in the overall frequency of adverse effects, although slightly more serious cardiovascular events were noted for romosozumab compared to alendronate [35].

7.3 Patient Preference

Where contraindications to specific treatments are absent, patient perceptions and fears with regard to possible side effects should be taken into account as these may affect adherence to therapy. As is the case with many chronic diseases, pharmacological intervention does not lead to symptomatic improvement and may cause side effects, whereas the benefit of not having a fracture can be hard to appreciate. The media has been active in drawing attention to possible side effects of bisphosphonates in particular and has often presented an unbalanced view about the benefits and risks of treatment [55, 56]. This has not only deterred patients from taking these drugs but has also made some healthcare professionals reluctant to prescribe them. It is therefore important that physicians and other health care professionals give adequate time to discussing the pros and cons of various treatments and pay heed to patient preferences.

8 Under-Treatment of Osteoporosis: Strategies to Improve Real World Effectiveness

In spite of their high incidence and substantial morbidity and mortality, fragility fractures are under-diagnosed and under-treated [57, 58]. This treatment gap exists despite the significant advances that have been made in fracture risk assessment and in the development of cost-effective pharmacological interventions. Low treatment rates have been identified even in very high-risk patients. In a recent study from the USA in people, mean age 80 years, who had recently sustained an incident hip fracture, the osteoporosis medication rate declined from 9.8% in 2004 to 3.3% in 2015 [59]. A recent report from the National Osteoporosis Foundation also highlights the neglect of such patients: only 9% of the two million people in the Medicare population who sustained an osteoporotic fracture in 2015 underwent bone density testing within the first 6 months after the fracture, and 6.5% sustained a further fracture [60].

These low treatment rates reflect a number of likely barriers to treatment. In particular, concerns about rare but serious side effects such as atypical femoral fractures and osteonecrosis of the jaw can make patients and healthcare professionals reluctant to undertake treatment, in spite of the well-documented benefit/risk balance of treating people at high risk of fracture. Care of people with a fracture is often fragmented, highlighting the need for better communication between all the agencies involved. In addition, healthcare professionals managing the disease come from a wide range of specialties and may lack the expertise to provide optimal care [61].

Although under-treatment of osteoporosis is a global phenomenon, higher treatment rates than in the USA have been reported from other parts of the world, and there are substantial variations both between and within individual countries. In the UK, treatment rates have increased and by 2013 had reached around 50% in older people with primary hip fracture [62]. These variations can be explained in part by the different models of care provided for individuals with incident fragility fracture. In particular, approaches such as Fracture Liaison Services that deliver multidisciplinary and integrated management have been shown to increase treatment rates, improve adherence to therapy and reduce subsequent fracture risk in a cost-effective manner [63–65]. Initiatives to increase the provision of Fracture Liaison Services are ongoing; these have been largely successful in many parts of the world, although less so in others [66, 67]. In particular, in the USA the proportion of the population currently served by these services is low, and strategies to improve coverage are currently being pursued.

In addition to addressing the under-treatment of high-risk individuals, the issue of more proactive screening programmes has been revisited in the light of several studies that have investigated the potential benefits of population-based screening. A trial in the UK (SCOOP) in women aged 70–85 years was conducted in a primary care setting with follow-up of 5 years [68]. When compared to standard clinical care, the use of FRAX, with femoral neck BMD in women at intermediate or high

risk, resulted in a significant decrease in hip fractures, although not in the primary outcome of all clinical fractures [69]. Another study, from Denmark in women aged 65–80 years, compared a two-step strategy (FRAX, followed by FRAX with BMD in those at increased fracture risk) with usual care and found no overall reduction in fractures, although a significant reduction was seen in women who complied with BMD measurement [70]. Finally, in the SALT osteoporosis study from Denmark, screening using FRAX, BMD, and vertebral fracture assessment did not result in overall fracture reduction, although post hoc analysis suggested a reduction in hip and major osteoporotic fractures in women with a recent history of fracture [71]. Current evidence is therefore, somewhat equivocal regarding the benefits of population-based screening but suggests that there may be some value, particularly for hip fracture prevention [72].

9 Future Prospects

The advances that have occurred in the assessment of fracture risk, together with the development of treatment options with a broad range of mechanisms, provide the potential substantially to reduce the burden of fractures in older people. The immediate challenge for the future is better implementation of strategies that have been shown to be successful, for example treatment of high-risk individuals within integrated models of care such as Fracture Liaison Services. In addition, the effectiveness of earlier identification and management of people at increased risk of the fracture using population-based screening programmes merits further investigation.

The development of new treatments for osteoporosis takes many years and is very costly, mainly due to the need for fracture reduction as the primary outcome. This, together with the recent failure of several interventions at late stages of their development, has reduced the motivation for commercial companies to embark on the long journey required to produce a successful drug. The search for a surrogate marker of fracture reduction, acceptable to regulatory agencies, is therefore key for the future of osteoporosis treatment and is currently being pursued [73].

The paradigm of treatment for osteoporosis is changing with the availability of bone anabolic agents, recognition of the high imminent fracture risk following a recent fracture, and acknowledgement that very long-term treatment is required in the majority of people embarking on therapy. In the very high-risk, initial anabolic therapy followed by anti-resorptive drugs is the preferred approach and is likely to prove cost-effective when appropriately targeted. For others who require treatment, long-term treatment with anti-resorptives is appropriate, tailored according to patient preference and safety considerations specific to the individual. Finally, in view of its long duration of action and the poor adherence to oral bisphosphonate therapy, the wider use of zoledronate merits further consideration.

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