



Mini-Review

Which treatment to prevent an imminent fracture?



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ABSTRACT

Purpose: To provide a summarized state of the art of the relative efficacy and rapidity of action of pharmacological treatments to prevent imminent osteoporotic fractures.

Methods: We reviewed metaanalyses (MA) and network metaanalyses (NMA) published during the last 10 years concerning the pharmacological treatment of osteoporosis. We compared the anti-fracture efficacy and the rapidity of action of various agents versus placebo and versus risedronate.

Results: All bisphosphonates decrease the incidence of vertebral fractures compared with placebo. Ibandronate is the only one without demonstrated efficacy against non-vertebral and hip fractures. Zoledronate, denosumab and anabolic therapy are associated with a higher fracture risk reduction than oral bisphosphonates. Compared with risedronate, which significantly reduces the rate of hip fractures, zoledronate, denosumab, teriparatide, abaloparatide and romosozumab are more efficient for vertebral fractures but not for non-vertebral or hip fractures reduction. No studies have compared bone anabolic treatments with zoledronate or denosumab. Oral bisphosphonates significantly reduce fracture risk only after more than one year of therapy. A faster reduction of fracture risk is observed with zoledronate and denosumab, or with anabolic agents. For denosumab and anabolic agents, a sequential treatment is required to keep gains after treatment withdrawal.

Conclusions: In patients at high risk of imminent fracture, starting therapy with potent antiresorptive agents or with an anabolic agent seems most appropriate to promptly reduce the fracture risk. Available NMA/MA suggest that, compared to zoledronate and denosumab, anabolic agents have a higher efficacy for vertebral fractures but head-to-head studies are lacking.

1. Introduction

Osteoporotic fractures are a major and increasing cause of mortality, morbidity, loss of independence and altered quality of life worldwide (Alarkawi et al., 2020). Because of population aging, osteoporosis is among the most important health crises for industrialized countries, with a high cost of incident fragility fractures, estimated at € 37 billion in European Union, and a predicted increase of 25% from now to 2025. The cost of treatment and long-term care of patients with fractures are considerably higher than those of pharmacological prevention, which remains largely underused (Hernlund et al., 2013).

Guidelines for the assessment and treatment of osteoporosis imperatively recommend work up and treatment for patients after a first fragility fracture, with secondary fracture prevention as an obvious first

step in the development of a systematic approach (Hernlund et al., 2013). The risk for recurrent fractures is maximal during the first two years after a fragility fracture (“imminent fractures” period) and decreases gradually afterward (Kanis et al., 2020a). This concept of imminent fracture is therefore central to the categorization of very high risk and has implications for the choice of therapy: these patients at high risk of imminent fractures are most at need of immediate treatment with agents that reduce fracture risk most efficiently and as promptly as possible. Hence the need to identify such agents.

Several anti-osteoporotic agents have a high antifracture efficacy, proven in many randomized controlled trials (RCT): anti-resorptive drugs such as oral bisphosphonates, denosumab and zoledronate, or anabolic agents of the first-generation, teriparatide, or newer ones, namely abaloparatide and romosozumab. However, they differ by their

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potency and the lag time before observing a significant fracture risk reduction.

The aim of the present paper is to provide the reader with a summarized view of the relative potency and rapidity of action of pharmacological treatments available to prevent osteoporotic fractures. For this purpose, we did not perform another metaanalysis but rather synthesized available metaanalyses (MA) and network metaanalyses (NMA) published in the last 10 years. We analysed the anti-fracture efficacy of active treatments versus placebo. To better appreciate differences in

efficiency, the power of the more recent agents (parenteral anti-resorptives and anabolics) was also systematically compared with that of risedronate, chosen as representative of oral bisphosphonate activity.

Three explicit questions were defined:

1. Which treatment would be the most powerful to prevent fracture?
2. What are the fastest anti-osteoporotic agents to promptly reduce fracture risk?
3. How to maintain the early benefits of treatment?

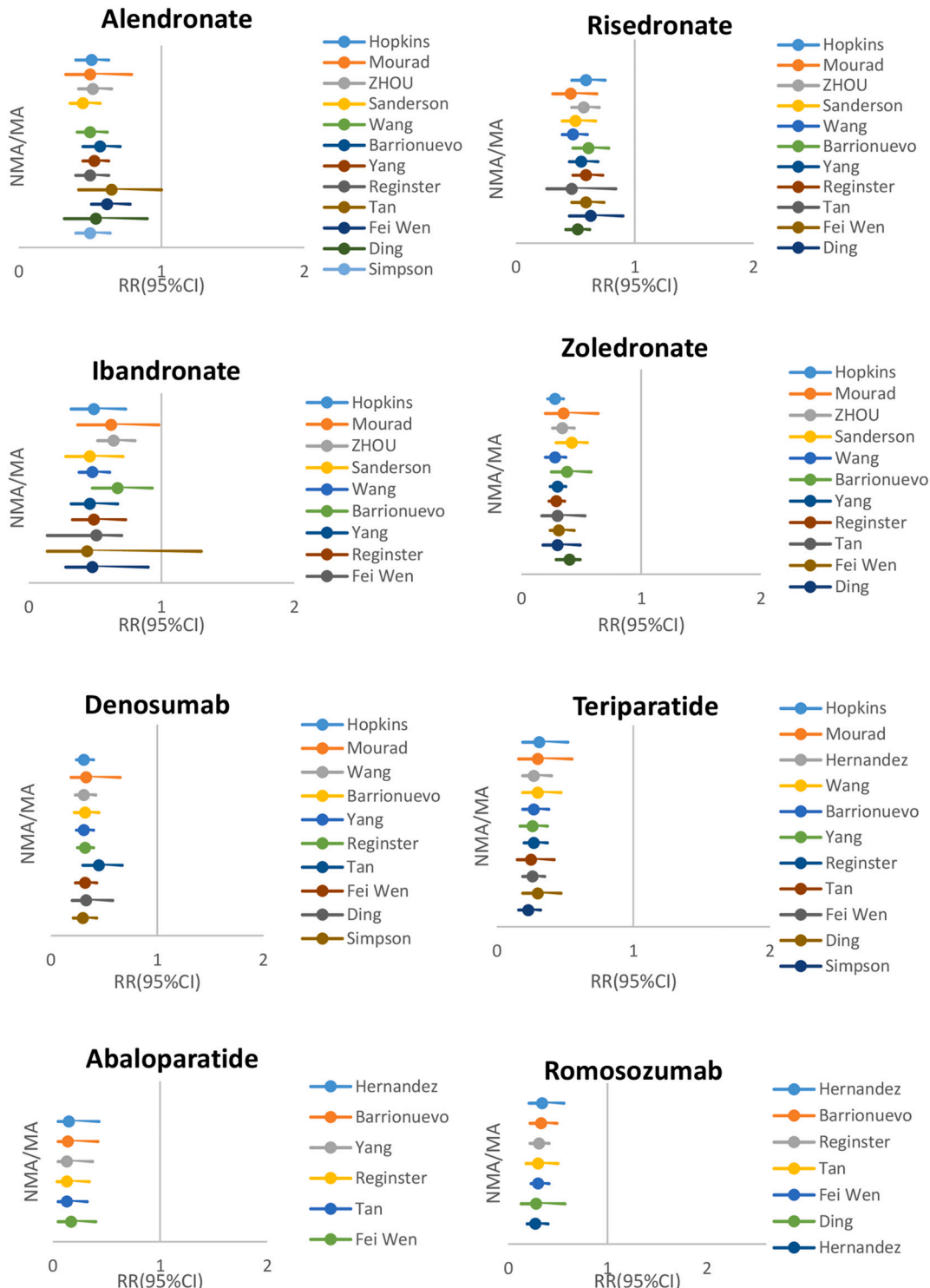


Fig. 1. Data reported in NMA/MA (efficacy vs placebo) for vertebral fractures.

2. Methods

A search of Scopus was performed to find NMAs and MAs published in the last 10 years. The language was limited to English for pragmatic reasons. Furthermore, the reference lists of studies selected for inclusion in the present review were screened for additional relevant reports.

Studies were eligible for this review if they met the following criteria: (a) MA/NMA included RCTs for which only postmenopausal women with primary osteoporosis or osteopenia were included; (b) one or more active agents were compared to placebo or to each other; and (c) the outcomes of interest (vertebral, hip, and nonvertebral fragility fractures) were reported as a primary or secondary outcome.

Three different types of pharmacological treatments were studied: 1) oral and parenteral bisphosphonates (alendronate, ibandronate, risedronate, and zoledronate), 2) denosumab, and 3) anabolic therapy (teriparatide, abaloparatide, and romosozumab). We present the efficacy versus placebo, versus risedronate and the head-to-head comparisons. Risedronate was chosen as representative of oral anti-resorptive treatments that has been shown in a placebo-controlled trial to reduce the rate of hip fractures (Barrionuevo et al., 2019; Murad et al., 2012).

Studies on the following topics were excluded: acute fracture care, high-energy fractures, fracture healing, secondary osteoporosis (including osteoporosis induced by glucocorticoid therapy or by cancer therapy), male osteoporosis, premenopausal osteoporosis, and studies in languages other than English.

We summarize the results of NMAs/MAs published during the last 10 years with available information on timing of action and efficacy of available osteoporosis treatments in relation to fracture risk reduction. No specific statistical analysis was performed.

3. Results

3.1. Which treatment would be the most powerful to prevent fracture?

For vertebral fractures, all bisphosphonates showed efficacy in preventing fractures compared with placebo (see Fig. 1 and Supplementary Table 1). Zoledronate was associated with a higher reduction (RR = 0.28–0.42) than the three oral bisphosphonates: alendronate (RR = 0.45–0.65), risedronate (RR = 0.46–0.60) and ibandronate (RR = 0.46–0.67). The efficacy of denosumab was similar to that of zoledronate (RR = 0.30–0.32). With respect to anabolics, the reduction of fracture risk following treatment with teriparatide and abaloparatide was substantially greater than that after anti-resorptives, even zoledronate or denosumab, with a RR at 0.23–0.31 and 0.13–0.15 vs placebo, respectively. In a head-to-head comparative trial (Kendler et al., 2017), teriparatide was more efficient than risedronate for prevention of vertebral fractures (RR = 0.44, $p < 0.0001$) (see Table 1). Moreover, the VERO study showed that the antifracture efficacy was superior in a subgroup of patients with imminent fracture risk (those with a prior clinical vertebral fracture (VFX) in the year before entering the study), with a reduction of new VFX, new and worsened VFX, and clinical fractures by 65%, 68%, and 62%, respectively, in patients treated with teriparatide as compared with risedronate (Geusens et al., 2018).

No difference in efficacy was apparent between risedronate and other oral bisphosphonates. Zoledronate, however, was more efficient, at the same level as denosumab. The three anabolic agents were slightly more potent than parenteral antiresorptives, particularly abaloparatide (for which there are only few data). The NMA of Ding et al. (2020) is the only one to assess the comparative anti-fracture effectiveness of various drugs according to the proportion of prevalent vertebral fractures (PVF): in the subgroup where more than 50% of the patients had a PVF, the greatest risk reduction was obtained for romosozumab (RR = 0.28); in the subgroup where PVF was <50%, abaloparatide was the most potent (RR = 0.16).

For non-vertebral fractures, bisphosphonates associated with a significant reduction in fractures were alendronate (RR = 0.53–0.83),

Table 1

Vertebral fracture data reported in head-to-head studies.

Trial name: first author and year (Ref.)	Treatments, n analysed	Follow-up (months)	Vertebral fracture outcomes n (%) (reported between-group difference)
Panico et al., 2011 postmenopausal women with severe osteoporosis	ALN, 39 TPTD, 42	18	ALN 6/39 (15.7) TPTD 1/42 (2.4) RR 0.15, 95% CI 0.02–1.23 NS
Hadji et al., 2012 postmenopausal women with osteoporosis	RIS, 350 TPTD, 360	6	RIS, 18/350 (5.1) TPTD, 15/360 (4.2), RR 0.83, 95% CI 0.41–1.58 NS
Miller et al., 2016a postmenopausal women with osteoporosis	ABL 824 TPTD 818	18	ABL 4/824 TPTD 6/818 RR 0.66, 95% CI 0.18–2.40, NS
ARCH: Saag et al., 2017 postmenopausal women with osteoporosis	ALN, 2047 ROMO, 2046	12	ALN, 128/2047 (6.3) ROMO, 82/2046 (4.0) RR 0.63, 95% CI 0.47 to 0.85 p = 0.003
VERO: Kendler et al., 2017 postmenopausal women with osteoporosis	RIS, 533 TPTD, 516	24	RIS, 64/533 (12.0) TPTD, 28/516 (5.0) RR 0.44, 95% CI 0.29–0.68; p < 0.0001

ALN – Alendronate, DEN – Denosumab, ROMO – Romosozumab, RIS – Risedronate, TPTD – Teriparatide, ZOL – Zoledronate, ABL-Abaloparatide, NS- not significant.

risedronate (RR = 0.55–0.81) and zoledronate (RR = 0.30–0.76) (see Fig. 2 and Supplementary Table 1). Ibandronate did not reduce non-vertebral fractures in the majority of NMA/MA. The same efficacy was obtained for teriparatide, denosumab and abaloparatide (RR = 0.31–0.81; 0.26–0.63 and 0.13–0.54, respectively). The few head-to-head comparisons showed no significant differences between the evaluated drugs (see Table 2). However, in the study of Saag (Saag et al., 2017), the risk of nonvertebral fractures was lower by 19% in the romosozumab-to-alendronate group than in the alendronate-to-alendronate group ($P = 0.04$). Cosman et al. (2016) did not obtain with romosozumab a significant reduction of the fracture risk within 12 months ($p = 0.10$) or 24 months ($p = 0.06$). In a post hoc analysis of the role of regional background fracture risk (Cosman et al., 2018), risk reductions were observed in “rest-of-world” ($p = 0.012$), with no treatment effect observed in Latin America.

For hip fractures, similar efficacies were observed for alendronate (RR = 0.45–0.64), risedronate (RR = 0.48–0.74), zoledronate (RR = 0.50–0.64) and denosumab (RR = 0.50–0.60). Teriparatide was efficient with RR = 0.35 (0.15–0.73) only in the NMA of Simpson et al., 2020. For romosozumab, only Barrionuevo et al. (2019) indicated a significant effect on the risk of hip fracture (RR = 0.44) (Fig. 3). Romosozumab followed by alendronate reduced the risk of hip fracture to a greater extent than alendronate alone ($P = 0.02$).

None of the parenteral drugs were apparently more potent than risedronate for non-vertebral and hip fractures prevention (see Supplementary Table 2 and Fig. 4).

3.2. What are the fastest anti-osteoporotic agents to reduce fracture risk?

For vertebral fractures, a significant reduction of fracture risk was only demonstrated after more than one year of treatment with oral bisphosphonates (Black et al., 2000; Chesnut et al., 2004; Harris et al., 1999; Liberman et al., 1995) (Table 3): after the first year for risedronate ($p < 0.001$) (Harris et al., 1999) and alendronate (Cosman et al., 2018),

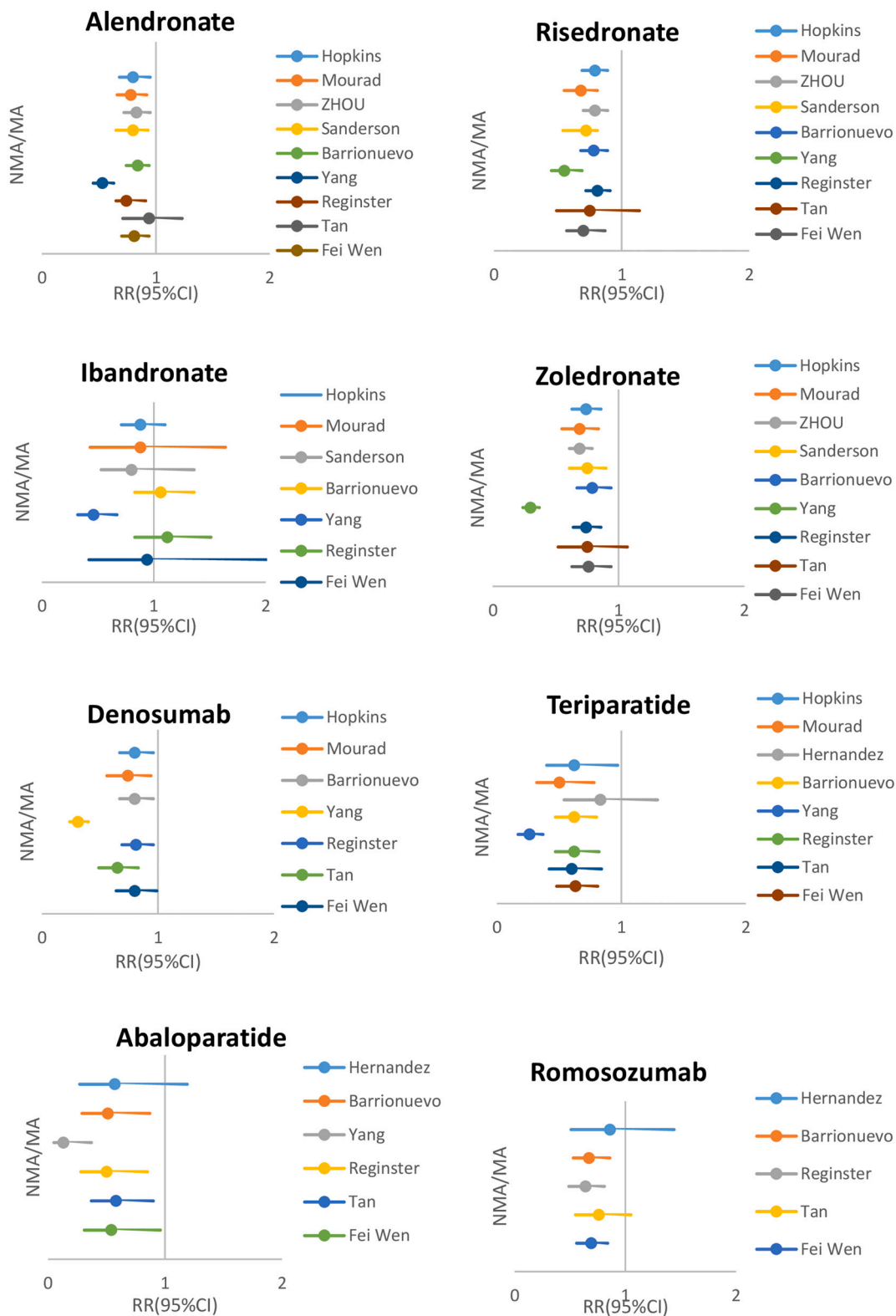


Fig. 2. Data reported in NMA/MA (efficacy vs placebo) for non-vertebral fractures.

and during the second year for ibandronate ($p < 0.001$) (Chesnut et al., 2004). With zoledronate (Dennis et al., 2007) and denosumab (Steven et al., 2007), a significant risk reduction was already observed after 6 months ($p < 0.001$). The protective effect of teriparatide became evident after 9 to 12 months (Neer et al., 2001). With romosozumab, a significant reduction of the risk of vertebral fracture was obtained within 12

months ($P < 0.001$) (Cosman et al., 2016). Abaloparatide had a similar efficacy ($p < 0.001$), but no data are available for the rapidity of action (Cosman et al., 2017; Miller et al., 2016a). However, only a small number of fracture events occurred across treatment groups, with the event rate in the placebo group being smaller than anticipated. Moreover, the result could be influenced by the fact that 63% of participants

Table 2

Non - vertebral fracture data reported in head-to-head studies.

Trial name: first author and year (Ref.)	Treatments, n analysed	Follow-up (months)	Non-vertebral fracture outcomes n (%) (reported between-group difference)
STAND: Kendler et al., 2010 postmenopausal women with osteoporosis	ALN, 249 DEN, 253	12	ALN, 4/251 (1.6) DEN, 8/253 (3.2) RR 0.5, 95% CI 0.15–1.65 NS
Hadji et al., 2012 postmenopausal women with osteoporosis	RIS, 350 TPTD, 360	6	RIS, 29/350 (8.30) TPTD, 28/360 (7.80) RR 0.94, 95% CI 0.57–1.54 NS
DAPS: Freemantle et al., 2012 postmenopausal women with osteoporosis	ALN, 124 DEN, 126	12	ALN, 1/118 (0.85) DEN, 1/125 (0.80) RR 1.06 95% CI 0.06–16.7 NS
Miller et al., 2016b postmenopausal women with osteoporosis	ZOL, 320 DEN, 320	12	ZOL, 11/320 DEN, 7/320 RR 0.63 95% CI 0.24–1.67 NS
ARCH: Saag et al., 2017 postmenopausal women with osteoporosis	ALN, 2047 ROMO, 2046	12	ALN, 95/2047 (4.60) ROMO, 70/2046 (3.40) RR 0.74, 95% CI 0.54–0.99 $p = 0.05$
VERO: Kendler et al., 2018 postmenopausal women with osteoporosis	RIS 680 TPTD 680	24	RIS, 38/680 (6.00) TPTD, 25/680 (4.00) RR 0.66, 95% CI 0.39–1.10 NS

ALN – Alendronate, DEN – Denosumab, ROMO – Romosozumab, RIS – Risedronate, TPTD – Teriparatide, ZOL – Zoledronate, NS- not significant.

had a prior fracture.

In the few available head-to-head comparisons, both teriparatide and romosozumab seem to be more efficient than the oral bisphosphonate already during the first year (Saag et al., 2017; Body et al., 2020). Body et al. (2020) compared teriparatide to risedronate. The largest difference in incidence rates of clinical fractures occurred during the 6- to 12-month period ($p = 0.03$). With regards to romosozumab, in the study of Saag et al., 2017, a significantly lower risk was observed in the romosozumab-to-alendronate group than in the alendronate-to-alendronate group ($P < 0.001$), but the difference was significant only after the first year of treatment ($p = 0.003$). Comparing the efficacy of abaloparatide and teriparatide, Miller et al. (2016a) found a significant reduction in the risk of new vertebral fractures in the abaloparatide vs placebo group (RR 0.14, $P < 0.001$) but without data for the rapidity of effect.

For non-vertebral fractures, the effect of oral bisphosphonates became significant after the first year only (Black et al., 2000; Chesnut et al., 2004; Harris et al., 1999; Liberman et al., 1995) (Table 3). For zoledronate (Dennis et al., 2007) and denosumab (Steven et al., 2007), a significant reduction of the risk of fractures was already observed after 6 months ($p < 0.001$). Regarding the effect of romosozumab, in the study of Saag et al. (2017), a significantly lower risk (19%) was observed in the romosozumab-to-alendronate group than in the alendronate-to-alendronate group for new non-vertebral fractures during the second year of treatment ($p = 0.037$). With abaloparatide, Miller et al. (2016a, 2016b) obtained an early significant reduction (RR = 0.57, $p = 0.049$). Kaplan-Meier curves for time to first nonvertebral fracture showed early separation (before 12 months) between the abaloparatide group and both the placebo and teriparatide groups. The curve of the abaloparatide- group continued to diverge from the placebo group and maintained consistent separation from the teriparatide group over the full course of the 18-month trial (Cosman et al., 2017; Miller et al., 2016a, 2016b).

For hip fractures, the same delay as for vertebral and non-vertebral fractures was observed after bisphosphonates and denosumab. For teriparatide, the effect became significant after 6 months ($p < 0.05$) (Eriksen et al., 2014). No significant effect was observed for romosozumab at 1 and 2 years by Cosman et al. ($p = 0.18$ and 0.06 respectively) (Cosman et al., 2016). However in the study of Saag et al., 2017, hip fractures occurred in 2.0% of patients in the romosozumab-to-

alendronate group as compared with 3.2% in the alendronate-to-alendronate group at the time of the primary analysis, representing a 38% lower risk with romosozumab (hazard ratio, 0.62; 95% CI, 0.42 to 0.92; $P = 0.02$) during the second year.

3.3. How to maintain the early benefits of treatment?

Because they are stored in bone, the anti-fracture effect of bisphosphonates (oral or parenteral) persists for several months or years after they are stopped. It is not the case with denosumab or anabolics. When denosumab is withdrawn, there is a rebound of bone turn-over and bone loss, and several cases of multiple vertebral fractures have been described (3.4% of patients in the post hoc analysis of the Freedom trial) (Anastasilakis et al., 2017; Cummings et al., 2018; Popp et al., 2016). Cummings et al. reported that the odds of developing multiple vertebral fractures after stopping denosumab were 3.9 times higher in those with prior vertebral fractures, sustained before or during treatment, than those without, and 1.6 times higher with each additional year of off-treatment follow-up. Thus, denosumab should be given life-long (Hansen et al., 2020) or, if stopped, replaced with another potent antiresorptive. Results of studies are still limited and controversial: one infusion of zoledronate did not prevent bone loss after discontinuing treatment according to studies of Solling and Horne (Horne et al., 2018; Sølling et al., 2020); conversely, Anastasilakis (Anastasilakis et al., 2017) showed that a single intravenous infusion of zoledronate given 6 months after the last denosumab injection prevented bone loss for at least 2 years independently of the rate of bone turnover.

The optimal timing to start a bisphosphonate treatment after denosumab is unknown, nor the dosage, nor the duration of treatment. A recent review (Tsourdi et al., 2021) concluded that the duration of denosumab treatment is an important determinant of the extent of the rebound phenomenon. A short duration of denosumab treatment (i.e. up to 2.5 years) in patients with otherwise low fracture risk could justify treatment with an oral bisphosphonate for 1–2 years. Patients having been treated with denosumab for a longer period (i.e., more than 2.5 years) or who are at persistently high risk for fracture should receive zoledronate.

Because the use of anabolic drugs for postmenopausal osteoporosis is limited to 12 to 24 months and the beneficial anti-fracture effect of

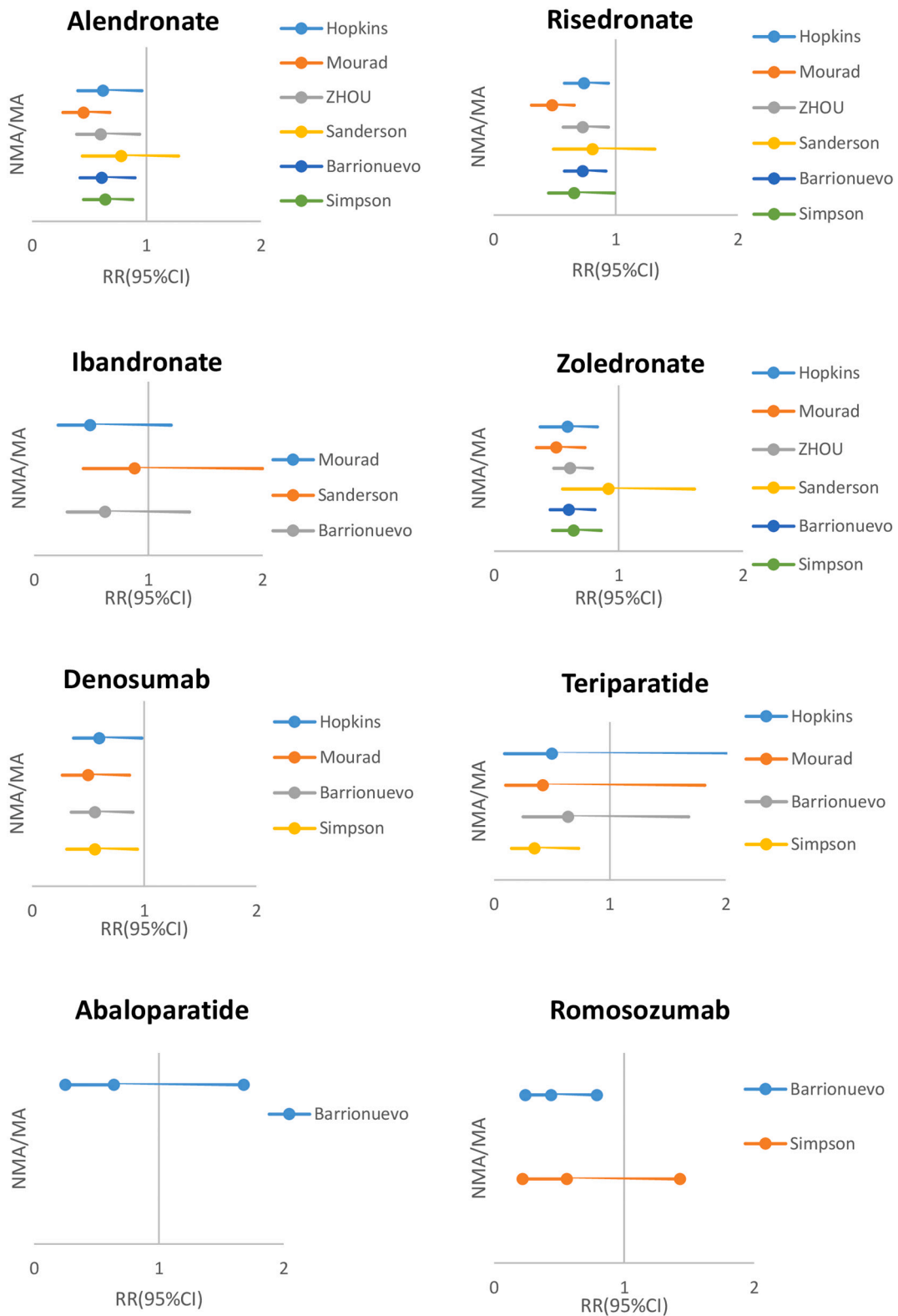


Fig. 3. Data reported in NMA/MA (efficacy vs placebo) for hip fractures.

anabolic therapy decreases rapidly when the treatment is stopped, a sequential treatment of antiresorptive therapy is required (Eastell et al., 2019; McClung et al., 2018). In postmenopausal women who have completed a course of teriparatide or abaloparatide, guidelines recommend treatment with antiresorptive therapy to maintain bone density

gains (V; Shoback et al., 2020). In the case of abaloparatide, efficacy was maintained with a subsequent 24-month treatment with alendronate; eighteen months of abaloparatide followed by 24 months of alendronate reduced the risk of vertebral, nonvertebral, clinical, and major osteoporotic fractures (Bone et al., 2017). For romosozumab, 12 months of

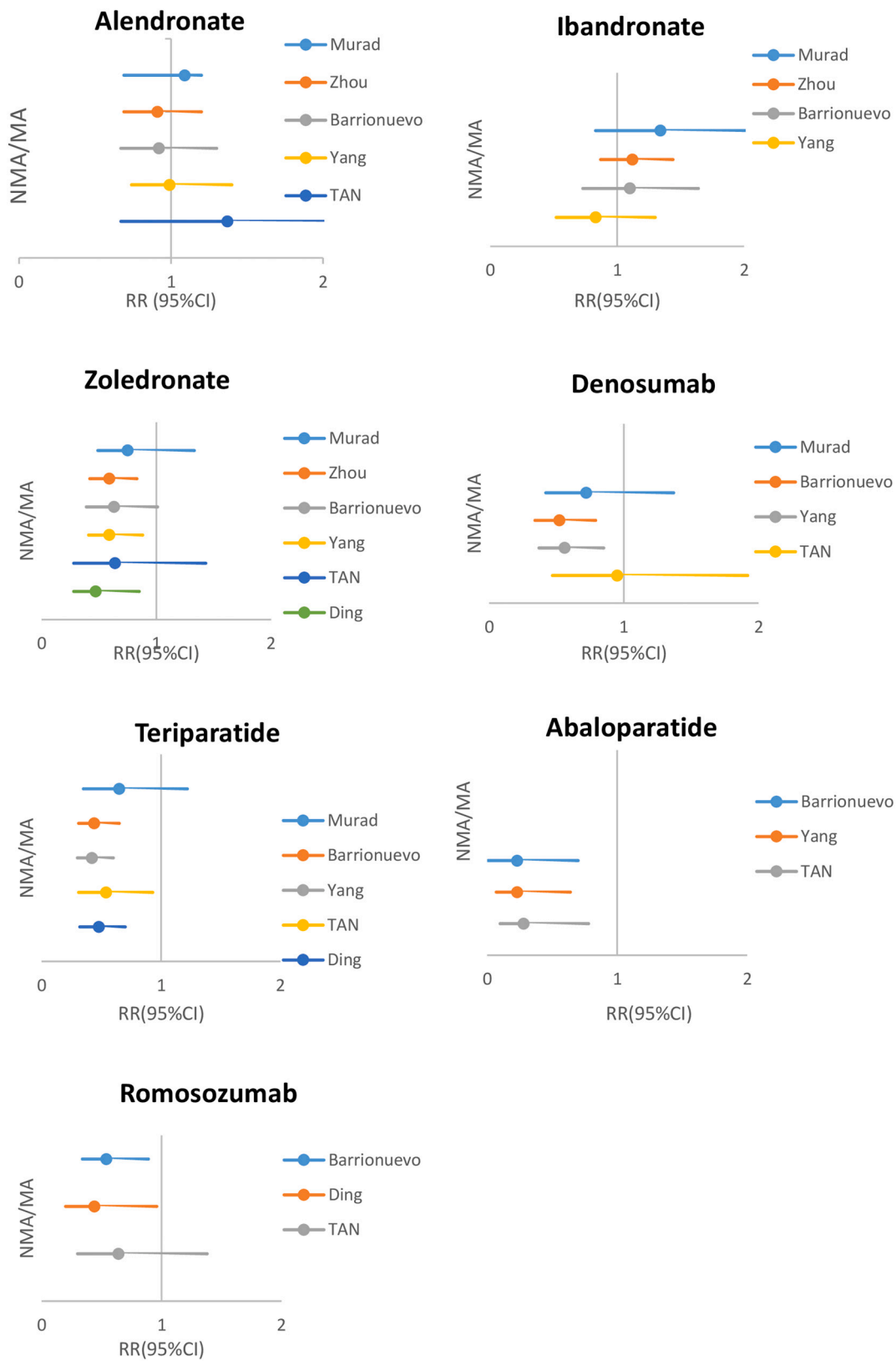


Fig. 4. Data reported in NMA/MA (efficacy vs Risedronate) for vertebral fractures.

alendronate after 12 months of romosozumab showed superior efficacy on fracture outcomes compared with alendronate alone (Saag et al., 2017). Treatment effects of romosozumab are reversible upon discontinuation and further augmented by denosumab (McClung et al., 2018):

women receiving romosozumab who transitioned to denosumab continued to accrue BMD, with additional mean gains of 2.6% at the lumbar spine, 1.9% at the total hip, and 1.4% at the femoral neck, whereas BMD returned toward pretreatment levels with placebo.

Table 3

Minimal duration of treatment before obtaining a significant risk reduction for a) vertebral fractures; b) hip fractures and c) non-vertebral fractures according to the included studies. (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, NS – not significant, NA - not analysed).

a) For vertebral fractures		
	Before 12 months	After 12 months
Oral bisphosphonates		
(Black et al., 2000; Chesnut et al., 2004; Harris et al., 1999; Liberman et al., 1995):	NS	***
Alendronate		**
Risedronate		**
Ibandronate		
Zoledronate (Dennis et al., 2007)	***	***
Denosumab (Steven et al., 2007; Boonen et al., 2011)	***	***
Teriparatide (Body et al., 2020; Lindsay et al., 2009)	**	**
Abaloparatide (Cosman et al., 2017; Miller et al., 2016a)	NA	***
Romosozumab (Cosman et al., 2016; Saag et al., 2017)	**	**
b) For non-vertebral fractures		
	Before 12 months	After 12 months
Oral bisphosphonates		
(Black et al., 2000; Harris et al., 1999; Liberman et al., 1995):	NS	*
Alendronate		*
Risedronate		
Zoledronate (Dennis et al., 2007)	***	***
Denosumab (Steven et al., 2007)	*	*
Teriparatide (Body et al., 2020)	**	**
Abaloparatide (Cosman et al., 2017; Miller et al., 2016a)	*	*
Romosozumab (Cosman et al., 2016; Saag et al., 2017)	NS	*
c) For hip fractures		
	Before 12 months	After 12 months
Oral bisphosphonates		
(Black et al., 2000; Liberman et al., 1995):	NS	*
Alendronate		
Zoledronate (Dennis et al., 2007)	***	***
Denosumab (Steven et al., 2007; Boonen et al., 2011)	*	*
Teriparatide (Eriksen et al., 2014; Lindsay et al., 2009)	*	*
Romosozumab (Saag et al., 2017)	NS	*

4. Discussion

There is a substantial body of evidence that the risk of a subsequent osteoporotic fracture is the highest immediately after the index fracture and wanes progressively with time (Kanis et al., 2020b). Therefore, the first 2 years after the index event is a period of “imminent risk” which requires that a pharmacological treatment should be given as soon as possible. Also, the chosen treatment should be most efficient to reduce the risk, and act promptly. The available pharmacologic treatments can be classified as anti-resorptive drugs: oral and parenteral bisphosphonates or inhibitors of RANK-ligand, and anabolic agents: activators of the PTH receptor and sclerostin inhibitors. These treatments differ in their mechanism of action and do not have the same power to reduce fracture risk. Also, the lag time before observing a significant risk reduction is variable. A number of RCT's, MA and NMA have been published about their relative efficiency and timing of action. The aim of the present narrative review was to summarize their results in order to

help choosing the best therapeutic approach in the prevention of imminent fractures.

The NMAs and MAs showed that all pharmacological treatments significantly reduce the fracture risk. All bisphosphonates decrease the incidence of vertebral fractures compared with placebo. In contrast to other oral bisphosphonates, ibandronate has no significant efficacy against non-vertebral and hip fractures in the majority of NMA/MA. Zoledronate and denosumab are associated with a higher fracture risk reduction than the oral bisphosphonates. Anabolic therapy (romosozumab, abaloparatide or teriparatide) are more efficient for fracture risk reduction than an oral bisphosphonate. Compared with risedronate, which has a proven efficacy in the reduction of fracture risk, chosen as representative of oral anti-resorptive treatments, zoledronate, denosumab, teriparatide, abaloparatide and romosozumab are more efficient for vertebral fractures reduction but not for non-vertebral and hip fractures. Therefore, given their greater antifracture efficacy on vertebral fractures, zoledronate, denosumab or an anabolic treatment would be a better option than oral bisphosphonates for patients at high and imminent risk of such fractures.

Regarding the rapidity of action, a significant reduction of fracture risk was demonstrated only after more than one year of treatment with oral bisphosphonates. A faster reduction of fracture risk is observed with more potent antiresorptive agents, intravenous zoledronate and denosumab, or with anabolic agents.

The rapidity of action of these parenteral antiresorptives is probably due to their much faster inhibition of bone remodeling (within a week), compared to the 3–6 months it takes to achieve remodeling inhibition with oral agents. These drugs have a protective effect already during the first year, especially for non-vertebral fractures and should be recommended for patients at very high risk of imminent fracture, even if they are more costly. Davis et al., 2020 showed indeed in a systematic review and economic evaluation that the incremental cost-effectiveness ratios for newer treatments are generally greater than the commonly applied threshold of £20,000–30,000 (23,000–34,000€) per quality-adjusted life-year. However, the incremental cost-effectiveness ratio for denosumab may fall below £30,000 (34,000€) per quality-adjusted life-year at very high levels of risk or for high-risk patients with specific characteristics. Nevertheless, a major problem arises from the fact that the beneficial anti-fracture effect of anabolic therapy and denosumab is reversible and quickly disappears when therapy is stopped (Eastell et al., 2019; McClung et al., 2018). Thus, when these treatments are discontinued, a bisphosphonate should be given to avoid a rebound fracture risk after denosumab (Hansen et al., 2020) and an anti-resorptive to keep the gains after an anabolic agent (Shoback et al., 2020). The optimal regimen to prevent rebound after denosumab, particularly if given for long periods, has yet to be investigated.

Unfortunately, despite the availability of effective treatments, the prescription and adherence to an osteoporosis therapy after a sentinel fracture is low (around 20% of eligible patients) and declining (Iconaru et al., 2020). The estimated probability of osteoporosis medication used in the year after hip fracture decreased significantly from 40% to 21% over a 10-year study period (Kanis et al., 2017; Solomon et al., 2014). This highlights the urgent need of additional education for the medical profession and patients regarding the risk-benefit balance of treatment (Iconaru et al., 2020).

A limitation of our review is that we could not find enough specific studies where the efficacy of treatment was investigated in patients with a recent fracture. However, studies of efficacy based only on patients with a recent index fracture would be quite impractical. We hypothesize that published data in patients with osteoporosis can be applied for those with an imminent fracture risk. Another limitation is the small number of studies and subjects with new agents, romosozumab and abaloparatide, which could explain the homogeneity of results concerning these treatments in the analysed MA/NMA. On the other hand, there are only a limited number of head-to-head studies which could allow a better comparison of the drug's efficiency and rapidity of action. Additionally,

no studies have compared bone anabolic treatments with zoledronate or denosumab, so it was not possible to analyse the benefit risk ratios of the anabolics compared with these drugs. Moreover, these analyses are done in different populations and there may be differences in many characteristics of the trials accounting for differences in fracture incidence other than the therapy.

In conclusion, in patients at high risk of imminent fracture, starting therapy with potent antiresorptive agents, intravenous zoledronate or denosumab, or anabolic agent seems most appropriate to promptly reduce the fracture risk because of their higher potency and faster effect on fracture risk reduction. In the absence of head-to-head studies to compare anabolic treatments with zoledronate and denosumab, the synthesis of NMA/MA suggests a higher efficacy of anabolics for vertebral fractures prevention, a moderate advantage for non-vertebral fractures and not enough data for hip fractures. For denosumab and anabolics, a sequential treatment is required to keep gains after treatment withdrawal, but the optimal regimen of these treatments remains to be defined with certainty. As these treatments are much more costly, a rigorous choice of patients is needed, underlying the need to develop a model for predicting imminent fractures.

Transparency document

The [Transparency document](#) associated with this article can be found, in online version.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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BP, BJJ, IL designed the study.

IL wrote the first draft of the manuscript.

IL, BJJ, BP revised subsequent versions of the manuscript. All authors read and approved the final version of the paper. IL accepts responsibility for the integrity of the data analyses.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bonr.2021.101105>.

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