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Meta-analysis

The sequential antifracturative treatment: a meta-analysis of randomized clinical trials

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Abstract

Background: Subjects with a fragility fracture have an increased risk of a new fracture and should receive effective strategies to prevent new events. The medium-term to long-term strategy should be scheduled by considering the mechanisms of action in therapy and the estimated fracture risk.

Objective: A systematic review was conducted to evaluate the sequential strategy in patients with or at risk of a fragility fracture in the context of the development of the Italian Guidelines.

Design: Systematic review and meta-analysis.

Data sources and methods: PubMed, Embase, and the Cochrane Library were investigated up to February 2021 to update the search of a recent systematic review. Randomized clinical trials (RCTs) that analyzed the sequential therapy of antiresorptive, anabolic treatment, or placebo in patients with or at risk of a fragility fracture were eligible. Three authors independently extracted data and appraised the risk of bias in the included studies. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation methodology. Effect sizes were pooled in a meta-analysis using fixed-effects models. The primary outcome was the risk of refracture, while the secondary outcome was the bone mineral density (BMD) change.

Results: In all, 17 RCTs, ranging from low to high quality, met our inclusion criteria. A significantly reduced risk of fracture was detected at (i) 12 or 24 months after the switch from romosozumab to denosumab *versus* placebo to denosumab; (ii) 30 months from teriparatide to bisphosphonates *versus* placebo to bisphosphonates; and (iii) 12 months from romosozumab to alendronate *versus* the only alendronate therapy (specifically for vertebral fractures). In general, at 2 years after the switch from anabolic to antiresorptive drugs, a weighted BMD was increased at the lumbar spine, total hip, and femoral neck site.

Conclusion: The Task Force formulated recommendations on sequential therapy, which is the first treatment with anabolic drugs or 'bone builders' in patients with very high or imminent risk of fracture.

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Plain language summary

A systematic review to evaluate the sequential therapy of antiresorptive (denosumab and bisphosphonate, such as alendronate, minodronate, risedronate, and etidronate), anabolic treatment (such as romosozumab, teriparatide), or placebo in patients with or at risk of a fragility fracture in the context of the development of the Italian Guidelines

Subjects with previous fragility fractures should promptly receive effective strategies to prevent the risk of subsequent events. Indeed, patients with a fragility fracture have a doubled risk of a new fracture. For this reason, it is essential to provide adequate sequential therapy based on the mechanisms and the rapidity of action. A systematic review was performed to identify the sequential strategy in patients at high- or imminent-risk of (re) fracture and to support the Panel of the Italian Fragility Fracture Guideline in formulating recommendations. Our systematic review included seventeen studies mostly focused on women and enabled us to strongly recommend the anabolic drugs as first-line treatment. Specifically, for the sequential therapy from anabolic to antiresorptive treatment, there was a significant reduction in the risk of different types of fractures after the switch from romosozumab to denosumab versus placebo to denosumab. These findings were confirmed at 24 months after the switch. Considering the sequential treatment from antiresorptive to anabolic medications, there was a decreased risk of fracture 12 months after the switch from placebo to teriparatide versus bisphosphonate or antiresorptive to teriparatide. Moreover, a greater bone mineral density increase after the switch from anabolic to antiresorptive medications was shown in the lumbar spine, total hip, and femoral neck. The results of this systematic review and meta-analysis confirm that initial treatment with anabolic drugs produces substantial bone mineral density improvements, and the transition to antiresorptive drugs can preserve or even amplify the acquired benefit. These findings support the choice to treat very high-risk individuals with anabolic drugs first, followed by antiresorptive drugs.

Keywords: anabolic, antiresorptive, fragility fracture, sequential therapy, systematic review

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Introduction

In subjects with a history of fragility fracture(s), effective prevention strategies are warranted to prevent subsequent events.[1,2] Indeed, patients with a fragility fracture have a doubled risk of a new fracture.[3] In particular, subjects who have recently had a fracture represent a concerning subset, defined by the term 'imminent risk', and are estimated to have a fivefold increased risk for a second fracture within 12–24 months.[4,5] In addition, the risk of recurrence dramatically increases with the number of previous fractures, regardless of their location.[6]

The resulting burden is significant, including limited walking, chronic pain, loss of independence, and reduced quality of life.[7] Therefore, patients should promptly receive an effective strategy to reduce the risk of new fractures.[8] Unfortunately, data show that many high-risk patients still do not receive any treatment.[1,2] It is crucial to enact strategies aimed at both identifying individuals at significant fracture risk and granting them an effective pharmacological treatment.[9]

Pharmacological therapies for the prevention and treatment of bone loss and mitigation of fracture risk have developed considerably in the last decades, with a significant increase in treatment options with different and innovative mechanisms of action available to the clinician. Among the antiresorptive drugs, denosumab represents the most recently developed compound, besides bisphosphonates, which are usually the first-line treatment. Denosumab is a monoclonal antibody directed against the receptor activator of NFkB ligand (RANKl) and acts by inhibiting the differentiation, activity, and survival of osteoclasts.[10] Meanwhile, classified as anabolics, teriparatide and abaloparatide are parathyroid hormone (PTH) analogs that act by stimulating osteoclast activity, favoring new bone formation.[11] Finally, romosozumab represents the last developed drug, recently licensed and introduced in clinical practice. Romosozumab is a novel agent that differs from prior anabolic drugs by blocking the action of sclerostin, an inhibitor of the Wnt pathway.[12] Romosozumab has been defined as a 'bone builder' as it assures a concurrent stimulation of neoformation and inhibition of bone resorption, leading to an accelerated and amplified anabolic therapeutic window.[13] The choice of therapy should be based on the estimated fracture risk, the mechanisms of action, and its rapidity of action as well as the medium-term to long-term strategy by scheduling combined or sequential approaches.[12,14] For this reason, it is essential to provide adequate sequential therapy after suspending these treatments.

A comparative analysis of different treatments and therapeutic strategies, both in terms of fracture protection and the onset of the protective effect, is still an unmet need. This systematic review aims to identify the sequential strategy in patients at high risk or imminent risk of (re)fracture.

Materials and methods

We performed a systematic review to support the Panel of the Italian Fragility Fracture Guideline (published on the platform of the Italian National Institute of Health)[15] in formulating recommendations. In accordance with the GRADE-ADOLOPMENT methodology[16] and the standards elaborated by the Sistema Nazionale Linee Guida,[17,18] the clinical question defined by the multidisciplinary panel was as follows: 'Which therapeutic strategy should be recommended in the short- and long-term treatment of patients at high- or imminent-risk of (re) fracture?' Specifically, we have updated a recent systematic review,[19] which assessed the sequential treatment in women with postmenopausal osteoporosis.

Inclusion and exclusion criteria

Randomized clinical trial (RCT) studies were detected if they met the following criteria: (1) population: patients who experienced a fragility fracture or were affected by osteoporosis; (2) intervention: antiresorptive (denosumab and bisphosphonate, such as alendronate, minodronate, risedronate, and etidronate), anabolic therapies (romosozumab, teriparatide, and PTH), or placebo; (3) comparison: sequential therapy of drugs abovementioned; (4) outcome: the primary outcome was a risk of the fracture using the dichotomized measure of risk ratio (RR), while the secondary outcome was mean change in bone mineral density (BMD) (at the lumbar spine, total hip, and femoral neck) considering the sequential treatment.

Studies were excluded if they (i) were not published in English; (ii) did not report original findings (i.e. letters, case report); (iii) did not identify patients affected by a fragility fracture or osteoporosis; or (iv) did not consider a sequential drug treatment.

Data source and search strategy

We performed a PubMed, Embase, and Cochrane Library search from 2019 to February 2021 and identified publications on sequential therapy among patients with fragility fracture or osteoporosis. The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses,[20,21] as reported in Supplemental Table S1. The search strategy (Supplemental Table S2) specified keywords and corresponding Medical Subject Headings (MeSH) terms related to fragility fracture/osteoporosis AND sequential therapy AND anabolic/antiresorptive drugs. We checked the reference lists of the studies and the systematic reviews identified during the search process.

Study selection and data extraction

Three independent authors (AB, GP, and RR) screened titles and abstracts according to the search strategy and then assessed the full text of the potentially relevant studies. Discrepancies between readers were discussed and resolved at the conference.

For each included RCT, the following information was extracted the name of the first author, year and country of publication, study setting, type of population, intervention and comparator, and follow-up period (Supplemental Table S3).

Studies quality

The updated systematic review was evaluated using the AMSTAR-2 checklist,[22] while the quality of each included publication was assessed using the Cochrane risk of bias (RoB) tool for RCTs.[23] The following domains of the Cochrane RoB tool were appraised: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias (such as funding bias). Each domain was classified as 'high', 'low', or 'unclear' RoB if the publication did not provide sufficient information to be classified (Supplemental Figure S1).

Quality of evidence

The quality of evidence of the primary outcome was judged through five dimensions (RoB, consistency of effect, imprecision, indirectness, and publication bias) by the GRADE approach.[24] The evidence was downgraded from 'high quality' by one level if serious or by two levels if very serious limitations were found for each of the five dimensions (Supplemental Table S4).

Statistical analysis

The measure of interest was the summary RR that evaluated the effect of sequential therapy (anabolic to antiresorptive, or vice versa) on the risk of fragility fracture. Estimates were summarized if at least three studies reported the association of interest. Heterogeneity between study-specific estimates was tested using χ^2 statistics[25] and measured with the I^2 index (a measure of the percentage variation across the studies).[26]

Moreover, a pooled estimate of BMD (mean change, %) was obtained for each site (lumbar spine, total hip, and femoral neck). A weighted average of the BMD was obtained by considering the sample size of the ith study and summing them across all studies.[27] p Values less than 0.05 for all tests were considered statistically significant.

Results

Study selection

A total of 283 studies were detected, as shown in Figure 1. After screening the title and abstract, eight papers were eligible for inclusion. Subsequently, six studies were discarded reading the full texts because they were duplicates (1) or because the intervention (1), outcome (1), population (1), or study design (2) were incorrect. In all, 14 studies were also included after the review of the references[28–41] and 3 by hand-searching.[13,42,43] The main characteristics of the included studies are reported in Supplemental Material (Table S3).

Study characteristics

The included papers were conducted in the United States,[29,33,43] Italy,[31] UK,[35] Japan,[37] Austria, and Czech Republic,[42] in addition to multicenter studies carried out in various countries.[13,28,30,32,34,36,38–41] Nine studies considered the sequential therapy from anabolic to antiresorptive treatment,[13,28,29,34,37,39–41,43] specifically (a) romosozumab to denosumab *versus* placebo to denosumab[13,34,40]; (b) teriparatide to denosumab or alendronate or minodronate[37]; (c) romosozumab to alendronate *versus* only alendronate[28,41]; (d) teriparatide to bisphosphonate *versus* placebo to bisphosphonate[39]; (e) PTH to bisphosphonate *versus* PTH to placebo[29]; and (f) romosozumab to denosumab *versus* romosozumab to placebo.[43] Seven papers evaluated the sequential treatment from antiresorptive to anabolic medications,[30–32,35,36,38,42] specifically (g) alendronate to teriparatide *versus* placebo to teriparatide[42]; (h) antiresorptive to teriparatide *versus* no treatment to teriparatide[35,38]; (i) antiresorptive to teriparatide *versus* only antiresorptive[31]; (j) alendronate to romosozumab or teriparatide[32]; and (k) risedronate or alendronate[30,36] or etidronate or non-bisphosphonate[30] to teriparatide.[30,36] Finally, one study reported the sequential treatment from anabolic to antiresorptive medications and vice versa.[33]

All studies, except one,[37] were focused on women. The proportion of patients with previous fragility fractures was reported by nine studies,[28–30,32,33,36,37,41,42] whereas the nature and severity of prior fractures were documented in eight[13,28,34–37,40,41] and five[13,28,34,40,41] studies, respectively. Moreover, secondary osteoporosis was indicated as an exclusion criterion in eight studies[30,31,33,35–38,42] (Supplemental Table S5).

RoB assessment and certainty of the evidence

According to the RoB assessment (Supplemental Figure S1), eight studies had an unclear risk for random sequence generation,[29–31,38–40,42,43] nine

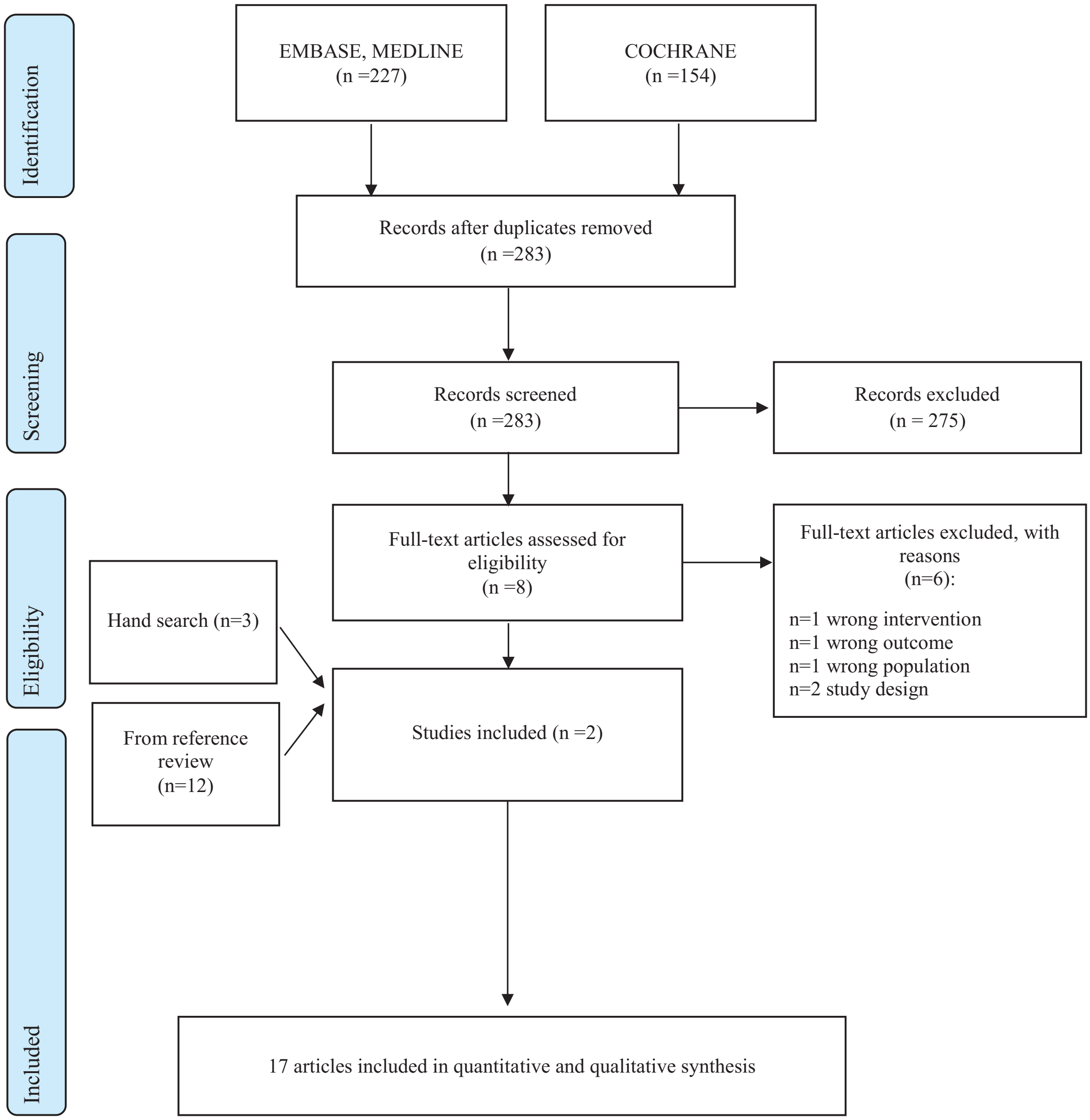

Figure 1. Flow chart of study selection.

for allocation concealment,[29–31,35,38–40,42,43] one for blinding of participants and personnel,[35] four for incomplete outcome data,[29,35,39,42] and other biases, such as funding bias.[31,35,37,40] A high RoB was found for random sequence generation in one study[35] and other biases in seven papers.[28,30,32,36,38,39,41]

The certainty of evidence ranged from moderate to high RoB for the sequential therapy from anabolic to antiresorptive treatment, while a low RoB was attributed to the sequential treatment from antiresorptive to anabolic medications (Supplemental Figure S1).

Primary outcome

The risk of refracture was measured after the switch from anabolic to antiresorptive or vice versa (Table 1). Regarding the sequential therapy from anabolic to antiresorptive treatment, there was a significant reduction in the risk of different types of fractures (vertebral, nonvertebral, major nonvertebral, and major osteoporotic fracture) after the switch from romosozumab to denosumab *versus* placebo to denosumab (RR from 0.25 to 0.75; 95% CI, 0.16–0.99), while a non-significant risk reduction was only detected for hip fracture (RR, 0.50; 95% CI, 0.24–1.04).[13]

Table 1. Risk of refracture: switching from anabolic to antiresorptive, or vice versa.

First author, year	Months from baseline	Months from switch	Site of fracture	Incidence of fracture			
				Group 1	Group 2		RR (95% CI)
Group 1: Romo to Dmab; Group 2: placebo to Dmab							
Cosman 2016 *FRAME Study*	24	12	Vertebral fracture	21/3325 (0.6%)	84/3327 (2.5%)		0.25 (0.16–0.40)
			Nonvertebral fracture	96/3589 (2.7%)	129/3591 (3.6%)		0.75 (0.57–0.97)
			Major nonvertebral fracture	67/3589 (1.9%)	101/3591 (2.8%)		0.67 (0.49–0.91)
			Hip fracture	11/3589 (0.3%)	22/3591 (0.6%)		0.50 (0.24–1.04)
			Major osteoporotic fracture	68/3589 (1.9%)	110/3591 (3.1%)		0.62 (0.46–0.84)
Lewiecki 2019 *Extension of FRAME study*	36	24	Vertebral fracture	32/3325 (1.0%)	94/3327 (2.8%)		0.34 (0.23–0.51)
			Nonvertebral fracture	139/3589 (3.9%)	176/3591 (4.9%)		0.79 (0.64–0.98)
			Major nonvertebral fracture	100/3589 (2.8%)	138/3591 (3.8%)		0.73 (0.56–0.93)
			Hip fracture	18/3589 (0.5%)	31/3591 (0.9%)		0.58 (0.33–1.04)
			Major osteoporotic fracture	103/3589 (2.9%)	147/3591 (4.1%)		0.70 (0.55–0.90)
Miyuachi 2019 *Subgroup analysis of FRAME Study*	36	24	Vertebral fracture	4/237 (1.7%)	11/243 (4.5%)		0.37 (0.12–1.15)
			Nonvertebral fracture	7/247 (2.8%)	15/245 (6.1%)		0.46 (0.19–1.12)
			Major nonvertebral fracture	4/247 (1.6%)	7/245 (2.9%)		0.57 (0.17–1.91)
			Hip fracture	0/247 (0.0%)	2/245 (0.8%)		0.20 (0.01–4.11)
			Major osteoporotic fracture	5/247 (2.0%)	8/245 (3.3%)		0.62 (0.21–1.87)
Group 1: Romosozumab to ALN; Group 2: only ALN							
Cosman 2020 *Post hoc analysis of ARCH Study*	24	12	Nonvertebral fracture	105/1739 (6.0%)	127/1726 (7.4%)		0.81 (0.63–1.05)[a]
			Hip fracture	25/1739 (1.4%)	42/1726 (2.4%)		0.60 (0.37–0.99)[a]
Saag 2017 *ARCH Study*	24	12	Vertebral fracture	127/2046 (6.2%)	243/2047 (11.9%)		0.52 (0.40–0.66)[b]
Group 1: Teriparatide 20 µg to BPs; Group 2: teriparatide 40 µg to BPs; Group 3: placebo to BPs							
Prince 2005		30	Nonvertebral fracture	Group 1 30/436 (6.9%)	Group 2 22/412 (5.3%)	Group 3 38/414 (9.2%)	20 µg: 0.70 (0.43–1.13)[c] 40 µg: 0.54 (0.32–0.91)[c]
Group 1: BPs or AR to teriparatide; Group 2: placebo to teriparatide							
Obermayer-Pietsch 2008 *EUROFORS Study*		24	Any fracture	3/134 (2.2%)	5/84 (5.9%)		0.38 (0.09–1.53)

[a]Adjusted for baseline BMD, age strata, and the presence of severe vertebral fracture at baseline.
[b]Adjusted for age (<75 *versus* ⩾75 years), the presence or absence of severe vertebral fracture at baseline, and baseline bone mineral density *T* score at the total hip.
[c]Adjusted for the duration of osteoporosis drug treatment.
ALN, alendronate; AR, antiresorptive; BPs, bisphosphonates; BMD, bone mineral density; CI, confidence interval; RR, risk ratio.

These findings were confirmed at 24 months after the switch.[34,40] Moreover, a reduced risk of non-vertebral fracture was reported 30 months after the switch from teriparatide to bisphosphonates *versus* placebo to bisphosphonates (RR, 0.54; 95% CI, 0.32–0.91).[39] Finally, there was a significant decrease in risk of vertebral and hip fractures (RR 0.52 and 0.60, respectively; 95% CI, 0.40–0.97)[28,41] 12 months after the switch from romosozumab to alendronate *versus* the only alendronate therapy, while a nonsignificant risk reduction in nonvertebral fracture was detected (RR, 0.81; 95% CI, 0.63–1.04).[41]

Considering the sequential treatment from antiresorptive to anabolic medications, there was a decreased risk of fracture 12 months after the switch from placebo to teriparatide *versus* bisphosphonate or antiresorptive to teriparatide (RR, 0.38; 95% CI, 0.09–1.53).[38]

Secondary outcome

Table 2 reports the change in BMD 2 years after the sequential therapy from anabolic to antiresorptive medications or vice versa. A greater BMD increase after the switch from anabolic to antiresorptive medications was shown in the lumbar spine (16.84%), total hip (8.47%), and femoral neck (7.31%).[28,34] Conversely, a lower BMD increase occurred in the (i) lumbar spine (7.50%) after the switch from placebo to antiresorptive drugs[34]; (ii) total hip (2.42%) after switching from antiresorptive to anabolic treatment[30]; and (iii) femoral neck (2.70%) for the only antiresorptive therapy[28] (Figure 2).

Discussion

This systematic review evaluated a clinical question for the Italian Guidelines,[15] and a panel of experts formulated recommendations through a structured and transparent process. Specifically, we conducted a systematic review and meta-analysis on sequential therapy in patients at very high risk of or with a fragility fracture that enabled us to strongly recommend the anabolic drugs as first-line treatment (moderate quality of evidence) as confirmed by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases.[44]

We found a relevant reduction in fracture risk at almost every skeletal site, especially when we considered the effects of the sequence: (i) romosozumab to denosumab *versus* placebo to denosumab; (ii) romosozumab to alendronate *versus* alendronate by alone; and (iii) teriparatide to bisphosphonates *versus* placebo to bisphosphonates. On the contrary, the sequence from bisphosphonate or antiresorptive to teriparatide *versus* no treatment to teriparatide[38] did not find a significant reduction of fracture risk 12 months after the switch (RR, 0.38; 95% CI, 0.09–1.53). Furthermore, the percent BMD changes were calculated by merging studies that evaluated the different therapeutic strategies. Greater improvement in BMD has been obtained using an anabolic by alone, such as romosozumab, or (a better choice) an anabolic followed by an antiresorptive drug, such as denosumab. We confirmed a significantly greater BMD benefit for the sequence: (i) romosozumab to denosumab *versus* placebo to denosumab; (ii) teriparatide to denosumab *versus* teriparatide to oral bisphosphonates; (iii) romosozumab to alendronate *versus* alendronate by alone; (iv) PTH to bisphosphonates *versus* PTH to placebo; and (v) romosozumab to denosumab *versus* romosozumab to placebo. In a representative open study, the DATA study,[33] postmenopausal women starting with teriparatide for 24 months and subsequently switching to denosumab for 24 months showed greater spine and hip BMD gains compared to the opposite treatment sequence. Notably, the results seen in the combination group (teriparatide plus denosumab followed by denosumab alone) showed an early BMD gain at the spine and hip sites.[45] This negative influence of antiresorptive pretreatment seems to be related to the antiresorptive potency of the used drug; the higher the antiresorptive potency (alendronate > risedronate > risedronate > etidronate > non-bisphosphonates), the lower the BMD gains induced by teriparatide.[30,36] Moreover, the study of Gonnelli *et al.*[31] showed an increase in spine BMD after switching from antiresorptive to teriparatide compared to only antiresorptive therapy, despite the limited sample size. Thus, the impact of post-anabolic treatment on the retention of densitometric gains is substantial, as evidenced by studies on both teriparatide[37] and romosozumab.[41] We believe the analysis by Cosman provides a valuable perspective. For patients at low risk, antiresorptive therapy on its own suffices, whereas the subsequent strategy for high-risk patients post-anabolic therapy should be contingent upon the densitometric outcome attained. Should the densitometric increase be deemed satisfactory, maintenance with bisphosphonates is appropriate; however, if the desired

Table 2. Bone mineral density changes from the switching: anabolic to antiresorptive, or vice versa.

First author, year	Months from baseline	Months from switch	Comparative LS BMD change from baseline (mean%)				Comparative TH BMD change from baseline (mean%)			Comparative FN BMD change from baseline (mean%)			
			Group 1	Group 2		*p* Value	Group 1	Group 2	*p* Value	Group 1	Group 2		*p* Value
Group 1: Romo to Dmab; Group 2: placebo to Dmab													
Cosman 2016 *FRAME Study*	18	6	*N* = 65 15.1	*N* = 61 3.3		$p < 0.001$	*N* = 66 8.4	*N* = 62 1.6	$p < 0.001$	*N* = 66 6.7	*N* = 62 −0.2		$p < 0.001$
	24	12	17.6	5.0		$p < 0.001$	8.8	2.9	$p < 0.001$	6.6	0.6		$p < 0.001$
Lewiecki 2019 *Extension of FRAME study*	24	12	*N* = 3169 16.6	*N* = 3176 5.5		$p < 0.001$	*N* = 3237 8.5	*N* = 3256 3.2	$p < 0.001$	*N* = 3237 7.3	*N* = 3256 2.3		$p < 0.001$
	36	24	18.1	7.5		$p < 0.001$	9.4	4.2	$p < 0.001$	8.2	3.4		$p < 0.001$
Miyauchi 2019 *Subgroup analysis of FRAME Study*	24	12	*N* = 205 20.2	*N* = 190 7.3		$p < 0.001$	*N* = 205 7.9	*N* = 200 2.9	$p < 0.001$	*N* = 205 7.8	*N* = 200 3.6		$p < 0.001$
	36	24	*N* = 207 22.1	*N* = 195 9.5		$p < 0.001$	*N* = 218 8.7	*N* = 210 4.5	$p < 0.001$	*N* = 218 8.6	*N* =2 10 4.4		$p < 0.001$
Group 1: Teriparatide to Dmab; Group 2: TPTD to ALN; Group 3: TPTD to minodronate													
Niimi 2018		12	Group 1 *N* = 100 4.3 ± 3.5	Group 2 *N* = 100 1.3 ± 5.1	Group 3 *N* = 100 0.5 ± 4.6	$p < 0.01$ Dmab *versus* Mino or ALN				Group 1 *N* = 100 1.4 ± 3.4	Group 2 *N* = 100 0.7 ± 4.6	Group 3 *N* = 100 0.2 ± 4.6	$p = 0.16$
Group 1: Romosozumab to ALN; Group 2: only ALN													
Saag 2017 *Extension of ARCH study*	36	24	*N* = 2046 14.9	*N* = 2047 8.5		$p < 0.001$	*N* = 2046 7.0	*N* = 2047 3.6	$p < 0.001$	*N* = 2046 5.9	*N* = 2047 2.7		$p < 0.001$
Cosman 2020 *ARCH Study*	24	12	*N* = 1739 15.5 ± 0.4	*N* = 1726 7.3 ± 0.3		$p < 0.001$	*N* = 1739 7.3 ± 0.2	*N* = 1726 3.5 ± 0.2	$p < 0.001$	*N* = 1739 6.1 ± 0.4	*N* = 1726 2.3 ± 0.3		$p < 0.001$
Group 1: PTH to BPs; Group 2: PTH to placebo													
Black 2005 *PATH study*	24	12	*N* = 12 12.1	*N* = 7 4.0		$p < 0.05$	*N* = 12 4.0	*N* = 7 0.0	$p < 0.05$	*N* = 12 4.0	*N* = 7 1.0		$p < 0.05$
Group 1: Romosozumab to Dmab; Group 2: Romosozumab to placebo													
Kendler 2019	24–36	0–12	*N* = 16 2.5 ± 1.5	*N* = 19 −9.1 ± 1.6			*N* = 16 2.0 ± 1.3	*N* = 19 −5.3 ± 2.0		*N* = 16 1.3 ± 1.3	*N* = 19 −4.3 ± 2.3		
Group 1: ALN to Teriparatide; Group 2: treatment naïve to TPTD													
Fahrleitner-Pammer 2016		12	*N* = 29 1.1	*N* = 16 6.2		$p = 0.004$							
		24	5.3	10.2		$p = 0.077$							

(Continued)

Table 2. (Continued)

First author, year	Months from baseline	Months from switch	Comparative LS BMD change from baseline (mean%)			Comparative TH BMD change from baseline (mean%)			Comparative FN BMD change from baseline (mean%)		
			Group 1	Group 2	*p* Value	Group 1	Group 2	*p* Value	Group 1	Group 2	*p* Value
Group 1: BisP or AR to TPTD; Group 2: no treatment to TPTD											
Middleton 2007		12	*N* = 38 9.0	*N* = 14 7.8	$p = 0.54$	*N* = 38 1.0	*N* = 14 −0.3	$p = 0.36$			
		18	9.8	6.1	$p = 0.30$	2.8	1.3	$p = 0.44$			
Obermayer-Pietsch 2008 *EUROFORS Study*		6	*N* = 134 3.5	*N* = 84 5.8	$p < 0.001$	*N* = 134 −0.3	*N* = 84 0.5		*N* = 134 −0.3	*N* = 84 1.2	$p < 0.05$
		12	6.6	9.3	$p < 0.001$	0.6	1.8	$p < 0.05$	1.1	2.2	
		18	8.6	11.1	$p < 0.01$	0.6	2.7	$p < 0.05$	2.1	3.1	
		24	10.2	13.1	$p < 0.01$	2.3	3.8	$p < 0.01$	3.4	4.8	
Group 1: AR to Teriparatide; Group 2: no change AR											
Gonnelli 2006		6	*N* = 27 5.6 ± 6.7	*N* = 28 1.2 ± 3.4	$p < 0.05$	*N* = 27 −2.1 ± 3.5	*N* = 28 0.20 ± 2.9	NS	*N* = 27 −1.8 ± 8.7	*N* = 28 1.6 ± 3.1	NS
		12	7.1 ± 5.9	1.5 ± 4.3	$p < 0.05$	−0.8 ± 2.7	1.2 ± 4.2	NS	2.6 ± 5.1	1.1 ± 3.8	NS
Group 1: ALN to Romosozumab; Group 2: ALN to TPTD											
Langdhal 2017 *STRUCTURE study*		6	*N* = 206 7.2 (6.6–7.8)	*N* = 209 3.5 (2.9–4.0)	$p < 0.0001$	*N* = 206 2.3 (1.9–2.7)	*N* = 209 −0.8 (−1.2 to −0.4)	$p = 0.0001$	*N* = 206 2.1 (1.6–2.7)	*N* = 209 −1.1 (−1.6 to −0.5)	$p = 0.0003$
		12	9.8 (9.0–10.5)	5.4 (4.7–6.1)	$p < 0.0001$	2.9 (2.5–3.4)	−0.5 (−0.9 to −0.0)	$p = 0.0357$	3.2 (2.6–3.8)	−0.2 (−0.8 to 0.4)	$p = 0.4566$
Group 1: RIS to Teriparatide; Group 2: ALN to TPTD											
Miller 2008		6	*N* = 158 3.0	*N* = 166 2.0		*N* = 158 −1.2	*N* = 166 −1.9	$p = 0.07$			
		12	5.1	3.6	$p < 0.05$	−0.3	−1.7	$p = 0.07$			
Group 1: RIS to Teriparatide; Group 2: ALN to TPTD; Group 3: ETN to TPTD; Group 4: Non-BPs to TPTD											
Boonen 2008 EUROFORS study		6	Group 1 *N* = 59 2.3 Group 2 *N* = 107 3.0	Group 3 *N* = 30 5.8 Group 4 *N* = 49 4.0	$p < 0.05$ ETN *versus* RIS, ALN	Group 1 *N* = 59 −1.6 Group 2 *N* = 107 −1.2	Group 3 *N* = 30 −0.7 Group 4 *N* = 49 −0.3	NS	Group 1 *N* = 59 −1.1 Group 2 *N* = 107 −1.8	Group 3 *N* = 30 −0.9 Group 4 *N* = 49 −1.4	NS
		12	5.6 5.4	8.8 5.3	$p < 0.05$ ETN *versus* RIS, ALN	−0.4 −0.6	1.1 −0.4	NS	0.2 −0.5	1.5 −0.3	NS
		18	7.7 7.8	11.6 8.2	$p < 0.05$ ETN *versus* NON-BPs	0.9 0.6	2.4 1.4	NS	1.6 1.3	3.8 2.3	$p < 0.005$ ALN *versus* ETI
		24	9.4 9.2	13.5 9.3	$p < 0.05$ ETN *versus* NON-BPs	2.9 2.1	3.7 1.8	NS	4.1 3.4	3.7 2.7	NS

ALN, alendronate; AN, anabolic; AR, antiresorptive; BMD, bone mineral density; ETN, etidronate; FN, femoral neck; LS, lumbar spine; PTH, parathyroid hormone; RIS, risedronate; TH, total hip; TPTD, teriparatide.

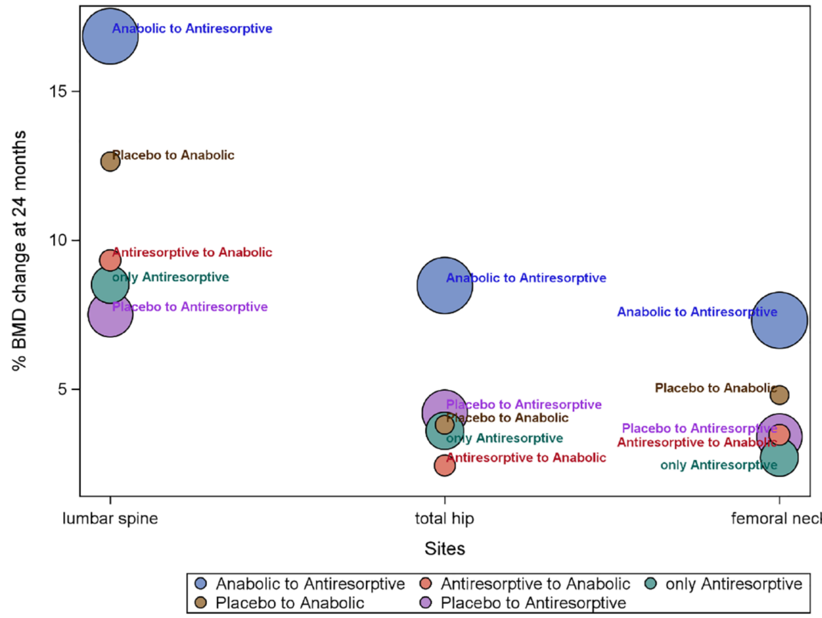

Figure 2. BMD change (mean % change) 24 months after the switch from anabolic, antiresorptive, or placebo.
Circles represent all studies related to the therapies and have a diameter proportional to the sample size.
AN, anabolic; AR, antiresorptive.

endpoint is not achieved, continuation with denosumab may be advisable until the target *T*-score (possibly −2.5) is reached. At that juncture, transitioning to bisphosphonates may be considered.

In general, antiresorptive agents, such as bisphosphonates, were the first developed drugs, and only later did an anabolic agent, such as teriparatide, become available.[46] Some pharmacological therapies can be used only for a limited timeframe, such as romosozumab and PTH analogs, which require a treatment cycle of 12 and 24 months, respectively. Furthermore, the discontinuation of certain treatments is followed by an undesired rebound effect, characterized by rapid bone loss that can undermine most of the densitometric benefits obtained over time and, consequently, loss of the clinical benefit in terms of fracture prevention. This can occur with anabolic, but it is especially alarming for denosumab.[47] Drugs currently available for the treatment of osteoporosis are classified by their mechanism of action. Antiresorptive drugs reduce osteoclastic bone resorption, and they include estrogens and selective estrogen receptor modulators, bisphosphonates, and denosumab. In addition, anabolic drugs increase osteoblastic bone formation activity, including teriparatide and abaloparatide. Finally, dual-action drugs, such as romosozumab, increase osteoblastic bone formation activity and reduce osteoclastic bone resorption.

Anabolic drugs, such as teriparatide, abaloparatide, and romosozumab, reduce the risk of fracture more rapidly and to a greater extent than antiresorptive medications.[41] Several head-to-head studies[28,48–50] showed that anabolic agents are more effective in reducing fracture incidence than oral bisphosphonates in the next 1 or 2 years, which have a higher refracture risk.[6,51–53] Anabolic medications not only provide bone mass accrual but are also associated with microstructural improvement, resulting in greater skeletal strength and resistance to fracture. Then, the sequential antiresorptive agents could sustain the BMD and strength gains, extending the protection against fractures over time.[54] With the newer drugs (denosumab and romosozumab), only head-to-head comparisons on densitometric effects are available.[55] However, there is increasing consensus on the appropriateness of estimating fracture risk reduction obtained with the densitometric gain associated with the therapy.[55] Unfortunately, anabolic drugs are widely underutilized in clinical practice, mostly due to their higher costs. For this reason, they are often used in high-risk patients, especially after the failure of a previous antiresorptive treatment for a new fracture or refracture.[45]

Sequential therapy in osteoporosis offers a pivotal means to augment the efficacy of individual treatments, provided the proper sequence (from anabolic to antiresorptive) is employed. Yet, it is regrettable that the reverse order is still prevalent in clinical settings, which is counterproductive and is thus inadvisable. It is now acknowledged that the increase in bone density achieved through therapy can be translated into a reduced risk of subsequent fractures. Consequently, the study's conclusions are pertinent to both high-risk and low-risk populations. Of course, in absolute numbers, the prevention of fractures will be considerably greater in the higher-risk cohort. This assertion is further corroborated by studies on romosozumab, where the romosozumab–alendronate sequence has demonstrated superiority over the alendronate–alendronate sequence in fracture outcomes, even though the study participants were of medium–low risk.

Limitations and strengths

Some limitations must be acknowledged. First, most studies were conducted in Europe, which may limit the generalizability of the results. Second, we have some concerns regarding the characteristics of patients and fracture sites at baseline. Moreover, few RCTs were included in each sequential therapeutic strategy, which might affect the interpretability of our findings. Third, the certainty of the evidence ranged from moderate to high RoB when considering anabolic as a first-line treatment. Conversely, a low RoB was attributed to sequential treatment from antiresorptive to anabolic medications.

Despite the above limitations, this study presents some strengths. The exhaustive search strategy identified an overview of RCTs focused on the sequential therapy from anabolic to antiresorptive and vice versa. In addition, the internal validity of the included studies was assessed using the RoB tool for RCTs.

Conclusion

The results of this systematic review and meta-analysis confirm that initial treatment with anabolic drugs produces substantial BMD improvements, both at the spine and at the hip sites, and the transition to antiresorptive drugs can preserve or even amplify the acquired benefit. These findings support the choice to treat very high-risk individuals with anabolic drugs first, followed by antiresorptive drugs, rather than using a reverse sequence.

Since osteoporosis is a chronic disease often requiring long-term treatments, clinicians are now asked not only to start a single drug but also to schedule long-term strategies based on the current and future fracture risk.

Declarations

Ethics approval and consent to participate

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Consent for publication

Not applicable.

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Availability of data and materials
No additional data are available.

Transparency declaration
The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supplemental material

Supplemental material for this article is available online.

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