Osteoporosis International
https://doi.org/10.1007/s00198-025-07440-1

REVIEW

PTH1 receptor agonists for fracture risk: a systematic review and network meta-analysis

Charlotte Beaudart[1,2] · Nicola Veronese[1,3] · Jonathan Douxfils[4,5,6] · Jotheeswaran Amuthavalli Thiyagarajan[7] · Francesco Bolzetta[8] · Paolo Albanese[8] · Gianpaolo Voltan[8] · Majed Alokail[9] · Nicholas C. Harvey[1,10] · Nicholas R. Fuggle[1,10] · Olivier Bruyère[1,11] · René Rizzoli[1,12] · Jean-Yves Reginster[1,9]

Received: 2 December 2024 / Accepted: 18 February 2025

Abstract

Osteoporosis, defined by reduced bone mineral density and macro- and micro-architectural degradation, leads to increased fracture risk, particularly in aging populations. While randomized controlled trials (RCTs) demonstrate that PTH1 receptor agonists, teriparatide and abaloparatide, are effective at reducing fracture risk, real-world evidence (RWE) remains sparse. This study reviews and compares the anti-fracture efficacy of these agents, against each other and against other osteoporosis treatments using both RCTs and RWE. We systematically searched Medline, Embase, and Cochrane up to May 2024, focusing on RCTs and RWE studies reporting reduction in vertebral, non-vertebral, hip, or all fractures as primary endpoint. A network meta-analysis (NMA) was conducted, first through pairwise meta-analyses of teriparatide versus abaloparatide, then a Bayesian NMA comparing each to other treatments. Safety assessments included adverse events classified by MedDRA, with a particular attention to hypercalcemia and cardiac events. Seventeen studies (11 RCTs, 6 RWE) met inclusion criteria. Teriparatide and abaloparatide were effective in reducing vertebral and non-vertebral fractures in all pairwise meta-analyses versus placebo. Abaloparatide showed an advantage over teriparatide for non-vertebral fractures (OR: 0.87, 95% CI: 0.80–0.95) and hip fractures (OR: 0.81, 95% CI: 0.71–0.93). In the NMA model, teriparatide and abaloparatide were superior to placebo, raloxifene, and calcitonin in reducing vertebral fracture while teriparatide was further superior to denosumab and risedronate. For non-vertebral fracture, abaloparatide was better than any other treatment while teriparatide was only superior to alendronate or placebo. PTH1 analogs were better than placebo at reducing all fractures while no difference was observed for the risk of hip fracture. Both abaloparatide and teriparatide demonstrate comparable safety to other osteoporosis treatments, with no increased cardiovascular risk**.** This review highlights that PTH1 receptor agonists effectively reduce fracture risk, with abaloparatide offering enhanced benefits for non-vertebral and hip fractures compared to teriparatide. Both agents exhibit acceptable safety profiles, suggesting their valuable role in managing osteoporosis, particularly for high-risk patients.

Keywords PTH-1 receptor agonists · Abaloparatide · Teriparatide · Osteoporosis · Fractures · Safety · MACE · Network meta-analysis · Randomized controlled trials · Real-world evidence studies

Introduction

Osteoporosis is a bone disease marked by reduced bone mineral density (BMD) and deterioration of bone structure, resulting in a heightened risk of fractures [1]. Often called the "silent disease" because it advances without noticeable symptoms until a fracture occurs, osteoporosis presents a major health concern, particularly within aging populations worldwide [1]. In Europe, the recent ScoreCard for OsteoPorosis in Europe (SCOPE) collaboration by the International Osteoporosis Foundation (IOF) projects that, over the next decade, osteoporotic fractures will affect more than 5 million individuals across the European Union, the UK, and Switzerland, a substantial rise of about 25% from 2019 levels [2].

It was overall reported that more than 50% of the patients affected by osteoporosis are not appropriately treated [3]. This is particularly true for patients at very high risk of osteoporotic fractures for whom the most potent treatments and comprehensive monitoring may be appropriate [4]. In this regard, bone-forming agents, such as abaloparatide and teriparatide, are of importance in osteoporosis management due to their efficacy in fracture prevention among high-risk

Extended author information available on the last page of the article

patients [5]. These anabolic agents have demonstrated the ability to improve vertebral and hip BMD and to reduce the risk of vertebral and non-vertebral fractures in clinical trials, systematic reviews, and network meta-analysis (NMA) [6–11].

Even if these works were of importance, they may suffer from some important limitations. First, we should point the lack of comprehensive real-world evidence (RWE) studies, as most randomized controlled trials (RCTs) do not adequately represent the broader patients' demographics and the patient "behavior" seen in clinical practice [12]. It is possible, for example, that some RCTs are underpowered to detect significant differences in fracture incidence, particularly for less common fracture types like those of the hip, which limits the generalizability of findings to everyday clinical settings [13]. In this regard, RWE is increasingly recognized for its value in capturing data from diverse, larger populations, reflecting actual clinical practice and long-term patient outcomes [12]. Observational studies and registry data provide insights into the sustained safety and efficacy of abaloparatide and teriparatide in routine care, supporting more informed decision-making for osteoporosis management [12]. This approach is essential for understanding the long-term effects, adherence rates, and comparative effectiveness of therapies, which can ultimately guide clinical guidelines and improve patient outcomes in managing osteoporosis-related fracture risks. Finally, new publications have recently emerged [14–17], overall suggesting that this information should be integrated into a new NMA clarifying the role of PTH1 receptor agonists in the management of patients at increased risk of osteoporotic fractures.

Given this background, with this systematic review and NMA, we aim to explore the risk of vertebral, non-vertebral, hip, and all fractures in primary osteoporosis in all studies (RCTs and RWE studies) including PTH1 receptor agonists (i.e., teriparatide or abaloparatide) versus other treatments (placebo, no treatment or any other active treatment). We also aim at evaluating the overall safety of these agents by compiling all adverse events reported in RCTs and RWE studies.

Materials and methods

The proposed systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) using the Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions (PRISMA-NMA) [18]. The completed PRISMA-NMA is available in Supplementary 1. A protocol has been developed and published in PROSPERO registry (RecordID: 558868). In the initial protocol, BMD was included as a secondary outcome. However, a slight deviation from the protocol was made, with safety analyses being prioritized for the current manuscript.

A project has been created on the Open Science Framework (OSF) (https://osf.io/fmbp2/), a platform for sharing scientific research. All materials and resources associated with this work are accessible through this open-access repository.

Research question

The research question can be summarized using the PICOs format: P (Population): primary osteoporosis, with or without history of fractures; I (Intervention): PTH1 receptor agonists (i.e., teriparatide or abaloparatide); C (comparator): placebo, no treatment or any other active treatment (i.e., denosumab, alendronate, risedronate, ibandronate, romosozumab, zoledronate); O (Outcome): main efficacy outcome: incidence of vertebral, non-vertebral, hip, and all fractures; secondary safety outcomes: all adverse events (AEs) classified according to MedDRA (English version 27.1) system organ class (SOC).

Literature search

Literature search was executed from database inception until 1 May 2024. Medline (via Ovid), Cochrane Central, and Embase databases used tailored search strategies to identify relevant papers. PRISMA-Search and Peer Review of Electronic Search Strategies (PRESS) guidelines were followed for literature searches conduct. A combination of terms of Medical Subject Headings (MeSH) and keywords was used in the search strategy (the complete search strategies for both databases are available in Appendix A). Additionally, a manual search within the bibliography of relevant papers was performed and experts in the field were contacted in order to complete the bibliographic search. Previous systematic reviews, meta-analyses, and network meta-analyses of interventions for osteoporosis were searched for backward/forward referencing. The search was limited to English studies [19, 20].

The search results from the electronic sources and hand searching were imported into Covidence software for data management. Covidence is a web-based collaboration software platform that streamlines the production of systematic and other literature reviews (https://support.covidence.org/help/how-can-i-cite-covidence).

Study selection

All identified articles were screened for their eligibility by two independent reviewers, in couples (N.V., F.B., P.A., and G.V.), first based on their titles and abstracts and, second,

based on their full texts. Any conflicts were resolved by a third reviewer (C.B.). Inclusion criteria (Table 1) guided the study selection process. Peer-reviewed RCTs or observational RWE studies were included if they reported the incidence of vertebral, non-vertebral, hip, or all fractures as the primary endpoint, involving at least two groups of treated patients, with one group receiving a PTH-1 receptor agonist (either abaloparatide or teriparatide) and the other group receiving placebo or any other active anti-osteoporosis treatment.

Studies with secondary causes of osteoporosis (e.g., cancer-related, hypogonadism, and glucocorticoid-induced osteoporosis), not original studies (case reports, review, letters to the editors, conference abstracts, opinion pieces), and protocols were excluded. To ensure robust statistical analyses, the following decisions were made: studies involving bisphosphonates were excluded if detailed information about the specific type of bisphosphonate was not provided since the efficacy of these agents is markedly different [21]; studies that used standard care as a definition of the comparator were excluded; studies that defined the placebo group as one receiving a low dose of active treatment (e.g., 1.4 µg teriparatide) were also excluded [22].

Data extraction

Study characteristics were extracted by one independent reviewer (N.V.) according to a standardized data extraction form pretested on a sample of four studies. A second reviewer checked data extraction (C.B.). The following data were extracted: information related to the study (author, year of publication, journal, DOI), demographics, and information related to the treatment (groups, type of treatment, dose, length of follow-up).

Efficacy data were extracted by two independent reviewers (C.B. and N.V.). The following data were extracted for efficacy assessment: absolute number of vertebral, non-vertebral, hip, or all fractures in each group.

Safety data were extracted by two independent reviewers (C.B. and J.D.). The following data were extracted for safety assessment: absolute number of AEs classified by the MedDRA system into SOC.

Any disagreements were resolved through consensus between reviewers. Authors of individual papers were contacted in case of any missing information.

Quality appraisal

The quality of individual studies was assessed using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB2) [23]. This tool evaluates five key domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and the selection of reported results. Each domain, as well as the overall risk of bias, was judged, categorizing studies as having a low risk of bias, some concerns, or a high risk of bias. Each study was independently evaluated by two reviewers (G.V., N.V.), with any disagreements resolved by consensus.

Strategy for efficacy data synthesis

Meta-analyses models were performed for the four efficacy outcomes separately, i.e., vertebral fractures, non-vertebral fractures, hip fractures, and all fractures. When at least two similar studies were available to be pooled in a meta-analytical model, an NMA was performed following two steps: (1) standard pairwise meta-analyses, considering only direct comparisons of PTH1 receptor agonists versus placebo; and (2) an NMA combining both direct and indirect comparisons versus other treatments.

For efficacy analyses, in the first step, random-effects pairwise meta-analyses were conducted by pooling studies that compared teriparatide versus placebo or abaloparatide versus placebo for each type of fractures (i.e., vertebral, non-vertebral, hip, and all fractures). A pooled Peto odds ratio (OR) and 95% CI were obtained using absolute number of fractures reported within each group of intervention. Peto ORs have been privileged to better account for the small number of observed outcomes [24]. Heterogeneity was assessed using the Q-test and quantified through I^2.

Table 1 Inclusion criteria

PICOS criteria	
Population	Adults with primary osteoporosis, with or without history of fracture
Intervention	PTH1 receptor agonists, namely teriparatide or abaloparatide
Comparator	Placebo, no intervention or any other active drugs (i.e., denosumab, alendronate, risedronate, ibandronate, romosozumab, zoledronate, teriparatide, abaloparatide). Both arms can include vitamin D and/or calcium)
Outcomes	Main outcome: incidence of vertebral, non-vertebral, hip fractures or all fractures Secondary outcome: absolute number of AEs classified by the MedDRA system into system organ classes (SOC)
Study design	Peer-reviewed randomized controlled trials (RCTs) and observational longitudinal real-world evidence (RWE) studies

In the second step, the transitivity assumption was assessed, which implied that studies comparing different sets of interventions were sufficiently similar to provide valid indirect inferences. For that, the distribution of the potential effect modifiers (e.g., gender, age, dose of treatment) of the primary outcome was compared across studies grouped by comparison. As the transitivity assumption was confirmed (i.e., no difference of distribution of potential effect modifiers), network meta-analyses were carried out for each outcome. A single heterogeneity parameter for each network was assumed. The available evidence was presented in a network diagram, where the width of each edge was proportional to the inverse of the variance of the summary effect of each direct treatment comparison. In each NMA model, PTH1 analogs should be considered as the comparator arm for any of the reported effect size, i.e., a positive OR indicates a higher risk of fracture for other treatment versus the PTH1 analog of interest.

The probability of each intervention being ranked as the most effective in reducing the risk of fracture was calculated, and a hierarchy of the competing interventions was determined using the surface under the cumulative ranking curve (SUCRA) and mean ranks. SUCRA values were expressed as percentages, indicating the relative probability of an intervention being among the best options.

Strategy for safety data synthesis

Safety analyses were performed on the same set of studies identified for efficacy. Nevertheless, as not all studies reported safety outcomes, especially RWE studies [14, 15, 25–28], the analysis primarily included RCTs [16, 17, 29–37].

The main analysis comprised "all AEs." A sub-analysis was performed on all AEs by excluding the preferred term (PT) "hypercalcemia" from the analysis since hypercalcemia is a well-known adverse effect associated with PTH1 analogs, as they promote osteoblast activity, leading to increased bone resorption and the release of calcium into the bloodstream. The MedDRA classification was then used to group adverse events into SOC [38]. The following SOC were investigated: cardiac disorders, gastrointestinal disorders, general disorders and administration site conditions, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, and, finally, neoplasms. Then, sub-stratifications were applied to PTs within the category of cardiac disorders, including the following groups: cardiac arrhythmias, coronary heart disease and stroke, heart failure, blood pressure disorders, and various definitions of major adverse cardiovascular events (MACEs). Specifically, MACE3 included myocardial infarction (MI), stroke, and cardiovascular death; MACE4 included these events plus heart failure; and MACE5 expanded this further to include heart rhythm problems (excluding palpitations). Stroke was classified under coronary heart disease and stroke. All SOC, PT, and supplementary safety analyses are described in Appendix B.

Statistical considerations

To avoid displaying studies in the NMA models comparing no treatment versus placebo as indirect evidence, placebo and no treatment have been merged to form one unique comparator option. For studies reporting outcomes across multiple follow-up periods, the outcomes for the longest follow-up period were selected. When the outcome "all fracture" was not directly reported by authors of individual studies, the outcome (i.e., vertebral, non-vertebral, or hip) with the highest cumulative incidence was used in the analyses. When a study had zero events in one arm, one event was added to each arm to allow for OR and its 95% CI calculation.

Potential publication bias was explored using a funnel plot (not reported in the manuscript) and Egger regression test.

All analyses were performed using the R package "meta," "netmeta," and its extensions. For all results, a two-sided p-value of 0.05 or less was considered significant.

Results

Study characteristics and risk-of-bias evaluation

A total of 7165 references were identified through the search strategies applied on bibliographic databases in May 2024. After removing duplicates, 5470 references were assessed for eligibility based on their title/abstract. Among those references, 178 were assessed based on their full text and 16 studies met the inclusion criteria. The list of excluded studies in the stage of full-text review as well as of the reason for exclusion is available on an Open Science Framework deposit (https://osf.io/fmbp2/). Manual search identified one additional reference, so a total of 17 studies were further included in this systematic review and meta-analysis (Fig. 1).

Among the 17 studies included, 11 were RCTs [16, 29–37, 39] and 6 were observation RWE studies [14, 15, 25–28]. Sample sizes ranged from 34 [39] to 1,278,296 individuals [26]. Length of treatment ranged from 12 to 36 months.

Ten different treatments were included, i.e., teriparatide, abaloparatide, alendronate, zoledronic acid, raloxifene, risedronate, ibandronate, denosumab, calcitonin, and placebo/no treatment. A visual netgraph presentation of all treatments direct and indirect evidence is available in Fig. 2.

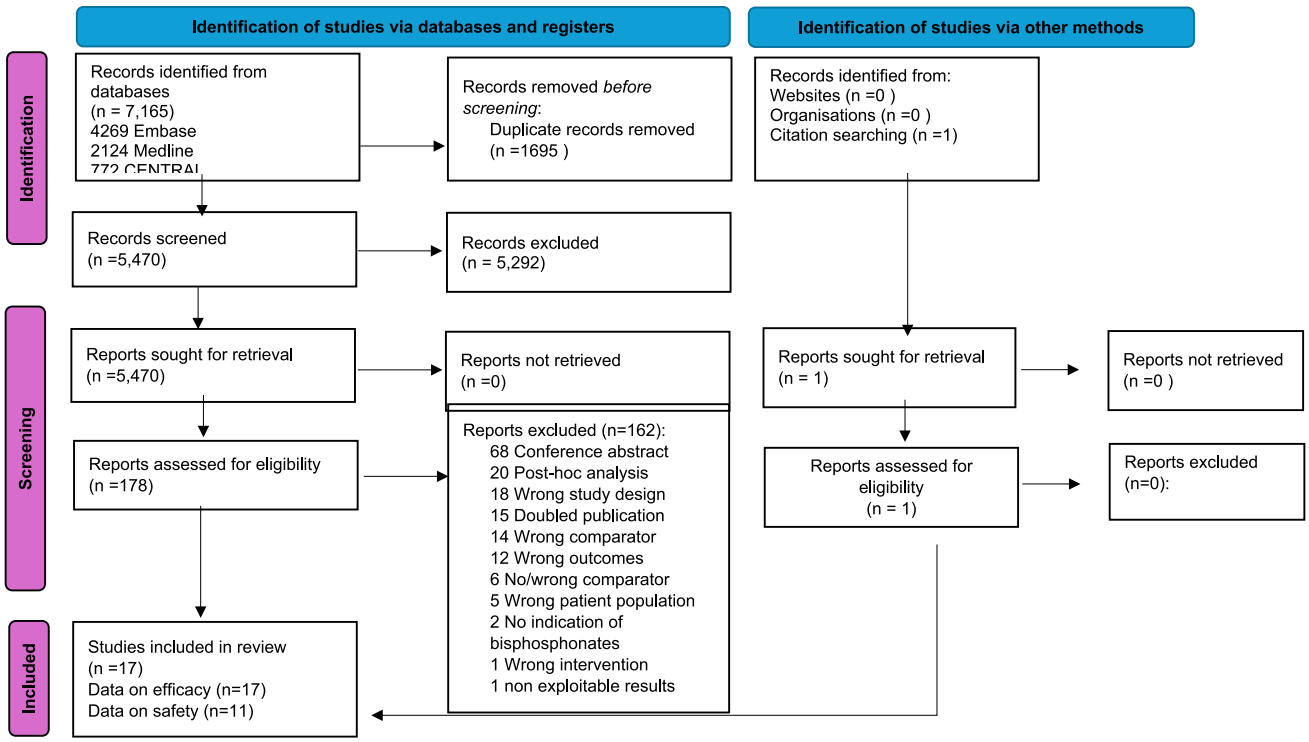


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) flowchart of study selection

All RWE studies were of good to excellent quality (7 to 9/9 stars on the NOS scale). RCTs were all rated at low risk of bias except the study of Li et al. [33], Neer et al. [29], and Lindsay et al. [39] that demonstrated some concerns in respectively domains 2, 1, and 1.

Characteristics and quality assessment of the 17 included studies are presented in Table 2.

Effect of PTH1 on fracture risk

Vertebral fractures

Eleven studies (i.e., nine RCTs and two observational RWE studies) reported vertebral fracture incidence [16, 26, 27, 29, 31, 32, 34–37, 39]. Pairwise meta-analyses reported a significant reduction of vertebral fractures for patients treated with teriparatide versus placebo ($k=4$, n individuals = 3822, Peto OR: 0.27, 95% CI: 0.20–0.36, $I^2=0\%$, p for heterogeneity = 1.00) and for patients treated with abaloparatide versus placebo ($k=2$, n individuals = 1850, Peto OR: 0.17, 95% CI: 0.06–0.45, $I^2=18\%$, p for heterogeneity = 0.27) (pairwise meta-analyses available in Appendix C).

In the NMA model, including the same 11 studies, 38 pairwise comparisons, and 10 treatments (Fig. 3), teriparatide is reported to provide a numerically greater benefit in preventing vertebral fractures than risedronate (OR risedronate vs. teriparatide for fracture risk: 1.98, 95% CI: 1.002–3.91), denosumab (OR: 2.99, 95% CI: 1.04–8.62), calcitonin (OR: 4.17, 95% CI: 1.21–14.29), raloxifene (OR: 4.08, 95% CI: 1.79–9.31), and placebo (OR: 4.38, 95% CI: 2.15–8.93). Abaloparatide, on the other hand, is reported to be significantly better in preventing vertebral fractures than calcitonin (OR: 7.17, 95% CI: 1.15–44.61), raloxifene (OR: 7.02, 95% CI: 1.44–34.18), and placebo (OR: 7.53, 95% CI: 2.21–26.7) (Fig. 4).

No publication bias has been detected in this meta-analysis model (Egger test $p=0.26$).

Non-vertebral fractures

Eleven studies (i.e., nine RCTs and two observational RWE studies) also reported non-vertebral fracture incidence [15–17, 30–32, 34–37]. Pairwise meta-analyses reported a significant reduction of non-vertebral fractures for patients treated with teriparatide versus placebo ($k=3$, n individuals = 3792, Peto OR: 0.62, 95% CI: 0.41–0.93, $I^2=16\%$, p for heterogeneity = 0.30) and for patients treated with abaloparatide versus placebo ($k=2$, n individuals = 1851, Peto OR: 0.56, 95% CI: 0.33–0.95, $I^2=0\%$, p for heterogeneity = 0.74). Two observational RWE studies [17, 34] also reported comparison between abaloparatide and teriparatide for reducing non-vertebral fracture. A pooled Peto OR of 0.87 (95% CI: 0.80–0.95) has been found using a pairwise

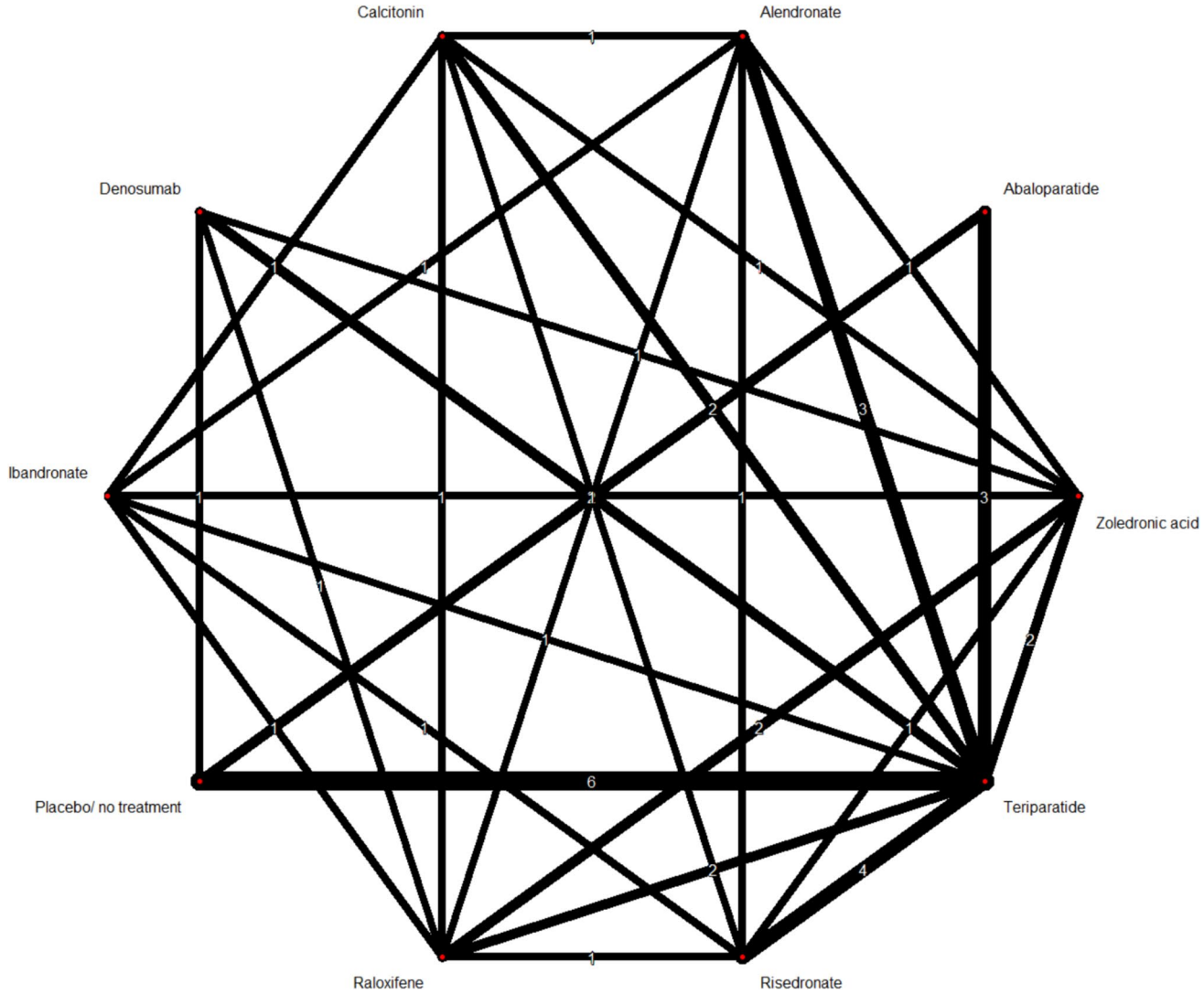


Fig. 2 Netgraph of included treatments (netgraph generated for the outcome "all fractures")

meta-analysis, in favor of abaloparatide (I^2 0%, p for heterogeneity 0.60).

In the NMA model, including the same 11 studies, 13 pairwise comparisons, and 5 treatments (Fig. 3), teriparatide is reported to be significantly less effective in preventing non-vertebral fractures than abaloparatide (OR for abaloparatide versus teriparatide for non-vertebral fracture risk: 0.88, 95% CI: 0.81–0.95). Teriparatide is reported to be significantly more effective than alendronate (OR: 2.00, 95% CI: 1.06–3.79) and placebo (OR: 1.63, 95% CI: 1.20–2.22) while no difference in terms of efficacy was observed compared to risedronate. Abaloparatide, on the other hand, demonstrated to be significantly better than any other treatments included in the model (namely, teriparatide (OR: 1.14, 95% CI: 1.06–1.23), risedronate (OR: 1.49, 95% CI: 1.03–2.15), alendronate (OR: 2.29, 95% CI: 1.20–4.35), and placebo (OR: 1.86, 95% CI: 1.36–2.55) (Fig. 4).

No publication bias has been detected in this meta-analysis model (Egger test $p = 0.79$).

Hip fractures

Nine studies (i.e., five RCTs and four observational RWE studies) also reported hip fracture incidence [15, 17, 26, 27, 29, 31, 35–37]. Only one RCT reported the incidence of hip fracture for teriparatide versus placebo [29]. This study did not report a significant reduction of hip fracture for teriparatide versus placebo. No RCT reported the incidence of hip fracture for patients treated with abaloparatide versus placebo. Two observational RWE studies [15, 17] reported comparison between abaloparatide and teriparatide for reducing non-vertebral fracture. A pooled Peto OR of 0.81 (95% CI: 0.71–0.93) has been found using a

Table 2 Studies' characteristics

Authors, year	Population description	Sample size per treatment	Treatment duration	Efficacy outcomes	Safety outcomes	Risk-of-bias assessment
Randomized controlled trials						
Body, 2002 [30]	146 postmenopausal women with osteoporosis (multi-country) Mean age of 65.5 years	Teriparatide 40 µg daily ($n=73$) Alendronate 10 mg daily ($n=73$)	14 months	NVF	All AEs, deaths, cardiac, musculoskeletal, MACE3, MACE4, MACE5	Low risk of bias
Hadji, 2012 [31]	710 postmenopausal women with osteoporotic vertebral fractures (multi-country) Mean age of 71 years	Teriparatide 20 µg daily ($n=360$) Risedronate 35 mg weekly ($n=350$)	18 months	VF, NVF, HF	All AEs, serious AEs, deaths, cardiac, gastro, metabolism, musculoskeletal	Low risk of bias
Hagino, 2021 [37]	1011 postmenopausal women of 75 years or older in Japan with primary osteoporosis and at high risk of fracture Mean age of 81.5 years *Japanese Osteoporosis Intervention Trial*	Teriparatide 56.5 µg weekly ($n=505$) Alendronate 5 mg tablet (daily), 35 mg tablet or jelly (weekly), or 900 µg infusion bag (once every 4 weeks) ($n=506$)	16.5 months	VF, NVF, HF, AF	All AEs, cardiac, gastro, general, metabolism, musculoskeletal, neoplasms	Low risk of bias
Kendler, 2018 [36]	1366 postmenopausal women with severe osteoporosis (multi-country) Mean age of 72.1 years *The VERO trial*	Teriparatide 20 µg daily ($n=683$) Risedronate 35 mg weekly ($n=683$)	24 months	VF, NVF, HF, AF	All AEs, deaths, gastro, general, metabolism, musculoskeletal	Low risk of bias
Li, 2013 [33]	453 postmenopausal women in China with osteoporosis Mean age of 65.1 years	Teriparatide 20 µg daily ($n=341$) Calcitonin 20 U weekly ($n=112$)	18 months	AF	All AEs, deaths, gastro	Some concerns
Lindsay, 1997 [39]	34 postmenopausal women in USA on estrogen with osteoporosis Mean age of 61.9 years	Teriparatide 25 µg daily ($n=13$) No treatment ($n=17$)	36 months	VF	NR	Some concerns
Malouf-Sierra, 2017 [35]	224 elderly patients with a recent petrochanteric hip fractures (multi-country) Mean age of 76.8 years (77% of women)	Teriparatide 20 µg daily ($n=111$) Risedronate 35 mg weekly ($n=113$)	18 months	VF, NVF, HF	All AEs, serious AEs, deaths, metabolism	Low risk of bias
Matsumoto, 2021 [16]	212 patients in Japan with osteoporosis Mean age of 68.4 years (88% of women) *The phase 3 ACTIVE-J Study*	Abaloparatide 80 µg daily ($n=140$) Placebo ($n=72$)	18 months	VF, NVF	All AEs, serious AEs, cardiac, gastro, general, metabolism, musculoskeletal, MACE5	Low risk of bias

Table 2 (continued)

Authors, year	Population description	Sample size per treatment	Treatment duration	Efficacy outcomes	Safety outcomes	Risk-of-bias assessment
Miller, 2016 [34]	2,463 postmenopausal women with osteoporosis (multi-country) Mean age of 68.8 years	Abaloparatide 80 µg daily ($n=824$) Teriparatide 20 µg daily ($n=818$) Placebo ($n=821$)	16.5 months	VF, NVF	All AEs, serious AEs, deaths, cardiac, gastro, general, metabolism, musculoskeletal, neoplasms, MACE3, MACE4, MACE5	Low risk of bias
Nakamura, 2012 [32]	578 patients in Japan with primary osteoporosis Mean age of 75.3 years (94% of women) *The TOWER trial*	Teriparatide 56.5 µg weekly ($n=290$) Placebo ($n=288$)	16.5 months	NVF	All AEs, serious AEs, deaths, cardiac, gastro, general, musculoskeletal, neoplasms, MACE3, MACE4, MACE5	Low risk of bias
Neer, 2001 [29]	1637 postmenopausal women with osteoporosis (multi-country) Mean age of 69 years	Teriparatide (20 µg daily or 40 µg daily) (n = 1,093 both doses combined) Placebo (n = 544)	24 months	VF, NVF, HF, AF	All AEs, gastro, general, metabolism, musculoskeletal, neoplasms	Some concerns
Real-world evidence studies						
Adami, 2022 [14]	Representative cohort of 3574 women in Italy at high risk of fracture Mean age of 66 years	No treatment ($n=3065$) Teriparatide ($n=26$) Denosumab ($n=154$) Bisphosphonates ($n=329$)	558 days	VF, NVF, AF	NR	Excellent quality: 9/9 stars on the NOS scale
Boytsov, 2015 [25]	1824 postmenopausal women in the USA with a recent fracture and treated with teriparatide to a matched cohort not treated with teriparatide Mean age of 73.8 years	Teriparatide ($n=912$) No treatment ($n=912$)	24 months	AF	NR	Excellent quality: 9/9 stars on the NOS scale
Cosman, 2022 [15]	23,234 women in the USA treated with abaloparatide or teriparatide Mean age 67.4 years	Abaloparatide ($n=11,616$) Teriparatide ($n=11,616$)	19 months	NVF, HF	NR	Good quality: 8/9 stars on the NOS scale
Reynolds, 2018 [27]	Patients in the USA starting a new osteoporosis medication Mean age 56 years (94% of women)	Alendronate ($n=26,395$) Calcitonin ($n=1074$) Ibandronate ($n=9956$) Raloxifene ($n=4753$) Risedronate ($n=8815$) Teriparatide ($n=524$) Zoledronic acid ($n=132$)	24 months	VF, HF, AF	NR	Good quality: 8/9 stars on the NOS scale
Tabatabai, 2024 [17]	43,352 women treated with abaloparatide or teriparatide (multi-country) Mean age of 66.1 (abaloparatide) and 67.1 years (teriparatide)	Abaloparatide ($n=21,676$) Teriparatide ($n=21,676$)	16.5 months	NVF, HF	All AEs, cardiac, MACE3, MACE4, MACE5	Excellent quality: 9/9 stars on the NOS scale

Table 2 (continued)

Authors, year	Population description	Sample size per treatment	Treatment duration	Efficacy outcomes	Safety outcomes	Risk-of-bias assessment
Yusuf, 2018 [26]	1,278,296 women in the USA enrolled in Medicare Mean age of 78 years	Teriparatide ($n=20,610$) Denosumab ($n=34,622$) Zoledronic acid ($n=124,857$) Raloxifene ($n=100,521$)	12 months	VF, HF, AF	NR	Good quality: 7/9 stars on the NOS scale

VF vertebral fractures, *NVF* non-vertebral fractures, *HF* hip fractures, *AF* all fractures, *NR* not reported

Nb. RoB assessment: Li et al. demonstrated some concerns in domain 2—deviations from the intended interventions; Neer et al. and Lindsay et al. demonstrated some concerns in domain 1—randomization process. All other studies were rated "low risk of bias" in any of the investigated domains

pairwise meta-analysis, in favor of abaloparatide (I^2 0%, p for heterogeneity = 0.73).

In the NMA model, including 9 studies, 34 pairwise comparisons and 10 treatments, neither teriparatide nor abaloparatide demonstrated to be more effective in reducing hip fractures compared to other treatments included in the model (Figs. 3 and 4).

No publication bias has been detected in this meta-analysis model (Egger test $p = 0.56$).

All fractures

All fractures were reported directly per se in eight studies (i.e., four RWE and four RCT studies) [14, 25–27, 29, 33, 36, 37]. In the nine other studies, the outcome (i.e., vertebral, non-vertebral or hip) with the highest cumulative incidence was used in the analyses (vertebral fractures in four studies and non-vertebral fractures in the last five studies). Among the 17 studies, 3 reported a direct comparison between teriparatide and placebo [14, 25, 29]. Pairwise meta-analysis indicated a significant reduction for teriparatide versus placebo (OR: 0.39, 95% CI: 0.27–0.56; $k = 3$, n individuals = 6552, $I^2 = 60\%$, p for heterogeneity = 0.08). Pairwise meta-analyses also demonstrated a superiority of abaloparatide versus teriparatide in reducing the risk of "all fractures" (OR: 0.88, 95% CI: 0.81–0.94, $k = 3$, n individuals = 68,226, $I^2 = 0\%$, p for heterogeneity = 0.84) [15, 17, 34].

In the NMA model, including 17 studies, 46 pairwise comparisons, and 10 treatments, both teriparatide and abaloparatide demonstrated to be significantly superior to placebo to reduce the incidence of all fractures (OR: 2.39, 95% CI: 1.61–3.56 for placebo vs. teriparatide and OR: 2.75, 95% CI: 1.57–4.82 for placebo vs. abaloparatide) (Figs. 3 and 4). No superiority of PTH1 receptor agonists was, however, found comparing to other treatments included in the model.

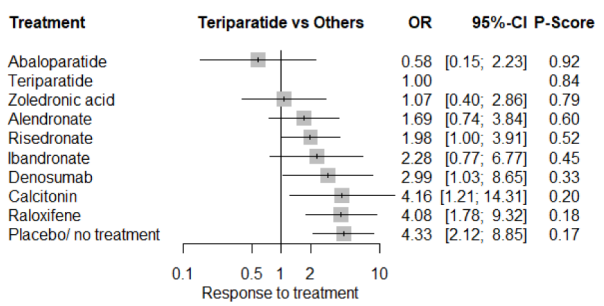
No publication bias has been detected in this meta-analysis model (Egger test $p = 0.78$).

Safety of PTH1 versus all other treatments

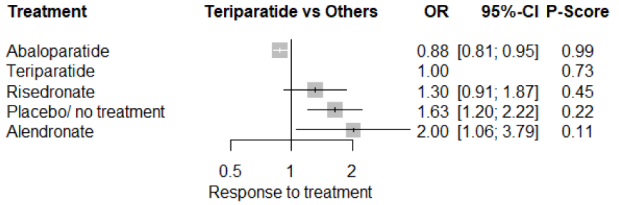
The full report of safety results is reported in Appendix C. A total of 11 studies among the 17 included reported safety analyses [16, 17, 29–37] (Fig. 1). The analysis was conducted for several outcomes, including all AEs, serious AEs, and SOC categories such as cardiac, gastrointestinal, and general disorders, metabolism and nutrition, musculoskeletal, and neoplasms.

All adverse events—serious adverse events—deaths

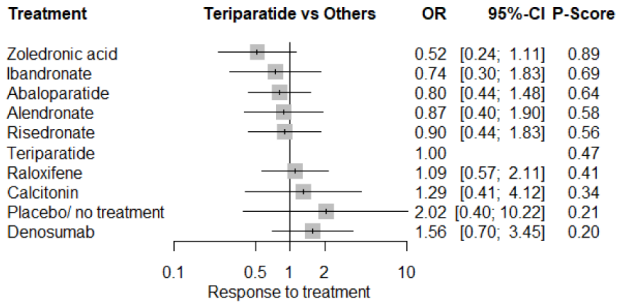
In the NMA on all AEs, placebo was shown to have a lower risk of AEs compared to both teriparatide and abaloparatide. However, this observation is driven by the higher rate of



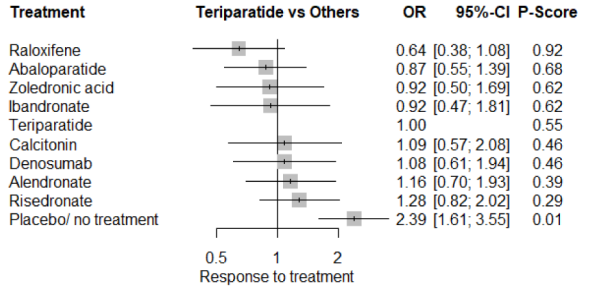
3.1. Vertebral fracture NMA - teriparatide



3.2. Non-vertebral fractures NMA - teriparatide

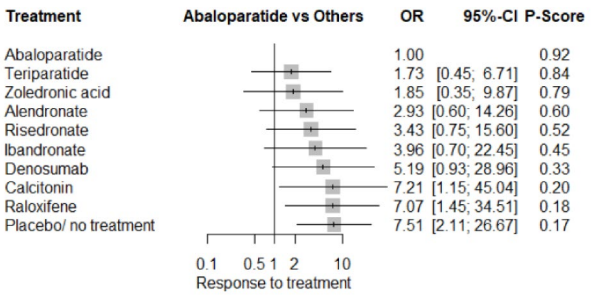


3.3. Hip fractures NMA - teriparatide

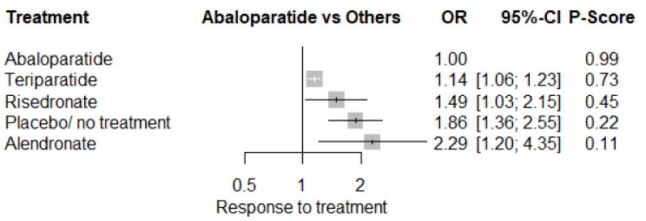


3.4. All fractures NMA - teriparatide

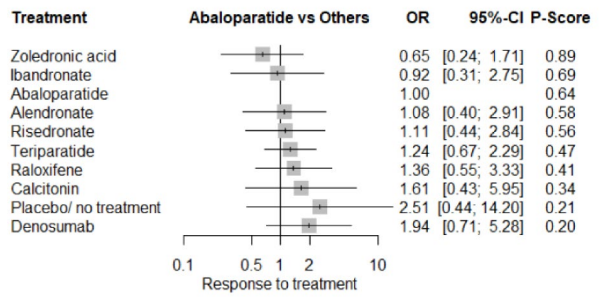
Fig. 3 Efficacy of teriparatide versus any other osteoporosis treatments on fracture risk



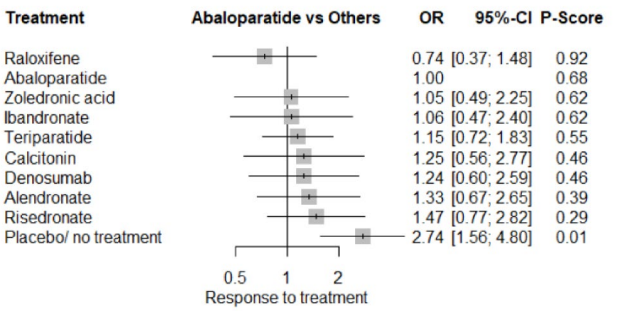
4.1. Vertebral fracture NMA - abaloparatide



4.2. Non-vertebral fractures NMA - abaloparatide



4.3. Hip fractures NMA - abaloparatide



4.4. All fractures NMA - abaloparatide

Fig. 4 Efficacy of abaloparatide versus any other osteoporosis treatments on fracture risk

hypercalcemia events reported in the teriparatide and abaloparatide arms since exclusion of these AEs leads to similar safety profile between all treatments including placebo/no treatment in the model. In terms of serious AEs and deaths, neither teriparatide nor abaloparatide was associated with a higher risk relative to other treatments or placebo.

System organ class specific analysis

Both teriparatide and abaloparatide demonstrated similar safety profiles to other treatments or placebo/no treatment for SOC gastrointestinal disorders, SOC musculoskeletal and connective tissue disorders, SOC neoplasms, and SOC cardiac disorders, including cardiac arrhythmias, coronary heart disease, and heart failure. Supplementary analyses were conducted on grouped cardiovascular events, including MACE3, MACE4, and MACE5. No significant differences in cardiovascular death or other MACE categories were observed between teriparatide, abaloparatide, and other treatments, suggesting a comparable cardiovascular safety profile between PTH R1 agonists and compared to other anti-osteoporosis treatments.

For SOC general disorders and administration site conditions, risedronate, alendronate, and placebo showed slightly better safety profiles compared to teriparatide and abaloparatide. For the SOC metabolism and nutrition disorders, placebo and risedronate were associated with fewer metabolic and nutrition-related AEs than teriparatide while only placebo was demonstrated safer than abaloparatide. Hypercalcemia accounts for 88% of the AEs classified in this SOC. Excluding hypercalcemia leads to no difference between treatments and placebo/no treatment.

Discussion

This NMA provides a robust evaluation of the anti-fracture efficacy of PTH1 receptor agonists (namely, abaloparatide and teriparatide) within a comprehensive network of osteoporosis treatments. This work highlights the distinct anti-fracture benefits of these PTH1 analogs, particularly emphasizing their comparative impact across vertebral and non-vertebral fractures. These findings contribute to the current understanding of the role of anabolic agents in osteoporosis therapy, offering novel insights beyond those previously reported in individual trials and observational studies.

This NMA demonstrates that both abaloparatide and teriparatide are highly effective in reducing vertebral, non-vertebral, and hip fracture risk compared to other osteoporosis treatments. In the direct comparison of teriparatide and abaloparatide, abaloparatide appears to have a distinct advantage over teriparatide, particularly in reducing non-vertebral and hip fractures. This finding is particularly relevant, as non-vertebral and hip fractures are associated with significant morbidity and mortality, and their prevention remains a central goal in osteoporosis management [40, 41]. The hip fracture reduction is mainly observed in RWE [15, 17], but the ACTIVE-ACTIVExtend study also showed a greater efficacy of abaloparatide on major osteoporotic fractures compared to teriparatide [34, 42]. In the same study, abaloparatide showed a significant reduction in non-vertebral fractures and clinical fractures, which was not reported for teriparatide. It should, however, be mentioned that the head-to-head comparison between abaloparatide and teriparatide was not blinded and that the patients included in the ACTIVE-ACTIVExtend study were at lower risk for fracture compared to the population included in the pivotal study of teriparatide [29]. Nevertheless, one hypothesis supports these results could be that the distinct receptor binding profile of abaloparatide, which promotes transient and targeted anabolic signaling, could potentially contribute to a more favorable bone quality and architecture, especially at cortical sites [43]. Indeed, PTH1 receptor has two high-affinity conformations: the G protein–independent R0 and G protein–dependent RG conformations. Thus, despite both teriparatide and abaloparatide binding to the PTH1 receptor [44], abaloparatide is more selective than teriparatide for the RG conformation of PTH1 receptor and induces a faster and more transient signaling response, consistent with a net anabolic effect [15, 44]. This selective binding of abaloparatide to the RG versus R0 conformation of PTH1 receptor, and the subsequent expected net anabolic effect [43, 45], translates into a greater anabolic window for abaloparatide compared to teriparatide, e.g., a lower rate of bone formation and bone resorption but a higher net anabolic effect [46]. In a meta-analysis published by Hong et al. including four RCTs assessing changes in BMD, at the lumbar spine, femoral neck, and total hip in patients treated with abaloparatide or teriparatide, abaloparatide showed a greater increase compared to teriparatide, after 48 weeks, at all skeletal sites [9]. When performing a three-dimensional analysis of Dual Energy X-Ray Absorptiometry (DEXA) data, abaloparatide significantly increases cortical volumetric BMD versus baseline and changes in both cortical volumetric BMD and cortical surface BMD were significantly greater with abaloparatide compared to teriparatide [47].

It is important to note that the results observed in the present study do not challenge the anti-fracture efficacy of teriparatide, which has been unequivocally demonstrated over more than two decades, for spinal and non-spinal fractures [29], confirmed in a sub-population of older patients [48] and confirmed at the level of the hip by meta-synthesis evidence [7]. More recently, anti-fracture efficacy of teriparatide on non-vertebral fragility fractures was shown to be greater than that observed with risedronate (a bisphosphonate which was previously shown to be effective at

fracture reduction), at all skeletal sites, in randomized controlled trials [36, 49] and in meta-analyses [50, 51]. Additionally (after the statistical analyses of the present studies were completed), a study comparing the effectiveness and cardiovascular safety of romosozumab and teriparatide in a Japanese population was published [52]. In this cohort study, based on health claims data, the antifracture efficacy (non-vertebral fracture and hip fracture) of teriparatide was reported as non-significantly different from what is observed in patients receiving romosozumab. In addition, the risk of MACE was comparable between the two drugs [52].

Results of this NMA, align with and expand on evidence from prior NMAs, which have often focused primarily on BMD outcomes rather than fracture-specific effects across diverse skeletal sites [53, 54]. This might have important implications for treatment strategies, particularly in tailoring osteoporosis management to individual patient needs. The most recent guidelines for the management of osteoporosis [55] suggest categorizing fracture risk to better target therapeutic interventions for the prevention of fragility fracture in post-menopausal women. Patients at very high fracture risk, e.g., immediately after a prevalent sentinel fracture, and the consequent further loss in quality of life, occurring immediately after a subsequent fracture, suggest that preventive treatment given as soon as possible after a fracture would avoid a higher number of new fractures and would reduce the mortality and morbidity compared to a delayed treatment. Such an immediate intervention justifies the use of agents that have a fast and strong effect on fracture reduction. Anabolic agents, like PTH R1 agonists, demonstrated a more rapid and a greater fracture risk reduction compared to anti-resorptive treatments [34, 36]. Thus, while current osteoporosis guidelines emphasize the importance of fracture risk reduction and categorization [55–59], our findings suggest that selecting an anabolic agent like abaloparatide could be particularly beneficial for patients at high risk of hip and non-vertebral fractures.

Given that non-vertebral fractures are often challenging to prevent and are associated with increased healthcare costs and burden [2], the use of abaloparatide could provide a strategic advantage in reducing these more debilitating fracture types. Currently, PTH R1 agonists are predominantly prescribed to patients at very high risk for osteoporotic fractures. The health economic studies conducted, to date, show that teriparatide and abaloparatide are cost-efficient or dominant compared to anti-resorptive agents in such patients. The lack of cost-efficiency of teriparatide and abaloparatide in patients at a lower risk for fracture is mainly driven by the relatively high price of PTH R1 agonists compared to oral bisphosphonates, particularly to generic alendronate or risedronate. However, since the greater efficacy of PTH R1 agonists compared to anti-resorptive agents is not limited to patients at very high risk for fracture, a decrease in the price of teriparatide or abaloparatide (i.e., when biosimilars will be widely available) may change the outcomes of the health economic studies and open the access to such medications in a greater subset of the osteoporotic population. Therefore, it is interesting to confirm the anti-fracture efficacy of teriparatide and abaloparatide both in patients with a prevalent fracture and in patients with low bone mineral density.

In terms of safety, this NMA primarily summarized data reported in RCTs, as no RWE studies, except for Tabatabai et al. (2024) which investigated cardiovascular events [17], described safety data in their manuscripts. The NMA highlights the long-standing, established safety profile of PTH receptor agonists compared to placebo and other osteoporosis therapies. An important concern which has been highlighted previously with these agents is the risk of osteoblastic osteosarcoma. This caution stems from findings in preclinical studies on rats, where dose-dependent increases in osteosarcoma were observed [60]. However, it is essential to analyze these preclinical findings in their context, especially because hypotheses regarding the mechanism of pathogenesis have not been observed in humans. The first difference to consider is the dosage used in animal studies, as even the lowest dose administered to rats (5 µg/kg for teriparatide and 10 µg/kg for abaloparatide) was respectively three and four times the typical human dose [60]. This excessive exposure may have contributed to the genesis of osteoblastic osteosarcoma. Importantly, these preclinical observations led to additional safety measures as teriparatide was initially limited in its treatment duration to 24 months of treatment [61–64]. However, the establishment of a 2-year treatment limit also needs to consider the relative lifespan exposure of rats which is totally different from humans' lifespan exposure. Indeed, in Fischer 344 rats, a 2-year treatment period represents approximately 90% of their lifespan, suggesting that the observed number of osteosarcoma cases could be unusually high under these conditions [60, 65, 66]. In contrast, the same duration does not represent a substantial portion of a human lifespan.

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have both adopted similar and divergent regulatory positions regarding the duration of restrictions for PTH1 analogs. For teriparatide, approved by the FDA in 2002, an initial 24-month treatment restriction was implemented due to concerns about osteosarcoma and insufficient long-term safety data [64]. In 2020, the FDA removed the black box warning on treatment duration but continues to recommend limiting cumulative use to 24 months unless the patient remains at high fracture risk. In contrast, the EMA, which approved teriparatide in 2003 with the same restriction, has maintained this limit despite US-based Post-Authorization Safety Studies (PASS) showing no increased osteosarcoma risk [67]. The EMA's cautious position may reflect a need for further safety monitoring or

differences in evaluation processes. For abaloparatide, the FDA approved it in 2017 with a 24-month lifetime treatment limit, consistent with its broader approach to minimize cumulative exposure to PTH1 analogs [63]. The EMA, however, approved abaloparatide in 2022 with a stricter 18-month restriction, likely based on the duration of clinical studies, which only assessed safety and efficacy for 18 months [61].

However, no causal link to osteosarcoma has been confirmed in human studies, including extensive PASS [66, 68, 69] and this NMA, which both suggest an absence of osteosarcoma cases among treated patients. These restrictions, while precautionary, may be excessive given the absence of clinical evidence indicating increased osteosarcoma risk in humans.

Hypercalcemia is also a known and expected effect of PTH1 analogs due to their mechanism of action, which stimulates bone turnover and leads to transient increases in serum calcium levels although the pharmacodynamic profile of abaloparatide suggests a lower risk with this agent [43]. This side effect is primarily responsible for 88% of AEs categorized under the SOC "metabolism and nutrition disorders" in studies of abaloparatide and teriparatide. Typically, hypercalcemia associated with these drugs is mild and transient, peaking within hours post-injection and returning to baseline by the next day [34, 70]. Routine calcium monitoring is not generally required unless patients have additional risk factors for hypercalcemia, making PTH1 analogs appropriate for most patients. However, patients with a history of urolithiasis or active hypercalcemia may require closer monitoring or alternative treatments, as hypercalcemia could exacerbate these conditions [61–64].

Regarding cardiovascular safety, the EMA, but not the FDA, recommends additional cardiovascular precautions before initiating abaloparatide therapy, as outlined in the Summary of Product Characteristics (SmPC) for Eladynos, but this statement warrants careful examination [61, 63]. The requirement to assess blood pressure, cardiac status, and ECG before beginning abaloparatide treatment is not mirrored in the SmPC for teriparatide (Forsteo) [62], despite the two drugs being in the same pharmacological class and sharing similar mechanisms of action. This discrepancy, if we refer to current evidence, may be considered overly cautious and lacking in sufficient scientific grounding. Indeed, our NMA and others demonstrate no statistically significant difference in cardiovascular safety between abaloparatide and teriparatide [17, 71]. The current CV safety sub-analysis, which includes 48,433 patients, evaluated various MACE categories, including MACE3, MACE4, and MACE5, and applied stratified assessments for conditions such as myocardial infarction and stroke. The consistent findings across all cardiovascular outcomes suggest that neither abaloparatide or teriparatide increases the risk of such events compared to placebo and other osteoporotic treatments, which is further confirmed in another recent NMA conducted by Seeto et al. [71]. Moreover, no difference was observed between abaloparatide and teriparatide themselves, challenging the necessity of additional cardiovascular screening exclusively for abaloparatide. The EMA's recommendation appears to rely on early clinical observations of transient orthostatic hypotension and increased heart rate within hours of abaloparatide administration, effects also noted with teriparatide but without the same degree of caution.

Consequently, the current statement from regulatory bodies regarding the safety of these agents may seem excessively cautious considering the documented low-risk profiles of both treatments. This could create an undue burden on healthcare providers and patients, potentially discouraging the use of safe and effective osteoporosis therapies.

Strength and weaknesses

Meta-analyses, including network meta-analyses, represent a high level of evidence as they integrate multiple sources of data, thereby enhancing the external validity of the results. Moreover, in this specific work, we took an additional step by including RWE studies alongside RCTs, rather than restricting the analysis to RCTs alone, thereby enhancing the pragmatic relevance of the results. To our knowledge, this is the first NMA investigating the efficacy of PTH1 receptor agonists for osteoporosis fracture prevention including also RWE studies, making these findings uniquely original in the field. Safety analyses, on the other hand, were only performed on RCT evidence as RWE studies did not report AEs related to the use of products. Nevertheless, these safety analyses have been carefully performed using the MedDRA classification to group adverse events into SOC. However, a common critique of such meta-syntheses is that they often combine studies that differ significantly in terms of interventions. Indeed, variations are frequently observed across studies regarding treatment dose, duration, and allowable rescue medications. This current analysis is not exempt from such methodological limitations. While doses of abaloparatide appear consistent between studies, reported doses of teriparatide vary between 20 and 40 µg per day, with treatment durations ranging from 12 to 36 months. However, focusing the meta-analysis assessing the anti-fracture efficacy of teriparatide on the currently marketed 20 µg daily dose and excluding the 40 µg daily dose arm of the currently published studies did not generate results which were significantly different from our primary analysis (a posteriori sensitivity analyses, available on https://osf.io/fmbp2/). Another limitation stands in the fact that the limited number of studies included in the pairwise meta-analyses restricted our ability to perform sensitivity and subgroup analyses. Specifically, performing a leave-one-out sensitivity analysis,

though included in our protocol, was deemed impractical given the small number of studies included in the pairwise meta-analyses (i.e., only two or three individual studies). Additionally, this work also slightly deviates from the initial protocol, as we did not analyze the impact of therapies on BMD. Since we chose to include only studies reporting fractures as the primary outcome, some RCTs that provided BMD data were excluded from the model. Conducting statistical analyses on BMD with a sample of studies biased for this outcome was therefore deemed irrelevant. A subsequent manuscript will address the effects on BMD, expanding the sample to include studies that report BMD as either a primary or secondary outcome.

Conclusion

In conclusion, this comprehensive NMA underscores the significant benefits of PTH1 analogs in reducing the risk of fractures across diverse skeletal sites. These findings highlight the potential for PTH1 analogs to serve as agents for the management of primary osteoporosis, particularly for patients at high risk of fractures. Despite longstanding concerns about their safety, particularly regarding cardiovascular events and osteosarcoma risk, this analysis, summarizing the most recent clinical evidence, confirms a highly satisfactory safety profile. Both abaloparatide and teriparatide demonstrate identical safety compared to other osteoporosis treatments, with no signal of increased cardiovascular risk, suggesting that cardiac evaluation at treatment initiation for abaloparatide may be unnecessary and could hamper patient access to these beneficial therapies. Given their effectiveness and favorable safety profile, PTH1 analogs should be considered essential in the therapeutic arsenal for osteoporosis, offering promising outcomes for most patients without unwarranted restrictions.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-025-07440-1.

Author contribution J-Y.R. and R.R. are at the initiative of the research question. C.B., N.V., and J.D. are the main investigators of the present research. C.B. and N.V. drafted the protocol. C.B. ran the search strategies and identified potential references to be included in the project. N.V., F.B., P.A., and G.V. screened the references and selected the relevant ones. Conflicts were resolved by C.B. N.V., C.B., and J.D. extracted the data. N.V., F.B., P.A., and G.V. performed the risk-of-bias assessment. C.B. ran all meta-analyses models. The results were interpreted by C.B., J.D., J-Y.R., and R.R. The first draft of the manuscript was written by C.B., N.V., and J.D. All authors reviewed and approved the final manuscript.

Funding This work was supported by the Distinguished Scientist Fellowships Programmes (DSFP) of the King Saud University, Riyadh, Kingdom of Saudi Arabia. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data availability and transparency All materials related to this work are freely available on the Open Science Framework deposit (https://osf.io/fmbp2/).

Declarations

Disclaimer The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

Conflict of interest C.B. reports personal speaker fees from Nutricia outside the submitted work. N.V. reports personal honoraria from IBSA, Mylan, Nestlè, and Viatris, all outside the submitted work. J.D. reports personal fees from Daiichi-Sankyo, Diagnostica Stago, Estetra, Gedeon Richter, GyneBio Pharma, Mithra Pharmaceuticals, Neuralis, Norgine, Roche, Roche Diagnostics, Technoclone, Werfen, and YHLO, all outside the submitted work. N.C.H. declares that he has received personal fees, consultancy, lecture fees, and/or honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, UCB, Kyowa Kirin, Servier, Shire, Consilient Healthcare, Theramex, and Internis Pharma, outside the submitted work. N.R.F. declares that he has received travel bursaries from Eli Lilly and Pfizer and speaker's fees from UCB and Viatris, outside the submitted work. R.R. declares that he has received fees as a speaker or consultant for Abiogen, Effryx, Nestlé, ObsEva, and Theramex, outside the submitted work. J-Y.R. declares that he has received consulting fees or has been on paid advisory boards for IBSA-Genevrier, Viatris, Radius Health, Rejuvenate Biomed, Celltrion, Promedius, and Theramex; received lecture fees when speaking at the invitation of the sponsor for IBSA-Genevrier, Theramex, and Viatris; and received grant support from IBSA-Genevrier, Viatris, Radius Health, and TRB, all through institutions and outside the submitted work. Other authors did not report any conflicts of interest in relation with this work.

References

1. Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D (1997) Guidelines for diagnosis and management of osteoporosis. The European foundation for osteoporosis and bone disease. Osteoporos Int 7:390–406
2. Kanis JA, Norton N, Harvey NC, Jacobson T, Johansson H, Lorentzon M, McCloskey EV, Willers C, Borgstrom F (2021) SCOPE 2021: a new scorecard for osteoporosis in Europe. Arch Osteoporos 16:82
3. Kanis JA, McCloskey EV, Harvey NC, Cooper C, Rizzoli R, Dawson-Hughes B, Maggi S, Reginster JY (2022) Intervention thresholds and diagnostic thresholds in the management of osteoporosis. Aging Clin Exp Res 34:3155–3157

4. Veronese N, Briot K, Guanabens N et al (2024) Recommendations for the optimal use of bone forming agents in osteoporosis. Aging Clin Exp Res 36:167
5. McClung MR (2021) Role of bone-forming agents in the management of osteoporosis. Aging Clin Exp Res 33:775–791
6. Reginster J, Bianic F, Campbell R, Martin M, Williams SA, Fitzpatrick LA (2019) Abaloparatide for risk reduction of nonvertebral and vertebral fractures in postmenopausal women with osteoporosis: a network meta-analysis. Osteoporos Int 30:1465–1473
7. Diez-Perez A, Marin F, Eriksen EF, Kendler DL, Krege JH, Delgado-Rodriguez M (2019) Effects of teriparatide on hip and upper limb fractures in patients with osteoporosis: a systematic review and meta-analysis. Bone 120:1–8
8. Ouyang Y, Chen S, Wan T, Zheng G, Sun G (2021) The effects of teriparatide and bisphosphonates on new fractures in postmenopausal women with osteoporosis: a protocol for systematic review and meta-analysis. Medicine (Baltimore) 100:e24839
9. Hong P, Liu R, Rai S, Liu J, Zhou Y, Zheng Y, Li J (2023) Is abaloparatide more efficacious on increasing bone mineral density than teriparatide for women with postmenopausal osteoporosis? An updated meta-analysis. J Orthop Surg Res 18:116
10. Beaudart C, Demonceau C, Sabico S, Veronese N, Cooper C, Harvey N, Fuggle N, Bruyere O, Rizzoli R, Reginster JY (2023) Efficacy of osteoporosis pharmacological treatments in men: a systematic review and meta-analysis. Aging Clin Exp Res 35:1789–1806
11. Han YX, Mo YY, Wu HX et al (2024) Safety and efficacy of sequential treatments for postmenopausal osteoporosis: a network meta-analysis of randomised controlled trials. EClinicalMedicine 68:102425
12. Moon RJ, Reginster JY, Al-Daghri NM et al (2023) Real-world evidence: new opportunities for osteoporosis research. Recommendations from a working group from the European society for clinical and economic aspects of osteoporosis, osteoarthritis and musculoskeletal diseases (ESCEO). Osteoporos Int 34:1283–1299
13. Bernstein J, Weintraub S, Morris T, Ahn J (2019) Randomized controlled trials for geriatric hip fracture are rare and underpowered: a systematic review and a call for greater collaboration. J Bone Joint Surg Am 101:e132
14. Adami G, Gavioli I, Rossini M, Viapiana O, Orsolini G, Benini C, Bertoldo E, Fracassi E, Gatti D, Fassio A (2022) Real-life short-term effectiveness of anti-osteoporotic treatments: a longitudinal cohort study. Ther Adv Musculoskelet Dis 14:1759720X221105009
15. Cosman F, Cooper C, Wang Y, Mitlak B, Varughese S, Williams SA (2022) Comparative effectiveness and cardiovascular safety of abaloparatide and teriparatide in postmenopausal women new to anabolic therapy: a US administrative claims database study. Osteoporos Int 33:1703–1714
16. Matsumoto T, Sone T, Soen S, Tanaka S, Yamashita A, Inoue T (2022) Abaloparatide increases lumbar spine and hip BMD in Japanese patients with osteoporosis: the phase 3 ACTIVE-J Study. J Clin Endocrinol Metab 107:e4222–e4231
17. Tabatabai L, Cosman F, Curtis JR et al (2024) Comparative effectiveness of abaloparatide and teriparatide in women 50 years of age and older: update of a real-world retrospective analysis. Endocr Pract 31:159–168
18. Hutton B, Salanti G, Caldwell DM et al (2015) The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 162:777–784
19. Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, Mierzwinski-Urban M, Clifford T, Hutton B, Rabb D (2012) The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care 28:138–144
20. Dobrescu AI, Nussbaumer-Streit B, Klerings I, Wagner G, Persad E, Sommer I, Herkner H, Gartlehner G (2021) Restricting evidence syntheses of interventions to English-language publications is a viable methodological shortcut for most medical topics: a systematic review. J Clin Epidemiol 137:209–217
21. Grey A, Reid IR (2006) Differences between the bisphosphonates for the prevention and treatment of osteoporosis. Ther Clin Risk Manag 2:77–86
22. Fujita T, Fukunaga M, Itabashi A, Tsutani K, Nakamura T (2014) Once-weekly injection of low-dose teriparatide (28.2 mug) reduced the risk of vertebral fracture in patients with primary osteoporosis. Calcif Tissue Int 94:170–175
23. Sterne JAC, Savovic J, Page MJ et al (2019) RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366:l4898
24. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A (2007) Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med 26:53–77
25. Boytsov N, Zhang X, Sugihara T, Taylor K, Swindle R (2015) Osteoporotic fractures and associated hospitalizations among patients treated with teriparatide compared to a matched cohort of patients not treated with teriparatide. Curr Med Res Opin 31:1665–1675
26. Yusuf AA, Cummings SR, Watts NB, Feudjo MT, Sprafka JM, Zhou J, Guo H, Balasubramanian A, Cooper C (2018) Real-world effectiveness of osteoporosis therapies for fracture reduction in post-menopausal women. Arch Osteoporos 13:33
27. Reynolds AW, Liu G, Kocis PT, Skowronski JN, Leslie DL, Fox EJ (2018) Comparison of osteoporosis pharmacotherapy fracture rates: analysis of a MarketScan((R)) claims database cohort. Int J Endocrinol Metab 16:e12104
28. O'Kelly J, Bartsch R, Kossack N, Borchert J, Pignot M, Hadji P (2022) Real-world effectiveness of osteoporosis treatments in Germany. Arch Osteoporos 17:119
29. Neer RM, Arnaud CD, Zanchetta JR et al (2001) Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344:1434–1441
30. Body JJ, Gaich GA, Scheele WH et al (2002) A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1–34)] with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 87:4528–4535
31. Hadji P, Zanchetta JR, Russo L et al (2012) The effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures. Osteoporos Int 23:2141–2150
32. Nakamura T, Sugimoto T, Nakano T et al (2012) Randomized Teriparatide [human parathyroid hormone (PTH) 1–34] Once-Weekly Efficacy Research (TOWER) trial for examining the reduction in new vertebral fractures in subjects with primary osteoporosis and high fracture risk. J Clin Endocrinol Metab 97:3097–3106
33. Li Y, Xuan M, Wang B et al (2013) Comparison of parathyroid hormone (1–34) and elcatonin in postmenopausal women with osteoporosis: an 18-month randomized, multicenter controlled trial in China. Chin Med J (Engl) 126:457–463
34. Miller PD, Hattersley G, Riis BJ et al (2016) Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA 316:722–733
35. Malouf-Sierra J, Tarantino U, Garcia-Hernandez PA et al (2017) Effect of teriparatide or risedronate in elderly patients with a recent pertrochanteric hip fracture: final results of a 78-week randomized clinical trial. J Bone Miner Res 32:1040–1051
36. Kendler DL, Marin F, Zerbini CAF et al (2018) Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 391:230–240

37. Hagino H, Sugimoto T, Tanaka S, Sasaki K, Sone T, Nakamura T, Soen S, Mori S (2021) A randomized, controlled trial of once-weekly teriparatide injection versus alendronate in patients at high risk of osteoporotic fracture: primary results of the Japanese Osteoporosis Intervention Trial-05. Osteoporos Int 32:2301–2311
38. Harrison J, Mozzicato P (2009) MedDRA®: the tale of a terminology: side effects of drugs essay. Side effects of drugs annual. Elsevier, pp xxxiii-xli
39. Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, Dempster D, Cosman F (1997) Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. Lancet 350:550–555
40. Sing CW, Lin TC, Bartholomew S et al (2021) Global epidemiology of hip fractures: a study protocol using a common analytical platform among multiple countries. BMJ Open 11:e047258
41. LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, Siris ES (2022) The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 33:2049–2102
42. Bone HG, Cosman F, Miller PD et al (2018) ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis. J Clin Endocrinol Metab 103:2949–2957
43. Hattersley G, Dean T, Corbin BA, Bahar H, Gardella TJ (2016) Binding selectivity of abaloparatide for PTH-type-1-receptor conformations and effects on downstream signaling. Endocrinology 157:141–149
44. Khosla S, Hofbauer LC (2017) Osteoporosis treatment: recent developments and ongoing challenges. Lancet Diabetes Endocrinol 5:898–907
45. Cheloha RW, Gellman SH, Vilardaga JP, Gardella TJ (2015) PTH receptor-1 signalling-mechanistic insights and therapeutic prospects. Nat Rev Endocrinol 11:712–724
46. Tabacco G, Bilezikian JP (2019) Osteoanabolic and dual action drugs. Br J Clin Pharmacol 85:1084–1094
47. Winzenrieth R, Ominsky MS, Wang Y, Humbert L, Weiss RJ (2021) Differential effects of abaloparatide and teriparatide on hip cortical volumetric BMD by DXA-based 3D modeling. Osteoporos Int 32:575–583
48. Boonen S, Marin F, Mellstrom D, Xie L, Desaiah D, Krege JH, Rosen CJ (2006) Safety and efficacy of teriparatide in elderly women with established osteoporosis: bone anabolic therapy from a geriatric perspective. J Am Geriatr Soc 54:782–789
49. McClung MR, Geusens P, Miller PD et al (2001) Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 344:333–340
50. Li M, Ge Z, Zhang B, Sun L, Wang Z, Zou T, Chen Q (2024) Efficacy and safety of teriparatide vs. bisphosphonates and denosumab vs. bisphosphonates in osteoporosis not previously treated with bisphosphonates: a systematic review and meta-analysis of randomized controlled trials. Arch Osteoporos 19:89
51. Jin YZ, Lee JH, Xu B, Cho M (2019) Effect of medications on prevention of secondary osteoporotic vertebral compression fracture, non-vertebral fracture, and discontinuation due to adverse events: a meta-analysis of randomized controlled trials. BMC Musculoskelet Disord 20:399
52. Masuda S, Fukasawa T, Matsuda S, Yoshida S, Kawakami K (2024) Comparative effectiveness and cardiovascular safety of romosozumab versus teriparatide in patients with osteoporosis: a population-based cohort study. Osteoporos Int 35:2165–2174
53. Yang XC, Deng ZH, Wen T, Luo W, Xiao WF, Zhao RB, Li YS (2016) Network meta-analysis of pharmacological agents for osteoporosis treatment and fracture prevention. Cell Physiol Biochem 40:781–795
54. Migliorini F, Maffulli N, Colarossi G, Eschweiler J, Tingart M, Betsch M (2021) Effect of drugs on bone mineral density in postmenopausal osteoporosis: a Bayesian network meta-analysis. J Orthop Surg Res 16:533
55. Kanis JA, Harvey NC, McCloskey E et al (2020) Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. Osteoporos Int 31:1–12
56. Kanis JA, Cooper C, Rizzoli R, Reginster JY, Scientific Advisory Board of the European Society for C, Economic Aspects of O, Osteoarthritis, the Committees of Scientific A, National Societies of the International Osteoporosis (2019) Executive summary of the European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Calcif Tissue Int 104:235–238
57. Kanis JA, Cooper C, Rizzoli R, Reginster JY, Scientific Advisory Board of the European Society for C, Economic Aspects of O, Osteoarthritis, the Committees of Scientific A, National Societies of the International Osteoporosis F (2019) Executive summary of European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Aging Clin Exp Res 31:15–17
58. Camacho PM, Petak SM, Binkley N et al (2020) American association of Clinical Endocrinologists/American College of endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis- 2020 update executive summary. Endocr Pract 26:564–570
59. Gregson CL, Armstrong DJ, Bowden J et al (2022) UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos 17:58
60. Vahle JL, Sato M, Long GG, Young JK, Francis PC, Engelhardt JA, Westmore MS, Linda Y, Nold JB (2002) Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1–34) for 2 years and relevance to human safety. Toxicol Pathol 30:312–321
61. European Medicines Agency (2024) Summary of Product Characteristics — Eladynos. https://www.ema.europa.eu/en/documents/product-information/eladynos-epar-product-information_en.pdf Accessed 21 Oct 2024
62. European Medicines Agency (2024) Summary of Product Characteristics — Forsteo. https://www.ema.europa.eu/en/documents/product-information/forsteo-epar-product-information_en.pdf Accessed 30 Oct 2024
63. Food and Drug Administration (2024) Prescribing Information — TYMLOS. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208743lbl.pdf Accessed 30 Oct 2024
64. Food and Drug Administration (2024) Prescribing Information — FORSTEO. https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/21318_forteo_lbl.pdf Accessed 30 Oct 2024
65. Vahle JL, Long GG, Sandusky G, Westmore M, Ma YL, Sato M (2004) Bone neoplasms in F344 rats given teriparatide [rhPTH(1–34)] are dependent on duration of treatment and dose. Toxicol Pathol 32:426–438
66. Abdulelah AA, Haddad BI, Alhajahjeh AA, AlQirem LM, El-Amayreh L (2023) The risk of developing osteosarcoma after teriparatide use: a systematic review. Orthop Res Rev 15:191–198
67. European Medicines Agency (2024) Forsteo — EPAR Procedural steps taken and scientific information after authorisation. https://www.ema.europa.eu/en/documents/procedural-steps-after/forsteo-epar-procedural-steps-taken-and-scientific-information-after-authorisation_en.pdf Accessed 19 Nov 2024
68. Andrews EB, Gilsenan AW, Midkiff K, Sherrill B, Wu Y, Mann BH, Masica D (2012) The US postmarketing surveillance study of adult osteosarcoma and teriparatide: study design and findings from the first 7 years. J Bone Miner Res 27:2429–2437
69. Gilsenan A, Midkiff K, Harris D, Kellier-Steele N, McSorley D, Andrews EB (2021) Teriparatide did not increase adult osteosarcoma incidence in a 15-year US postmarketing surveillance study. J Bone Miner Res 36:244–251

70. Sherpa C, Shrestha BC, Nallala D, Gabriely I (2021) Hypercalcemia in a patient treated with abaloparatide. J Endocrine Soc 5:A196–A197
71. Seeto AH, Tadrous M, Gebre AK, Lewis JR, Fink HA, Ebeling PR, Rodriguez AJ (2023) Evidence for the cardiovascular effects of osteoporosis treatments in randomized trials of post-menopausal women: a systematic review and Bayesian network meta-analysis. Bone 167:116610

Authors and Affiliations

Charlotte Beaudart[1,2] · Nicola Veronese[1,3] · Jonathan Douxfils[4,5,6] · Jotheeswaran Amuthavalli Thiyagarajan[7] · Francesco Bolzetta[8] · Paolo Albanese[8] · Gianpaolo Voltan[8] · Majed Alokail[9] · Nicholas C. Harvey[1,10] · Nicholas R. Fuggle[1,10] · Olivier Bruyère[1,11] · René Rizzoli[1,12] · Jean-Yves Reginster[1,9]

✉ Charlotte Beaudart
charlotte.beaudart@unamur.be

1 World Health Organization (WHO) Collaborating Center for Epidemiology of Musculoskeletal Health and Ageing, University of Liège, Liège, Belgium

2 Public Health Aging Research & Epidemiology (PHARE) Group, Research Unit in Clinical, Pharmacology and Toxicology (URPC), Namur Research Institute for Life Sciences (NARILIS), Faculty of Medicine, University of Namur, Namur, Belgium

3 Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo, Palermo, Italy

4 Research Unit in Clinical Pharmacology and Toxicology (URPC), Namur Research Institute for Life Sciences (NARILIS), Faculty of Medicine, University of Namur, Namur, Belgium

5 QUALIresearch, QUALIblood S.a., Liège, Belgium

6 Department of Biological Hematology, Centre Hospitalier Universitaire Clermont-Ferrand, Hôpital Estaing, Clermont-Ferrand, France

7 Ageing and Health Unit, Department of Maternal, Newborn, Child and Adolescent Health and Ageing, World Health Organization, Geneva, Switzerland

8 Azienda ULSS (Unità Locale Socio Sanitaria) 3 "Serenissima", 30174 Venice, Italy

9 Protein Research Chair, Biochemistry Department, College of Science, King Saud University, Riyadh, Kingdom of Saudi Arabia

10 MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton SO16 6YD, UK

11 Research Unit in Public Health, Epidemiology and Health Economics, University of Liege, Liege, Belgium

12 Service of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, Geneva 14 1211, Switzerland