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Review article

Monoclonal antibodies in patients with osteoporosis and renal insufficiency: An updated systematic review and meta-analysis

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ABSTRACT

Objectives: There are challenges for the treatment of osteoporosis in patients with kidney failure and monoclonal antibodies (MAb) might be a suitable therapy. However, the efficacy and safety of MAb among patients with osteoporosis and renal insufficiency remains unclear.
Methods: We systematically searched PubMed, Embase, and Cochrane Central for studies evaluating the efficacy and safety of the use of MAb in patients with osteoporosis and renal insufficiency. We pooled risk ratios (RR) and 95% confidence intervals (CI) for binary outcomes. Mean difference (MD) was used for continuous outcomes.
Results: We included 5 studies with 33,550 patients. MAb therapy decreased the risk of vertebral fractures (RR 0.32; 95% CI 0.26–0.40; $P < 0.01$) when compared to placebo and no statistical difference was found when comparing to bisphosphonate (RR 0.71; 95% CI 0.49–1.03; $P = 0.07$). MAb therapy also decreased the risk of nonvertebral fractures (RR 0.79; 95% CI 0.69–0.91; $P = 0.0009$). Lumbar spine bone mineral density (BMD) was higher in the MAb therapy when compared to both placebo (MD 10.90; 95% CI 8.00–13.80; $P < 0.01$) and bisphosphonate (MD 7.66; 95% CI 6.19–9.14; $P < 0.01$). There was no statistically significant difference in the change of estimated glomerular filtration rate and in the incidence of hypocalcemia and serious adverse events between groups.
Conclusions: There were reductions in both vertebral and nonvertebral fracture risks, alongside improvements in BMD among patients with renal insufficiency treated with MAb.

1. Introduction

Osteoporosis is a long-term asymptomatic disease that involves low bone mass and weakened bone structure typically associated with postmenopausal women and the elderly [1]. Complications are vertebral and hip fractures that represent great risk of illness and death [2]. Bisphosphonates are the first-line treatment for osteoporosis, however, their use is contraindicated in patients with severe renal dysfunction [3]. Monoclonal antibodies (Mab), including denosumab and romosozumab might represent a good option for patients with impaired kidney function and have been approved by the U.S. Food and Drug Administration for postmenopausal women at high risk of fracture [4].

However, there is a lack of standardized treatment recommendations for the osteoporosis management of patients with known kidney function impairment. Current guidelines, including those from The Kidney Disease Improving Global Outcomes (KDIGO), provide no definitive recommendations on the use of MAb in this population [5]. Prior meta-analyses on osteoporosis medications in patients with chronic kidney disease (CKD) or kidney transplantation yielded inconclusive results due to limited evidence or found no significant difference between denosumab and placebo in fracture risk [6,9]. Consequently, the effectiveness and safety profile of MAb in patients with impaired renal

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function remains unclear.

Therefore, we performed an updated systematic review and meta-analysis comparing MAb with standard care (bisphosphonates and raloxifene) or placebo in the management of osteoporosis in patients with renal insufficiency on efficacy and safety endpoints. In our study, renal insufficiency was defined based on estimated glomerular filtration rate (eGFR) values, which reflect kidney function. Specifically, renal insufficiency was defined as an eGFR below 90 mL/min/1.73 m^2, ranging from mild impairment to kidney failure.

2. Methods

This meta-analysis was performed in accordance with the recommendations of the Cochrane Collaboration, directed by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [10,11]. This study was registered on PROSPERO in December 2023 under protocol number CRD42023493748, where the statistical procedures and analyses were prespecified. We had no access to patient-level data and conducted no direct interventions.

2.1. Eligibility criteria and endpoints

The inclusion criteria were as follows: (1) enrollment of patients with osteoporosis and renal insufficiency; (2) incorporation of randomized controlled trials (RCT) or observational studies comparing MAb with placebo or non-MAb therapy; and (3) assessment of the primary outcome of vertebral fracture or any of the following secondary outcomes of interest – nonvertebral fracture, BMD, change in the eGFR, hypocalcemia and serious adverse events (SAEs). Exclusion criteria were: (1) exclusion of population of interest; (2) absence of control group; (3) no outcomes of interest; and (4) language other than English, Spanish or Portuguese. There were no exclusions based on the population size or year of publication.

2.2. Search strategy and data extraction

We systematically searched PubMed, Embase, and Cochrane Library on December 2023, with the following search strategy: (Osteoporosis) AND ("Chronic kidney disease" OR "Renal insufficiency" OR "Kidney disease" OR "Kidney failure") AND ("Monoclonal antibodies" OR Denosumab OR Romosozumab). We also searched the references from included studies, previous systematic reviews, and meta-analyses for additional studies.

Two authors (M.L.R.D. and V.A.) independently conducted the search, performed the screening, and extracted data following predefined search criteria. Disagreements between these authors were resolved by consensus among them.

2.3. Quality assessment

Risk of bias and quality assessment of individual studies was performed independently by two authors (M.L.R.D. and V.A.) using the Cochrane tool for assessing risk of bias in randomized trials (RoB 2) for RCTs, while non-randomized studies were assessed with the tool for non-randomized studies (ROBINS-I) [12,13]. Post-hoc analyses of RCTs were assessed as cohort studies because the exposure of interest was not randomized. Disagreements were resolved by consensus among them. Publication bias was investigated by using funnel-plot graphs and checking for symmetrical distribution of studies with similar weights.

2.4. Statistical analysis

Risk ratios (RR) were used to compare treatment effects for binary outcomes and mean differences (MD) for continuous data with the corresponding 95% confidence intervals (CI). We considered P-values < 0.05 as statistically significant. To assess heterogeneity, Cochran's Q-test and I^2 statistics were used. Values of $P > 0.10$ and $I^2 < 25\%$ were considered of low heterogeneity. We used the DerSimonian and Laird random-effects model for all outcomes. We conducted sensitivity analyses in the presence of significant heterogeneity ($I^2 > 25\%$). The leave-one-out sensitivity analyses were performed by systematically removing each study from the pooled estimate. Baujat plot was used to explore heterogeneity. If the included studies did not provide mean and standard deviation and data were not significantly skewed, we estimated their values using the method by Wan and Luo [14]. We used the Review Manager 5.4 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and R version 4.3.2 for statistical analyses.

3. Results

3.1. Study selection and characteristics

The search strategy yielded 855 results. After removing duplicate records and screening titles and abstracts, 33 studies were fully reviewed. Of these, 5 studies met all inclusion criteria and were included in the meta-analysis, as detailed in Fig. 1, with one of these being a post hoc analysis of two different RCTs [19]. The main characteristics of the studies are shown in Table 1. Data from the FREEDOM trial was assessed through a prior publication, when unavailable in the included study [20].

3.2. Pooled analysis of all studies

3.2.1. Primary outcome

The frequency of vertebral fracture was significantly lower in the group receiving MAb therapy (100/6613; 1.5%) compared with the placebo group (311/6606; 4.7%) (RR 0.32; 95% CI 0.26–0.40; $P < 0.01$; Fig. 2). There was no statistically significant difference in occurrence of vertebral fracture when comparing MAb therapy with bisphosphonate

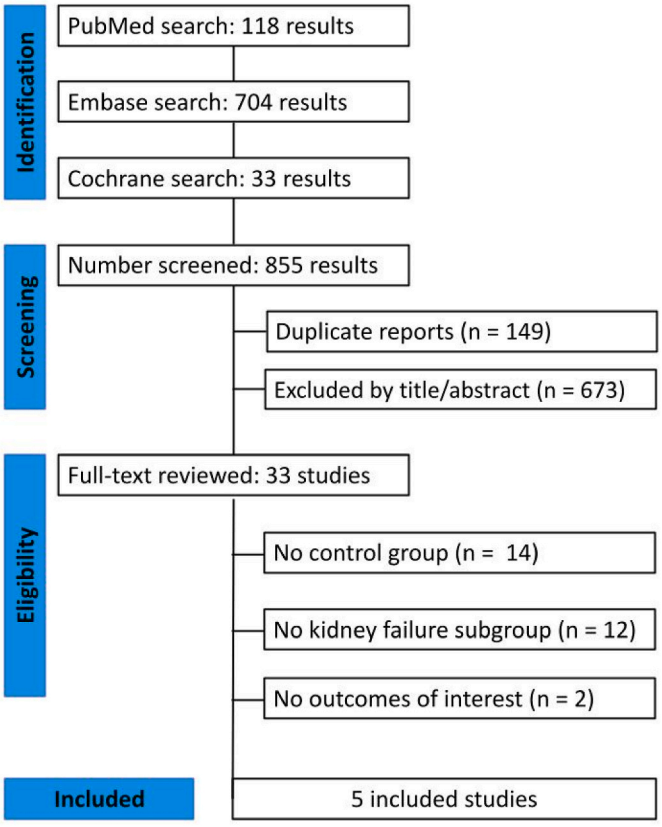

Fig. 1. PRISMA flow diagram of study selection.

Table 1
Baseline characteristics of included studies.

Study	Design	MAb/Control	Number of patients MAb/No MAb	Mean age (year) MAb/No MAb	Percentage of female MAb/No MAb	Mean baseline eGFR (mL/min/1.73 m^2) MAb/No MAb	Percentage of eGFR <60 ml/min/1.73 m^2 MAb/No MAb	Mean lumbar spine BMD MAb/No MAb	No of prior fracture MAb/No MAb
Chen 2022[a] [15]	Retrospective cohort	Denosumab/Raloxifene	4722/4722	71.9/71.9	100/100	72.4/71.5	34.9/34.4	NA	NA
Hsu 2019[a] [16]	Retrospective cohort	Denosumab/Alendronate	2523/2523	71.5/71.2	82.6/84.0	78.3/78.7	NA	NA	865/842
Iseri 2018 [17]	RCT	Denosumab/Alendronate	14/14	66.5/65.5	42.8/42.8	61.1/49.0	NA	−1.3/−1.2[c]	2/3
Jamal 2011[d] [18]	RCT	Denosumab/Placebo	3902/3906	72.3/72.3	100/100	NA	37.0[b]	−2.82/−2.84[c]	NA
Miller 2022 FRAME [19]	Post hoc – RCT	Romosozumab/Placebo	3572/3575	70.7/71.4	100/100	NA	20.5/17.5	−2.7/−2.7[c]	1264/1251
Miller 2022 ARCH [19]	Post hoc – RCT	Romosozumab/Alendronate	2039/2038	75.5/75.2	100/100	NA	24.9/23.7	−2.9/−2.9[c]	2015/2022

RCT, randomized controlled trial; Mab, monoclonal antibodies; eGFR, estimated glomerular filtration rate; BMD, bone mineral density; NA, not available.

[a] Values are propensity score matched.

[b] Value for the entire population.

[c] T-score.

[d] FREEDOM trial.

(RR 0.71; 95% CI 0.49–1.03; P = 0.07; Fig. 2).

3.2.2. Secondary outcomes

3.2.2.1. Nonvertebral fracture. The risk of nonvertebral fracture was significantly lower in the MAb group (348/8809; 3.9%) compared with the control group, composed of placebo and bisphosphonates (437/8762; 4.9%) (RR 0.79; 95% CI 0.69–0.91; P < 0.01; Fig. 3).

3.2.2.2. Bone mineral density. Lumbar spine BMD was significantly higher in the MAb therapy compared with either placebo (MD 10.90%; 95% CI 8.00–13.80%; P < 0.01; Fig. 4) or bisphosphonate (MD 7.66%; 95% CI 6.19–9.14%; P < 0.00001; Fig. 4). Femoral neck BMD significantly increased in the MAb therapy compared with placebo (MD 5.10%; 95% CI 4.80–5.41%; P < 0.01; Fig. 5) or bisphosphonate (MD 2.94%; 95% CI 2.36–3.52%; p < 0.01; Fig. 5). Total hip BMD increased significantly in the MAb therapy compared with placebo (MD 5.89%; 95% CI 5.36–6.42%; P < 0.01; Fig. 6) and bisphosphonate (MD 3.15%; 95% CI 2.89–3.40%; P < 0.01; Fig. 6).

Leave-one-out sensitivity analyses and Baujat plot showed that studies with patients with higher baseline eGFR contributed to heterogeneity (Figs. S1–S3) and a RCT highly contributed to the overall results along with a higher heterogeneity (Figs. S4–S6).

The significant heterogeneity found in the BMD analysis can be most likely attributed to (1) different follow-ups between the studies, that varies from 12 to 36 months, (2) inclusion of randomized and non-randomized studies, (3) heterogeneous severity of kidney disease among studies, and (4) difference in the number of prior fractures between the studies' populations.

3.2.2.3. eGFR change. The eGFR change showed no statistically significant difference between groups (MD 0.27 mL/min/1.73 m^2; 95% CI -0.14~0.68 mL/min/1.73 m^2; P = 0.20; Fig. 7a). One study was found to contribute to the heterogeneity and overall results [16] (Figs. S7–S8). It may be explained by the difference in the population, since this was the only study in this pooled analysis with both males and females, as opposed to the others, which were exclusively composed of females.

3.2.2.4. Adverse events. There was no statistically significant difference in the incidence of hypocalcemia (RR 1.54; 95% CI 0.30–8.01; P = 0.61; Fig. 7b) and SAEs (RR 1.02; 95% CI 0.94–1.10; P = 0.65; Fig. 7c) between groups. The definition of SAEs for each study is available at Table S3.

3.3. Quality assessment

RoB 2 identified two studies at some concerns of bias due to deviations from intended interventions and selection of the reported results [17,18] (Table S1). ROBINS-I identified three studies at moderate risk of bias, due to confounding adjustment and selection of reported results [15,16,19] (Table S2).

On funnel plot analysis, a symmetrical distribution according to weight is seen for vertebral fracture, nonvertebral fracture, change in eGFR, hypocalcemia and SAEs, indicating no apparent evidence of small study effect (Figs. S9–S13). However, in lumbar spine, femoral neck, and total hip BMD, studies had an asymmetrical distribution according to weight, which may indicate an overestimation of the intervention effect (Figs. S14–S16). This may be due to the small number of studies and the heterogeneity found in the pooled analysis of these outcomes.

4. Discussion

In this systematic review and meta-analysis of 33,550 patients, we evaluated the efficacy and safety of monoclonal antibodies among patients with decreased renal function. The main findings were: (1) lower

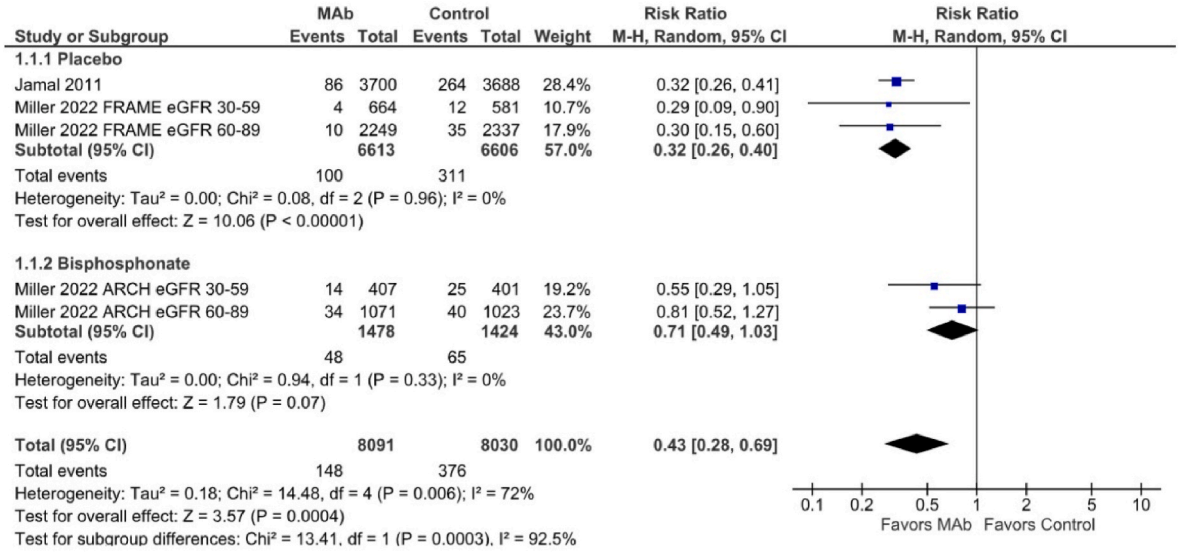

Fig. 2. Forest plot of the incidence of vertebral fractures.

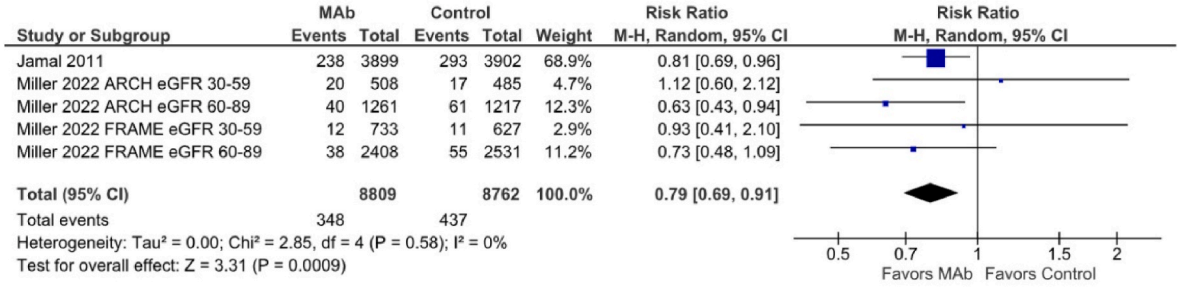

Fig. 3. Forest plot of the incidence of nonvertebral fractures. MAb, monoclonal antibodies.

risk of vertebral and nonvertebral fractures in the MAb group; (2) higher lumbar spine, femoral neck, and total hip BMD in the MAb group; (3) comparable eGFR change between groups, and (4) no statistically significant difference in the occurrence of hypocalcemia and SAEs between groups.

A monoclonal antibody is designed to specifically target and bind to a single type of antigen, such as a protein, cell, or molecule [23,24]. Denosumab and romosozumab are both monoclonal antibodies used in osteoporosis treatment. Denosumab works by targeting the receptor activator of NFκB ligand (RANKL), leading to reduced bone resorption [23]. On the other hand, romosozumab functions by inhibiting sclerostin, a protein that negatively regulates bone formation, and promoting bone formation while enhancing bone mass [24]. Both drugs have a predominantly reticuloendothelial system clearance, with only minimal renal excretion, because of their large molecular size [25].

The results of this study related to lower risk of fracture and BMD increase when in MAb are in accordance with a previous network meta-analysis among patients with CKD or a history of kidney transplantation

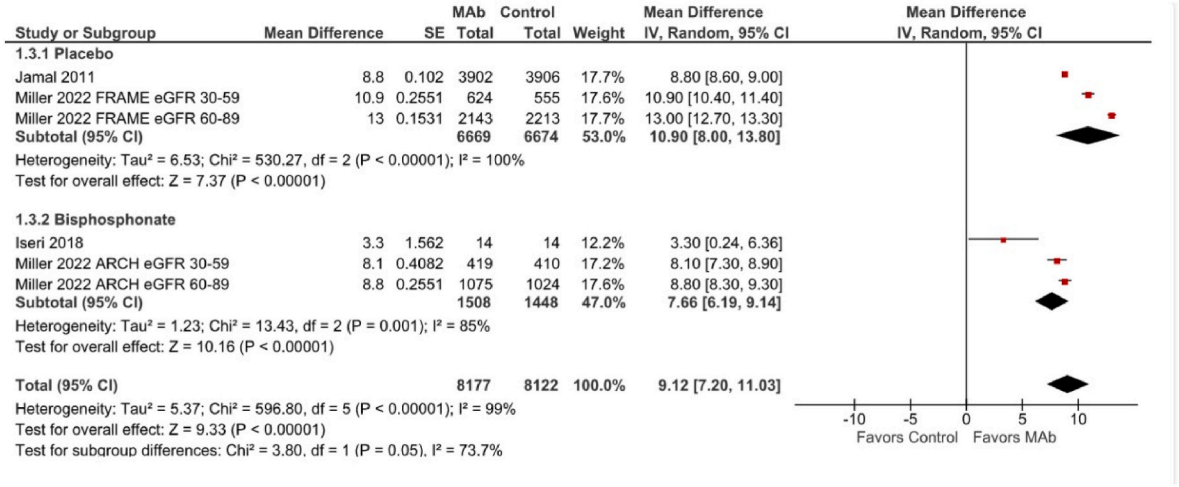

Fig. 4. Forest plot of lumbar spine bone mineral density. MAb, monoclonal antibodies.

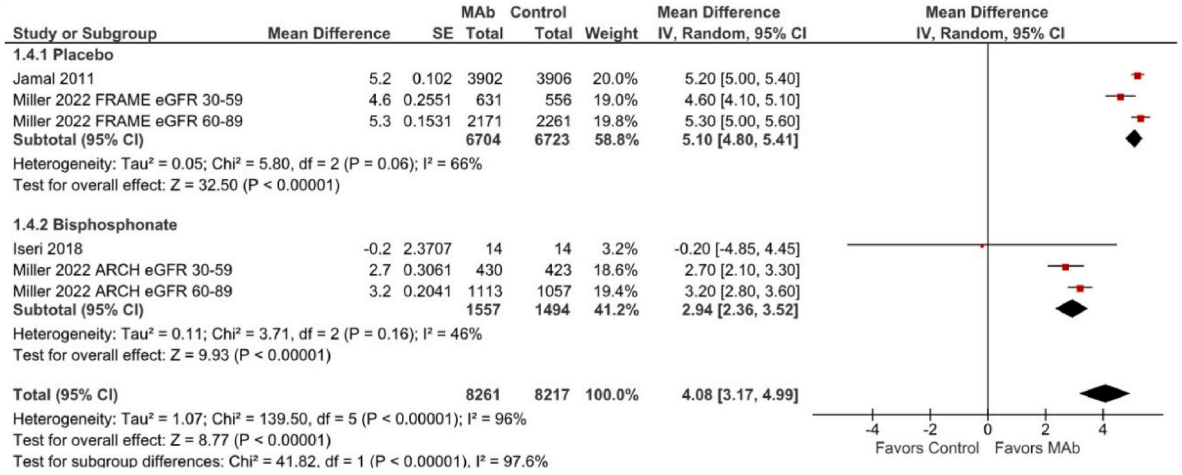

Fig. 5. Forest plot of femoral neck bone mineral density. MAb, monoclonal antibodies.

[8] and in contrast with prior meta-analyses which found inconclusive outcomes [6–9]. It may be attributed to population differences since we did not include kidney transplant patients and that we added the up to date data from ARCH and FRAME post-hoc analyses, increasing the population by over 30%. This expanded population may have contributed to the more definitive findings observed in this study.

On eGFR change, there was no statistical difference between the groups, with a comparable result between MAb and control groups. However, it should be carefully interpreted, since Chen 2022 [15] indicated a higher rate of eGFR decline in the denosumab group, and Hsu 2019 [16] found denosumab treatment to be associated with a significantly higher risk of eGFR $\geq$ 30%. Thus, it is encouraged to eGFR be complemented with objective findings such as quantification of urinary albumin to improve kidney function assessment and optimally predict worsening renal function [26]. Although no difference in the incidence of hypocalcemia and serious adverse events was found, in three included trials patients underwent calcium and calcitriol regimens, which may have attenuated the adverse events rate [18–22].

There are important limitations in our study. First, 3 of the 5 studies are observational and are potentially affected by confounding, which can introduce biases and may compromise the robustness of our findings. Second, substantial heterogeneity was found in the outcomes of BMD measurements. However, it can be explained by (1) the different follow-ups between studies (12 vs 36 months), (2) grouped randomized and nonrandomized data, (3) different baseline eGFR between the studies, which may contribute to the variability in the BMD, as severe decrease of renal function impairs BMD, and (4) important differences in the number of prior fractures among studies, indicating fragility differences in the overall population. Third, the demographic characteristics of the included study populations pose challenges to the generalizability of our findings. With the majority of studies focusing exclusively on women, particularly postmenopausal women, which have a specific physiopathology linked to estrogen decrease, the applicability of our results to broader patient demographics may be limited. Fourth, there was a small number of studies, precluding Egger's regression test and meta-regression analyses. Finally, the absence of access to patient-level data and the reporting of data of the included studies did not allow to investigate the impact of MAbs on renal function across different levels of eGFR decline.

5. Conclusions

In this systematic review and meta-analysis of 33,550 patients with osteoporosis and renal insufficiency, we found a significant reduction in vertebral and nonvertebral fracture risks, alongside improvement in BMD associated with MAb. There were similar eGFR changes, hypocalcemia, and SAEs between groups.

Our findings underscore the potential of MAb therapy as an intervention for addressing the challenges of osteoporosis management in individuals with renal insufficiency. However, further validation through high quality RCTs and a diverse population is essential to increase the robustness and generalizability of the results.

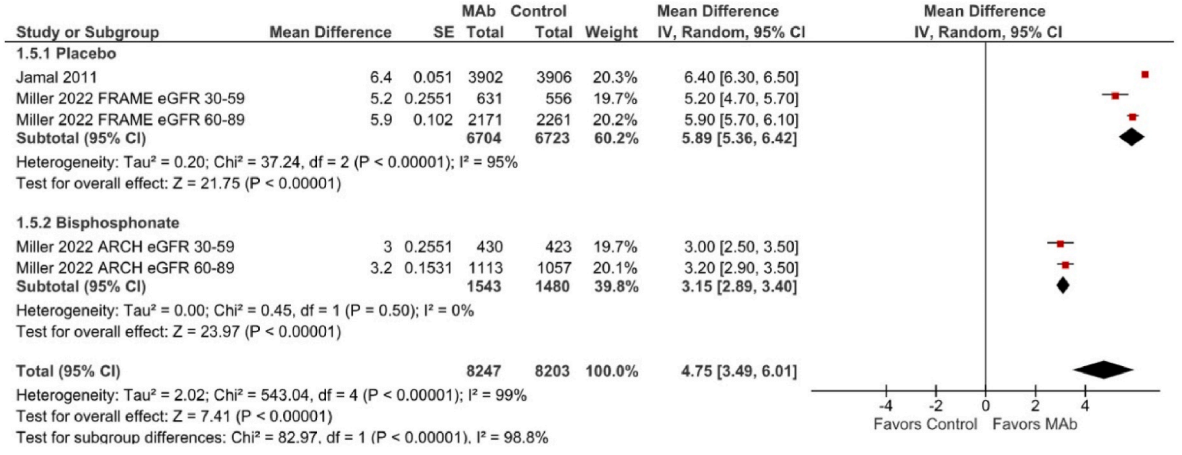

Fig. 6. Forest plot of total hip bone mineral density. MAb, monoclonal antibodies.

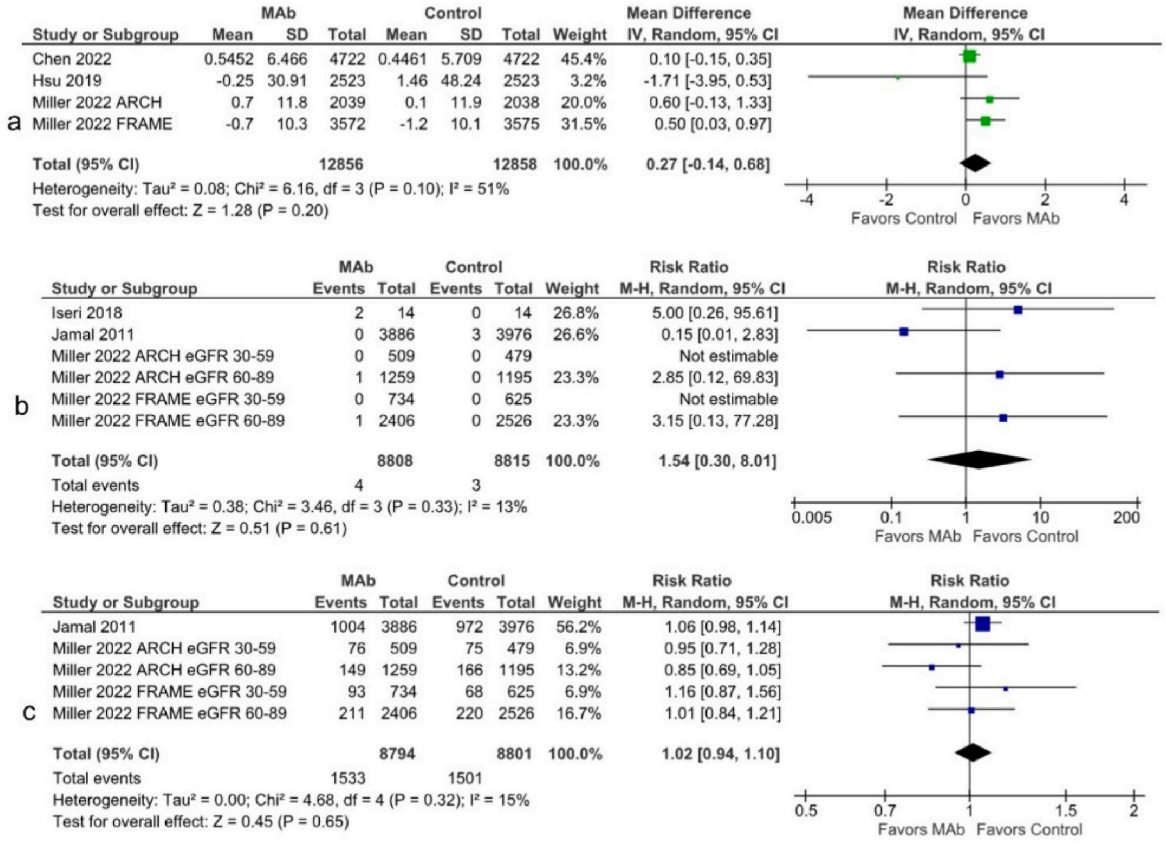

Fig. 7. Forest plot of change of estimated glomerular filtration rate (a), the occurrence of hypocalcemia (b), and the occurrence of serious adverse events (c) between groups. MAb, monoclonal antibodies.

CRediT author statement

Maria Luiza Rodrigues Defante: Conceptualization, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Victoria Alzogaray**: Formal analysis, Investigation, Methodology, Software, Validation, Writing – review & editing. **Davi Said Gonçalves Celso**: Methodology, Software, Writing – review & editing. **Lucas Antônio Torres**: Methodology, Software, Writing – review & editing. **Mayara Bearse**: Methodology, Software, Supervision, Writing – review & editing. **Ana Claudia Frota Machado de Melo Lopes**: Methodology, Software, Supervision, Validation, Writing – review & editing.

Conflicts of interest

The authors declare no competing interests.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.afos.2024.05.004.

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