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Original Article

Comparison of Cardiovascular Events among Users of Different Classes of Anti-Osteoporosis Medications

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SUMMARY

Background: Osteoporosis or cardiovascular disease prevalence increase with age. Osteoporosis medicine's cardiovascular safety should be monitored. We evaluate the cardiovascular effects of anti-osteoporosis medications, namely hormone therapies, bisphosphonates, parathyroid hormone analogs, anti-receptor activator of nuclear factor kappa-B ligand, and romosozumab.
Method: We performed a standard, random-effect, pairwise meta-analysis for cardiovascular disease risk to estimate the available direct evidence of each drug class. The literature search was conducted in PubMed, Embase, and ClinicalTrials.gov on December 31, 2021. Parallel group randomized and controlled trials were eligible if they compared one kind of anti-osteoporosis agents. For every possible pairwise comparison, the association between treatment and outcomes was obtained using odds.
Results: The search yielded 10,162 records. Screening and full-text article analysis identified 77 trials, including 106,982 patients, comparing five classes of anti-osteoporosis drugs and a placebo. Anti-receptor activator of nuclear factor kappa-B ligand, revealed a significantly higher risk of cardiovascular disease than placebo (risk ratio 1.25 [95% confidence interval 1.07% to 1.45%]). The Surface Under the Cumulative Ranking confirmed that anti-receptor activator of nuclear factor kappa-B ligand use was most likely to result in cardiovascular disease in patients with osteoporosis; it had a significantly higher risk of coronary artery disease, cerebrovascular disease, angina, and transient ischemic accident (risk ratio 1.26 [95% confidence interval 1.01% to 1.58%]).
Conclusions and Relevance: In this network meta-analysis of clinical trials of patients with osteoporosis, different classes of anti-osteoporosis medications were associated with different effects on cardiovascular events.

1. Introduction

The risks of osteoporosis or cardiovascular disease (CVD) increase with age progression. Those two disorders usually have comorbidity in the same patient.[1] Besides age, they have other common risk factors, such as menopause in women, sedentary lifestyle and inactivity, excessive alcohol consumption, and smoking. The progression of osteoporosis is related to cardiovascular morbidity and mortality. Furthermore, since both disorders' prevalence increase with age, osteoporosis medicine's cardiovascular safety should be monitored.[2] Several studies have demonstrated that vascular cells may be differentiated into osteoblast-like cells in human calcified atherosclerosis.[3] Vascular calcification was found relative to bone regulatory factors.[4] Hence, ensuring the cardiovascular safety of anti-osteoporosis drugs is important. Hormone replacement therapy could maintain bone mineral density (BMD) and prevent vertebral and non-vertebral fractures.[5] However, the cardiovascular effects of hormone replacement therapy are controversial.[6] Selective estrogen receptor modulators (SERMs) include raloxifene, bazedoxifene (which is combined with conjugated estrogens), and lasofoxifene (which is limited in parts of Europe) are used for osteoporosis treatment. Recently, hormone relative therapies (HRTs), including hormone replacement therapy and SERMs, were thought to increase the risk of venous thromboembolism (VTE).[2] Some clinical trials have demonstrated that bisphosphonates are neutral in atherosclerotic cardiovascular events.[7,8] However, an increase in atrial fibrillation from zoledronic acid has been observed.[3]

Two parathyroid hormone (PTH) analogs, teriparatide and abaloparatide, are commonly used for osteoporosis management. However, PTH had pleiotropic effects on cardiac myocytes and peripheral vessels.[2] Human monoclonal antibodies were approved for the clinical treatment of osteoporosis. Denosumab is an anti-receptor activator of nuclear factor kappa-B ligand (anti-RANKL) antibody, which prevents the maturation and effects of osteoclasts.[9] Romosozumab promotes bone formation and inhibits bone resorption by inhibiting sclerostin.[10]

However, these studies do not have sufficient randomized or cohort trials; therefore, a comprehensive meta-analysis is needed. Hence, this study aimed to evaluate the cardiovascular effects of anti-osteoporosis medications, namely HRT, bisphosphonates, PTH analogs, denosumab, and romosozumab.

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2. Methods

This network meta-analysis of randomized clinical trials of anti-osteoporosis medications was performed according to the checklist of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions. This study was approved by institutional review board of MacKay Memorial Hospital, Taiwan.

2.1. Search strategy and study selection

The literature search was conducted in PubMed, Embase, and ClinicalTrials.gov on December 31, 2021, without language restriction. The search terms used included osteoporosis, osteoporosis and agents, and anti-osteoporosis medications (eTable 1 in the Supplement).

The studies were included with the following criteria: (1) randomized clinical trials; (2) published during or after 1990; (3) evaluated anti-osteoporosis medications, including hormone therapies, bisphosphonates, PTH analogs, anti-RANKL, and romosozumab. compared with control groups receiving placebo, standard treatment, or health education; (4) reported incidence of CVD events (cardiovascular death, angina, myocardial infarction, transient ischemia accident, stroke, venous thromboembolism, arrhythmia, heart failure); and (5) we included studies reporting outcomes at 24 weeks or longer. In addition, we excluded studies of combined treatment was excluded. Parallel group randomized and controlled trials were eligible if they compared one kind of anti-osteoporosis agent with another or placebo in adults with osteoporosis. Two reviewers screened citations and evaluated full-text records for eligible studies.

2.2. Data extraction

For each eligible study, two reviewers independently extracted the study characteristics (year of publication, name of the author, and duration), population (sample size, patient demographics), description of interventions (drug class, name), and outcomes (CVD events). The overall cardiovascular events were calculated as the aggregation of cardiovascular death, myocardial infarction, stroke, venous thromboembolism and revascularization.

2.3. Risk of bias assessment

Two reviewers independently assessed the risk of bias using the Cochrane tool for assessing the risk of bias in randomized trials, which includes the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

2.4. Data synthesis and analysis

We initially performed a standard, random-effect, pairwise meta-analysis for CVD risk to estimate the available direct evidence of each drug class. For every possible pairwise comparison, the association between treatment and outcomes was obtained using odds ratios (ORs), and a different heterogeneity parameter was assessed by statistical heterogeneity and its 95% confidence intervals. Network meta-analysis was then used to compare available treatment strategies within a single analytical framework in a Bayesian setting.

Transitivity that one can validly and indirectly compare treatments A and B via one or more anchor treatments is a fundamental assumption underlying the performance of a network meta-analysis and requires careful evaluation of the consistency of direct and indirect evidence. The plausibility of transitivity in our data was examined by comparing the similarities of the competing interventions when estimated in studies with different designs and then assessing the distribution of the potential effect modifiers with sufficient data across the different direct comparisons. The consistency was obtained by calculating the difference between direct and indirect treatment effects in all closed loops and assuming loop-specific heterogeneity. To examine the inconsistency in each loop, the magnitude of inconsistency factors and their respective p values were used. Significant disparity between direct and indirect evidence ($p <$ .10) signified the presence of inconsistent loops. To explore the design inconsistency in the entire network, we used the design-by-treatment model. To judge the evidence of intra-network inconsistency, we separated indirect evidence from direct evidence using the back-calculation method.

The surface under the cumulative ranking (SUCRA) curves was estimated for the relative ranking probability of each treatment. Compared with a hypothetical treatment, mean ranks always express the effectiveness and acceptability of each treatment first without uncertainty. We conducted the heterogeneity in each network analysis by comparing the heterogeneity parameter, Q statistics, and tau with the empirical distribution.

To evaluate the evidence of small-study effects, we drew a comparison-adjusted funnel plot containing all comparisons of different studies and sets of interventions to estimate the drug classes on fracture risk. Statistical significance was indicated by the two-sided testing with $p < .05$. Network meta-analysis was performed in R version 4.1.1 using the network command.

3. Results

3.1. Description of included studies

The electronic search yielded 10,162 unique records. Screening and full-text article analysis identified 77 trials, including 106,982 patients (Figure 1), comparing five classes of anti-osteoporosis drugs and a placebo. A total of 4,633 patients had CVD. Figure 2 shows the network plot of trials evaluating CVD risk for osteoporosis. The most frequently compared drug was hormone therapy, compared with the placebo. The search for keywords and the characteristics of the included trials are described in eTable 1 in the Supplement and Table 1.

3.2. Network meta-analysis – effect of anti-osteoporosis agents on CVD risk

The forest plot for the meta-analysis of the association between CVD and the different kinds of drug classes is demonstrated in Figure 3. Patients using hormone therapy, bisphosphonates, romosozumab, and PTH had a neutral risk of CVD than those using a placebo. Anti-RANKL revealed a significantly higher risk of CVD than placebo (risk ratio [RR] 1.25 [95% confidence interval (CI) 1.07% to 1.45%]). In Table 1, the league table for CVD risk reveals that patients taking anti-RANKL had a higher risk of CVD than those taking bisphosphonates (RR 1.23 [95% CI –1.04% to 1.47%]). Placebo exhibited better protective effects on CVD than anti-RANKL (RR 0.8 [95% CI 0.69% to 0.93%]). Figure 4 presents the SUCRA result that emerged from these data. The SUCRA ranking confirmed that anti-RANKL was most likely cause CVD in patients with osteoporosis. In Figure 5, we further stratified the definition of CVD and observed that all classes

of anti-osteoporosis drugs had a neutral effect on arrhythmia and heart failure. In contrast, anti-RANKL had a significantly higher risk of coronary artery disease, cerebrovascular disease, angina, and transient ischemic accident (RR 1.26 [95% CI 1.01% to 1.58%]), while HRT demonstrated a higher risk of a venous thromboembolic event (RR 1.96 [95% CI 1.53 to 2.51]).

3.3. Publication bias and risk of bias

Comparison-adjusted funnel plots did not suggest any publication bias (eFigure 1 in the Supplement). The risk of bias is presented in eTable 3 in the Supplement.

3.4. Inconsistency

No inconsistency was detected in the direct and indirect comparisons (eTables 4 and 5 in the Supplement).

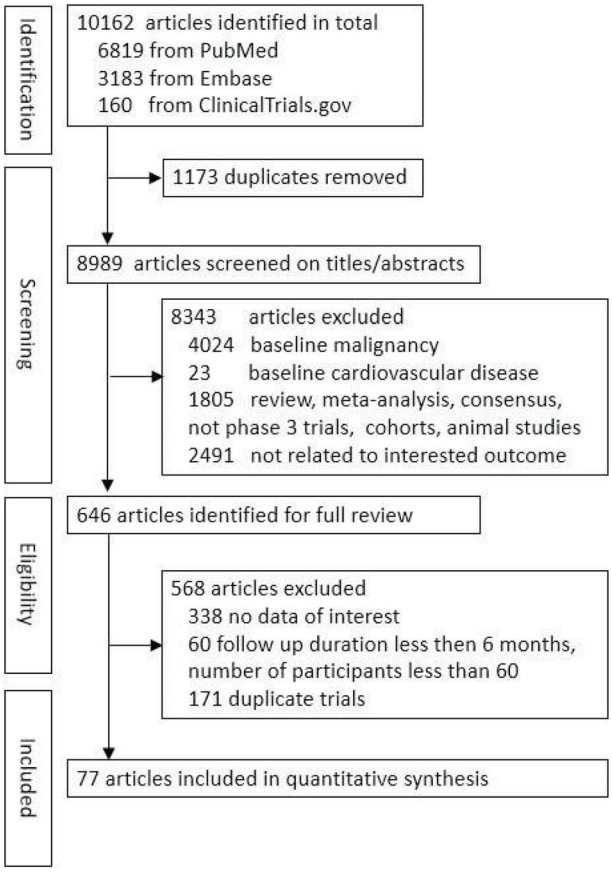

Figure 1. Flow chart.

4. Discussion

Our study is the first network meta-analysis to investigate the cardiovascular safety of HRT, bisphosphonates, anti-RANKL, PTH analogs, and romosozumab in patients with osteoporosis. This network meta-analysis found that treatment with anti-RANKL would increase CVD risk for patients with osteoporosis but the phase 3 study of denosumab revealed no significant difference in cardiovascular events.[11] All anti-osteoporosis medicines had neutral effects on arrhythmia and heart failure. HRT increased the risk of venous thromboembolism in patients with osteoporosis. Anti-RANKL had the highest risk of coronary artery disease, cerebrovascular disease, angina, and transient ischemic accident.

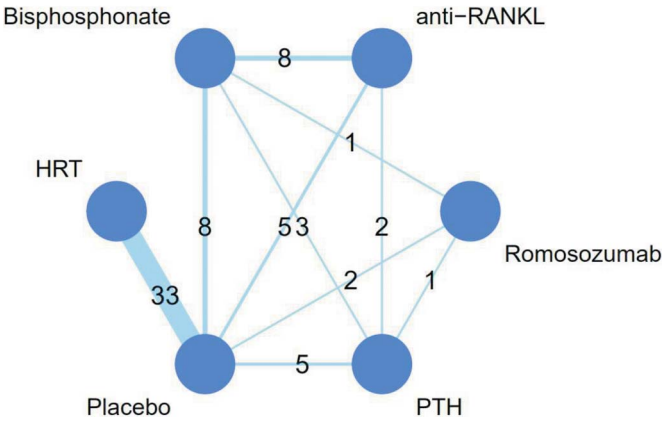

Figure 2. Network plot of trials evaluating CVD risk for osteoporosis. The network shows the number of trials assigned to each drug class. Line widths are proportional to the number of trials comparing the corresponding pair of treatments. Anti-osteoporosis drug classes: HRT, hormone relative therapies, including hormone replacement therapy and selective estrogen receptor modulators; bisphosphonates; PTH, parathyroid hormone; anti-RANKL, anti-receptor activator of nuclear factor kappa-B ligand; and romosozumab.

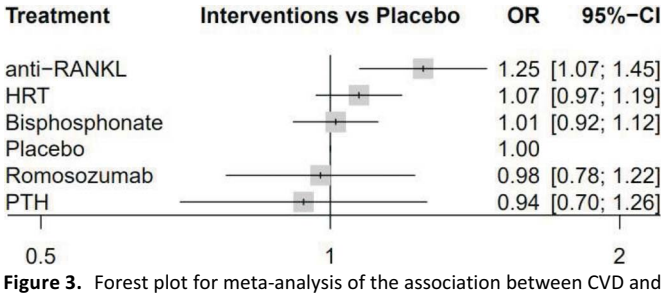

Figure 3. Forest plot for meta-analysis of the association between CVD and different drug classes. anti-RANKL, anti-receptor activator of nuclear factor kappa-B ligand; HRT, hormone relative therapies; PTH, parathyroid hormone.

Table 1
League table.

Placebo					
0.93 (0.84; 1.03)	**HRT**				
0.8 (0.69; 0.93)	0.86 (0.71; 1.03)	**Anti-RANKL**			
0.99 (0.89; 1.09)	1.06 (0.92; 1.22)	1.23 (1.04; 1.47)	**Bisphosphonate**		
1.07 (0.79; 1.43)	1.14 (0.84; 1.56)	1.33 (0.96; 1.85)	1.08 (0.8; 1.45)	**PTH**	
1.02 (0.82; 1.28)	1.1 (0.86; 1.41)	1.28 (0.98; 1.67)	1.04 (0.83; 1.29)	0.96 (0.67; 1.37)	**Romosozumab**

anti-RANKL, anti-receptor activator of nuclear factor kappa-B ligand; HRT, hormone relative therapies; PTH, parathyroid hormone.

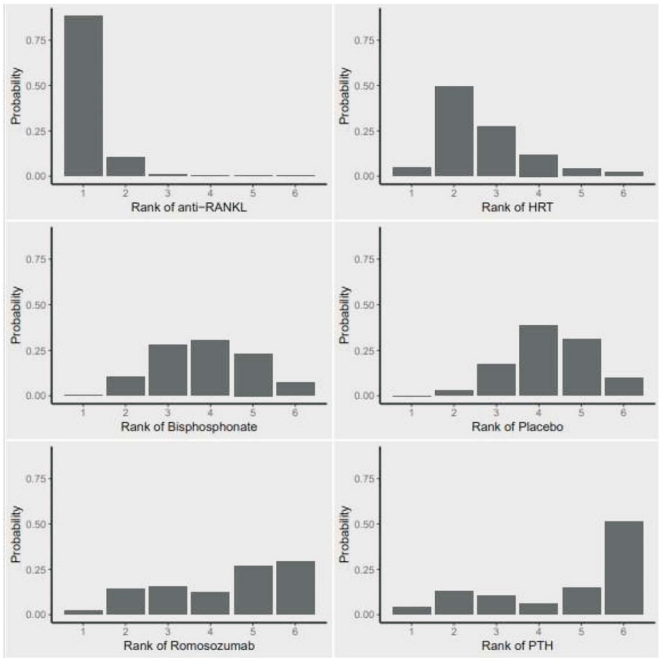

Figure 4. SUCRA.

Several meta-analyses were pooled with clinical trials to investigate the cardiovascular effects of treatment with anti-osteoporosis agents. A meta-analysis of randomized controlled trials in 2013 by Yang et al. revealed that HRT had no effects on the incidence of coronary events, cardiac death or total mortality but more risk of stroke.[6] For bisphosphonates, a meta-analysis of 58 trials in 2015 performed by Kim et al. demonstrated that bisphosphonates have neutral effects on atherosclerotic cardiovascular events; however, a modest increase in the risk of atrial fibrillation from zoledronic acid was observed.[7] Another meta-analysis of 61 trials in 2016 by Kranenburg et al. showed that bisphosphonates do not prevent arterial stiffness or cardiovascular events.[8]

In our meta-analysis, romosozumab showed no significant effects on cardiovascular events. But a controversy about the cardiovascular safety of romosozumab presented in the previous meta-analyses published in 2021, one meta-analysis to evaluate the efficacy and safety of romosozumab, including four studies that recorded cardiovascular events, showed no significant differences in cardiovascular events between anti-sclerostin antibodies and other treatments.[10] Another meta-analysis of three studies on 11,954 individuals found a higher risk of major cardiovascular events from romosozumab use.[12]

Our network meta-analysis found that treatment with anti-RANKL would increase CVD risk for patients with osteoporosis, but a controversy exists in the previous meta-analyses of the cardiovascular safety of anti-RANKL. A meta-analysis of cardiovascular safety of denosumab across multiple indications was published in 2021.[9] It included 27 trials (12 eligible for meta-analysis) on 13,202 postmenopausal women. There were more cardiovascular events in postmenopausal women treated with denosumab than with bisphosphonates, but not placebo. Another meta-analysis that addressed the effect of denosumab or romosozumab therapy on cardiovascular outcomes in patients with primary osteoporosis was published in 2020 and showed that denosumab had no more risk of composite and specific cardiovascular outcomes than active comparators or placebo.[13] A meta-analysis that investigated the cardiovascular effects in postmenopausal women with osteoporosis treated with anti-RANKLs or PTH analogs was published in 2020. The meta-analysis showed that the anti-RANKL and PTH analogs had neutral effects on cardiovascular risk and overall mortality.[14]

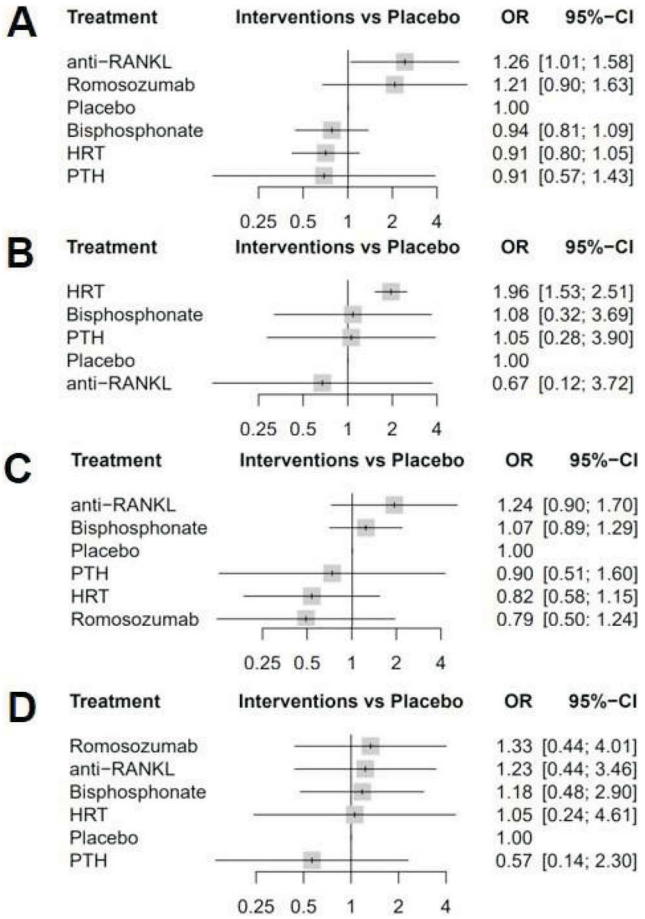

Figure 5. Subgroup analysis of cardiovascular disease. (A) Coronary artery disease, cerebrovascular disease, angina, transient ischemic accident. (B) Venous thromboembolic event. (C) Arrhythmia. (D) Heart failure. anti-RANKL, anti-receptor activator of nuclear factor kappa-B ligand; HRT, hormone relative therapies; PTH, parathyroid hormone.

Denosumab, the human anti-RANKL mono-antibody, is an antagonist of the RANKL. The RANKL binds the RANK receptor on the osteoclast precursor's surface and induces osteoclasts' differentiation and activation. Osteoprotegerin (OPG) produced by osteoblasts is a natural inhibitor of RANKL. RANKL induces calcification of vascular smooth muscles. OPG could potentially inhibit vascular calcifications by blocking the RANKL.[2,9] Hence, denosumab treatment was considered to provide a cardiovascular benefit. However, the phase 3 study of denosumab (the FREEDOM study) which enrolled 7,868 women, revealed no significant difference in cardiovascular events, stroke, coronary heart disease, peripheral vascular disease, or atrial fibrillation.[11] Subgroup analysis with 2,363 females at a high risk of CVD from the FREEDOM study found no significant difference in aortic calcification over the 3 years of the study. The frequency of cardiovascular adverse events was not significantly different between the denosumab and placebo groups.[15] However, there is a conflict between the result of our meta-analysis and the result of those clinical trials. For further studies, more clinical trials about the CV risk of human anti-RANKL mono-antibody would be in need and the possible mechanism should be investigated.

5. Limitations

Our study had some limitations. First, the heterogeneity of CVD

events was moderate to high in most analyses. Thus, the generalizability of the results is limited. Second, the clinical studies registered on ClinicalTrials.gov. might have more comprehensive cardiovascular event records; however, not all studies in our meta-analysis have such detailed records. Third, one case would have more than one cardiovascular event, such as myocardial infarction and heart failure. However, it would be reported as two events in a clinical trial. Fourth, the differences in the follow-up duration between these trials might contribute to different results. Some trials, especially those on HRTs, had different cardiovascular effects in different follow-up durations.

6. Conclusion

From our network meta-analysis, anti-RANKL, denosumab, had a higher risk of composite cardiovascular outcomes. HRT increases the risk of VTE. Romosozumab had no impact on cardiovascular risk in this study; however, its effect on CVD risk was observed in other meta-analyses. In clinical practice, attention should be paid to every individual's composite or specific cardiovascular risk, and proper medical management of osteoporosis should be conducted. In the further studies, the cardiovascular risk of anti-RANKL and the possible mechanism should have more investigations.

Supplementary materials

Supplementary materials for this article can be found at http://www.sgecm.org.tw/ijge/journal/view.asp?id=27.

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