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Short Report

Cardiovascular outcomes of romosozumab treatment—real-world data analysis

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Abstract

Romosozumab is a potent treatment for osteoporosis, with significant effects on bone density and fracture prevention. This study evaluated the cardiovascular safety of romosozumab in a real-world cohort of postmenopausal women at high fracture risk. We retrospectively evaluated postmenopausal women who initiated treatment with romosozumab between January 1, 2020, and June 30, 2023. We examined the occurrence of a major adverse cardiovascular event (MACE) across two distinct segments during the treatment period and after its conclusion. After applying inclusion and exclusion criteria, 847 women were followed for a median of 729 days (IQR: 445-1060). The incidence rate of MACE was 24.0 (95% CI 17.7-32.5) per 1000 person-years during the study period. The change in the rate of MACE from 0-90 days and 90-365 days post-treatment initiation was 0.04 and 0.06 events per 1000 days, respectively. The difference in the rate between these intervals was not statistically significant ($p = .09$). After 1 yr of treatment, the slope of MACE increased to 0.10, differing significantly from the preceding 12 mo on treatment ($p < .001$). The incidence of MACE was higher in those with a background of previous cardiovascular disease or diabetes at all timepoints, as expected. The consistency in event rates during treatment suggests that romosozumab is not associated with an increase in MACE in postmenopausal women. This finding challenges reports suggesting an increase in cardiovascular events within the first year of romosozumab treatment.

Keywords: romosozumab, sclerostin inhibitor, cardiovascular safety, osteoporosis, real world

Lay Summary

This study assessed the cardiovascular safety of romosozumab in a real-world cohort of postmenopausal women at high fracture risk. Major adverse cardiovascular events were evaluated during and after treatment. The findings do not support increased risk of cardiovascular events during romosozumab therapy; instead, they emphasize the significant role of comorbidities in influencing cardiovascular outcomes. These results add to the current body of safety data on romosozumab.

Introduction

Romosozumab is approved for treating osteoporosis in postmenopausal women at high fracture risk.[1] Despite favorable tolerability in clinical trials, the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) study reported higher rates of major adverse cardiovascular events (MACE) with romosozumab vs alendronate during the first year of treatment.[2,3] Conversely, no difference was reported in the first year of the larger FRActure study in postmenopausal woMen with ostEoporosis (FRAME) study.[4] Still, a black-box warning cautions against starting romosozumab in patients with history of myocardial infarction (MI) or stroke within the past year.[5] Recently, two real-world studies demonstrated a lower rate of cardiovascular events with romosozumab vs teriparatide.[6,7] However, these findings may be influenced by the fact that patients treated with romosozumab are preselected for their lower cardiovascular risk, potentially introducing bias.[8] We thus conducted a retrospective study of postmenopausal women treated with romosozumab, comparing the incidence of cardiovascular events during and following treatment.

Materials and methods

This observational, retrospective cohort study utilized anonymized data from Clalit Health Services (CHS) using the Clalit Research Data sharing platform powered by MDClone (https://www.mdclone.com). The study was approved by the Helsinki and Data-Utilization committees of CHS. Individual patient consent was not required due to the retrospective design.

Women aged ≥50 yr who filled at least two romosozumab prescriptions between January 1, 2020, and June 30, 2023, were included. Participants were followed from the index date (first purchase) until February 29, 2024. The primary outcome was the incidence of MACE, defined as hospitalization for cerebrovascular accident (CVA), acute MI, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG), or all-cause mortality. We also calculated the slope of MACE incidence during the first 3, 3-12 mo, and beyond 12 mo of treatment.

To account for the lack of a comparator group, we compared our findings to a published retrospective analysis from the TriNetX database with similar baseline characteristics.

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Table 1. Baseline demographic and clinical characteristics of overall cohort.

Characteristic	All ($N = 847$)
Age (yr), mean ± SD	73.1 ± 8.4
BMI (kg/m^2), mean ± SD	25.4 ± 5.2
Smoking status	
Ever	176 (20.9)
Never	361 (42.6)
Unknown	310 (36.6)
Charlson Comorbidity Index, mean ± SD	4.7 ± 2.3
eGFR, mean ± SD	81.4 ± 17.2
≥60 mL/min/1.73 m^2	746 (88.1)
<60 mL/min/1.73 m^2	101 (11.9)
Prior medications	
Beta blockers	206 (24.3)
ACE/ARB/ARNI	273 (32.2)
Anti-platelet therapy	173 (20.4)
Statins	399 (47.1)
Medical history	
Hypertension	866 (51.1)
Diabetes	370 (21.8)
CVA	132 (7.8)
Acute MI	17 (2.0)
CABG/PTCA	2 (0.2)
IHD	49 (5.8)
CHF	51 (6.0)
Prior fracture	
Any	489 (57.7)
Hip fracture	204 (24.1)

Values reported as *N* (%) unless otherwise stated. Abbreviations: eGFR, estimated glomerular filtration rate; CVA, cerebrovascular accident; MI, myocardial infarction; CABG/PCI, coronary artery bypass graft/percutaneous transluminal coronary angioplasty; IHD, ischemic heart disease; CHF, congestive heart failure.

The study authors provided data on MACE incidence in women treated with teriparatide or romosozumab.[6]

The incidence rate and 95% CI of each outcome are reported. Major adverse cardiovascular event is stratified according to background MACE (history of stroke or MI) and diabetes. Kaplan–Meier estimates were used to graph the probability of outcomes. Statistical analyses were performed with SAS Enterprise Guide 8.3.

Results

We included 1081 patients who initiated treatment with romosozumab during the study period. After applying inclusion and exclusion criteria, 847 women were followed for a median duration of 729 days (IQR: 415-1060). Baseline characteristics are shown in Table 1. The cohort included women aged 73.1 ± 8.4 yr, BMI 25.4 ± 5.2 mg/kg^2, and Charlson Comorbidity Index of 4.7 ± 2.3 (mean ± SD). Notable medical history included cerebrovascular disease in 132 (7.8%) individuals, ischemic heart disease in 49 (5.8%), and diabetes in 147 (17.4%). Previous osteoporotic fracture was documented in 489 (57.7%), including 204 (24.1%) with a hip fracture.

Following index date, 42 (5%) patients experienced MACE; 9 (1.1%) patients experienced a CVA, 4 (0.5%) suffered an acute MI, 2 (0.2%) underwent PTCA/CABG, and 32 (3.8%) died during the follow-up period. Figure 1 illustrates failure curves for outcomes of interest over time. The incidence of MACE was higher in those with a history of MI/PTCA/CABG or diabetes, at all timepoints. The incidence of MACE during the follow up period was 24.0 (95% CI, 17.7-32.5) and 2.3 (95% CI, 0.9-6.1), 5.1 (95% CI, 2.7-9.9), and 18.1 (95%CI, 12.8-25.6) per 1000 person-years for acute MI, CVA, and death, respectively.

The rate of change in MACE from 0-90 days to 90-365 days post-treatment initiation was 0.04 and 0.06 per 1000 days, respectively. The difference between these intervals was not statistically significant ($p = .09$). After 1 yr of treatment, the rate of change in MACE increased to 0.10, showing a significant difference compared with the preceding 12 mo ($p < .001$).

Discussion

We observed a consistent rate of adverse cardiovascular events during romosozumab treatment, while the rate increased during follow-up post-treatment. Higher comorbidity burden correlated with increased mortality risk as expected, irrespective of romosozumab treatment.

The cardiovascular safety of romosozumab was questioned following the ARCH trial, which reported a significant imbalance in cardiovascular risk between romosozumab-treated patients and controls receiving alendronate.[2] The absence of MACE in the alendronate group during the initial 3 mo, with sustained low rates up to 18 mo, raises questions about differential effects between romosozumab and alendronate. Conflicting evidence regarding bisphosphonates' cardiovascular benefits complicates interpretation, especially considering the unprecedented reduction in cardiovascular events with these drugs.[3,9,10] Furthermore, the consistent event rates over 3 yr, even after transitioning to alendronate, suggest these findings may be due to chance.

Recent real-world data from the TriNetX database also examined the cardiovascular safety of romosozumab, comparing it with PTH analogs over a 1-yr follow-up period.[6] After propensity score matching, the incidence of 3-point MACE was significantly lower in the romosozumab group. Similar outcomes were reported in a study by Hartz et al.[7] Our data align with these findings, indicating that cardiovascular event rates remain steady during and after romosozumab treatment. We also compared our results with those from the TriNetX database. The incidence of MACE in women during the first year of romosozumab treatment was 27.2 (95% CI, 23.0-32.0) per 1000 person-years, compared with 34.0 (95% CI, 29.2-39.4) with teriparatide. In our study, the incidence was 18.6 (95% CI, 11.2-30.8) per 1000 person-years. This suggests that the cardiovascular event rate in our study is comparable to that reported by Stokar et al. and does not indicate an increased risk compared with PTH analogs.

Several limitations of our study should be noted. The retrospective design limits our ability to infer a causal relationship between romosozumab and cardiovascular outcomes. Additionally, the absence of a comparator group precludes direct comparisons with alternative treatments or placebo. However, the black-box warning leads to the pre-selection of low cardiovascular risk patients, potentially resulting in a lower incidence of MACE compared with other therapies. This bias may explain the reduced cardiovascular events observed with romosozumab in the Stokar and Hartz studies, despite adjustments for baseline characteristics.[6,7] Nonetheless, we observed a similar MACE incidence to that reported by Stokar et al.[6]

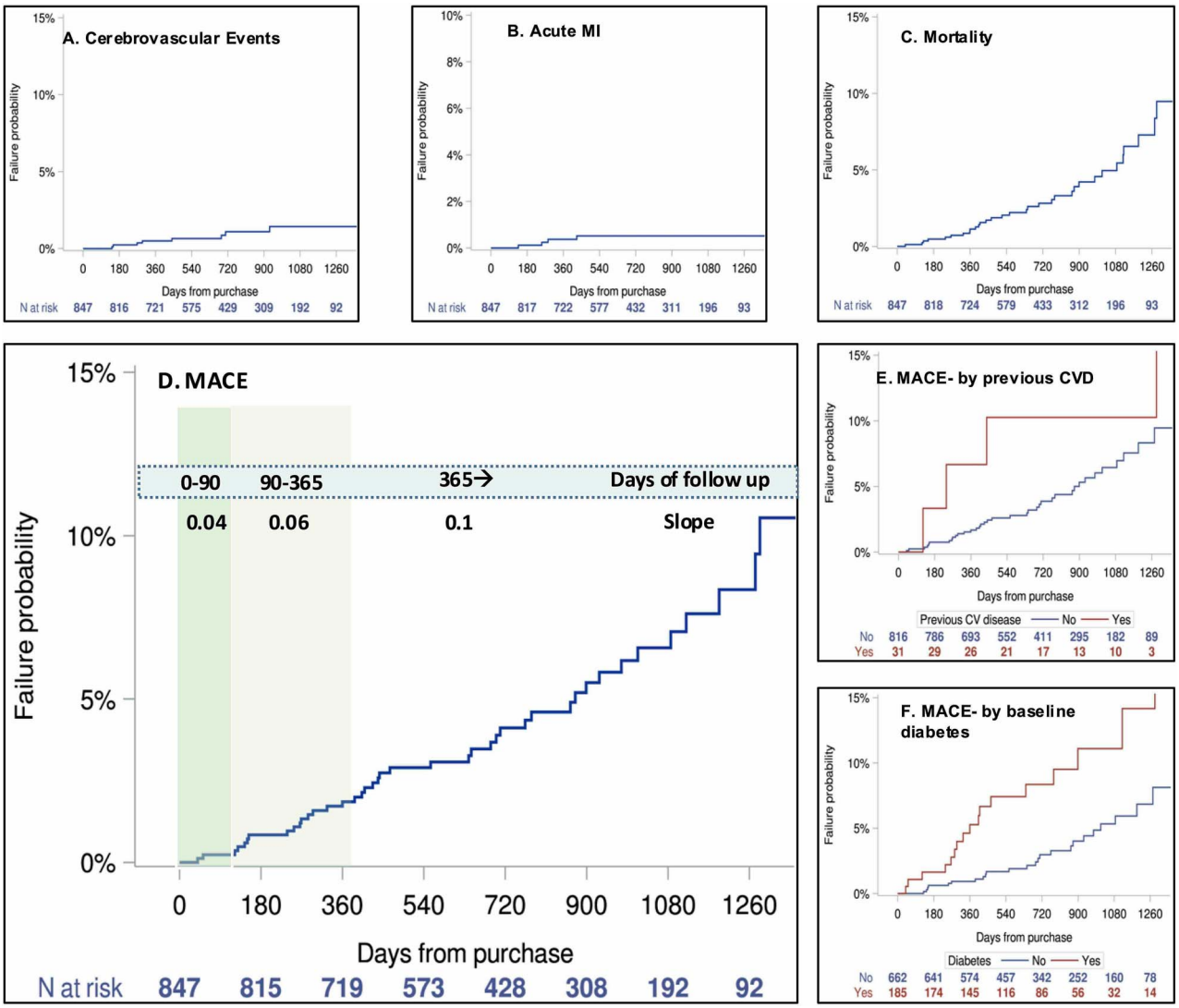

Figure 1. Cardiovascular outcomes of romosozumab treatment. (A-D) Failure curves over time for key outcomes, including CVA (A), acute MI (B), mortality (C), and MACE (D). In (D), the dark shading represents the period from 0 to 90 days of romosozumab treatment, while the light shading covers 90 to 365 days; the unshaded portion corresponds to the follow-up period post-treatment. The slopes for each interval are provided. (E, F) Illustration of the time to MACE based on the presence of previous cardiovascular disease (CVD) or diabetes. Abbreviations: CVA, cerebrovascular accident; MI, myocardial infarction; MACE, major adverse cardiovascular event.

In summary, we demonstrate consistency in cardiovascular event rates in postmenopausal women during treatment with romosozumab. This finding challenges reports suggesting an increase in cardiovascular events within the first year of romosozumab treatment.

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Author contributions

A.T. and L.L. conceived and designed the study and collected the data. A.T., R.P., and A.C. analyzed the data and interpreted the results. A.T. and R.P. wrote the manuscript. All authors reviewed and commented on the manuscript.

Anat Tsur (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing—review & editing), Avivit Cahn (Conceptualization, Formal analysis, Investigation, Methodology), Ludmila Levy (Conceptualization, Data curation), and Rena Pollack (Conceptualization, Investigation, Methodology, Writing—original draft, Writing—review & editing).

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Conflicts of interest

The authors have no conflict of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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