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Romosozumab Use and Cardiovascular Events

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To the Editor:

We have read with interest the article by Miller and colleagues recently published in *JBMR*.[(1)] The authors show a post hoc analysis of two randomized, phase 3 clinical trials (Fracture Study in Postmenopausal Women with Osteoporosis [FRAME] and Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk [ARCH]) investigating the efficacy and safety of romosozumab in postmenopausal women with osteoporosis and mild-to-moderate chronic kidney disease (CKD). Romosozumab significantly reduced the relative risk of new vertebral fractures at month 12 among patients with estimated glomerular filtration rate (eGFR) of 30–59, 60–89, and ≥90 mL/min by 72%, 70%, and 84%, respectively, in FRAME versus placebo, and by 51%, 19%, and 57%, respectively, in ARCH versus alendronate. The authors conclude that romosozumab is an effective treatment option for postmenopausal women with osteoporosis and mild-to-moderate reduction in kidney function, with a similar safety profile across different levels of kidney function.

In Table 1, we summarize the absolute number and the percentage of patients experiencing cardiovascular events (CV) leading to death, serious myocardial infarction, or stroke over a 12-month follow-up period in the ARCH trial according to baseline eGFR values and allocation arm. It is noticeable that the cumulative proportion of patients having these adverse events was consistently higher in patients on romosozumab than in those on alendronate across all eGFR categories (Table 1). Although the between-arms difference of the percentage of patients experiencing such events did not achieve the statistical significance, it is crucial, noting that the number needed to harm[(2)] (NNH, ie, how many patients must receive romosozumab versus alendronate over a 12-month period for one additional patient to experience a CV event leading to death, serious myocardial infarction, or stroke) raises some safety concern. Indeed, the NNH is 91, 141, and 77, respectively, among patients with eGFR of 30–59, 60–89, and ≥90 mL/min over a restricted time period (12 months). These findings in perspective highlight as follows: for every 77 patients with eGFR ≥90 mL/min who receive romosozumab for 12 months, one additional patient experiencing a CV event leading to death, serious myocardial infarction, or stroke is observed versus alendronate. Remarkably, the NNH is lower (that is, less favorable) in patients with eGFR ≥90 mL/min (NNH = 77) than in those with eGFR between 60 and 89 mL/min/1.73 m^2 (NNH = 143) and with eGFR ranging from 30 to 59 mL/min/1.73 m^2 (NNH = 91).

These results suggest that further clinical studies, particularly observational studies of safety, are needed to evaluate the use of romosozumab, especially the association with cardiovascular events leading to death, serious myocardial infarction, or stroke over a 12-month follow-up, in postmenopausal women with osteoporosis and mild-to-moderate chronic kidney disease.

Table 1. Absolute Number and Percentage of Patients Experiencing Cardiovascular Events Leading to Death, Serious Myocardial Infarction, or Stroke in the ARCH Trial by Baseline eGFR Over a 12-Month Follow-Up Period

	Baseline eGFR (mL/min/1.73 m^2)					
	eGFR ≥90		eGFR 60–89		eGFR 30–59	
	Alendronate $n = 333$	Romosozumab $n = 267$	Alendronate $n = 1195$	Romosozumab $n = 1259$	Alendronate $n = 479$	Romosozumab $n = 509$
CV events leading to death, serious myocardial infarction, or stroke[a], *n* (%)	2 (0.6)	5 (1.9)	12 (1.0)	22 (1.7)	8 (1.7)	14 (2.8)
Number needed to harm	77		143		91	

ARCH = Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk; eGFR = estimated glomerular filtration rate; CV = cardiovascular event.
[a]Positively adjudicated CV events.

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Disclosures

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Peer Review

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