Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors and Stroke — Reply —

We thank Dr. Kimura for his interest in our study. As he highlighted, in our recent analysis of the Asian subgroup of patients in the EMPA-REG OUTCOME trial, empagliflozin given in addition to standard of care was associated with a reduction in cardiovascular (CV) mortality but no difference in the risk of stroke.1 This was consistent with the results observed in the overall patient population, in which no significant increase in stroke was observed.2

Dr. Kimura comments that combined use of empagliflozin and other diuretics might result in “massive” diuresis. Reassuringly, the published data demonstrate that this was not the case. The pharmacodynamic effects of empagliflozin combined with a thiazide or loop diuretic in patients with type 2 diabetes were investigated in a mechanistic study.3 The mean (SD) increase in urine volume was 54 (93) mL/day after treatment with empagliflozin alone for 5 days and 429 (92) mL/day with empagliflozin in combination with hydrochlorothiazide for 5 days (difference of <400 mL/day compared with empagliflozin alone).3 In a separate group, the mean (SD) increase in urine volume was 215 (168) mL/day after treatment with empagliflozin alone for 5 days and 353 (116) mL/day with empagliflozin in combination with torasemide for 5 days (difference of approximately 100 mL/day compared with empagliflozin alone).3 No hypertensive events were reported in this study.3

As Dr. Kimura notes, in the EMPA-REG OUTCOME trial, the use of diuretics at baseline was lower in Asian patients than in the overall population in both the empagliflozin and placebo groups. However, in a subgroup analysis of the overall trial population, the risk of stroke with empagliflozin vs. placebo was comparable in patients taking and not taking diuretics at baseline (P=0.25 for interaction) or loop diuretics at baseline (P=0.08 for interaction).4 The reduction in the risk of hospitalization for heart failure with empagliflozin vs. placebo was also consistent in patients taking vs. not taking diuretics or loop diuretics at baseline (P>0.05 for interactions).4 Hemodynamic changes in response to empagliflozin are reflected as reductions in systolic blood pressure (SBP) and increases in hematocrit. In the EMPA-REG OUTCOME trial, patients with the largest decreases from baseline in SBP (>30 mmHg) or with the largest increases from baseline in hematocrit (>90th percentile) did not have an increased risk of stroke.4 Further, the proportion of patients with a stroke event was no higher in patients who had an adverse event consistent with volume depletion in either the empagliflozin or placebo groups.4

In conclusion, while we agree that effects on volume may be one of the mechanisms behind the observed reductions in the risk of CV death and heart failure outcomes with empagliflozin, we find no evidence that concomitant use of diuretics and empagliflozin was associated with an increased risk of stroke in patients in the EMPA-REG OUTCOME trial.

Conflict of Interest Disclosures

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