the DAPA-HF trial. However, neither trial was designed or adequately powered to evaluate the effect of SGLT2 inhibitors on cardiovascular death. The duration of follow-up in both trials was short (i.e., 16 months in EMPEROR-Reduced and 18 months in the DAPA-HF trial). Therefore, patients who were hospitalized for heart failure were not followed long enough to discern their higher risk of cardiovascular death. The DAPA-HF trial recorded 25% more cardiovascular deaths than EMPEROR-Reduced and thus had greater statistical power for this outcome.[4] Yet, because that trial was not powered for cardiovascular death, the nominal P value for the effect of dapagliflozin was close to 0.05. A meta-analysis of the two trials showed no heterogeneity in the effects of the two SGLT2 inhibitors on the risk of cardiovascular death.[3]

Bhattacharyya and Kar, Kumar and Sinha, and others propose that the benefits of SGLT2 inhibitors are mediated by a natriuretic or osmotic diuretic effect. However, the effect of SGLT2 inhibitors on urinary sodium excretion and plasma volume is transient,[5] the effect of these drugs on circulating NT-proBNP levels is modest, the dose of diuretics is not modified in the vast majority of patients with heart failure who are treated with these drugs, and a diuretic effect cannot explain the action of these drugs in slowing the decline in glomerular function. Instead, their clinical benefits may be related to an action of these drugs to induce nutrient-deprivation signaling, with its attendant effects in mitigating cellular stress and prolonging cellular survival in the heart and kidneys.[5]

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Since publication of their article, the authors report no further potential conflict of interest.

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Dapagliflozin in Patients with Chronic Kidney Disease

TO THE EDITOR: The results of the DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial reported by Heerspink et al. (Oct. 8 issue)[1] suggest that an alternative to the restriction of daily sodium intake and the use of diuretic agents to correct volume expansion associated with both heart failure and proteinuric chronic kidney disease may be sodium–glucose cotransporter 2 (SGLT2) inhibitors, owing to their natriuretic effects. Whether the improvements in long-term cardiovascular and kidney outcomes that were observed in this trial could be attributed solely to the correction of volume expansion or to class-specific effects is unknown. Information from the authors regarding the daily sodium consumption of the trial participants and the dose and type of diuretics they received would be helpful, as would information as to whether these variables influenced the protective effects of SGLT2 inhibition. After all, restricting dietary sodium consumption, changing the diuretic dose, and combining diuretic classes have all been shown to be highly efficacious in the management of therapy-resistant volume overload, and these measures may prove to have a similar effect on long-term cardiovascular and renal protection.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: One of the kidney-protective effects of SGLT2 inhibitors is the correction of glomerular hypertension by afferent arteriolar constriction mediated by tubuloglomerular feedback.[1] The existence of glomerular hypertension and the capacity of SGLT2 inhibitors to trigger tubuloglomerular feedback during normoglycemia are necessary for SGLT2 inhibitors to be able to suppress the progression of nondiabetic chronic kidney disease. A third of the participants in the DAPA-CKD trial had received a diagnosis of nondiabetic chronic kidney disease, in which a kidney-protective effect equivalent to or greater than that of diabetes was shown. These results suggest that SGLT2 inhibitors could correct glomerular hypertension by activating tubuloglomerular feedback even without dysglycemia. To what extent did dapagliflozin reduce albuminuria among the participants without diabetes?

In addition to the presence of albuminuria, the use of amino acid loading as a test of renal functional reserve may be an index of the degree of intraglomerular pressure attributed to afferent arterioles, which are common sites of action for SGLT2 inhibitors.[2] A renal functional reserve index might identify patients with earlier stages of chronic kidney disease in whom SGLT2 inhibitors might provide renal protection; such patients were not enrolled in the DAPA-CKD trial.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Vogt suggests that the benefits of dapagliflozin on heart and kidney outcomes in the DAPA-CKD trial may be mediated by the natriuretic properties of the drug. We agree that volume restriction with the use of diuretic treatment, as well as moderation of dietary sodium consumption, are important strategies in the treatment of heart failure and chronic kidney disease and may improve long-term kidney and cardiovascular outcomes. In the DAPA-CKD trial, 1882 participants (43.7%) were using diuretics at baseline. The 39% lower relative risk in the dapagliflozin group than in the placebo group with respect to the primary composite outcome (a sustained ≥50% decline in the estimated glomerular filtration rate, end-stage kidney disease, or death from renal or cardiovascular causes) was consistent among participants who were using diuretics at baseline and those who were not (P for interaction=0.96). Other clinical trials have also shown that the effects of SGLT2 inhibitors on cardiovascular or kidney outcomes are not modified by the concomitant use of diuretics.[1,2] However, in the DAPA-CKD trial, we did not obtain 24-hour urine samples or measure urine volume to assess dietary sodium intake.

Yasuda and Isobe question whether SGLT2 inhibitors could correct glomerular hypertension by activating tubuloglomerular feedback, even without dysglycemia. Glomerular hypertension and proteinuria, as they point out, are common manifestations of many causes of chronic kidney disease. Correction of glomerular hypertension during dapagliflozin treatment has been associated with reductions in albuminuria in previous trials involving patients with or without type 2 diabetes and may explain the protective effects of dapagliflozin in chronic kidney disease resulting from various underlying causes.[3,4] Our data indicate that the effects of dapagliflozin on all the primary and secondary outcomes were consistent among participants with and those without type 2 diabetes and were present regardless of the underlying cause of chronic kidney disease; these findings support the use of dapagliflozin in a broad range of patients with chronic kidney disease.[5]

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