explore whether red meat, and possibly other dietary components, can lead to de novo ESRD in subjects without identifiable ESRD risks. These data also increase the urgency to identify kidney toxic dietary components and if these components can promote ESRD even in subjects who have no identifiable risk factors.

Diet remains a relatively underused component of the clinician’s armamentarium in the fight to prevent patients with CKD progressing to ESRD and its detrimental consequences. The study of Lew et al. gives more direction to the research needed to clarify how the increasingly important tool of diet can help reduce ESRD incidence and its associated morbidity and mortality.

**ACKNOWLEDGMENTS**

The authors acknowledge the support of the Academic Operations division of Baylor Scott and White Health in the studies by our research group quoted in this manuscript.

**DISCLOSURES**

None.

**REFERENCES**


**SGLT2 Inhibitors—Sweet Success for Diabetic Kidney Disease?**

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*SGLT2 inhibitors—Sodium-glucose cotransporter 2 inhibitors—have provided the opportunity to learn about other benefits and risks of these agents. They also provide an interesting model to learn about how to take advantage of the development of new drugs to increase the potential for benefits in diabetes care. This is an exciting time for diabetes therapeutics. In addition to insulin, biguanides (e.g., metformin), sulfonylureas, α-glucosidase-inhibitors, and thiazolidinediones, a number of new classes of glucose-lowering medications have recently been developed and brought to the clinic. These new classes include the glucagon-like peptide 1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, which target the incretin system, and, most recently, the sodium glucose transporter-2 (SGLT2) inhibitors. Further, well over 100,000 patients with diabetes have been enrolled in large trials required by the regulatory authorities overseeing drug development to ensure the cardiovascular safety of these new drugs. Such trials have also provided the opportunity to learn about other benefits and risks of these agents.

*Published online ahead of print. Publication date available at www.jasn.org.

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Of the new diabetes drug classes, the SGLT2 inhibitors are of particular interest to the nephrology community. First, the kidney is the main site of action for SGLT2 inhibitors, which waste glucose in the urine by blocking sodium-coupled glucose reabsorption in the proximal tubule. Second, there is good reason to believe that SGLT2 inhibitors may be renoprotective. By increasing distal tubular sodium delivery and stimulating tubuloglomerular feedback, SGLT2 inhibitors increase afferent arteriolar tone and decrease intraglomerular pressure. In addition, SGLT2 inhibitors lead to modest decreases in weight and BP, presumably through natriuretic effects. Decreased sodium reabsorption could also plausibly affect proximal tubular cell energetics and therefore other functions of these metabolically active cells.

In this setting, Lambers-Heerspink et al. present provocative new data on the renal effects of canagliozin, an SGLT2 inhibitor currently available for clinical use. The new data are a secondary analysis of the Canagliozin Treatment and Trial Analysis versus Sulphonylurea (CANTATA-SU) study, which included 1450 participants with type 2 diabetes and baseline eGFR $\geq$ 55 ml/min per 1.73 m$^2$. All participants were treated with metformin, and approximately 60% were treated with an inhibitor of the renin-angiotensin system (RAS). Each participant was randomly assigned to add-on therapy with one of two doses of canagliozin or with glimepiride, a sulfonylurea used as an active control. Over 2 years of follow-up, decline in eGFR was significantly slower with either canagliozin dose (0.5 ml/min per 1.73 m$^2$ per year with 100 mg daily [95% confidence interval (95% CI), 0.0 to 1.0] and 0.9 ml/min per 1.73 m$^2$ per year with 300 mg daily [95% CI, 0.4 to 1.4]), compared with glimepiride (3.3 ml/min per 1.73 m$^2$ per year [95% CI, 2.8 to 3.8]). Among the subset of participants with urine albumin-to-creatinine ratio $\geq$ 30 mg/g at baseline, canagliozin also reduced albuminuria, compared with glimepiride. These differences occurred with little difference in hemoglobin A1c between treatment groups, suggesting effects are not mediated by blood glucose.

These new data on canagliozin are consistent with recent data demonstrating that empagliozin, another SGLT2 inhibitor, improved clinical renal outcomes in the EMPA-REG OUTCOMES study. In EMPA-REG OUTCOMES, 7020 participants with type 2 diabetes at high cardiovascular risk and a baseline eGFR $\geq$ 30 ml/min per 1.73 m$^2$ were randomly assigned to empagliozin or to placebo for a median observed follow-up of 3.1 years. Compared with placebo, empagliozin reduced the risk of a composite renal outcome (incident or worsening nephropathy or cardiovascular death) by 39% (hazard ratio [HR], 0.61; 95% CI, 0.55 to 0.69), with significant reductions in progression to macroalbuminuria, doubling of serum creatinine, and initiation of RRT of similar magnitudes. Empagliozin reduced mean eGFR over the first 4 weeks of follow-up, after which eGFR stabilized compared with placebo, consistent with a mechanism of action involving decreased intraglomerular pressure. Approximately 80% of EMPA-REG OUTCOMES participants were using a RAS inhibitor at baseline, and the beneficial effects of empagliozin were confirmed in the subgroup of participants using a RAS inhibitor. Together, the canagliozin and empagliozin studies provide replication of renal effects and suggest that renoprotection may be a class effect of SGLT2 inhibitors that is additive to RAS blockade.

Moreover, the apparent renoprotective effects of SGLT2 inhibitors add to exciting results suggesting that this class of medications may also reduce cardiovascular events. The primary outcome of the EMPA-REG OUTCOMES study was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, which was reduced by 14% (HR, 0.86; 95% CI, 0.74 to 0.99), compared with placebo. In addition, hospitalization for heart failure was reduced by 35% (HR, 0.65; 95% CI, 0.50 to 0.85) and all-cause mortality was reduced by 32% (HR, 0.68; 95% CI, 0.57 to 0.82). Given the early occurrence of this beneficial impact of empagliozin on cardiovascular outcomes in the face of rather modest effects of the SGLT2 inhibitor on glycemia, along with recognition from other clinical trials of a long lag time between glycemcic control and any cardiovascular benefit, the cardiovascular benefits observed in EMPA-REG OUTCOMES are not likely to be mediated primarily by its actions on blood glucose.

How will the new data from CANTATA-SU and EMPA-REG OUTCOMES affect frontline treatment of type 2 diabetes by primary care providers and endocrinologists? The American Diabetes Association provides a logical framework for choosing treatments to control glycemia. In this framework, metformin is recommended as standard first-line treatment for type 2 diabetes. When additional agents are required to meet glycemia targets, the benefits and risks of adding a sulfonylurea, thiazolidinedione, GLP-1 receptor agonist, DPP-4 inhibitor, SGLT2 inhibitor, or basal insulin are weighed in the context of an individual patient’s clinical presentation.

The apparent renal and cardiovascular benefits of SGLT2 inhibitors will encourage primary care physicians and endocrinologists to use these agents more frequently in the care of patients with type 2 diabetes. Of course, adverse effects, costs, alternative agents, and individual patient characteristics must also be taken into account. Adverse effects of SGLT2 inhibitors include genital infections and an increased risk of fracture, which is well described but for which mechanisms remain unclear. In addition, the US Food and Drug Administration recently strengthened a warning that canagliozin and dapagliozin may increase the risk of AKI, though empagliozin was not associated with increased risk of AKI in EMPA-REG OUTCOMES. Alternative agents also offer potential benefits with low risks: three DPP-4 inhibitors have been shown to have neutral effects on cardiovascular risk with low risk of hypoglycemia; one GLP-1 agonist was recently reported to decrease cardiovascular events, a broad composite renal outcome, and mortality; and pioglitazone was reported to reduce the risk of recurrent stroke among stroke survivors with insulin resistance. Because many recent trials of glucose-lowering medications were conducted among participants with high
cardiovascular risk, results may not extrapolate to all patients with type 2 diabetes. Thus, the beneficial renal and cardiovascular effects of SGLT2 inhibitors should be important factors for primary care physicians and endocrinologists to consider when choosing glucose-lowering medications, but other important factors must also be considered.

How do the new data affect the care of patients with type 2 diabetes and established CKD? Even with the recent, more liberal advisory for use of metformin issued by the US Food and Drug Administration, CKD often constrains choice of glucose-lowering medications. Fortunately, available SGLT2 inhibitors are approved for use in moderate CKD, with specific restrictions varying by agent. The glucose-lowering effects of SGLT2 inhibitors are reduced in type 2 diabetes patients with moderate CKD compared with those with normal renal function, probably due in part to reduced glucose filtration. Despite the reduced glucose-lowering effect, the renal and cardiovascular benefits of empagliflozin were not diminished in EMPA-REG OUTCOMES participants with CKD at baseline, compared with those with normal eGFR at baseline.4 However, CANTATA-SU and EMPA-REG OUTCOMES were conducted among populations with type 2 diabetes and predominantly normal baseline kidney function. Further studies are needed to test the long-term renal effects of SGLT2 inhibitors among patients with prevalent CKD. To this end, the ongoing Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation study is testing the effects of canagliflozin versus placebo on the occurrence of ESRD, doubling of serum creatinine, and renal or cardiovascular death (Clinicaltrials.gov identifier: NCT02065791).

Ultimately, recent advances in diabetes therapeutics should help prevent kidney disease among the large and growing diabetes population by directly targeting the kidney, providing an expanded menu of options to effectively and safely control glycaemia, or both. New glucose-lowering medications will hopefully also improve outcomes for patients with diabetes and established CKD, though further studies in this population are needed, as are new classes of drugs targeting other injury pathways leading to CKD progression. Given the ongoing exponential growth in the number of people with diabetes and the enormous health impact of diabetic kidney disease, it is promising that advances in physiology, vigilant development of new drugs, and investment in large clinical trials may soon begin to yield sweet success for prevention and treatment.

ACKNOWLEDGMENTS

I.H.d.B. receives support from grants R01DK088762 and R01DK099199 from the National Institute of Diabetes and Digestive and kidney Diseases (NIDDK), grant 4-15-CKD-20 from the American Diabetes Association, an unrestricted gift from the Northwest Kidney Centers to the Kidney Research Institute, and the Veterans Affairs (VA) Puget Sound Health Care System. S.E.K. receives support from grant 101BX001060 from the Department of Veterans Affairs, grant P30DK017047 from the NIDDK, and the VA Puget Sound Health Care System.

DISCLOSURES

I.H.d.B. received research support from Abbvie (North Chicago, IL) and MedTronic (Minneapolis, MN) and consulted for Amgen (Thousand Oaks, CA), Bayer (Whippany, NJ), Boehringer-Ingelheim (Ridgefield, CT), Ironwood (Cambridge, MA), and Janssen (Raritan, NJ). S.E.K. received research support from Eli Lilly (Indianapolis, IN) and consulted for Astra Zeneca (Wilmington, DE), Boehringer-Ingelheim, Elielyx (San Diego, CA), GlaxoSmithKline (Seattle, WA), Intarcia (Hayward, CA), Janssen, Merck (Whitehouse Station, NJ), Novo Nordisk (Seattle, WA), and Receptos (San Diego, CA).

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See related article, “Canagliflozin Slows Progression of Renal Function Decline Independently of Glycemic Effects,” on pages 368–375.