Prior to the advent of sodium/glucose cotransporter 2 (SGLT2) inhibitors, the treatment of diabetic kidney disease (DKD) remained relatively unchanged for close to 2 decades. The mainstay of therapy centered on aggressive glycemic control in conjunction with managing hypertension with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers. Recently, multiple randomized controlled trials have unequivocally demonstrated the cardiovascular and renoprotective benefits of SGLT2 inhibitors, revolutionizing the management of diabetes and DKD (Table 1). But these drugs are not cheap: the wholesale cost of empagliflozin is $530 per month. The elephant in the room is whether the benefits of SGLT2 inhibitors sufficiently offset the outsized costs of kidney replacement therapy (KRT) to justify their expensive price tag.

In this issue of AJKD, Reifsnider et al1 sought to answer this question. They did so with a cost-effectiveness analysis, by weighing the costs and benefits of empagliflozin over standard of care without an SGLT inhibitor. The main measure of interest is the incremental cost-effectiveness ratio (ICER), or the increase in costs from adding empagliflozin to DKD treatment divided by the gains in quality-adjusted life-years (QALYs). Simply put, the ICER is the price of 1 additional QALY, or 1 additional year of perfect health. Cost-effectiveness analyses typically use QALYs to account for differences in health: an additional year of health. Cost-effectiveness analyses under various scenarios. Most scenarios resulted in ICERs less than $50,000/QALY, and all had ICERs less than $150,000/QALY. Moreover, the authors simultaneously varied all areas of uncertainty in a probabilistic sensitivity analysis, with 91% of simulations having ICERs less than $50,000/QALY and 99.8% less than $150,000/QALY.

A major strength of the study is that the model was calibrated to closely match clinical events for the DKD subgroup in EMPA-REG OUTCOME, a process described in the supplementary material of Reifsnider et al. The results were also robust to a wide range of sensitivity analyses that varied key assumptions, including the time horizon of the study, cost of treatment, drug pricing, and copayments (Table 4 in Reifsnider et al). Furthermore, the model captured a substantial amount of clinical complexity and heterogeneity.

As with all modeling studies, the plausibility of the results relies on whether we believe the underlying assumptions. For instance, because EMPA-REG OUTCOME followed patients for a maximum of 4 years, Reifsnider et al needed to extrapolate their parametric assumptions through the end of life. The authors tested this concern over a shorter 3-year time horizon: empagliflozin remained cost-effective but at a substantially more expensive $113,234/QALY. Additionally, EMPA-REG OUTCOME did not have sufficient power to obtain precise estimates of certain cardiovascular outcomes, leading to high uncertainty in some parameters. However, even when the authors only considered statistically significant outcomes, they estimated an ICER of $34,337/QALY. Finally, the authors did not explicitly model the costs of standard of care. Although empagliflozin reduced DKD spending on an annual basis, patients receiving empagliflozin lived longer and might have been more expensive over their entire lifetimes. Notwithstanding these limitations, the ICER was so low that empagliflozin is likely
cost-effective even if some parameters were incorrectly specified. In short, we can confidently state that empagliflozin (and likely the SGLT2 inhibitors overall) is a high-value drug.

The standard of care for DKD has long been glycemic optimization, blood pressure control, and prevention of both macro- and microvascular complications of diabetes. The angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in particular reduce proteinuria and slow DKD progression above and beyond simply achieving normotension. Even in the absence of hypercholesterolemia, guidelines recommend using statins in patients with DKD, owing to the high rate of cardiovascular events. SGLT2 inhibitors provide a welcome innovation for patients with diabetes. Their putative mechanism for reducing DKD progression is blocking sodium and glucose uptake in the proximal convoluted tubule and restoring tubuloglomerular feedback and glomerular hemodynamic irregularities. Multiple clinical trials have demonstrated the efficacy of SGLT2 inhibitors in preventing cardiovascular disease and slowing DKD progression (Table 1). National and international professional societies now universally recommend their use in patients with diabetes and estimated glomerular filtration rate ≥30 mL/min/1.73 m².

Although this study suggests that SGLT2 inhibitors are relatively inexpensive, the findings come with important caveats. First, the certainty of the cost-effectiveness estimates wanes over longer time horizons, and the true economic impact of empagliflozin might not correlate with long-term use. Second, the drug’s cost varies substantially depending on the payer, wholesale price, and market competition with other SGLT2 inhibitors. Not surprisingly, the sensitivity analyses (Table 4 in Reifsnider et al) demonstrate that empagliflozin’s price was the most important contributor to the drug’s overall cost-effectiveness. To the extent drug prices tend to fall over time, empagliflozin might be an even better bargain than this study suggests. Third, medication adherence in real-world clinical settings is likely lower than in a trial and likely mitigates the drug’s cost-effectiveness.

Still, SGLT2 inhibitors are cheaper than other novel therapies considered standard of care. While not as cheap as statins (ICER: $3,700/QALY), empagliflozin is cheaper than metformin (ICER: $31,300/QALY) and sofosbuvir-containing treatments for hepatitis C (ICER: $47,304/QALY). SGLT2 inhibitors might also have a synergistic effect in combination with other therapies. Multidisciplinary care has been shown to be cost-effective in chronic kidney disease (ICER: $51,285/QALY without SGLT2 inhibitors), and SGLT2 inhibitors could make multidisciplinary care an even better bargain.

We remain cautiously optimistic that health insurance payers (and society more broadly) will universally recognize the value of SGLT2 inhibitors. However, kidney disease is unique in that Medicare ultimately bears the responsibility of paying for KRT. A previous study demonstrated that private health plans often do not pay for the full cost of KRT because patients shift to Medicare coverage early. Reifsnider et al suggest that SGLT2 inhibitors are less cost-effective at shorter timeframes. Consequently, health plans might decide that SGLT2 inhibitors are not worthwhile to cover. We hope they do not. This study adds to the preponderance of data

### Table 1. Summary of Sodium/Glucose Cotransporter 2 Inhibitor Trials in Patients With Diabetic Kidney Disease

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug and Dose</th>
<th>Patient Inclusion Criteria</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME11,12</td>
<td>Empagliflozin 10 mg or 25 mg</td>
<td>T2DM; high-risk for CV disease; eGFR ≥ 30 mL/min/1.73 m²</td>
<td>Relative risk reductions of: 14% for 3-point MACE 44% for Scr doubling 55% for KRT initiation</td>
</tr>
<tr>
<td>CANVAS13 (2017); N = 10,142</td>
<td>Canagliflozin 100 mg or 300 mg</td>
<td>T2DM; symptomatic CV disease; eGFR ≥ 30 mL/min/1.73 m²</td>
<td>Relative risk reductions of: 14% for 3-point MACE 40% for the composite kidney outcome (40% reduction in eGFR, KRT, or renal death)</td>
</tr>
<tr>
<td>CREDENCE14 (2019); N = 4,401</td>
<td>Canagliflozin 100 mg</td>
<td>T2DM; eGFR ≥ 30 mL/min/1.73 m²; albuminuria 300-5,000 mg/g; stable dose of ACEI or ARB for ≥4 wk</td>
<td>Relative risk reductions of: 30% for primary composite outcome (incident KRT, Scr doubling, renal or CV death) 31% for CV death or hospitalization for HF 34% for incident KRT, Scr doubling, or renal death</td>
</tr>
<tr>
<td>DAPA-CKD15 (2020); N = 4,304</td>
<td>Dapagliflozin 10 mg</td>
<td>With or without T2DM (68% with T2DM); eGFR 25-75 mL/min/1.73 m²; albuminuria 200-5,000 mg/g; stable dose of ACEI or ARB for ≥4 wk</td>
<td>Relative risk reductions of: 29% for CV disease mortality or hospitalization for HF 44% for ≥50% decline in eGFR, incident KRT, or renal mortality</td>
</tr>
</tbody>
</table>

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; KRT, kidney replacement therapy; MACE, major cardiovascular events (first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke); Scr, serum creatinine; T2DM, type 2 diabetes mellitus.
demonstrating that we need to remove all barriers to the uptake of SGLT2 inhibitors, especially the financial ones.

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