Sodium glucose cotransporter two inhibitors (SGLT2i) slow CKD progression, decrease mortality and heart failure (HF), and have shown evidence for the guided standard of care therapies in patients with or without diabetes (1). Although wide adoption of SGLT2i will provide clinical benefits for patients, whether these agents will ultimately decrease the health care costs of CKD and ESKD is far from clear. Patients with CKD and type 2 diabetes (T2DM) or HF account for 7% (US$21B) and 4% (US$11.2B) of Medicare fee-for-service expenditures, which far exceeds their representation in the Medicare population, of 5% and 2% respectively (2). Although the cost for treating ESKD has remained stable in inflation-adjusted terms since 2009, it still comprises a significant proportion of Medicare expenditure (about 7%, or US$36B annually) (2).

Let us consider the payer’s perspective: “is there robust evidence to justify paying for SGLT2i?” The answer to this requires the enumeration of four related questions:

Q1. Does the drug prolong survival?
Q2. Does the drug improve health related quality of life (HRQoL)?
Q3. Does the drug reduce need of renal replacement?
Q4. Does the drug reduce frequency/severity of costly events, such as hospitalization for HF (hHF)?

If these questions are answered affirmatively, then we can ask about the cost of achieving these goals. A comparison with the angiotensin receptor blocker (ARB) trials will allow us to frame the cost/coverage question using the same pharmacoeconomic arguments (3) that were applied to ARBs when they were still under patent, and thus not widely used. Published trial data about Q1, Q3, and Q4 from Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDiENCE) (4) and Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) (5) show these drugs outperform ARBs for all outcomes considered (Table 1). QoL data from the SGLT2i randomized controlled trials only recently have been reported, and it appears there is either a benefit (e.g., when used in HF [6]) and a beneficial (7) or neutral (8) effect when they are used as antihyperglycemics. Although HRQoL data from the DAPA-CKD trial are not yet available, the association of progressive CKD and HF events with declining HRQoL make it unlikely SGLT2i will be associated with a decrement in HRQoL.

To simplify the argument, we will assume there is a neutral effect of SGLT2i on HRQoL, and judge their value proposition on Q1, Q3, and Q4 alone. Although the other questions are pertinent, we will focus on Q3, which is uniquely relevant to our specialty. The answer to the same question about ARBs, which is the benchmark with which SGLT2i should be compared, was given shortly after Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) (3); in that analysis, losartan resulted in net cost savings of US$5298 over 4 years (or US$7523 after accounting for inflation).

How do SGLT2i compare with ARBs in terms of their ability to decrease costs associated with renal replacement and other complications of CKD? The relevant data come from a recently developed cost model on the basis of CREDiENCE (9). The six events considered were the composite outcome for ESKD (dialysis, transplantation, or a sustained eGFR of <15 ml/min per 1.73 m²), nonfatal myocardial infarction, nonfatal stroke, hHF, renal death, and cardiovascular death. Unit costs were derived from the United States Renal Data System (USRDS) (renal replacement, encompassing both dialysis and transplant) and for other events from commercial plans. The analysis assumed that SGLT2i will be used only in patients that would have been included in CREDiENCE: patients with T2DM, eGFR of ≥30 to <90 ml/min per 1.73 m², and urinary albumin-creatinine ratio ≥300 to <5000 mg/g. Under the assumption that event rates in the real world will be the same as those observed in the trial, the greatest cost avoided per member per year was US$2.92 for ESKD with a range of US$1.28–US$4.20. There were additional positive costs avoided per member per year for nonfatal myocardial infarction (US$0.54), nonfatal stroke (US$0.30), hHF (US$1.56), renal death (US$0.06), and cardiovascular death (US$0.51). The cost avoided per patient with diabetes per year for ESKD was approximately US$49. Restricting analysis to patients with T2DM and CKD would have resulted in a “per patient with CKD per year cost” of

1Pharmacy Department, University of New Mexico Hospitals, Albuquerque, New Mexico
2Department of Internal Medicine, Division of Nephrology, University of New Mexico School of Medicine, Albuquerque, New Mexico

Correspondence: Christos P. Argyropoulos, Chief Division of Nephrology, University of New Mexico School of Medicine, 1 University of New Mexico, MSC04-2785, Albuquerque, NM 87131. Email: cargyropoulos@salud.unm.edu

www.kidney360.org Vol 2 June, 2021 Copyright © 2021 by the American Society of Nephrology
Table 1. Hazard ratios in CKD: Sodium glucose cotransporter two inhibitors versus angiotensin receptor blocker

<table>
<thead>
<tr>
<th>COLUMN HEADING</th>
<th>Sodium Glucose Cotransporter Two Inhibitors, Hazard Ratio (95% Confidence Interval)</th>
<th>Angiotensin Receptor Blockers, Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canagliflozin (CREDENCE)</td>
<td>Dapagliflozin (DAPA-CKD)</td>
</tr>
<tr>
<td>All-cause mortality (Q1)</td>
<td>0.83 (0.68 to 1.02)</td>
<td>0.69 (0.53 to 0.88)</td>
</tr>
<tr>
<td>Composite kidney outcome (Q2)</td>
<td>0.66 (0.53 to 0.81)</td>
<td>0.56 (0.45 to 0.68)</td>
</tr>
<tr>
<td>ESKD (Q2)</td>
<td>0.68 (0.54 to 0.86)</td>
<td>0.64 (0.50 to 0.82)</td>
</tr>
<tr>
<td>Heart failure hospitalizations (Q4)</td>
<td>0.61 (0.47 to 0.80)</td>
<td>0.51 (0.34 to 0.76)</td>
</tr>
<tr>
<td></td>
<td>Losartan (RENAAL)</td>
<td>0.98 (0.73 to 1.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.92 (0.69 to 1.23)</td>
</tr>
<tr>
<td></td>
<td>Irbesartan (IDNT)</td>
<td>0.79 (0.66 to 0.95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.71 (0.59 to 0.86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.78 (0.58 to 0.89)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.77 (0.57 to 1.03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.74 (0.55 to 0.98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.72 (0.52 to 1.00)</td>
</tr>
</tbody>
</table>

Composite Kidney Outcome: doubling creatinine/ESKD/decrease in eGFR >40% (doubling of serum creatinine in the angiotensin receptor blocker trials). CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; IDNT, Irbesartan Diabetic Nephropathy Trial.
approximately US$986 for ESKD and approximately US$1900 for all outcomes combined. Absent in these impressive cost-avoidance calculations is the cost of SGLT2i per se, which is considerable for both the payor and the patient. As we show below, although the cost avoidance by SGLT2i is substantial, the cost reduction (cost avoidance – drug cost) may not be, because of the high price of these drugs in the United States. This is an example of American exceptionalism, because a microsimulation model on the basis of the data from CREDENCE showed these drugs may achieve net cost savings under the pharmaceutical and dialysis costs of the United Kingdom’s National Health Service (10).

We now consider the drug costs of SGLT2i from the lens of recent analysis (11) for Medicare Part D: out-of-pocket costs were more than US$1000/year, and costs to Part D ranged from US$3600/year (ertugliflozin, a drug that currently only has an antihyperglycemic indication) to approximately US$6000/year (all other SGLT2i, which in addition to the antihyperglycemic have variable cardiac/HF and CKD indications). The sobering reality is that, despite the high clinical value of SGLT2i, the price may not be right for many US insurance carriers; the break even point suggested by the cost analysis of US$1900 is smaller than the US$3600–US$6000 direct drug costs, leading to restricted formularies, onerous prior authorization processes, and frequent denials. Furthermore, out-of-pocket expenses may simply be too high, and the benefit too far in the future to be tangible for patients, who will frequently drop prescriptions. However, many clinicians can get these agents covered for their commercially insured patients, whereas some federal programs (e.g., the Department of Veteran Affairs and the Indian Health Services) include a SGLT2i in their formularies. We can get a perspective into these coverage decisions by considering the annualized net cost savings per patient on SGLT2i, which for any complication is given by:

\[
\text{Net savings} = \text{annual drug cost} - \text{cost of treatment}.
\]

The net saving is the difference between treating the complication (e.g., cost of renal replacement) minus the drug expenditure. Net cost can be negative, indicating an unfavorable value proposition for SGLT2i. To construct the graph, we assumed a hazard ratio of 0.66 (the average hazard ratio seen in CREDENCE and DAPA-CKD 95% CI, 0.56 to 0.79) and the USRDS RRT cost, which includes costs for both dialysis and transplant as previously reported. Negative net savings (the white area in the plot) represents increased expenditures under universal adoption of these drugs. In 2018, the SGLT2i ranolazine was used by the CREDENCE cost model (9), and annual drug costs set to US$3600/year, which is the Part D cost of an SGLT2i inhibitor with a cardiorenal indication (11). Horizontal grid lines mark the event rates of the placebo arm in CREDENCE (17.7 events per 1000 patient years) and RENAAAL (91 events per 1000 patient years), and vertical grid lines different scenarios of the cost of treating a complication over the annual drug cost: x1, x4, x8 multiples of the cost of RRT/current annual drug cost to Part D for an SGLT2i with a cardiorenal indication As can be seen from the figure, the current drug prices (left vertical line) intersects with the baseline rates in CREDENCE (or even RENAAAL) in an area of the figure associated with increased total costs. Thus, wide adoption of SGLT2i, as currently priced, will not result in net cost savings, despite their overwhelming clinical benefit. SGLT2i, sodium glucose cotransporter two inhibitors; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; RENAAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; USRDS, United States Renal Data System.

Figure 1. | Net savings (per patient, as a fraction of annual drug cost) associated with the use of SGLT2i as a function of baseline risk (event rate per 1000 person-years) and the cost of treating a complication (also as a ratio of the annual drug cost). The net saving is the difference between the current cost of treating complications (DMP cost) and the drug expenditure. Net cost can be negative, indicating an unfavorable value proposition for SGLT2i. To construct the graph, we assumed a hazard ratio of 0.66 (the average hazard ratio seen in CREDENCE and DAPA-CKD 95% CI, 0.56 to 0.79) and the USRDS RRT cost, which includes costs for both dialysis and transplant as previously reported. Negative net savings (the white area in the plot) represents increased expenditures under universal adoption of these drugs. In 2018, the SGLT2i ranolazine was used by the CREDENCE cost model (9), and annual drug costs set to US$3600/year, which is the Part D cost of an SGLT2i inhibitor with a cardiorenal indication (11). Horizontal grid lines mark the event rates of the placebo arm in CREDENCE (17.7 events per 1000 patient years) and RENAAAL (91 events per 1000 patient years), and vertical grid lines different scenarios of the cost of treating a complication over the annual drug cost: x1, x4, x8 multiples of the cost of RRT/current annual drug cost to Part D for an SGLT2i with a cardiorenal indication As can be seen from the figure, the current drug prices (left vertical line) intersects with the baseline rates in CREDENCE (or even RENAAAL) in an area of the figure associated with increased total costs. Thus, wide adoption of SGLT2i, as currently priced, will not result in net cost savings, despite their overwhelming clinical benefit. SGLT2i, sodium glucose cotransporter two inhibitors; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; RENAAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; USRDS, United States Renal Data System.
Commercial insurers pay, on average, higher rates than Medicare for services: four times the Medicare rate for dialysis (12) and nearly double the rate for hospital services, such as hospitalizations (13). However, they can negotiate prices with drug manufacturers while also receiving rebates from them, which effectively reduce annual drug costs. Nevertheless, a plan that does not cover many patients who are high risk to require dialysis, or one that could be reasonably assured that patients will switch to Medicare soon after dialysis, would have little financial incentive to cover SGLT2i. The equation may also balance some Medicaid programs and the Department of Veteran Affairs by restricting the use of SGLT2i to those at high risk for complications and through price negotiations. In Figure 1, we visualize these complex coverage scenarios, using the hazard ratios of SGLT2i for ESKD from Table 1, for annual drug costs that are multiples ($\times1, \times4, \times8$) of the USRDS RRT/Medicare Part D cost for a SGLT2i with a cardiorenal indication. The event rates in CREDENCE and RENAAL are shown as horizontal dashed lines, and indicate nephrology’s success in decreasing the risk of ESKD over the last 25 years. It is this success, in combination with cost control of dialysis expenses through bundling and the increasing costs of drug therapy, that make SGLT2i a tough proposition for Medicare in pure dollar terms. These system-level barriers to widespread adoption of SGLT2i become even higher if one considers out-of-pocket expenses. Recent research (14) shows that an increase in coinsurance of approximately US$10 per drug covered by Part D, results in large drops in total drug consumption and increases in mortality. The latter tracks the cutbacks in utilization of cardiovascular medications (*i.e.*, antihypertensives, statins, and noninsulin antihyperglycemics, including SGLT2i).

SGLT2i offer patients several advantages because they are once-daily oral drugs, with cardiorenal benefits, an acceptable 0.6%–1% hemoglobin A1c lowering effect (15), with low risk of hypoglycemia, although also lowering BP and inducing weight loss. There are four SGLT2i currently available on the US market, and coverage is highly variable and unpredictable. When prescribing these agents, it is important to become familiar with the patient’s formulary (*i.e.*, Medscape or Fingertip Formulary application) and which SGLT2i will be available to avoid unnecessary prior authorizations and denials. Communicating the benefits to the insurance carrier in the clinical documents may also help, and we do so via a “smartphrase” that may be found at https://bit.ly/3uNpYKA. For patients with commercial insurance, coupons and vouchers are available to cover the costs of the drug. Patient-assistance programs are also available from the drug manufacturers for those who meet the criteria. With the expansion of their FDA-labeled indications, it may be prudent to prescribe under the cardiac indications or renal indication if patients meet the criteria, because prescriptions are less likely to be “blocked” under these indications. As we enter an era of increasing experimentation with alternative payment models, strong consideration should be given to the development of programmatic innovations that would allow these agents to be covered, without necessarily inducing the type of price controls that would stifle innovation by the pharmaceutical sector.

**Disclosures**

C. Argyropoulos reports having consultancy agreements with Momenta Pharma; reports receiving research funding from Dialysis Clinic, Incorporated, University of Pennsylvania; reports being a scientific advisor or member of Baxter Healthcare, Health Services Advisory Group, and Bayer; and reports other interests/relationships as Medical Director—Outpatient Dialysis Unit of Dialysis Clinic, Incorporated in Cuba, New Mexico, site Principal Investigator in two phase 3 trials of an investigational product for the correction and maintenance of anemia in patients with nondialysis-dependent CKD and one phase 3 study of the same agent in dialysis at Akebia, site sub-investigator in a phase 3 study of an experimental agent in diabetic nephropathy at AbbVie, and site Principal Investigator for CKD Outcomes and Practice Patterns Study. All remaining authors have nothing to disclose.

**Funding**

None.

**Acknowledgments**

The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendations. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or Kidney360. Responsibility for the information and views expressed herein lies entirely with the author(s).

**Author Contributions**

C.P. Argyropoulos was responsible for visualization and developed the figure; S. Koppula and N.-Y.T. Pham wrote the original draft; and all authors contributed to the final version of this paper and approved it for publication.

**References**

1. Johansen ME, Argyropoulos C: The cardiovascular outcomes, heart failure and kidney disease trials tell that the time to use sodium glucose cotransporter 2 inhibitors is now. *Clin Cardiol* 43: 1176–1387, 2020 [https://doi.org/10.1002/clc.23508](https://doi.org/10.1002/clc.23508)


Received: February 19, 2021 Accepted: March 17, 2021