Payment Coverage and Health Economics of SGLT2 inhibitors

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Sodium Glucose Cotransporter Two Inhibitors (SGLT2i) slow Chronic Kidney Disease (CKD) progression, decrease mortality and heart failure (HF) on top of evidence guided standard of care therapies in patients with or without diabetes\textsuperscript{1}. While wide adoption of SGLT2i will provide clinical benefits for patients, whether these agents will ultimately decrease the healthcare costs of CKD and End Stage Kidney Disease (ESKD) is still far from clear. Patients with CKD and Type 2 diabetes (T2DM) or HF account for 7.1\% ($21B) and 3.8\% ($11.2B) of Medicare fee-for-service expenditures, figures which far exceed their representation in the Medicare population, 4.5\% and 1.6\% respectively\textsuperscript{2}. Though the cost for treating ESKD has stayed stable in inflation adjusted terms since 2009, it still comprises a significant proportion of Medicare expenditures (about 7\%, or $36B annually)\textsuperscript{2}.

Let us consider the the payor’s perspective: “is there robust evidence to justify paying for SGLT2i?” The answer to this question requires examination 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 e.g., hospitalization for HF (hHF)?

If these questions are answered affirmatively, then we can ask about the cost required to achieve these goals. A comparison against the Angiotensin Receptor Blocker (ARB) trials, will also allow us to frame the cost/coverage question using the same pharmaco-economic arguments\textsuperscript{3} that were applied to the ARBs when they were still under patent and thus not widely used. Published trial data about Q1,Q3,Q4 from CREDENCE\textsuperscript{4} and DAPA-CKD\textsuperscript{5}, show that these drugs outperform ARBs for all outcomes considered (Table 1). Quality of life data from the SGLT2i RCTs have only recently been reported, and it appears that there is either a benefit (e.g., when used in HF\textsuperscript{6}) and a beneficial\textsuperscript{7} or a neutral\textsuperscript{8} effect when they are used as antihyperglycemics. While HRQoL data from the DAPA-CKD trial is not yet available, the association of
progressive CKD and HF events with declining HRQoL make it unlikely that 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,Q4 alone. While 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 SGLT2i should be compared to, was given shortly after RENAAAL; in that analysis losartan resulted in net cost-savings of $5,298 over 4 years (or $7,523 after accounting for inflation).

How do the SGLT2i compare against the 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 based on CREDENCE. The six events considered were the composite outcome for ESKD (dialysis, transplantation, or a sustained eGFR of <15 ml/min/1.73 m²), non-fatal myocardial infarction (MI), non-fatal stroke, hHF, renal death, and CV death. Unit costs were derived from the 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 CREDENCE: patients with T2DM, eGFR of ≥ 30 to <90 ml/min/1.73 m² and urinary albumin-to-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 (PMPY) was $2.92 for ESKD with a range of $1.28-$4.20. There were additional positive costs avoided PMPY for non-fatal MI ($0.54), non-fatal stroke ($0.30), hHF ($1.56), renal death ($0.06), and CV death ($0.51). The cost avoided per patient with diabetes per year (PDPY) for ESKD was ~$49. Restricting analysis to patients with T2DM and CKD would have resulted in a “per patient with CKD per year cost” of ~$986 for ESKD and ~$1,900 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, while 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 US. This is yet another example of American exceptionalism, since a microsimulation model based on the data from CREDENCE showed that these drugs may achieve net cost-savings under the pharmaceutical and dialysis costs of the UK’s National Health System.

We now consider the drug costs of SGLT2i from the lens of a recent analysis for Medicare Part D: out of pocket costs were more than $1,000/year, and costs to Part D ranged from $3,600/year (ertugliflozin, a drug that as of this writing only has an antihyperglycemic indication) to ~$6,000 per 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 since the breakeven point suggested by the cost analysis of $1,900 is smaller than the $3,600 - $6,000 of direct drug costs, leading to restricted formularies, onerous prior authorization processes and frequent denials. Furthermore, out-of-pocket expense 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, while some federal programs (e.g., the Department of Veteran Affairs (VA) 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:

$$\text{Absolute Baseline Rate of Complication} \times (1 - HR) \times \text{Cost of Complication} - \text{Annual Drug Cost} = \text{Annual Drug Cost} \times \left( \text{Baseline Rate of Complication} \times (1 - HR) \times \frac{\text{Cost of Complication}}{\text{Annual Drug Cost}} - 1 \right)$$

Commercial insurers pay on average higher rates than Medicare for services: four times the Medicare rate for dialysis nearly double the rate for hospital services e.g., hospitalizations. However, they can negotiate prices with drug manufacturers while also receiving rebates from them (i.e., reduced annual drug costs). Nevertheless, a plan that does not cover many high-risk patients to incur the dialysis
expenditures, or one which 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 for some Medicaid programs and the VA 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 HR of SGLT2i for ESKD from Table 1, for annual drug costs that are multiple (x1, x4, x8) of the USRDS Renal Replacement Therapy/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 twenty-five 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 shows that an increase in co-insurance of ~$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 non-insulin antihyperglycemics, including SGLT2is).

SGLT2i offer patients several advantages as they are once-daily oral drugs, with cardiorenal benefits, an acceptable 0.6%-1% HbA1c lowering effect, with low risk of hypoglycemia while also lowering blood pressure and inducing weight loss. There are currently four SGLT2is 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 app) and which SGLT2is 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 here: 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, as 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.
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C Argyropoulos developed the figure. All authors contributed in the final version of this paper and approved it for publication.
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### Table 1. Hazard Ratios in CKD: SGLT2i vs ARB

|                        | SGLT2i                  | ARB                     |
|------------------------|-------------------------|-------------------------|
|                        | Canagliflozin (CREDENCE)| Dapagliflozin (DAPA – CKD) | Losartan (RENAAL) | Irbesartan (IDNT) |
| All-Cause Mortality (Q1)| 0.83 (0.68 – 1.02)      | 0.69 (0.53 – 0.88)      | 0.98 (0.73 – 1.19) | 0.92 (0.69 – 1.23) |
| Composite Kidney Outcome (Q2) | 0.66 (0.53-0.81)    | 0.56 (0.45 – 0.68)      | 0.79 (0.66 – 0.95) | 0.71 (0.59 – 0.86) |
| End Stage Kidney Disease (Q2) | 0.68 (0.54 – 0.86)      | 0.64 (0.50 – 0.82)      | 0.78 (0.58 – 0.89) | 0.77 (0.57 – 1.03) |
| Heart Failure Hospitalizations (Q4) | 0.61 (0.47-0.80) | 0.51 (0.34 – 0.76)      | 0.74 (0.55 – 0.98) | 0.72 (0.52 – 1.00) |

Composite Kidney Outcome: doubling creatinine/End Stage Kidney Disease/decrease in eGFR > 40% (doubling of serum creatinine in the Angiotensin Receptor Blocker Trials)
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 years) and the Cost of treating a complication (also as a ratio of the annual drug cost). The Net Savings 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 0.65 (the average hazard ratio seen in CREDENCE and DAPA-CKD) and the USRDS R(enal) R(eplacement) T(herapy) 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. USRDS RRT cost set to $104,932 used by the CREDENCE cost model, and annual drug costs set to $6,000 per year, which is the Part D cost of an SGLT2i inhibitor with a cardiorenal indication. Horizontal grid lines mark the event rates in CREDENCE (29.4 events /1000 patient years) and RENAAL (91 events/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 most vertical line) intersects with the baseline rates in CREDENCE (or even RENAAL) in an area of the figure associated with increased total costs. Thus wide adoption on SGLT2i, as currently priced will not result in net-cost savings despite their overwhelming clinical benefit.
