Are the protective effects of SGLT2 inhibitors a "class-effect" or are there differences between agents?

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The cardiorenal benefits of sodium glucose cotransporter 2 inhibitors (SGLT2i) are transforming the care of chronic kidney disease (CKD). An inherent challenge of practice-changing advances on this scale is how to best incorporate them into daily practice. In this vein, while there are four SGLT2i commercially available in the United States; the question remains whether these SGLT2i may be viewed as interchangeable or if specific agents offer unique benefits or harms in specific clinical settings. The more similarities between the agents within a pharmacologic class (e.g., chemical structure, pharmacodynamics, and pharmacokinetics), the greater the likelihood of shared class effects. Preclinical data, starting with largely comparable chemical structures provide a foundation where class effects might be anticipated. Nevertheless, on- and off-target effects may be expected to modify the response to any drug, an area of particular interest when considering the potential for drug, rather than class-specific effects (1). While translational, toxicological, and pharmacological investigations carried out in model systems may shed a light into class versus drug specific effects, the ultimate adjudicator of this question is data from sufficiently powered, rigorously controlled human randomized clinical trials (RCT). Before delving into the trial data, it may be helpful to briefly review the preclinical data regarding SGLT2i to explore the a-priori bioplausibility of class versus drug specific effects.

The origins of SGLT2i can be linked to two earlier tracks of research: Familial Renal Glucosuria (FRG) and phlorizin rodent studies(2). The presence of patients with a familiar tendency to produce elevated levels of glucose in the urine despite normal blood glucose had been identified for some time and as early as the 1920s work had begun to identify the pattern of inheritance (2,3). The precise molecular mechanism for this clinical finding would take considerably longer to come to light(4). One observation from these patients that is directly
applicable to the SGLT2i era is that individuals with FRG tend to have little in the way of adverse effects attributable to this defect (2), except the tendency of these patients to develop ketosis when stressed perioperatively. Phlorizin, a compound extracted from unripe apple, had been shown to induce glucosuria as early as the nineteenth century. Starting in the last 1980s, a series of studies involving rat models of diabetes employed Phlorizin to gain additional insights into the anti-glycemic effects of SGLT2 blockade (5). Further studies, found that in blocking glucose absorption in the proximal tubule this agent was able to mitigate hyperfiltration and that tubuloglomerular feedback was felt to be the likely mechanism of this action (6). Investigations marrying the evidence of FRG and the phlorizin rodent studies, demonstrated that in SGLT-2 knock-out mice given diabetes, showed attenuated hyperfiltration (7) providing the rationale for testing these agents in (diabetic) CKD.

Notwithstanding these encouraging observations, phlorizin which is a dual inhibitor of the SGLT1 and SGLT2, was never developed for human use because of two un-appealing properties. First, it has a limited oral bioavailability, necessitating the use of rather high doses to achieve a systemic exposure and a significant potential for gastrointestinal side effects as a result of the inhibition of the glucose absorption in the small bowel (8). To overcome the limited bioavailability, drug development shifted away from O-glycoside structures to C-glycoside ones because of the latter’s resistance hydrolysis by intestinal glucosidases. All SGLT2i interact with the SGLT2 cotransporter at the luminal side after filtration in the glomerulus. All SGLT2i are highly selective inhibitors of the cotransporter, with selectivity for SGLT2 over SGLT1 ranging from 1:414 for canagliflozin to 1:2,500 for empagliflozin. This variable selectivity is unlikely to be of physiological or clinical importance, as the SGLT2i are concentrated in the luminal side
due to proximal filtrate fluid reabsorption, thus saturating their target. Furthermore, they exhibit broad pharmacokinetic similarities: very fast absorption with time to peak within 2 hours, extremely high bioavailability (ranging from 65% in the case of canagliflozin to nearly 100% for ertugliflozin), high protein binding (>85%), large volume of distributions (e.g., 74L for empagliflozin to 119L for canagliflozin) and half lives between (12-17 hours). Elimination of metabolites is roughly equal between renal and gastrointestinal routes (except for dapagliflozin in which urinary excretion predominates); of all the four SGLT2i currently approved in the United States, only empagliflozin is recovered intact in the urine in a substantial amount (20% of administered dose v.s. <2% for all others. All SGLT2i variably activate the AMP-activated protein kinase, though the precise role this shared off-target effect plays on the cardiorenal benefit of these drugs is still not clear(9,10). While these differences in pharmacokinetic, selectivity and off-target effects are of scientific interest, they are unlikely to explain the variation in the RCT results noted by these agents as we detail below.

The first SGLT2i was approved by the FDA for the treatment of diabetes in 2013 and three others soon followed. The overall effectiveness of SGLT2i as antiglycemics are broadly similar. The average benefit in treatment naïve patients with diabetes was approximately a 1% (0.81-1.02%) reduction in hemoglobin A1C and when SGLT2i are added to metformin the A1C only improves an additional 0.6% (0.57-0.63%)(11). The approval of SGLT2i as antiglycemics was followed by a series of trials to document the cardiovascular safety of these agents. Such studies have been mandated by the FDA since 2008 because of the increased rate of cardiovascular adverse events seen in the Phase 2/3 studies of the antiglycemic proliferator-activated receptor agonist rosiglitazone and in the aftermath of the ACCORD trial, in which
intense glycemic control was associated with 22% higher risk of death. The first Cardiovascular safety Outcomes (CVOT) trials of empagliflozin (empagliflozin: EMPA-REG Outcomes, canagliflozin: CANVAS/CANVAS-R) established the superiority of SGLT2i over the standard of care against the composite outcome of composite of cardiovascular death, non-fatal myocardial infarction, or stroke. While dapagliflozin and ertugliflozin only achieved non-inferiority in their CVOT trials (DECLARE-TIMI-58 and VERTIS-CV), studies in Heart Failure with reduced ejection fraction (HFrEF, dapagliflozin’s DAPA-HF and empagliflozin’s EMPEROR-Reduced) and kidney disease (canagliflozin’s CREDENCE and dapagliflozin’s CKD) documented the broad efficacy of SGLT2i as cardiorenal protective agents.

So, is the cardiorenal benefit of SGLT2i a class or a drug effect? This is a reasonable question to ask, considering the numerically variable outcomes with SGLT2is noted in the large RCTs. A recent systematic meta-analysis(12) of the eight randomized controlled trials of the available SGLT2-inhibitors (SGLT2i) was undertaken to explore this question. The open data and software code of this meta-analysis are re-used here to illustrate that there is little heterogeneity in the cardio-renal benefits of SGLT2i.

SGLT2i reduce all-cause (Figure 1A) by 15% ($p < 0.0001$) and cardiovascular mortality (Figure 1B) by 16% ($p = 0.0006$) with little evidence for heterogeneity ($p$ values for the Q test 0.07, 0.10 respectively). When analyzing the composite kidney outcome (Figure 1C) of worsening kidney function (defined variably as doubling of serum creatinine or more than 40% drop in the eGFR), end stage kidney disease, or need for renal replacement therapy, SGLT2i reduced the outcomes by 39% ($p < 0.001$), with no evidence of heterogeneity by study drug. All trials reported consistent decreases in the number for hospitalization for heart failure (Figure 1D) with hazard
ratios in the narrow range 0.61-0.73. We also contrasted the composite outcomes of worsening kidney function, end stage kidney disease and mortality (Figure 1E) between the two CKD-SGLT2i trials and the two pivotal angiotensin receptor blockers (ARB) trials in diabetic kidney disease: IDNT (irbesartan) and RENAAL (losartan). The comparison depicted a meta-regression with SGLT2i showing a rate which is 85% of the ARB (95% CI 0.73,0.99), p = 0.04. Again, the beneficial effect of the SGLT2i were observed irrespective of the study drug. The reported common risks associated with SGLT2i such as DKA, volume depletion, genital mycotic infections, and urinary tract infections also appear to be similar between the individual drugs (12).

Based on the available clinical trial data thus far, and basic considerations from pharmacology and physiology it can be inferred that both the benefit and the side effects of the SGLT2i are part of their class features and not specific to individual drug members of the class. While one may be tempted to attribute the variable outcomes noted in some of the trials (e.g., VERTIS-CV) to drug effects, highly variable outcomes were observed for all SGLT2i that completed more than one trial. RCTs, as with any other experiment, are subject to noise, and one should simply resist the tendency to follow the noise in the data. In summary, SGLT2i as a class demonstrate cardiovascular and renal benefits in patients with diabetes mellitus type 2 at risk for cardiovascular disease, cardiovascular benefit in patients with diabetic or non-diabetic kidney disease, and heart failure benefit in patients with known HFrEF or CKD with or without diabetes. The physician prescription practice at the current time should be guided by the approved FDA indications which do differ among drugs (Table 1), insurance coverage and
patient affordability of the copay, because at the end of the day *any SGLT2i is better than no SGLT2i*. 

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**Author Contributions**

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N Singh: Conceptualization; Writing - original draft; Writing - review and editing

All authors contributed in the final version of this paper and approved it for publication.
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<th>Indication</th>
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<th>Dapagliflozin</th>
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<td>Cardiovascular Disease</td>
<td>Reduce the risk of Major Adverse Cardiovascular Events in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) MACE: cardiovascular death, nonfatal myocardial infarction and nonfatal stroke</td>
<td>Reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple risk factors</td>
<td>Reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.</td>
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<td>Renal Disease</td>
<td>Reduce the risk of end-stage kidney disease doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria &gt; 300 mg/day</td>
<td>Breakthrough Therapy Designation (BTD) in the US for patients with CKD with and without type-2 diabetes (indication pending)</td>
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Figure 1 Effects of SGLT2i on all cause death (A) and cardiovascular death (B), the composite kidney outcome (C) (defined variably as doubling of serum creatinine or more than 40% drop in the eGFR, end stage kidney disease, or need for renal replacement therapy), Hospitalizations for Heart Failure (HHF) and comparison between SGLT2i and Angiotensin Receptor Blockers (ARB, E). Random effects model synthesizes the effect across all studies. CVOT: Cardiovascular Outcome Trial, HFREF: Heart Failure with reduced Ejection Fraction, CKD: Chronic Kidney Disease, HR: Hazard Ratio Event rates (per 1000 patient years) are shown for both the SGLT2i and the placebo arms.