SGLT2 Inhibitors and Cardiorenal Outcomes

By Brendon L. Neuen, Edgar V. Lerma, and Joel Topf

Our top area to watch for 2019 is the advent of sodium glucose cotransporter 2 (SGLT2) inhibitors, oral anti-hyperglycemic agents that have been recently approved for the treatment of type 2 diabetes mellitus (T2DM).

Aside from their glucose-lowering effect, SGLT2 inhibitors have also been shown to reduce blood pressure, body weight, and albuminuria. These multiple beneficial metabolic effects have contributed, at least in part, to reductions in cardiovascular and renal outcomes observed in large cardiovascular outcome trials. As a result, the American Diabetes Association’s 2019 Standards of Medical Care in Diabetes (1) now recommends SGLT2 inhibitors as second-line therapy after metformin in patients with T2DM and atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease (CKD).

These agents promote glycosuria by selectively inhibiting SGLT2 transporters, which are expressed in the proximal tubule and are responsible for more than 90% of filtered glucose reabsorption. In addition to this, SGLT2 inhibitors also augment urinary sodium excretion, which contributes to plasma volume contraction and alterations in intrarenal hemodynamics (discussed below).

SGLT2 inhibitors currently approved by the US Food and Drug Administration include empagliflozin (Jardiance), canagliflozin (Invokana), dapagliflozin (Farxiga), and eragliflozin (Steglatro). Combination formulations are also available: empagliflozin/metformin (Symjula), canagliflozin/metformin (Inveglin), dapagliflozin/metformin (Xigduo XR), and eragliflozin/metformin (Segluromet).

Several large randomized controlled trials have recently been published, demonstrating the cardiovascular and renal benefits of these new agents.

The first of these was the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Event Outcome Trial in Type 2 Diabetes Mellitus Patients) (2), reported in 2015 (Figure 1). EMPA-REG OUTCOME was a randomized double-blind placebo-controlled trial that included 7020 participants with T2DM and established cardiovascular disease. This trial demonstrated that empagliflozin reduced the risk of major adverse cardiovascular events in addition to standard of care, driven by a 38% relative risk reduction in cardiovascular death. Empagliflozin also reduced the risk of heart failure by 35% and the composite renal outcome of doubling of serum creatinine, ESKD, or renal death by 46%.

The CANVAS (Canagliflozin Cardiovascular Assessment Study) Program (4) integrated data from two parallel randomized trials involving 10,142 participants with T2DM and high cardiovascular risk (Figure 2). The CANVAS program demonstrated that canagliflozin also reduced the risk of major adverse cardiovascular events, heart failure, and adverse renal outcomes but increased the risk of amputations, mainly at the toe/metatarsal level.

In November 2018, The DECLARE-TIMI 58 trial was published. This trial enrolled 17,160 participants with T2DM, two-thirds of whom did not have prior cardiovascular disease (i.e., a majority primary prevention cohort). While dapagliflozin did not reduce the risk of major adverse cardiovascular events, it did reduce the risk of hospitalization for heart failure and the renal composite outcome (40% decrease in eGFR, ESKD, or renal death), without any major safety concerns.

A characteristic feature of SGLT2 inhibitors is that their glycemic efficacy is dependent on glomerular filtration, and thus their effect on Hba1c diminishes with declining kidney function. In contrast, effects on blood pressure and albuminuria appear to be preserved in people with reduced kidney function, and secondary analyses of the EMPA-REG OUTCOME trial (4) and the CANVAS Program (5) suggest that the cardiovascular and renal benefits are similar regardless of baseline kidney function down to eGFR 30 mL/min per 1.73 m² (Figure 3).

A frequently cited explanation for the renoprotective effect of SGLT2 inhibitors is that they reduce intraglomerular pressure, which is critical in the pathogenesis of diabetic kidney disease. These agents increase distal sodium delivery to the macula densa, which activates tubuloglomerular feedback to promote afferent arteriolar vasoconstriction, and thus reduce intraglomerular pressure. This is reflected in an acute ‘dip’ in eGFR, similar to that seen with inhibition of the renin-angiotensin-aldosterone system (RAAS). Importantly, approximately 80% of participants in these SGLT2 inhibitor trials were also receiving RAAS inhibition, which suggests that the renoprotective effects of these two classes of medications are additive, without any additional risk of acute kidney injury. However, participants with eGFR <30 mL/min per 1.73 m² were excluded from these trials, so the effects in this population are still unknown.

In July 2018, the CREDENCE (Canagliflozin and Renal Endpoint in Diabetes with Established nephropathy Clinical Evaluation) trial was prematurely terminated because prespecified efficacy criteria had been achieved at a scheduled interim analysis (6). CREDENCE is a randomized double-blind placebo-controlled trial, which enrolled 4401 participants with stage 2 or 3 CKD and macroalbuminuria. Approximately 60% of these participants had an eGFR <60 mL/min per 1.73 m² at enrollment, and all were required to be on a maximally tolerated dose of ACE inhibitor or ARB for at least 4 weeks prior to rand-
Health systems—new mergers and existing ones—are also regional hubs: A growing trend

The year 2019 promises to be a busy one in healthcare. In the face of a great deal of volatility, Kidney News readers can expect the following.

**Mergers and acquisitions: Expect more, and sooner rather than later**

A recent Capital One survey found that three-quarters of 291 senior executives across the healthcare spectrum are planning for better business performance in 2019. To exceed 2018 performance levels, 44% support more mergers and acquisitions (M&A), and 25% also expect to revamp or update existing merger offerings already on the table. In the latest figures from 2018, the third quarter saw 261 healthcare M&A deals according to PricewaterhouseCoopers (PwC). Value-based care policies and rising healthcare costs are seen as the main drivers in these deals, and 43% of the study’s respondents said their greatest challenge for 2019 is regulatory and reimbursement changes.

These mergers are becoming increasingly vertical, in which the merging parties are not current competitors and are actually operating at different levels of the healthcare distribution chain. Examples include deals like UnitedHealth Group’s acquisition of DaVita Medical Group; CVS and Aetna; Cigna and Express Scripts; and Humana and two private equity companies buying post-acute care provider Kindred Healthcare.

**Regional hubs: A growing trend**

Health systems—new mergers and existing ones—are also building regional care hubs within and across state lines. The objective is achieving a scale that can help them negotiate better rates with suppliers and payers and expanding patient access through outpatient facilities and telemedicine. Nephrology is already at the forefront of payment reforms to encourage telemedicine and support Medicare’s stated goal of significantly increasing home dialysis cases. Aligning systems with regional population data can also reveal the most profitable service lines. Analysts have pointed to that approach in the Advocate Health Care and Aurora Health Care merger paving the way for a 27-hospital system spanning Illinois to Wisconsin with $10.7 billion in combined revenue.

**Prescription drug prices: The fight is heating up**

The midterm elections made it clear that a leading issue for 2019 is prescription drug pricing. Analysts have pointed to that approach in the Advocate Health Care and Aurora Health Care merger paving the way for a 27-hospital system spanning Illinois to Wisconsin with $10.7 billion in combined revenue.

**Repeal of the Affordable Care Act: Enter the courts**

On December 14, 2018, a federal district court judge in Texas struck down the Affordable Care Act, siding with a group of 18 Republican state attorneys general and two GOP governors who brought the case. The ruling said the tax bill passed by Congress in late 2017 effectively rendered the entire health law unconstitutional. That tax bill eliminated the penalty for not having insurance.

Simultaneously, another federal district judge in Washington, DC, is presiding over a lawsuit brought by 12 Democratic state attorneys general to block a 2018 final rule issued by the Department of Labor making it easier for small firms and individuals to band together in association health plans by the Department of Labor making it easier for small firms and individuals to band together in association health plans.

**Canagliflozin consistently prevents CV and renal outcomes across different levels of kidney function**

Visual abstract by Brendon Neuen

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**Policy Update**

**2019: A Lot is Happening Fast**

By David White

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