

CLINICAL PRACTICE UPDATE IN  
**ENDOCRINOLOGY & DIABETES****LMC**

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## SGLT2 Inhibitors in my Patients – Am I treating their Heart, their Kidneys, or their Diabetes?

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### In Heart Failure – Diabetes' Most Common CV event

In 2008, the FDA set out new requirements that required all new treatments for diabetes to prove that they were safe from a cardiovascular (CV) point of view in high risk patients with type 2 diabetes. At the time, concerns had been raised regarding the possibility of increased myocardial infarctions and CV deaths with Rosiglitazone in a 2007 NEJM meta-analysis. All new diabetes medications were mandated to undergo a rigorous outcome trial program in the Cardiology model where a composite of major adverse cardiovascular events (MACE) outcomes were tracked in order to rule out anything more than a 30% increase in CV ischemic events. Since then, MACE has been made up of non-fatal MI + non-fatal stroke along with deaths from those events +/- hospitalizations for acute coronary syndrome.

In the "first wave" of these CV outcome trials (CVOTs), 12 trials of new diabetes therapies have been published since 2013: 4 with DPP4 inhibitors (all neutral), 5 with GLP1 receptor agonists (2 neutral and 3 superior), and 3 with SGLT2 inhibitors (2 superior for MACE, and 1 neutral). In fact, in the recently released 2018 Diabetes Canada Clinical Practice Guidelines, the results of the 3 superior trials (CANVAS for Canagliflozin, EMPA-Reg for Empagliflozin and LEADER for Liraglutide) have been incorporated in our new recommendations to consider use of these 3 AHAs in patients with clinical CV disease (and GFR > 30) who need additional therapy to achieve A1c target. Two more trials are nearing completion (1 GLP1 RA, 1 SGLT2i), and we can expect the next wave of SGLT2 inhibitor trials will also include heart failure and renal outcomes.

All these trials have provided CV safety reassurance. All - including those with TZDs - have met the FDA criteria for non-inferiority against placebo but many questions remain unanswered. Foremost is the generalizability of the findings to patients with lesser degrees of CV risk (which we commonly refer to as "primary prevention" patients), as well as other important outcomes, including hospitalization for heart failure (HHF), and progression of chronic kidney disease (CKD). DECLARE, the most recent SGLT2i outcome trial to publish, demonstrated significant reductions in the dual primary endpoint of HHF/CV death in the dapagliflozin group compared to placebo. In fact, despite the historical focus on MACE events, heart failure is actually the most common cause for CV hospitalizations (Fig 1) in patients with diabetes. Many HF admissions occur without a prior MI or ischemic event and may result from global diastolic dysfunction (often with preserved systolic ejection fraction). Furthermore, there is a high rate of unrecognized subclinical heart failure contributing to fatigue and poor exercise tolerance in patients with type 2 diabetes.

Secondary outcomes (such as heart failure endpoints) in the CANVAS and EMPA-Reg outcome trials are suggestive of significant benefits but are considered only “exploratory” and “hypothesis generating”. Since these endpoints analyses raise the risk of a false positive finding in the sense that multiple additional analyses ‘after the fact’ might eventually find an imbalance between groups which may have been there only by chance. The same concern of trusting the validity of certain unintended findings applies to other analyses with very small numbers, including recently reported safety outcomes like fractures or amputations. There is a growing confidence, though, that the heart failure benefits are actually real as real world evidence of large international databases (including CVD REAL, OBSERVE-4D) consistently points in the same direction.

Let’s return to our other knowledge gap – the primary prevention (or low risk) patient. In CANVAS, 35% of patients had CV risk factors but had not had a prior CV event. Although this group was underpowered to show overall MACE benefits, recent analyses have found that canagliflozin provided similar risk reductions for heart failure hospitalizations (and renal events) in both groups – primary and secondary prevention patients. This finding then represents the first prospective trial evidence of CV benefit in patients without established clinical CVD. Primary heart failure outcome trials are underway but while we await those results, Diabetes Canada has recommended considering canagliflozin and empagliflozin for reducing HF events in patients with type 2 diabetes at high CV risk (if A1c not at target and GFR > 30).

**“Canagliflozin provided similar risk reductions for heart failure hospitalizations (and renal events) in both groups – primary and secondary prevention patients.”**

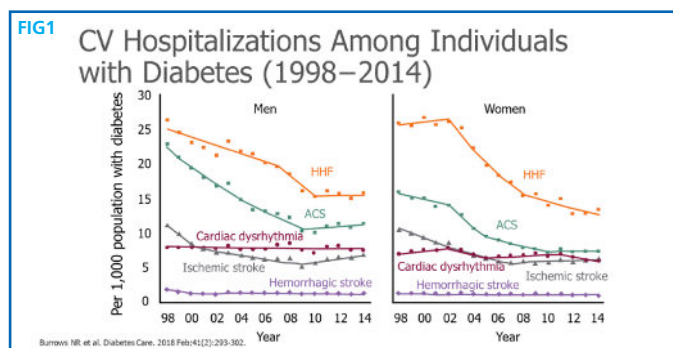
The importance of these outcome trials should not be underemphasized as there is now ample evidence to justify the increased use of SGLT2 inhibitors (as well as GLP1 receptor agonists) as the preferred next treatment after metformin. For the primary prevention patient, the SGLT2i’s and GLP1-RA’s overall appear to have key advantages over DPP4i’s and sulfonylureas (SU’s) – previously established greater A1c lowering, weight benefit and relative hypoglycemia safety, and now the likely benefit in reducing HF events – the most common CV event in these patients (Fig 1).

## In Diabetic Kidney Disease – Still the #1 Cause of ESRD

Diabetic kidney disease (DKD) (Fig2) remains the number one cause of kidney failure requiring renal replacement therapy in Canada. Among adults who come to require dialysis or a renal transplant, >50% have their end stage renal disease (ESRD) attributable to diabetes.

**“three-pillared approach to reduce the rate of progression of DKD – namely i) hypertension control ii) glycemic control and iii) the use of renin angiotensin aldosterone system inhibitors (RASi).”**

Diabetes Canada defines DKD as either elevated urine albumin (ACR > 2.0mg/mmol) or an eGFR < 60 ml/min/1.73m<sup>2</sup>. Approximately 40 - 50% of people living with diabetes will develop DKD. Since 1998, Diabetes Canada has advocated a three-pillared approach to reduce the rate of progression of DKD – namely i) hypertension control ii) glycemic control and iii) the use of renin angiotensin aldosterone system inhibitors (RASi). The current “gold standard agents” for DKD are the renin angiotensin system inhibitors (RASi) - ACE inhibitors and ARBs - each recommended for DKD (but not their combination). The pivotal RASi trials had found that these agents did reduce the progression of doubling the serum creatinine, ESRD or renal death - but only by ~20%. Therefore, a significant degree of residual renal risk still exists even with current best practice therapy. Since 2001, many trials have explored novel treatment mechanisms: dual RAS inhibitors, direct renin inhibitors, antioxidant inflammation modulators, endothelin receptor antagonists - but nothing has emerged to add additional clinical benefits for people living with DKD. More recently, the positive renal (secondary) outcomes in the two CV trials, EMPA-REG and CANVAS, have generated enthusiasm that SGLT2 inhibitors may be a fourth pillar of nephroprotection.



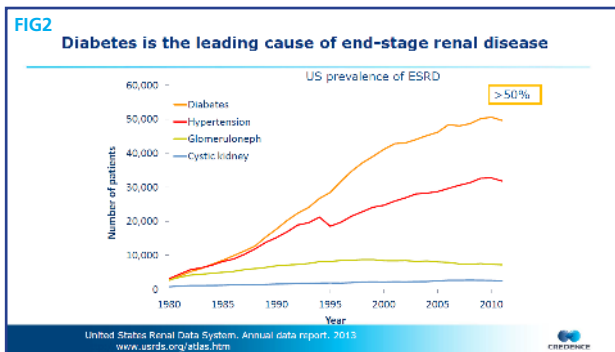
Burns NB et al. Diabetes Care. 2018 Feb;41(2):293-302.

SGLT2 inhibitors appear to exert renal protection in a number of ways. These medications lead to the renal excretion of 70 - 120gm of glucose per day, depending on the serum glucose level and on the GFR. As GFR declines, glycosuria declines so that there is a corresponding reduction in the magnitude of blood glucose lowering. For example, if the GFR is 50% of normal, one typically sees ~50% of the expected reduction in A1c from an SGLT2i treatment. This reduced glycemic benefit in patients with CKD 3b (eGFR < 45) and below led to the initial indications for this class to be limited to patients with eGFR >45). However, experimental data and clinical trial data have shown that the no-glucose benefits - hypertension, weight loss, renal protection and vascular protection - are dissociated from their glucose lowering effect and actually seem to persist down to an GFR of 30. These findings have now led Diabetes Canada to recommend SGLT2 inhibitors as second line agents after metformin for those patients not at target A1c with any of: established CVD, risk of hypoglycemia or weight gain, as well as for nephroprotection – even down to an eGFR of 30.

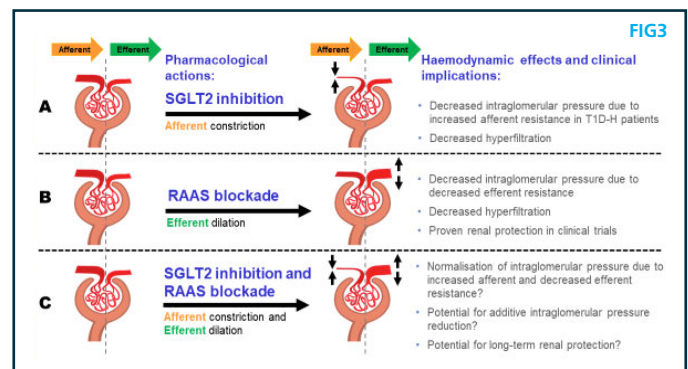
resulting tubuloglomerular feedback reduces glomerular hypertension by tightening the afferent arteriolar tone, thus reducing glomerular pressure and hyperfiltration (Fig 3). This effect on afferent arteriolar tone is somewhat parallel to that of RAS inhibitors, which have a relaxing effect on the smooth muscle of the efferent arteriole. Both approaches have the effect of reducing glomerular hypertension.

Experimental studies have demonstrated reduced hyperfiltration and decreased inflammatory and fibrotic activity in the kidney with SGLT2i. Clinical studies, have also shown a stabilization of GFR with SGLT2i not been seen with comparator agents. These same studies have consistently demonstrated reductions in albuminuria of 30 to 50% similar to that seen with RAS inhibitors.

Neither the EMPA-REG Trial nor the CANVAS Program were dedicated DKD trials. Nonetheless, a fairly large number of patients in either trial had either albuminuria (approximately 30% in both trials) or an eGFR < 60 (~20% in CANVAS and 26% in EMPA-REG). In CANVAS, patients randomized to canagliflozin achieved a 36% reduction in albuminuria amongst those with “macro-albuminuria” at baseline. In EMPA-REG, nephropathy was reduced 39% with empagliflozin. The composite renal outcomes (40% drop in eGFR, renal replacement therapy or renal death) and (doubling serum creatinine, renal replacement therapy or renal death) were reduced in CANVAS by 40% and 47% respectively. In a retrospective analysis of EMPA-REG, a similar composite outcome was reduced by 46% in the empagliflozin group. In both studies, the vast majority of patients (80-85%) were receiving baseline therapy with ACE or ARB. Although the magnitude of the renal benefit in CANVAS and EMPA-REG appear to be larger than those seen in ARB trials, these are secondary outcomes and they are simply starting points for further study.



How do SGLT2 inhibitors benefit renal disease? At first glance, it may appear that excess renal glucose from hyperglycemia might appear similar to the glucosuria generated by SGLT2 inhibitors. They're actually quite different. In simple hyperglycemia, glucose flooding the proximal tubule is associated with glomerular hyperfiltration and leads to intraglomerular hypertension (IGH) and albuminuria. In contrast, patients with the genetic disease familial renal glycosuria (FRG) lack SGLT transport proteins and have lifelong glucose excretion but do not develop albuminuria or CKD. There further appears to be nephroprotection associated with SGLT2 inhibitors through renal effects other than glycosuria and BP reduction. The two most plausible renal mechanisms by which SGLT2i exert nephroprotection are through (a) tubuloglomerular feedback and (b) inhibition of sodium hydrogen exchange (NHE3). SGLT2 inhibitors increase distal nephron sodium delivery (along with glucose). The





# CVOT Perspectives

## ...from an Endocrinologist

Following publication of the new 2018 Diabetes Canada guidelines, we find ourselves in a unique situation whereby the newest treatment classes have the best evidence for efficacy, safety and outcome benefits, yet are significantly underutilized compared with older medications. There are multiple contributing factors including cost/coverage issues and resistance to change (“inertia”). It will be interesting to see how quickly physicians, patients and payors embrace the new paradigm shift recommended in the 2018 Diabetes Canada Clinical Practice Guidelines, especially as new evidence comes to light.

## ...from a Nephrologist

From a safety point of view, it was very encouraging that there was no increase in renal adverse events, or acute kidney injury, with these agents in either CANVAS or EMPA-REG. However, only ~26% of patients had a GFR < 60 ml/min/1.73m<sup>2</sup> in these trials and it remains prudent to be cautious of using these agents in patients with eGFR < 45 ml/min/1.73m<sup>2</sup>. This caution should be most applied to certain at risk groups of patients (frail, elderly, low BP, large dose diuretics, etc.) until dedicated renal trials have further demonstrated renal safety. Thankfully, several dedicated trials of SGLT2i in DKD are underway including CREDENCE (canagliflozin), DAPA-CKD (dapagliflozin), EMPA-KIDNEY (empagliflozin) and SCORED (sotagliflozin). These long term trials of SGLT2i in patients with more advanced diabetic kidney disease will include primary outcomes of hard renal endpoints and will better address whether these agents are nephroprotective. Until these trials are completed, however, there at least exists encouraging early data of a 4th pillar of nephroprotection in DKD and this approach has already been adopted by Diabetes Canada with the following recommendation: In adults with type 2 diabetes with clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with an eGFR >30 mL/min/1.73 m<sup>2</sup>, an SGLT2 inhibitor with proven renal benefit may be considered to reduce the risk of progression of nephropathy for empagliflozin and canagliflozin.

