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CLINICAL PRACTICE UPDATE IN
ENDOCRINOLOGY & DIABETES

Beyond 'JUST GLUCOSE' in choosing a Diabetes therapy—with CREDENCE, its now prevention of Renal Disease

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Over my past three decades in diabetes care, we appear to have come to an unprecedented expansion of therapy options for type 2 diabetes (T2D). We have more options for our patients of both oral and injectable therapies than ever before.

In parallel, there's been a remarkable expansion in the added value that each of these therapies brings, beyond simply controlling a glucose level. We've been glucose-focused for decades, hoping that more effective glucose lowering would bring long-term health to our patients. Our new line-up of therapies are now proven to offer particular value in preventing microvascular disease, vascular disease (MACE - MI, Stroke and vascular death), heart failure events, and now, the progression of renal disease.

Chronic Kidney Disease (CKD) affects at least 40% of people living with T2D - more prevalent than cardiovascular disease (CVD). And it has considerable impact – among Americans with T2D, developing albuminuria quadrupled their 10-year mortality from 4.1% to 17.8%. It doubled again if it was associated with an impaired GFR. And conversely, diabetes remains the leading cause of end-stage kidney disease (ESKD) in Canada. In any dialysis unit, 50% are also affected with diabetes.

For two decades, controlling A1C and blood pressure (BP), and using a RAAS therapy (ACEi or ARB) has successfully cut CVD in half but ESKD incidence has not changed, and is actually increasing among our elderly patients.

Several therapies have proven effective in slowing renal disease progression: irbesartan (IDNT), losartan (RENAAL) and perindopril (ADVANCED, with indapamide) with renal outcomes reduced by 16 to 21%. In the two decades since, we haven't seen any new effective treatments. Many new molecules have undergone clinical trials (avosentan, aliskiren, bardoloxone and others), but failed either due to inadequate efficacy or unfortunate adverse events.

SGLT2 inhibition has, for years, held promise of effective renal benefit based on its known favourable impact on reducing glomerular pressure, plasma volume, and arterial stiffness. Indirectly, better glucose control, less inflammation, and down regulation of angiotensinogen may further contribute.

CREDENCE

Canagliflozin became the first to primarily explore its renal efficacy with the 2014 design of the CREDENCE. Phase 3 studies had already shown SGLT2i efficacy and safety in individuals with T2D and moderate renal impairment (GFR ranges 30 – 50/60 ml/min/1.73 m²). And in meta-analyses of the well-known outcome trials (EMPA-REG, CANVAS, DECLARE), this class showed a 33% reduction of renal composite outcomes, in participants with GFR < 60. In fact, each of the SGLT2i's have a renal outcome trial underway (DAPA-CKD with 4000 participants; EMPA-KIDNEY with 5000 patients and due to report in 2022).

CREDENCE explored a composite renal endpoint of ESKD, doubling of serum creatinine, or renal/CV death. Planned secondary outcomes included heart failure, MACE outcomes (CV death, MI, Stroke) and their usual components. CREDENCE included adults with T2D, 30 years of age and older, with a broad range of A1C of 6.5 to 12%, and impaired renal function: eGFR as low as 30 ml/min/1.73m² and uACR > 33.9 mg/mmol. All patients used a RAAS therapy for at least four weeks prior to enrolment. The study excluded those with other causes of kidney disease, hyperkalemia, or recent CV event.

CREDENCE was stopped early in July 2018, after a planned interim analysis found a significant difference in renal outcomes favouring canagliflozin

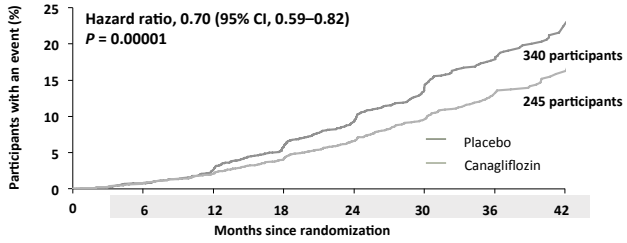
Participants were randomized to receive either canagliflozin 100 mg daily or placebo, and monitored regularly. Therapy continued until either dialysis or renal transplant occurred, even if GFR dropped < 30. CREDENCE was stopped early in July 2018, after a planned interim analysis found a significant difference in renal outcomes favouring canagliflozin

In all, 4401 people participated: 66.1% male, mean of 63 years of age, BMI of 31, A1C of 8.3%, and a 15.8 year duration of diabetes. The mean eGFR was 56.2, and median uACR of 105 mg/mmol. CKD stage distribution was somewhat evenly distributed: Stage 2 with 35%, Stage 3A with 29%, and Stage 3B with 27%.

As expected, A1C improved in the canagliflozin arm with an initial drop of nearly 0.5%. Over the entire study, the difference between treatment and placebo group averaged 0.25%. Patients in the placebo group were treated with other glucose lowering therapies and a difference in A1C was not intended. Systolic BP improved by 3.3 mmHg and weight dropped by 0.8kg in the canagliflozin group.

PRIMARY ENDPOINT

Composite of ESKD, doubling of serum creatinine, and renal or CV death

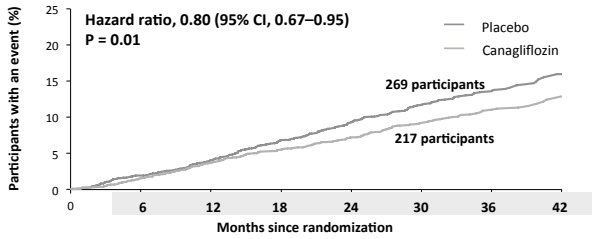


No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

Perkovic et al., *N Engl J Med* 2019, DOI: 10.1056/NEJMoa1811744. 1

SECONDARY ENDPOINT

MACE (CV DEATH, MI, or stroke)

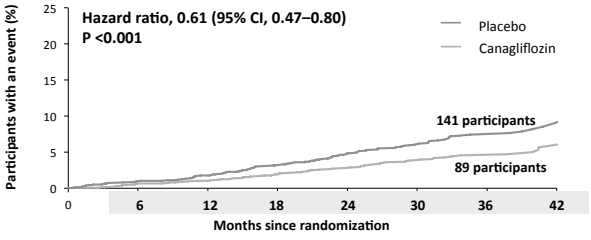


No. at risk								
Placebo	2199	2152	2100	2022	1717	1143	635	168
Canagliflozin	2202	2163	2106	2047	1756	1196	642	198

Mahaffey KW. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-361. 2

SECONDARY ENDPOINT

Hospitalization for heart failure



No. at risk								
Placebo	2199	2165	2122	2043	1735	1147	638	170
Canagliflozin	2202	2171	2131	2076	1789	1226	668	199

Mahaffey KW. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-361. 3

The primary outcome (composite of ESKD, doubling of creatinine, and renal/CV death) occurred in 340 participants in a placebo group and 245 participants in the treatment group, a relative risk reduction of 30%. ESKD alone, defined as dialysis or GFR < 15 for >30 days or transplantation, was also significantly reduced, by 32%.

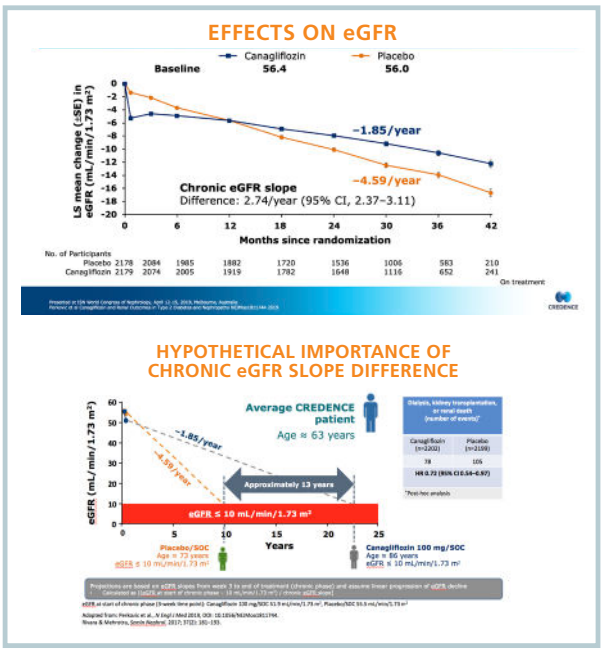
Planned subgroup analyses showed a consistent effect across all degrees of kidney function and in patients with more or less than 1gm/day proteinuria. Similarly, there were no consistent effects of gender, age > 65, BMI > 30, A1C > 8.0%,

and BP elevation.

GFR declined initially in the canagliflozin group but by one year, the faster pace of GFR decline of the placebo group had overtaken the canagliflozin GFR decline pace. Projections to a GFR < 10 would, on average, take only 10 years in the placebo group vs. 23 years in the canagliflozin group - a difference of approximately 13 years.

CREDENCE found that for those with both T2D and renal disease, a clinically meaningful composite outcome was delayed by 30% and was consistent across a broad range of pre-specified subgroups. Canagliflozin also reduced the risk of ESKD by 32% and doubling of serum creatinine by 40%.

Interestingly, the secondary endpoint of MACE also showed a significant 20% risk reduction in favour of canagliflozin for this renal disease T2D population. Hospitalization for heart failure also showed a 39% risk reduction.



A Paradigm Shift: Patients with T2D & CKD

When SGLT2i were introduced, our initial prescribing concerns were centred on potential adverse events, and especially acute kidney injury events. In CREDENCE, among participants with advanced renal disease, 'all adverse events (AE)' and 'serious AE' were both lower in the canagliflozin arm. Specifically, hyperkalemia was 20% lower, acute kidney injury 15% lower, and all renal-related AE's reduced by 29%.

Other specific AE's of interest include genital mycotic infections were extremely rare (< 1%) but were higher in canagliflozin-treated women and men. There were minor trends to increased UTI's and volume depletion AEs that were not significant and there were 11 cases of ketoacidosis in the canagliflozin (vs. one in the placebo group). Reassuringly, fracture and lower extremity amputations were not different between the two groups. The CANVAS program had reported a doubling in a rare event of lower extremity amputation. In this presumably higher risk group of participants, no difference was found.

It's worth noting that the benefits seen with canagliflozin in CREDENCE were in addition to the known benefits of the adjunct RAAS therapy effects, which were present in 99.9% of participants.

The number needed to treat (NNT) for renal and CV outcomes, over 2.5 years of therapy, was 22 for the primary composite, 28 for renal outcomes alone and 40 for MACE outcomes; and 46 for heart failure. In the GFR 30 - 45 group, NNT was even lower at 16.

Subsequent post hoc analyses of CREDENCE data have produced a number of further interesting findings. Although GFR cut-off for entry had been 30 ml/min/1.73m², the length of the randomization process produced some participants with GFR < 30 by the time they entered the study. These 174 participants were analyzed separately and showed similar outcomes to the overall group: 33% reduction in proteinuria and a 43% reduction in the rate of GFR decline. Their AE profiles were similar as well.

Our current DM clinical practice guidelines already endorse SGLT2i therapy in established CV disease, directing caregivers to an SGLT2i with proven renal benefit (canagliflozin and empagliflozin). With the CREDENCE findings, we predict that the guidance will be expanded to all patients with advanced renal disease, regardless of their CV disease risk status – for both renal and CV event risk reductions. The ADA guidelines have already been updated to suggest that in patients with diabetes and kidney disease, "…consider use of an SGLT2i in patients with an GFR > 30, particularly in those with > 20mg albuminuria, to reduce the risk of CKD progression, cardiovascular events or both." Health Canada has also followed suit by approving a new indication for Invokana® to to reduce the risk of ESKD, doubling of serum creatinine and CV death in adults with T2D and diabetic nephropathy with albuminuria.

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Making sense of the Renal Diet

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The Renal Diet is one of the most complex nutrition regimens, and is almost always prioritized over other therapeutic diets. This poses a challenge to both patients and practitioners because the conventional renal diet contradicts some of the recommendation for diabetes. We know that about 40% of people living with diabetes also have kidney disease.

. . .emerging research tells us that a holistic dietary approach promotes better outcomes versus demonizing specific foods

Current Preconceptions

The primary goal of the renal diet is to prevent, or at least slow, the progression of chronic kidney disease (CKD) to end-stage kidney disease by limiting dietary sodium, potassium, and phosphorus. The go-to dietary recommendation given by most physicians is to omit bananas, oranges, and tomatoes, but emerging research tells us that a holistic dietary approach promotes better outcomes versus demonizing specific foods.

A Modern Approach

Newer evidence recommends patients with renal disease to cut out processed meats, cheeses, and refined grains, and adhere to a vegetarian diet rich in vegetables, fruits, low-fat dairy, and tofu, which is associated with a decreased risk in CKD progression. And this includes liberalizing the intake of potassium-rich foods, as the link between dietary potassium and serum potassium concentrations is not evidence-based.

Despite more research supporting a vegetarian diet for both patients with renal disease and patients with diabetes, many physicians prescribe the ever-so-popular ketogenic diet because it promotes rapid weight loss and A1c reduction. The results of keto are enticing, but strict adherence puts SGLT2i-prescribed patients at risk of euglycemic-DKA. An alternative and safer dietary intervention is therefore essential. Fad diets, like keto, are a tempting quick fix, but we know most patients can't sustain it over a lifetime. We also know that many vegetarians eventually go back to eating meat.

So what key recommendations can I make for my patients?

A great starting point is a modified vegetarian diet where two meals are plant-based and one meal includes animal sources. This compromise allows patients to enjoy meat while reaping the rewards of vegetarian eating, which include improvements in glycemic control, weight reduction, and favourable benefits to kidney function preservation.

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