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Diabetic Nephropathy – Updating the Pillars of Renal Protection

LMC

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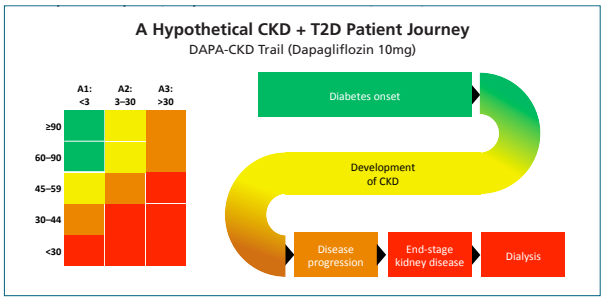
In today's day-to-day clinical practice, kidney disease is defined by both the stages of estimated glomerular filtration rate (eGFR) and the stages of urinary albumin to creatinine ratio (UACR). These generate the KDIGO heat curve that not only allows us to more easily identify patients that are at risk of kidney disease progression, but also to score this risk using the 4-point Kidney Failure Risk Equation (KFRE) formula narrowing in on our patients' 2-year and 5-year risk of end stage kidney disease (ESKD).

Guide to frequency of monitoring (number of times per year) by GFR and albuminuria category

GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

GFR and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year).

Unfortunately, diabetes continues to be the number one cause of ESKD in North America even today. About 50% of our patients develop microvascular complications 10 years after the diagnosis of diabetes. At 4 years following the diagnosis of diabetes, the risk of hospitalization for heart failure increases 33%, and at 5 years, the risks of cardiovascular events and stroke increase by 54% and 72%, respectively. The development of diabetic nephropathy is associated with not only an increased risk of ESKD, but also an increased risk of cardiovascular and all-cause mortality



The Standard of Care

Until very recently, the three pillars for renal protection consisted of blood pressure reduction, adequate glycemic control, and Renin-Angiotensin-Aldosterone System (RAAS) blockers. Even with these strategies, there was still a significant residual risk cardiovascular mortality (4-5% annually). Further, eGFR declined approximately 5% per year, leading to a 30% increased risk of either ESKD or death within 3-4 years.

From the Endocrinology & Diabetes Specialists of LMC Diabetes & Endocrinology. The opinions expressed in this paper are those of the authors and do not necessarily reflect the opinions of LMC Diabetes & Endocrinology or the editorial board of Clinical Practice Update.

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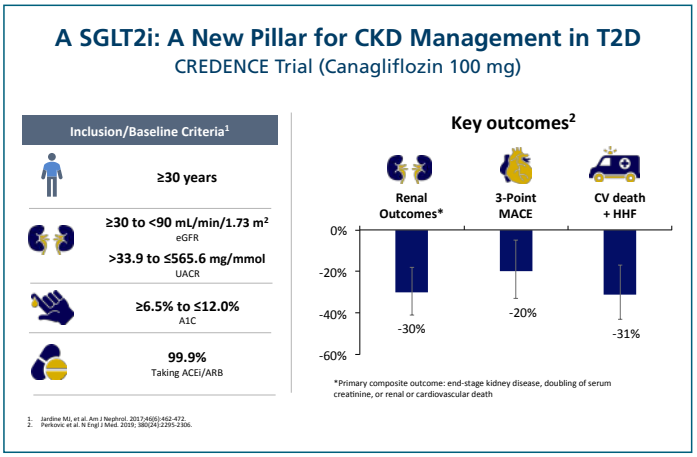
The Newest Pillar

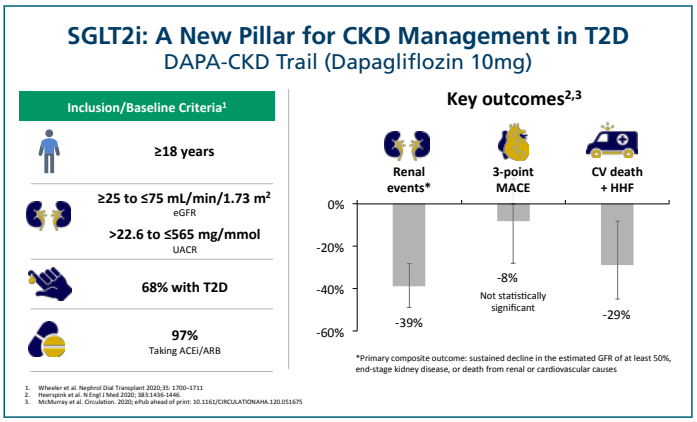
The requirement for cardiovascular trial outcome trials mandated by various regulatory agencies has given us our first glimpse of a novel renal protection strategy with SGLT2 inhibition. The EMPA-REG, CANVAS, and DECLARE trials all suggested renal protection in patients with diabetes and established cardiovascular disease or cardiovascular risk factors. The patients enrolled in these trials had relatively normal kidney function.

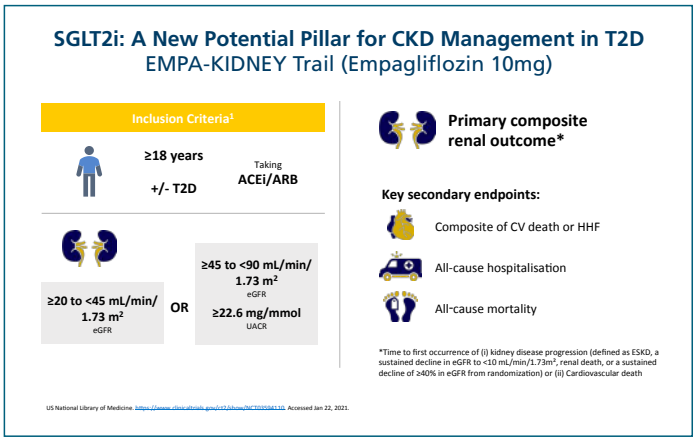
Renal outcome trials in patients with advanced diabetic nephropathy soon followed. CREDENCE included patients with type 2 diabetes who had an eGFR between 30-90 and UACR above 33.9 mg/mmol. The composite primary endpoint of ESKD, doubling of serum creatinine, renal and cardiovascular death demonstrated a relative risk reduction of 30%. The annual slope of eGFR decline was reduced from 4.59 ml/min/1.73m^2/yr to 1.85ml/min/1.73m^2/yr. A look at most of the secondary composite or individual renal endpoints like of ESKD, hospitalization for heart failure, and major adverse cardiovascular events were also all significantly reduced. Reassuringly, adverse events were minimal and most importantly the signal for lower limb amputation was neutral for canagliflozin during this trial in a higher risk group of patients.

There were also strongly positive signals both for regression and for slowing down progression of UACR with dapagliflozin.

The DAPA-CKD trial was unique since it included patients with both diabetic and nondiabetic nephropathy. Patients were included with UACR greater than 22.6 mg/mmol and eGFR between 25 and 75. The results were again positive with the renal composite primary endpoint reduced by 39%. Renal specific secondary endpoints also demonstrated benefits for dapagliflozin compared with placebo, including reductions in ESKD, renal or cardiovascular death, hospitalization for heart failure, and all-cause mortality. There were also strongly positive signals both for regression and for slowing down progression of UACR with dapagliflozin. Amongst the non-diabetic population enrolled in the DAPA-CKD trial, patients with IgA nephropathy and focal segmental glomerulosclerosis (FSGS) showed consistent benefit in the primary renal composite endpoint.







The EMPA KIDNEY trial is still ongoing. Enrolled patients have an eGFR ≥20 to <45 mL/min/1.73m^2, or ≥45 to <90 mL/min/1.73m^2 with UACR ≥22.6 mg/mmol. This study also includes patients with nondiabetic nephropathy and one of the arms has no UACR requirement. Hopefully, the results will be ready around June 2022.

Emerging Renal Protection

Aside from SGLT2 inhibitors, another class of therapeutic agents, the non-steroidal mineralocorticoid receptor antagonist, namely finerenone, has recently shown positive results amongst patients with diabetic kidney disease in the FIDELIO and FIGARO trials. Primary renal endpoints were relatively reduced by 18%, and major adverse cardiovascular events by 13%.

What's Good for Kidney is Good for the Heart

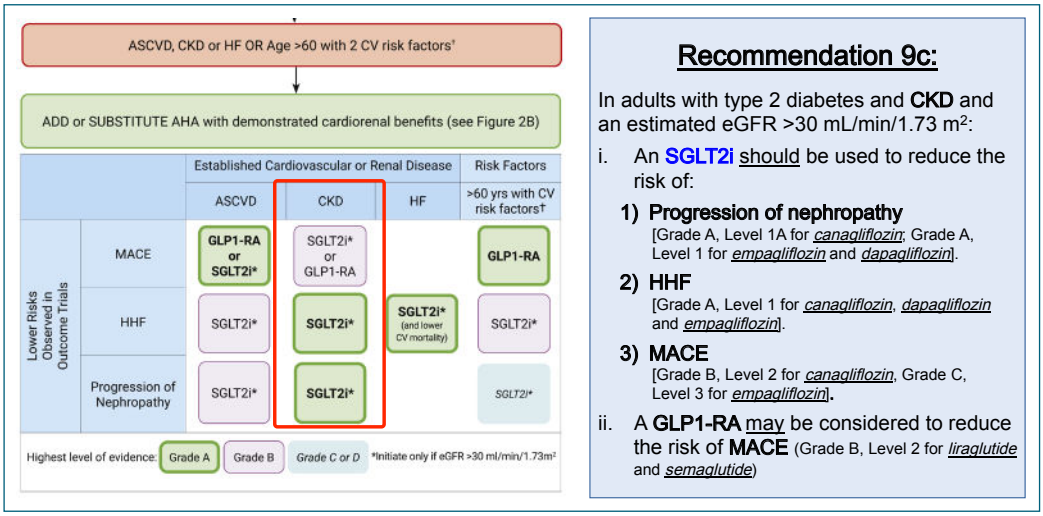
Considering the strength of the heart failure benefit demonstrated in cardiovascular and renal outcome trials, trials in patients with all stages of heart failure were initiated to further evaluate this benefit. These trials included patients with and without diabetes, and enrolled patients with reduced left ventricular ejection fraction (HFrEF) and preserved ejection fraction (HFpEF).

The HFrEF trials DAPA-HF and EMPEROR-REDUCED both showed improvement in primary cardiac endpoints and preservation of renal function in patients managing heart failure. A meta-analysis of the of the heart failure trials suggest that both patients with diabetic and nondiabetic heart disease and HFrEF similarly reduce the risk of hospitalization for heart failure or cardiovascular death by 26% and 25%, respectively. the primary composite endpoint of cardiovascular death, and hospitalization for heart failure in patients receiving empagliflozin compared to placebo.

Practical Pearls

SGLT2 inhibitors have shown to be effective in the management of type 2 diabetes without the risk of hypoglycemia or weight gain. Further benefits include cardiovascular protection in primary and secondary cardiovascular populations, renal protection across the entire spectrum of diabetic nephropathy, and reductions in the risk of hospitalization and cardiovascular death amongst patients with HFrEF and HFpEF. Renal protection is also evident in nondiabetic kidney disease, although additional data is still forthcoming in patients with impaired renal function and normal UACR.

When prescribing SGLT2 inhibitors, consider the following important issues related to the mechanism of action of the class:



Recommendation 9c:

In adults with type 2 diabetes and **CKD** and an estimated eGFR >30 mL/min/1.73 m²:

i. An **SGLT2i** should be used to reduce the risk of:

1) **Progression of nephropathy**
[Grade A, Level 1A for *canagliflozin*; Grade A, Level 1 for *empagliflozin* and *dapagliflozin*].

2) **HHF**
[Grade A, Level 1 for *canagliflozin*, *dapagliflozin* and *empagliflozin*].

3) **MACE**
[Grade B, Level 2 for *canagliflozin*, Grade C, Level 3 for *empagliflozin*].

ii. A **GLP1-RA** may be considered to reduce the risk of **MACE** (Grade B, Level 2 for *liraglutide* and *semaglutide*)

- Recognize that as renal function declines the effectiveness of A1C reduction is diminished but the cardiorenal benefits are maintained.
- Evaluate the volume and blood pressure status. For euvolemia or hypovolemia, consider reducing the dose of diuretics. For normotension or hypotension, consider reducing antihypertensive medication.
- Caution patients about the risk of genital mycotic infections and management options.
- Warn about the risk of euglycemic diabetic ketoacidosis (especially in patients on insulin or going for surgery) and provide sick day medication counselling.

The 2020 update to the Diabetes Canada clinical practice guidelines support the use of SGLT2 inhibitors in patients with CKD

The 2020 update to the Diabetes Canada clinical practice guidelines support the use of SGLT2 inhibitors in patients with CKD. Our established pillars of renal protection have shown us that all patients with diabetic kidney disease should receive adequate glycemic control, blood pressure reduction, lipid management and lifestyle counselling. Today, we also recognize that most benefit from RAAS blockers, and even more recently, the addition of SGLT2i inhibitors.

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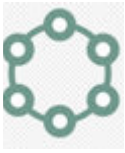

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