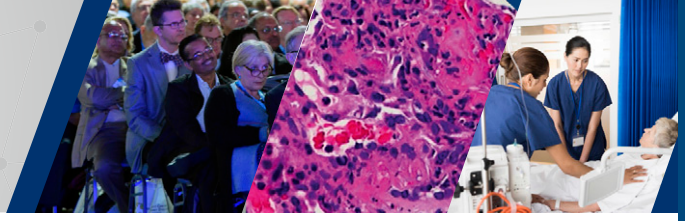

SGLT2 Inhibitors in Diabetic Kidney Disease

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Introduction

Type 2 diabetes, increasing in prevalence globally, is a major cause of CKD and kidney failure. Sodium-glucose transport protein 2 inhibitors (SGLT2i) significantly reduced progression of CKD, major adverse cardiovascular events, heart failure, and all-cause mortality in large clinical trials of people with type 2 diabetes (1,2).

Studies suggest a substantial gap between evidence-based recommended practices and the care currently received by people with diabetes and CKD (3). The 2020 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for management of diabetes and CKD aims to address this issue by providing new clinical recommendations and practical points for clinicians (2). The guideline recommends treatment with SGLT2i for patients with type 2 diabetes, CKD, and eGFR≥30 ml/min per 1.73 m^2 at any level of current glycemic control. Here, we describe our approach to initiating an SGLT2i in patients with type 2 diabetes and CKD, guided by recommendations and practice points from the new KDIGO guideline.

Patient Presentation

A 69-year-old man with type 2 diabetes and hypertension was referred for declining eGFR. He was diagnosed with diabetes 32 years prior to referral, and over time, developed both retinopathy and neuropathy. Urine albumin-creatinine ratio was first recorded as elevated 10 years prior to referral and rose to 2291 mg/g. eGFR was 70 ml/min per 1.73 m^2 10 years prior to referral and declined in a sawtooth pattern to 32 ml/min per 1.73 m^2. Comorbidities included obstructive sleep apnea, hyperlipidemia, and back pain. Medications included metformin, glipizide, insulin, losartan, amlodipine, hydrochlorothiazide, and spironolactone. BP was 132/68, and hemoglobin A1c was 7.2%

Selecting Appropriate Patients

The KDIGO guideline recommends initiating an SGLT2i for patients with type 2 diabetes and CKD across all albuminuria levels and eGFR stages (≥30 ml/min per 1.73 m^2) (2). SGLT2i initiation is particularly important for patients at high risk of CKD progression or heart failure—the two outcomes most strongly improved with SGLT2i—who derive the greatest absolute benefit (Figure 1). Initiation at early stages of CKD is optimal to maximize potential lifetime benefits.

The threshold of 30 ml/min per 1.73 m^2 is drawn from inclusion criteria of large clinical trials. However, an eGFR of 30 ml/min per 1.73 m^2 or slightly higher should not dissuade from SGLT2i initiation because there is no increased risk of harm at low eGFR. In addition, the initiation eGFR threshold may change as data from newer trials evaluating patients with lower eGFR emerge (4,5).

The KDIGO SGLT2i recommendation does not apply to immunosuppressed patients with a kidney transplant for whom benefits and risks have not yet been adequately studied. SGLT2is show great promise for patients with CKD who do not have diabetes (4), but evidence is most abundant and implementation most strongly supported for patients with type 2 diabetes.

Incorporating Sodium-Glucose Transport Protein 2 Inhibitor into Existing Glucose-Lowering Regimens

In large outcome trials, SGLT2is were added to diverse background antihyperglycemic therapies, with little or no increased risk of hypoglycemia (6). Notably, effects on glycemia are attenuated with lower eGFR. SGLT2i can simply be added to other glucose-lowering drugs when glycemic targets are not being met or when glycemic targets can safely be lowered further (*e.g.*, patients with hemoglobin A1c at goal treated with metformin alone). For patients currently using drugs that increase risk of hypoglycemia (*i.e.*, insulin or sulfonylureas) whose glycemic control is at goal or who have a history of severe hypoglycemia, we advise regular blood glucose monitoring and consideration of sulfonylurea or insulin dose reduction or sulfonylurea cessation when initiating an SGLT2i (Figure 1) (2).

Assessing Volume and Diuretic Use

SGLT2is cause natriuresis and modest volume contraction. This has led to concerns for volume depletion and AKI, particularly when used in combination with

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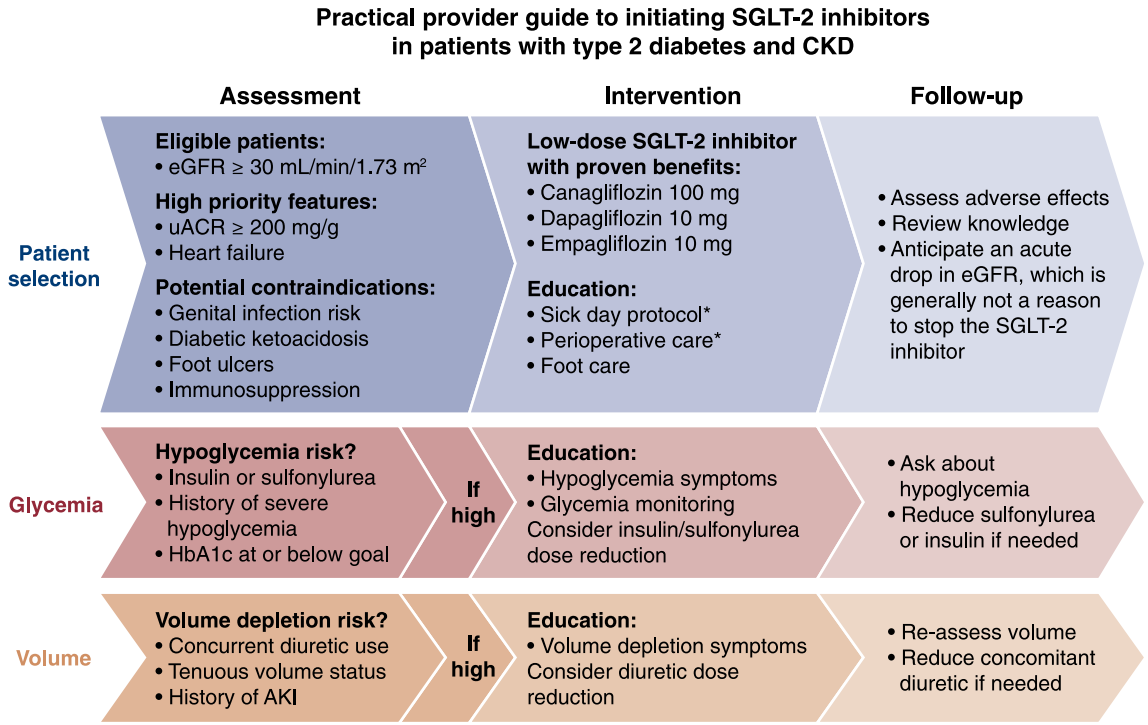

Figure 1. | **Practical approach to initiating sodium-glucose transport protein 2 (SGLT2) inhibitors in patients with type 2 diabetes and CKD.** *Sick day protocol (for illness or excessive exercise or alcohol intake): temporarily withhold sodium-glucose transport protein 2 inhibitor (SGLT2i), keep drinking and eating (if possible), check blood glucose and blood ketone levels more often, and seek medical help early. Periprocedural/perioperative care: inform patients about risk of diabetic ketoacidosis, withhold SGLT2i the day of day-stay procedures and limit fasting to minimum required, withhold SGLT2i at least 2 days in advance and the day of procedures/surgery requiring one or more days in hospital and/or bowel preparation (which may require increasing other glucose-lowering drugs during that time), measure both blood glucose and blood ketone levels on hospital admission (proceed with procedure/surgery if the patient is clinically well and ketones are <1.0 mmol/L), and restart SGLT2i after procedure/surgery only when eating and drinking normally. HbA1c, hemoglobin A1c; uACR, urinary albumin-creatinine ratio.

renin-angiotensin system inhibitors or diuretics. However, observed rates of AKI are lower with SGLT2i than placebo (7). In addition, reported benefits and risks are similar among patients with or without use of renin-angiotensin system inhibitors or diuretics. Nonetheless, vigilance is warranted for patients with tenuous volume status. This may include warning patients of symptoms of volume depletion, considering reducing dose of a concomitant diuretic, and most importantly, following up to reassess volume status after SGLT2i initiation (Figure 1).

Patient Education Regarding Potential Adverse Effects

All patients initiating SGLT2i should be educated on potential adverse effects, including polyuria and genital mycotic infections (6). Patients commencing SGLT2i should also be informed about the risk of diabetic ketoacidosis (DKA) associated with intercurrent illness or surgery/procedures requiring prolonged fasting. Clinicians should be aware that DKA associated with SGLT2i may present with symptoms of abdominal pain, nausea, vomiting, fatigue, or metabolic acidosis and normal or only modestly elevated blood glucose levels.

For surgery and procedures requiring one or more days in the hospital or bowel preparation, including colonoscopy, patients should be advised to stop an SGLT2i 2 days prior to surgery and the day of procedure to reduce risk of DKA. This may require temporarily increasing other glucose-lowering medications. Blood glucose and ketones should be monitored in the perioperative period if the patient is unwell or fasting or has limited oral intake. For day-stay procedures, patients should be advised to withhold SGLT2i on the day of the procedure and to recommence it when eating and drinking normally.

Amputations and fractures were observed at rates higher than placebo in one study of canagliflozin. These adverse events were not increased in other SGLT2i trials but require further study (6).

Reversible Effects on Glomerular Filtration Rate

Initiation of an SGLT2i is associated with an acute decline in eGFR (1). This decline is at least partially hemodynamic in origin and is reversible with discontinuation of the drug. Exploratory *post hoc* analyses of trial participants treated with an SGLT2i suggest that an acute eGFR drop >10% is not associated with risk of adverse events, whereas an acute eGFR drop >30% may be associated with increased risk of adverse events (8,9). Overall, long-term kidney benefit is observed despite an initial decline in eGFR, as with renin-angiotensin system inhibitors. Therefore, a drop in eGFR should be expected with SGLT2i initiation and is generally not an indication to

stop the drug, particularly when the drop is <30% of the eGFR prior to drug initiation.

Protocols of the CREDENCE and DAPA-CKD trials included continuing study drug even when eGFR fell below eligibility thresholds (4,10). We follow this approach in clinical practice, stopping an SGLT2i only when adverse effects are noted or for kidney failure requiring dialysis.

Prescribing

The benefits of SGLT2i appear to be class effects rather than drug specific. However, it is optimal when possible to use drugs that have demonstrated clinical benefits, such as canagliflozin, dapagliflozin, and empagliflozin (2). As clinical trials have not observed dose-response effects for clinical benefits, use of the lowest dose demonstrated to be effective in clinical trials is advisable (Figure 1).

Patient Follow-Up

The patient was started on empagliflozin 10 mg daily. Subsequent eGFR values varied between 25 and 29 ml/min per 1.73 m^2, which was attributed to hemodynamic effects of the SGLT2i or progression of underlying disease. Weight and BP also fell modestly. The SGLT2i was continued, and the metformin was discontinued. The patient noted several episodes of hypoglycemia, attributed to a combination of antihyperglycemic medications, decreased eGFR, and weight loss. Glipizide was discontinued, with stabilization of blood glucose.

SGLT2is have been proven to improve kidney and cardiovascular outcomes among people with type 2 diabetes, CKD, and eGFR≥30 ml/min per 1.73 m^2. Appropriate implementation is needed to improve outcomes in this population. Considerations for patient selection, assessment, treatment, education, and follow-up are increasingly well defined and can be effectively applied by diverse providers, including nephrologists.

Disclosures

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