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Sodium-Glucose Cotransporter-2 Inhibitors: Who, When & How? Guidance for Use from a Multidisciplinary Practical Approach

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Abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors) have transformed diabetes management by targeting renal glucose reabsorption. Designed initially as antidiabetic agents, their ability to lower blood glucose levels independently of insulin is well-documented. Beyond glycemic control, emerging research has unveiled their profound cardiorenal benefits. By inhibiting SGLT-2 protein, these drugs enhance glucose excretion in urine, reducing blood glucose levels. This mechanism has translated into significant cardiovascular and renal protection, establishing SGLT-2 inhibitors as pivotal in managing not only diabetes but also cardiovascular and renal diseases. Recent studies have illuminated the broader therapeutic potential of SGLT-2 inhibitors beyond diabetes. Evidence indicates their efficacy in managing heart failure, chronic kidney disease (CKD), and cardiovascular complications in individuals with or without diabetes. This expanded therapeutic landscape has catalyzed a paradigm shift in SGLT-2 inhibitor use, positioning them as key agents in the cardiorenal metabolic continuum. Moreover, their role in the secondary prevention of cardiovascular events and slowing CKD progression in T2DM patients has garnered considerable attention. This consensus-based review aims to offer practical guidance in

an algorithmic approach to primary care healthcare professionals to optimize SGLT-2 inhibitors utilization and maximize their benefits. The review seeks to empower clinicians to effectively manage patients who may benefit from SGLT-2 inhibitor therapy by addressing common initiation barriers and optimizing treatment strategies. Additionally, it aims to raise awareness among primary care physicians regarding the multifaceted benefits of these medications and overcome clinical inertia in their adoption into routine clinical practice.

Keywords

Sodium-Glucose Cotransporter-2 Inhibitors, Cardiorenal Benefits, Therapeutic Potential, Cardiovascular Protection, Primary Care Optimization

1. Introduction

Since their advent, the sodium-glucose cotransporter 2 inhibitors (SGLT-2 inhibitors) as a class of medications first licensed and primarily used in the treatment of type 2 diabetes mellitus (T2DM), underwent tremendous investigations for many other indications [1] [2].

These drugs work by inhibiting the action of the SGLT-2 protein in the proximal renal tubule, which plays a role in the reabsorption of glucose from the glomerular filtrate back into the bloodstream. By blocking this protein, SGLT-2 inhibitors increase the excretion of glucose in the urine, lowering blood glucose levels. When the estimated glomerular filtration rate (eGFR) is sufficient, SGLT-2 inhibitors, such as dapagliflozin, empagliflozin, canagliflozin, and ertugliflozin, are now commonly approved glucose-lowering medications that can lower glucose levels independent of insulin [3]-[5].

Recent research has shown that sodium-glucose cotransporter 2 inhibitors (SGLT-2 inhibitors) offer more than just glycemic control—they also exhibit protective effects on the heart and kidneys across the cardiorenal metabolic continuum [6]-[11]. This wealth of data has led to the development of new therapeutic models for SGLT-2 inhibitors, expanding their use beyond type 2 diabetes mellitus (T2DM). These models include managing heart failure (HF) and chronic kidney disease (CKD) in individuals with or without T2DM, as well as secondary prevention of cardiovascular disease (CVD) and delaying the progression of CKD in people with T2DM [2] [5] [7] [12] [13].

To optimize the use of SGLT-2 inhibitors, this review-based consensus seeks to give healthcare professionals, in the primary care setting who manage those patients who might benefit from treatment by these medications, some helpful simple guidance to increase their assurance when starting these medications. The goal extends beyond raising awareness among primary care physicians about the positive impacts of SGLT-2 inhibitors. It involves addressing the barriers related to doctors that contribute to clinical inertia [14].

2. The Cardio-Metabolic-Renal Interconnections

More than 500 million individuals worldwide are estimated by the International Diabetes Federation to have diabetes, with T2DM accounting for the great majority of cases [15]. In addition, it is estimated that 64 million people worldwide have HF, and 700 million people suffer from CKD, making these three conditions the primary pandemics of the twenty-first century [16] [17]. When considered separately, each of these three conditions is linked to significant morbidity and mortality [18]-[21].

However, it is widely acknowledged that these conditions frequently coexist [18]-[21]. This recognition has led to the establishment of the term cardio-metabolic-renal (CMR) disease, a significant concept that characterizes the systemic interdependence of T2DM, CVD, and CKD, as there is increasing data on their strong interrelationship [22]. In a recent cross-sectional study including 1.4 million adults, 12.6% had at least one condition within the CMR spectrum (± T2DM ± HF ± CKD) [23].

Epidemiological investigations suggest a multidirectional relationship between T2DM, CVD, and CKD. For instance, in a cohort study of almost 1.2 million T2DM patients who did not originally have concomitant CVD or CKD, 24% of first events were HF, and 36% were CKD [24]. Claims-based research of almost 1.2 million T2DM patients starting oral glucose-lowering medication in the US revealed that 16% of participants had CVD or CKD during follow-up, with heart failure and/or CKD accounting for the majority of diagnoses (65%) [25].

On the other hand, T2DM prevalence is higher in HF cohorts than in the general population; data indicate that it is 24% among all HF patients and 40% among hospitalized patients with deteriorating HF [26]. Additionally, diabetes is found to be highly prevalent, ranging from 31% - 40%, among individuals with CKD [27]-[29].

Moreover, CKD is regarded as a significant risk factor for CVD, including HF. As estimated Glomerular Filtration Rate (eGFR) declines, there is an increased risk of CV events and death [30] [31]. Increased serum creatinine level is an independent predictor of CVD, HF, and all-cause mortality [32]. Conversely, incident CKD and a rapid eGFR drop are more than twice as likely to occur in people with HF [33].

3. Benefit of SGLT-2 Inhibition and Mechanism of Action

Understanding the direct and indirect physiological mechanisms and effects of SGLT-2 inhibition is crucial to clarify why they offer a diversity of clinical benefits. They cause glucosuria by decreasing the renal threshold for glucose; they also increase the sensitivity to insulin and enhance beta-cell function, leading to improvement in glucose control, reflected by a reduction in HbA1c of ~0.5% - 1%. On the other hand, natriuresis improves blood pressure and reverses the tubuloglomerular feedback stimulation. Albuminuria improves, as demonstrated in clinical trials on diabetic and non-diabetic patients with CKD. They also in-

duce weight loss (2 - 4 kg after 6 - 12 months of treatment) initially related to volume contraction and then to caloric wasting through glucosuria. This is in addition to other benefits such as improvement in proximal tubular work, oxygen consumption, oxygen delivery, and anemia [34].

4. SGLT-2 Inhibitors: Valuable Multi-Indication Therapeutic Tool

4.1. T2DM

It is crucial for the management of people with T2DM to understand the eight core defects, collectively known as "the ominous octet," that contribute to its pathophysiology. These include decreased insulin secretion, decreased incretin effect, increased lipolysis, increased glucose renal reabsorption, decreased muscle glucose uptake, neurotransmitter dysfunction, increased hepatic glucose production, and increased glucagon secretion [35]-[37]. Therapy choices should target these established pathophysiologic defects in T2DM as well as follow a patient-centered approach that considers factors beyond glycemic control, including reduction of microvascular and macrovascular complications, including the CV risk [35] [36] [38]-[40].

Achieving ideal glycemic goals has traditionally been the primary objective of treatment interventions for people with T2DM to prevent microvascular and macrovascular complications [2]. Old oral anti-diabetic drugs have been linked to a lower risk of microvascular complications; however, results for macrovascular complications were conflicting [41] [42]. Because of this, a significant proportion of people with T2DM still have a high remaining risk of renal and CV disease development [43]. Notably, several of these drugs have been related to additional adverse effects such as hypoglycemia and weight gain, and they may potentially increase the risk of CV events [44]-[46].

In this context, SGLT-2 inhibitors emerge as a significant therapeutic option for T2DM. Unlike many traditional antidiabetic medications, SGLT-2 inhibitors offer a unique mechanism of action by inhibiting glucose reabsorption in the kidneys, thereby promoting urinary glucose excretion and reducing blood glucose levels. By targeting increased glucose renal reabsorption, SGLT-2 inhibitors directly address one of the core defects of T2DM, leading to improved glycemic control [43] [47]-[73].

Novel therapies that provide glycemic and non-glycemic benefits are of great importance. In this regard, SGLT-2 inhibitors have become a viable treatment choice due to their numerous benefits, which include blood pressure regulation, weight loss, glycemic control, and renal and cardiac protection [2]. A substantial amount of data, including several randomized controlled (RCT) studies and meta-analyses, showed that SGLT-2 inhibitors used as monotherapy and in addition to other DM medications significantly reduced HbA1c, fasting plasma glucose (FBG), 2-h postprandial glucose (PPBG), body weight, systolic and diastolic blood pressure compared to placebo [43] [47]-[73].

In addition, they also demonstrated reductions in overall morbidity and mortality by reducing CV and renal complications as demonstrated by several cardiovascular outcome trials (CVOTs) so far evaluating their impact on CV outcomes: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME), Canagliflozin Cardiovascular Assessment Study (CANVAS), the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes trial (VERTIS-CV), and Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58). It was obvious that the cardioprotective advantages of these drugs vs. placebo were self-evident in terms of decrease in hospitalizations because of heart failure (hHF), a composite of CV mortality, non-fatal myocardial infarction and non-fatal stroke, and any cause mortality [73]-[79].

4.2. HFrEF

4.2.1. Pathophysiology of HFrEF

Heart failure with reduced ejection fraction (HFrEF) results from various pathophysiologic processes, including myocardial injury and abnormal cardiac loading, leading to maladaptive responses and neurohormonal activation. Despite neurohormonal blockade therapies, HFrEF mortality remains high, and new treatments targeting cardiac mechanics are being explored [80].

4.2.2. Public Health Burden of HFrEF

Heart failure (HF) is a significant health problem with increasing cases of even preserved ejection fraction HF. Despite stable or declining HF incidence, mortality and hospitalization rates are high, with disparities in occurrence and outcomes, especially among younger populations. Omics science offers new insights into HF mechanisms, calling for holistic, multidisciplinary management approaches [81].

4.2.3. Prognosis of HFrEF

Patients with HFrEF have poor long-term outcomes. A study found that those with mid-range ejection fraction HF (HFmrEF) had lower all-cause mortality and hospitalization rates than HFrEF or HF with preserved ejection fraction (HFpEF). In Egypt, the median survival time for decompensated HF patients is 34.5 months [82] [83].

4.2.4. SGLT2i Efficacy and Safety in HFrEF

Trials like DAPA-HF and EMPEROR-REDUCED showed that SGLT-2 inhibitors like dapagliflozin and empagliflozin reduce heart failure events and cardiovascular death in HFrEF patients. Adverse events were similar between the treatment and placebo groups [84] [85].

4.2.5. Benefits of SGLT2i for Hospitalized Patients

Trials like SOLOWIST-HF and EMPULSE demonstrated that SGLT-2 inhibitors like Sotagliflozin and empagliflozin, provide benefits to hospitalized HF patients,

including reduced cardiovascular deaths and HF events [86] [87].

4.2.6. Updated Guidelines for HFrEF Treatment

The American College of Cardiology (ACC) and the European Society of Cardiology (ESC) now recommend SGLT-2 inhibitors for HFrEF patients, regardless of diabetes status [88]-[91].

4.2.7. Cost-Effectiveness of SGLT-2 Inhibitors in HFrEF

Economic evaluations indicate that dapagliflozin and empagliflozin are cost-effective in treating HFrEF, improving quality-adjusted life-years at acceptable costs [92] [93].

4.2.8. Sequencing HFrEF Therapies

A proposed new treatment algorithm suggests initiating treatment with a combination of drugs, achieving complete therapy within four weeks to prevent deaths and hospitalizations [7].

4.2.9. Practical Considerations for SGLT-2 Inhibitors Prescription

Recommendations include in-hospital initiation, prioritizing ARNI or SGLT-2 inhibitors, considering renal function, adjusting concurrent HF and diabetes therapies, and managing adverse effects. Multidisciplinary care is emphasized [7] [94] [95].

4.2.10. Potential Mechanisms of SGLT-2 Inhibitors Benefits

SGLT-2 inhibitors may benefit HFrEF through various mechanisms, including volume regulation, cardiorenal effects, metabolic improvements, cardiac remodeling, direct cardiac effects, and inflammation and oxidative stress reduction [96].

4.2.11. Practical Considerations When Prescribing SGLT-2 Inhibitors in Patients with HFrEF

In-Hospital Initiation: Starting SGLT-2 inhibitors in-hospital for stabilized HF patients not on vasopressors or Nitroglycerine is safe and improves outcomes. The STRONG-HF trial supports early and rapid up-titration in HFrEF, endorsed by guideline [84]-[95].

- ARNI or SGLT-2 inhibitors First? Combining ARNIs and SGLT-2 inhibitors is safe, with evidence showing that comprehensive HF therapy extends event-free survival by eight years in adults aged 50.
- Metformin in HFrEF and T2DM: SGLT-2 inhibitor is the preferred first-line therapy for HFrEF patients with new T2DM, even without prior metformin use, as per the ESC 2019 DM guidelines.
- Choosing SGLT-2 inhibitors and Dosage: The efficacy of SGLT-2 inhibitors in HF treatment is consistent across the class, regardless of receptor affinity differences.
- Renal Considerations: SGLT-2 inhibitors are safe for HF patients with an eGFR down to 20 ml/min/1.73 m^2 BSA, initially reducing eGFR but provid-

ing long-term renal protection.

- Adjusting HF and T2DM Therapies: HFrEF patients with T2DM often need polypharmacy. Reducing non-evidence-based and fluid-retaining medications and individualizing loop diuretics is advised when starting SGLT-2 inhibitors.
- Adverse Effects and Guidance: SGLT-2 inhibitors side effects are less in nondiabetic HFrEF patients. Diabetic patients should pause SGLT-2 inhibitors during low oral intake, with diabetic ketoacidosis being a rare risk. Counseling on its symptoms and risks, including genital infections and amputations, is important.
- Multidisciplinary Care: SGLT-2 inhibitor is a key HFrEF therapy, not just for diabetes. Collaboration among cardiologists, endocrinologists, and pharmacists is crucial for effective use and guideline adherence.

4.3. HFpEF

4.3.1. Challenges in the Diagnosis of HFpEF

It is not easy to diagnose HFpEF. However, there are different algorithms that help in the identification of cases. Including the H2FpEF score, which is a scoring system out of 9, and a score of 6 or more is highly diagnostic of the disease. The European HFA-PEFF score is more complex, with a preliminary assessment of the probability, followed by morphological changes in the LV and LA, incorporated with cut-off levels of NT BNP. If the case is inconclusive, invasive tests or a stress test can also be performed also, and finally the etiology is investigated to aid in the management [97].

4.3.2. SGLT-2 Inhibitors and Prevention of HFpEF

The optimal strategy to prevent HFpEF is to manage the risk factors [88] [98]. Some of the most prevalent risk factors for HFpEF are obesity and diabetes mellitus. People with T2DM are reportedly 2.5 times more likely to develop HF than those without the condition [99]. As such, there is a great focus on treatments with the potential to prevent HF in patients with diabetes.

While some glucose-lowering agents have a good cardiovascular safety profile in patients with T2D, SGLT-2 inhibitors such as empagliflozin and dapagliflozin may also prevent incident HF in at-risk patients with diabetes. In the EMPA-REG OUTCOME TRIAL [73], patients with T2DM and high CV risk were randomized to receive empagliflozin or placebo alongside background diabetes therapy. Empagliflozin reduced the primary outcome (composite of death from CV causes, non-fatal MI or non-fatal stroke) as well as decreasing all-cause death and hospitalization for HF compared with placebo [73]. Similarly, the SGLT-2 inhibitors dapagliflozin, canagliflozin and ertugliflozin were shown to reduce hospitalization for HF in the DECLARE-TIMI [77], CANVAS [75] and VERTIS-CV [76] [78] trials, respectively. Hence, several SGLT-2 inhibitors are recommended in the AHA/ACC/HFSA 2022 and ESC 2021 HF guidelines for patients with T2DM at high risk of CV disease or with CV disease to prevent HF hospitalizations [88]

[97].

4.3.3. SGLT-2 Inhibitors and Management of HFpEF

Management of HFpEF has proven to be difficult because of the heterogeneity of risk factors and complex pathophysiology. Thus, treatments have focused mainly on managing comorbidities and improving symptoms. Management of the commonly prevalent hypertension and CAD in patients with HFpEF includes treatment with ACEIs, ARBs, beta-blockers, or MRAs. Diuretics are also recommended to improve congestion [89].

Clinical HFpEF trials using different medications (e.g., perindopril, candesartan, irbesartan, spironolactone, digoxin and sacubitril/valsartan) did not show a significant reduction of mortality and morbidity [98]-[103]. However, there were improvements in specific sub-cohorts of patients with HFpEF or HFmrEF. For example, both the MRA spironolactone and the ARB candesartan have been shown to reduce CV death and HF hospitalizations in patients with low baseline LVEF [104] [105]. The angiotensin receptor-neprilysin inhibitor sacubitril/valsartan also reduced cardiovascular death and hospitalizations in patients with an LVEF ≤ 57% compared with renin-angiotensin-aldosterone-system inhibitors and in higher LVEF in women [106].

Over the past few years, SGLT-2 inhibitors have emerged as important therapies for HF, although their use has previously been reserved for patients with HFrEF. However, findings from the EMPEROR-Preserved trial and DELIVER have had a great impact on the approval of these medications in HFpEF [107] [108]. The SGLT-2 inhibitor empagliflozin showed a reduction of the combined risk of CV death or HF hospitalization (primary outcome) in patients with HFmrEF/HFpEF in the Phase III, double-blind, randomized EMPEROR-Preserved trial. This effect was observed regardless of the presence or absence of diabetes, or age, the presence or absence of AF, body mass index (BMI), or baseline systolic blood pressure (BP). The main reduction was in the hHF [107].

This was also noted with dapagliflozin with a reduction of the risk of cardiovascular death and worsening HF (HF hospitalization or urgent HF visit; primary composite outcome) in patients with HFmrEF/HFpEF in the Phase III, double-blind, randomized DELIVER trial [108]. Over a median of 2.3 years, the primary composite outcome occurred in 16.4% of patients in the dapagliflozin group and in 19.5% of patients in the placebo group (HR 0.8; 95% CI: 0.7 - 0.9; $P < 0.001$). The effect of dapagliflozin was consistent across all prespecified subgroups, being unaffected by variables such as age, the presence or absence of T2D or AF, BMI, eGFR at enrolment, systolic BP at randomization, and previous LVEF being ≤ 40%. Additional evidence for improvement in health status and quality of life with SGLT-2 inhibitors use in HFpEF was observed in the PRESERVED-HF (Dapagliflozin in PRESERVED Ejection Fraction Heart Failure) trial [109].

Therefore, SGLT-2 inhibitors should be initiated in all individuals with HFpEF lacking contraindications as suggested by the ACC and European guide-

lines [97] [110].

4.3.4. Practical Considerations

HFpEF prevalence is ever-increasing and is causing significant morbidity and mortality. The main obstacle is the detection and provided algorithms may help reach a definite diagnosis. The management of comorbidities is essential in such cases. SGLT-2 inhibitors dapagliflozin and empagliflozin are the only medications to show significant improvements of outcomes in such patients, and should be provided in all patients with HFpEF, or HFmrEF unless contraindicated [97] [110].

4.4. CKD

Chronic kidney disease (CKD) is a common and serious health problem characterized by the gradual loss of kidney function over time, with an estimated 800 million people worldwide living with the condition. CKD is more common in older adults and is often associated with other chronic conditions such as diabetes (DM) and hypertension [111]. Diabetic kidney disease (DKD) is a frequent long-term complication of diabetes, and the leading cause of CKD and end-stage kidney disease (ESKD). Typically, DKD is defined by the presence of CKD characterized by persistently (at least three months) elevated urinary albumin excretion (ACR ≥ 30 mg/g) and/or low eGFR (≤60 mL/min/1.73m^2) in a person with diabetes. Individuals with a GFR below 30 mL/min/1.73m^2 (*i.e.*, CKD stages 4-5) are at especially high risk across all albuminuria categories [112].

4.4.1. Mechanism of Renoprotection by SGLT-2 Inhibitors

The potential mechanism of the renal benefits of SGLT-2 inhibitors is an area of ongoing investigation. Increased proximal tubular glucose and sodium reabsorption in diabetics may be due to overexpression of SGLT2 mRNA and increased transporter activity. As a result, decreased sodium transport to the macula-densa inhibits tubule glomerular feedback, which decreases the eGFR by causing afferent arteriolar vasodilation, hyperfiltration, and hyperperfusion. Therefore, SGLT-2 inhibitors decrease the workload on the glomeruli and tubules. Additionally, SGLT-2 inhibitors prevent proximal sodium and glucose reabsorption, which causes natriuresis. SGLT-2 inhibitors reduce arterial stiffness, an indicator of both renal and cardiovascular risk. In addition to promoting anti-inflammatory and antifibrotic pathways, SGLT-2 inhibitors enhance the positive effects of decreased glomerular hypertension, hyperfiltration, and renal oxygenation. Therefore, SGLT-2 inhibitors have also been shown to reduce albuminuria [113]-[115].

4.4.2. SGLT2i: Renal Effects across the Cardiorenal Continuum

The EMPA-REG OUTCOME, CANVAS Program, DECLARE-TIMI 58, and VERTIS-CV trials originally aimed to assess the CV safety of SGLT-2 inhibitors. However, they also provided significant data on renal effects [113]-[115].

4.4.3. Kidney Outcomes from CVOTs

CVOTs including EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI-58, VERTIS CV, and SCORED revealed the benefit of SGLT-2 inhibitors in improving cardiovascular outcomes in patients with T2DM with varying risks for ASCVD. Secondary analysis of renal outcomes from CVOTs was the first to suggest potential benefit in patients with kidney disease. In EMPA-REG OUTCOME which included 7020 patients with T2DM with established ASCVD and enrolled patients with eGFR > 30 ml/min per 1.73 m^2, the renal composite outcome of ESKD and doubling of serum creatinine was lower with empagliflozin, with a reduction in ESKD and doubling in serum creatinine [86].

As a consequence of the reduction in intraglomerular hypertension and other protective pathways, albuminuria decreases by 30% to 50% regardless of baseline albuminuria within the span of weeks in response to SGLT2 inhibition. On stopping these agents, albuminuria increases within weeks suggesting a contribution from underlying hemodynamic mechanisms [116].

In the CANVAS Program, which enrolled patients with T2DM with high cardiovascular risk and eGFR > 30 ml/min per 1.73 m^2, the renal composite outcome was also lower with canagliflozin. DECLARE-TIMI 58, which only included patients with T2DM with established or multiple risk factors for ASCVD and eGFR > 60 ml/min per 1.73 m^2, similarly favored SGLT-2 inhibitors use, which reduced the composite renal outcome of sustained eGFR decline of >40%, ESKD, or renal death. Despite the positive outcomes, CVOTs were not powered for kidney-related outcomes and patients with CKD comprised <30% of the study cohorts but informed subsequent dedicated trials for patients with kidney disease. In VERTIS CV, ertugliflozin was associated with preservation of eGFR decline by >0.75 ml/min per 1.73 m^2 per year with greater benefit in reducing heart failure hospitalizations in those with more advanced CKD [116]-[118].

In SCORED, which included patients with CKD with eGFR 25 to 60 ml/min per 1.73 m^2, a secondary kidney endpoint was not significantly different between sotagliflozin and placebo, although the trial was terminated early and likely not of a sufficient duration to detect these differences in composite endpoints [86].

4.4.4. CKD Trials

CREDENCE and DAPA-CKD specifically evaluated the effect of SGLT-2 inhibitors on a primary kidney endpoint and ultimately provided the strongest evidence for use in patients with CKD. In **CREDENCE**, the primary composite of doubling of creatinine, ESKD, and death from renal or cardiovascular causes was reduced by 30% with canagliflozin. Benefit was consistent across renal endpoints with a lower risk of doubling serum creatinine and ESKD. Decline in eGFR was lower in the canagliflozin group (3.19 ml/min per 1.73 m^2 per year) in comparison to 4.71 ml/min per 1.73 m^2 per year in the placebo group. This finding was observed despite only modest changes in blood glucose, weight, and BP [119].

DAPA-CKD enrolled 4304 adults with both diabetic and nondiabetic kidney diseases with eGFR 25 to 75 ml/min per 1.73 m^2, ACR 200 to 5000 mg/g

on maximal tolerated RAAS blockade and followed participants for a median of 2.4 years. Dapagliflozin reduced the primary composite outcome of sustained decline in the estimated GFR by > 50%, ESKD, and renal or cardiovascular death by 39% with a number needed to treat 19. Importantly, the effects of dapagliflozin were similar in patients with T2DM or without T2DM. All individual components of the renal endpoint had benefits with the risk of ESKD reduced by 36% and 50% eGFR decline reduced by 47%. The risk for hospitalization for heart failure or cardiovascular was reduced by 29% like previous CVOTs. Both CREDENCE and DAPA-CKD represent a strong win for the field of nephrology, collectively revealing the impressive benefit of SGLT-2 inhibitors on hard renal endpoints in patients with CKD with albuminuria regardless of diabetes status [119].

4.4.5. Practical Considerations

1) Contraindications

It is contraindicated to initiate SGLT-2 inhibitors in patients with eGFR < 15 ml/min/1.73 m^2, receiving dialysis, Polycystic kidney disease, Patient with a solid organ transplant and/or receiving cytotoxic therapy, immunosuppressive therapy, or other immunotherapy (despite having ongoing studies on their use in those therapeutic areas), Type 1 diabetes mellitus, Previous diabetic ketoacidosis (DKA), and Pregnancy or breastfeeding [120].

2) Accepting the Acute "Dip" in eGFR

SGLT-2 inhibitors are believed to slow down CKD progression primarily by reducing glomerular hyperfiltration. This causes a temporary drop-in glomerular filtration rate (GFR), like the mechanism of RAAS blockade, which raises concerns among clinicians, leading to potential discontinuation. However, it is recommended to resist stopping SGLT-2 inhibitors due to a rise in serum creatinine up to 30 %from baseline, as these drugs offer significant cardiorenal benefits. A greater dip in eGFR is associated with more substantial long-term benefits, indicating a positive hemodynamic effect [120].

It is reasonable to monitor kidney function 1 month after initiation in higher risk patients, including those with a history of prior acute kidney injury, advanced CKD, or in those in whom there is increased concern regarding volume depletion. This careful assessment of volume status and a decision made about whether to hold the SGLT-2 inhibitor temporarily and then consider rechallenging the patient once appropriate [121].

5. SGLT-2 Inhibitors: Critiques and Barriers for Optimum Use

For the optimal prescription of SGLT-2 inhibitors, it is crucial to possess a comprehensive understanding of both their benefits and potential risks. Key safety considerations include volume depletion and associated acute kidney injury (AKI), hypoglycemia, DKA, and genitourinary infections [18]. However, it is important to note that adverse events with SGLT-2 inhibitors are generally man-

ageable, and serious adverse events are rare [122]. By making tailored minor adjustments and addressing intermittent illness or major surgery, adverse effects can be managed [123].

5.1. Diabetic Ketoacidosis

Diabetic ketoacidosis in patients taking SGLT-2 inhibitor can present with normal or only mildly elevated glucose concentrations. This is due to the ongoing SGLT-2 inhibitor-induced glycosuria. It is therefore important to test for ketones in any unwell patient taking an SGLT-2 inhibitor regardless of their blood glucose concentration [122]-[124].

5.2. Diuretic Effect and Volume Status

In euvolemic patients consider reducing the dose of any diuretics to avoid further volume depletion. SGLT-2 inhibitors should be withheld when a patient is at risk of dehydration, such as during an episode of gastroenteritis, when systemically unwell and during medical and surgical procedures [122]-[124].

5.3. Genital Mycotic Infections and UTIs

Monitoring is required for a rare but serious genital infection called Fournier's gangrene for which the FDA has issued a warning [123].

5.4. Acute Kidney Injury

The risk of AKI with SGLT-2 inhibitors is considered to be due to volume depletion resulting from natriuresis and consequent kidney medullary hypoxia [123].

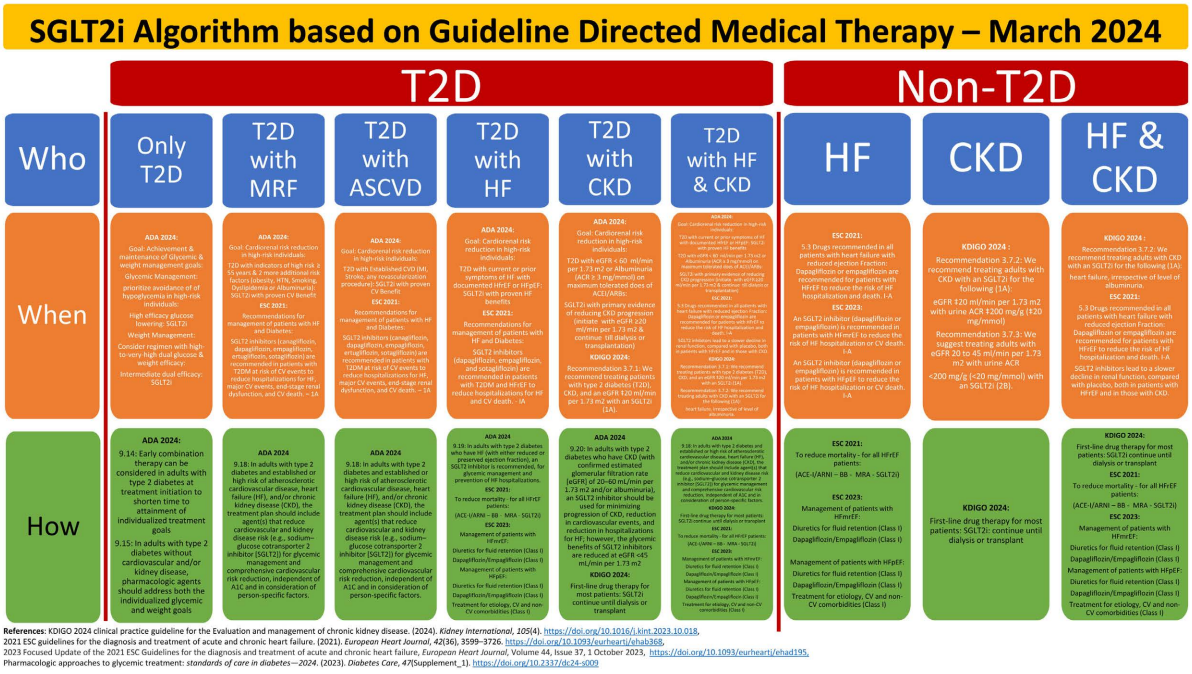

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Figure 1. SGLT-2 inhibitors: Algorithm based on Guideline Directed Medical Therapy—March 2024.

5.5. Lower Extremity Amputations

Donnan et al. highlight the lack of data for a causal association of SGLT-2 inhibitors with the risk of amputations and fractures, and they also confirm that the present evidence for this association is available from CANVAS and CANVAS-R trials only [124].

6. SGLT-2 inhibitors: Algorithm Based on Guideline Directed Medical Therapy—March 2024 (Figure 1)

Based on the recent updates on guideline-directed medical therapy, the following algorithmic approach can help healthcare professionals on how to use SGLT-2 inhibitors in an individualized case scenario [12] [40] [89] [110].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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