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Science, Perception, and Reality of Using SGLT2 Inhibitors in Clinical Practice

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Abstract

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have revolutionized the management of type 2 diabetes mellitus (T2DM), extending benefits beyond glycaemic control. This review explores the scientific basis, clinical efficacy, real-world applications, and future implications of SGLT2 inhibitors. We discuss cardiovascular and renal benefits, as well as emerging applications in hepatology, neurology, and oncology. Despite robust evidence, the real-world utilization remains suboptimal. This article evaluates perception vs. reality in prescribing practices and highlights the need for more comprehensive patient management strategies.

Keywords: Type 2 Diabetes Mellitus; Sodium-Glucose Cotransporter-2

Abbreviations

SGLT2: Sodium-Glucose Cotransporter-2; T2DM: Type 2 Diabetes Mellitus; CV: Cardiovascular; CKD: Chronic Kidney Disease; HF: Heart Failure; HFrEF: HF With Reduced Ejection Fraction.

Introduction

Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), is a global epidemic contributing significantly to morbidity and mortality. The burden of diabetes is exacerbated by its associated complications, including microvascular (neuropathy, nephropathy, retinopathy) and macrovascular (coronary artery disease, cerebrovascular disease, peripheral vascular disease) complications. The evolution of diabetes management has shifted from glucose-centric approaches to comprehensive risk reduction strategies addressing cardiovascular (CV) risks, heart failure (HF), and chronic kidney disease (CKD). Sodium-glucose co-transporter-2 (SGLT2) inhibitors have emerged as a cornerstone in the management of T2DM, offering benefits beyond glucose control, including weight reduction, blood pressure control, and CV risk reduction [1,2]. This review evaluates the scientific evidence, clinical perceptions, and real-world application of SGLT2 inhibitors.

Mechanisms and Established Benefits

The Science of SGLT2 Inhibitors

SGLT2 inhibitors, such as empagliflozin, canagliflozin, and dapagliflozin, were initially approved for their glucose-lowering effects. These drugs reduce glucose reabsorption in the proximal renal tubules, promoting glucosuria and lowering blood glucose levels [3]. This mechanism also leads to natriuresis, blood pressure reduction, and metabolic benefits, positioning these agents as multifaceted therapeutic options [4]. Clinical trials have demonstrated their efficacy in reducing CV events, HF hospitalizations, and the progression of CKD.

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Mechanisms of Action

The mechanisms underlying the benefits of SGLT2 inhibitors are multifactorial. These drugs reduce glucose reabsorption in the kidney, leading to glycosuria and a reduction in blood glucose levels. Additionally, SGLT2 inhibitors promote weight loss, reduce blood pressure, and improve endothelial function. They also have diuretic and natriuretic effects, which contribute to their benefits in HF and CKD. Furthermore, SGLT2 inhibitors reduce oxidative stress, inflammation, and fibrosis, which are key pathways in the progression of CV and kidney disease.

Cardiovascular Outcomes

The EMPA-REG OUTCOME trial was a landmark study that demonstrated the CV benefits of empagliflozin. The trial showed a significant reduction in the risk of CV death, non-fatal myocardial infarction, and non-fatal stroke (3-point major adverse cardiovascular events, 3P-MACE) in patients with T2DM and established CV disease [5]. Similar benefits were observed in the CANVAS program (canagliflozin) and the DECLARE-TIMI 58 trial (dapagliflozin) [6,7].

Heart Failure and Kidney Outcomes

SGLT2 inhibitors have also shown significant benefits in reducing HF hospitalizations and slowing the progression of CKD. The DAPA-HF and EMPEROR-Reduced trials demonstrated the efficacy of dapagliflozin and empagliflozin, respectively, in reducing HF hospitalizations and improving outcomes in patients with HF with reduced ejection fraction (HFrEF) [8,9]. Additionally, the CREDENCE trial showed that canagliflozin reduced the risk of kidney failure and CV events in patients with T2DM and CKD [10].

Emerging Therapeutic Roles

- **Metabolic and Weight Management** by promoting caloric loss through glucosuria, these drugs support weight reduction and improved metabolic profiles, beneficial for patients with obesity-related T2DM [11].
- **Hepatic Benefits:** Evidence suggests SGLT2 inhibitors may ameliorate nonalcoholic fatty liver disease (NAFLD) and metabolic-associated fatty liver disease (MAFLD) by improving insulin sensitivity and reducing hepatic steatosis [12].
- **Neuroprotection and Dementia Risk Reduction:** Studies indicate a lower incidence of dementia among SGLT2 inhibitor users, possibly due to enhanced ketogenesis and reduced oxidative stress [13].
- **Cardio-oncology:** Preclinical studies suggest that SGLT2 inhibitors may mitigate anthracycline-induced cardiotoxicity in cancer patients undergoing chemotherapy [14].
- **Erectile Dysfunction:** Preliminary data indicate improved endothelial function and cavernosal relaxation in diabetic models, highlighting potential benefits in managing erectile dysfunction [15].

Perception Amongst Clinicians

Despite strong evidence supporting SGLT2 inhibitors, their clinical adoption varies. A Karnataka Endocrine Society (KES) survey of 100 endocrinologists revealed that 100% of endocrinologists recommended SGLT2 inhibitors for T2DM patients with atherosclerotic cardiovascular disease (ASCVD) or HF, 98% for patients with diabetic kidney disease (DKD) and 96% for patients with two or more risk factors but without established CVD, HF, or CKD. Hesitancy persisted due to concerns about side effects (genital mycotic infections (GMI), urinary tract infections, volume depletion), cost (especially in low- and middle-income countries), and rare risks like DKA and AKI. Limited long-term safety data further contributed to cautious prescribing, highlighting barriers to broader use despite proven benefits.

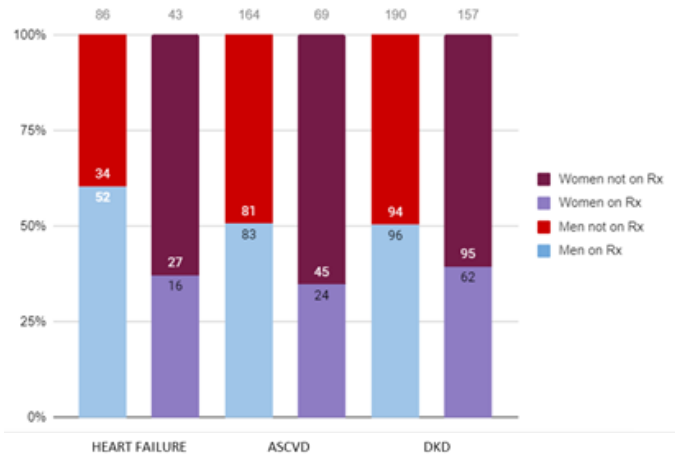

Figure 1: SGLT2 inhibitor use in high cardiovascular risk populations – heart failure, ASCVD and DKD.

Real-World Utilization

A cross-sectional study by Dr. Bhattacharyya and colleagues evaluated the real-world use of SGLT2 inhibitors in 1450 adults with T2DM, focusing on patients with risk factors such as obesity, hypertension, dyslipidemia, ASCVD, age over 60 years, and diabetes duration exceeding ten years. Patients with other types of diabetes, GMI in the last 1 year or an estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m^2 were excluded, leaving 1322 participants. Of these, 42.1% were prescribed SGLT2 inhibitors, with higher use among men (44%) compared to women (38%). Among patients with heart failure, which affected 9.7% of the cohort, 52.7% were on SGLT2 inhibitors, with men (60.4%) more likely to receive them than women (37.2%). Similarly, 44.9% of ASCVD patients and 45.5% of DKD patients were on SGLT2 inhibitors, again showing gender disparities (Figure 1). Despite the known benefits of SGLT2 inhibitors, the study underscored their underutilization, particularly among high-risk individuals (Figure 2) and women.

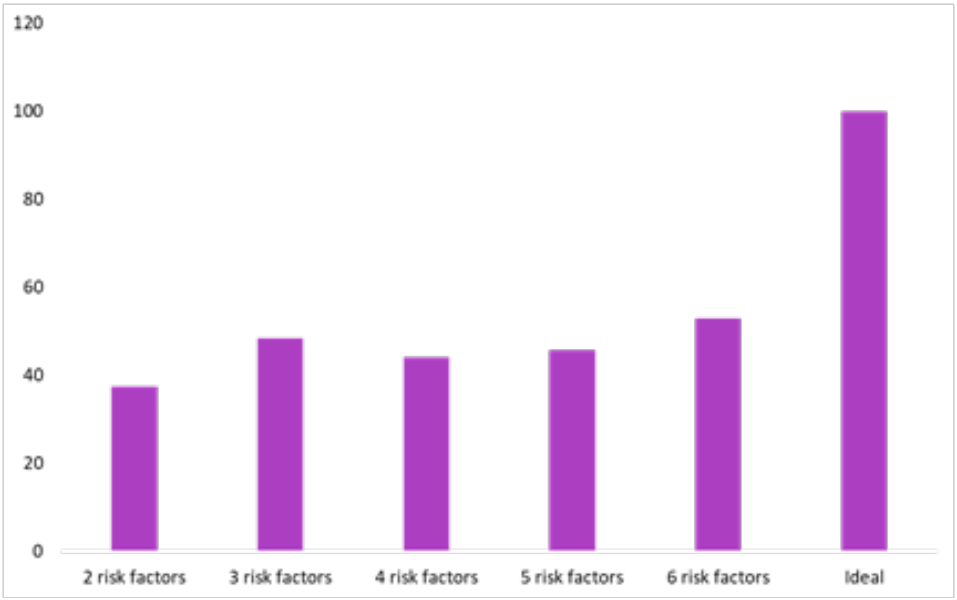

Figure 2: SGLT2 inhibitor use based on the number of cardiovascular risk factors. Risk factors included: obesity, hypertension, dyslipidemia, atherosclerotic cardiovascular disease (ASCVD), age over 60 years, and diabetes duration exceeding ten years.

Potential Reasons for Disparity and Implications for Equitable Care

The observed disparity in SGLT2 inhibitor utilization, particularly the lower prescription rates among women and high-risk individuals, raises important concerns about equitable care. Several factors may hypothetically contribute to this disparity:

- **Clinician Bias:** Unconscious or implicit biases among healthcare providers can influence treatment decisions. For example, there might be an underestimation of cardiovascular risk in women or a perception that certain treatments are more suitable for men.
- **Patient Factors**: Patient preferences, adherence to medication, and access to healthcare can vary significantly. Postmenopausal women, for instance, may be more likely to develop GMI, and maybe to hesitant to restart the medication post resolution.
- **Socioeconomic Factors:** Differences in availability in government hospitals, insurance coverage and access to healthcare can also lead to disparities in treatment.

This disparity has significant implications for equitable care. Underutilization of SGLT2 inhibitors in certain populations means that these individuals are not receiving the full benefits of these life-saving medications. This can lead to poorer health outcomes, increased morbidity and mortality, and a higher burden of disease. Addressing these disparities requires a multi-faceted approach:

- **Education and Awareness**: Healthcare providers need to be educated about the benefits of SGLT2 inhibitors and the importance of equitable prescribing practices. Public awareness campaigns can also help to inform patients about the importance of these medications.
- **Addressing Bias:** Implicit bias training can help healthcare providers to become aware of their biases and take steps to mitigate them.
- **Improving Access:** Efforts to reduce the cost of SGLT2 inhibitors and improve access to healthcare can help to ensure that all patients who could benefit from these medications are able to receive them.

Future Directions

Further research should explore novel indications, including heart failure with preserved ejection fraction (HFpEF), liver fibrosis, and neurodegenerative disorders. Improved clinician education and guideline dissemination can bridge the gap between evidence and practice.

Conclusion

SGLT2 inhibitors represent a paradigm shift in T2DM management, offering cardiovascular, renal, and metabolic benefits. However, real-world utilization remains suboptimal, necessitating enhanced awareness and targeted interventions. Future research and education initiatives should focus on optimizing patient outcomes through appropriate use of these agents.

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