Review Article

The expanding role of SGLT2 inhibitors in cardiovascular and renal protection

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ABSTRACT

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, initially designed for glycemic control in type 2 diabetes mellitus, have emerged as transformative agents in cardiovascular and renal protection. Landmark trials such as DAPA-HF, EMPA-REG OUTCOME, and DAPA-CKD have demonstrated their ability to reduce hospitalizations, cardiovascular mortality, and progression to end-stage renal disease, even in non-diabetic patients. These benefits are attributed to mechanisms beyond glucose lowering, including reducing intraglomerular pressure, promoting natriuresis, enhancing mitochondrial efficiency, and mitigating oxidative stress. SGLT2 inhibitors now offer disease-modifying effects across conditions such as heart failure and chronic kidney disease, reshaping therapeutic strategies. Despite their demonstrated efficacy, clinical adoption remains suboptimal, particularly in non-diabetic populations. Expanding awareness of their broad indications and unique mechanisms is crucial to leveraging their full potential. As ongoing research continues to uncover additional benefits, SGLT2 inhibitors are poised to play an increasingly vital role in improving cardiovascular and renal outcomes across diverse patient populations.

Keywords: SGLT2 inhibitors, cardiovascular protection, renal protection, heart failure

Introduction

A new horizon for SGLT2 inhibitors

Initially developed to manage hyperglycemia in patients with type 2 diabetes mellitus, sodium-glucose co-transporter 2 (SGLT2) inhibitors have demonstrated far-reaching benefits that extend well beyond glucose control. Recent studies have revealed their pivotal roles in protecting both cardiovascular and renal systems, marking a paradigm shift in how we manage patients with heart failure (HF), chronic kidney disease (CKD), and cardiovascular disease, irrespective of diabetic status.[1]

Cardiovascular Benefits: A Game Changer

The heart failure revolution

The breakthrough in cardiovascular protection came with the DAPA-HF trial, where dapagliflozin reduced hospitalizations and cardiovascular death in patients with heart failure with reduced ejection fraction (HFrEF), irrespective of diabetes status. This finding transformed the therapeutic landscape of heart failure, making SGLT2 inhibitors an essential option for heart failure management in both diabetic and non-diabetic populations.[2]

Cardiovascular outcomes trials (CVOTs)

The CVOTs conducted for SGLT2 inhibitors initially focused on reducing the risk of major adverse cardiovascular events (MACEs) in patients with diabetes. EMPA-REG OUTCOME (empagliflozin), CANVAS (canagliflozin), and DECLARE-TIMI 58 (dapagliflozin) were pivotal in showing that these agents not only lower blood sugar but also reduce cardiovascular mortality and hospitalizations for heart failure, expanding their indications into cardiology.[2]

Renal Protection: Preserving Kidney Function

From glucose lowering to kidney preservation

CKD is one of the most significant comorbidities associated with diabetes and heart disease. The CREDENCE and DAPA-CKD trials

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demonstrated that canagliflozin and dapagliflozin reduce the risk of CKD progression, including progression to end-stage renal disease (ESRD), even in patients without diabetes. This revelation has established SGLT2 inhibitors as key players in the management of kidney disease, offering benefits that extend well beyond their original indication for diabetes control.[3]

Mechanisms of renal protection

SGLT2 inhibitors exert renal protective effects through multiple mechanisms, including reducing intraglomerular pressure, promoting natriuresis, and mitigating inflammation and oxidative stress. These benefits make SGLT2 inhibitors a versatile treatment option for slowing kidney disease progression in a broad range of patients, even those without diabetes.[4]

Mechanisms of Action: Beyond Glycemic Control

Blood pressure and diuresis

SGLT2 inhibitors provide additional benefits, including blood pressure reduction and weight loss, primarily through their effects on natriuresis and osmotic diuresis. These mechanisms make them particularly effective in managing heart failure by reducing fluid overload and lowering blood pressure, which contributes to their cardiovascular and renal protective effects.[5]

Mitochondrial Efficiency and Inflammation Reduction

Emerging evidence suggests that SGLT2 inhibitors enhance mitochondrial function and reduce oxidative stress, two key factors in cellular damage and disease progression. By improving metabolic efficiency and mitigating inflammation, these drugs offer protective benefits for the heart and kidneys beyond glucose lowering.[6]

Expanding Indications: More Than a Diabetes Drug

Non-Diabetic indications in focus

With mounting evidence from clinical trials, SGLT2 inhibitors are now being used to treat conditions such as heart failure and CKD in patients without diabetes. This expansion highlights their broader potential as disease-modifying agents, offering significant therapeutic benefits across various conditions previously managed with different drug classes.[7]

Overcoming clinical inertia

Despite compelling evidence, SGLT2 inhibitors remain underutilized, particularly in non-diabetic patients with heart failure and CKD. Greater efforts are needed to raise awareness among clinicians about their expanding indications and to overcome the hesitancy that often accompanies the adoption of new therapeutic strategies. By broadening their use, many more patients could benefit from these life-saving medications.[8]

Conclusion: The Future of Cardiovascular and Renal Protection

The role of SGLT2 inhibitors in cardiovascular and renal protection is only just beginning to be fully appreciated. These drugs, originally developed for diabetes management, are now at the forefront of therapies for heart failure and CKD, marking a revolutionary shift in treatment paradigms. Clinicians must embrace the expanding potential of these medications to improve outcomes in a broader range of patients, not just those with diabetes.

As research continues to uncover new mechanisms of action and benefits, SGLT2 inhibitors are likely to become even more integral to managing cardiovascular and renal diseases, offering hope to millions of patients worldwide.

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