



# SGLT2 Inhibitors and the Cardiorenal Continuum: A Paradigm Shift in the Treatment of Patients with T2D

Javier Escalada

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## EDITORIAL

Type 2 diabetes mellitus (T2D) represents a significant public health problem, with a dramatically increasing prevalence. T2D is considered a progressive disease that develops macro- and microvascular complications such as cardiovascular disease (CVD), heart failure (HF), and chronic kidney disease (CKD), which are closely interconnected and constitute the main causes of morbidity and mortality in these patients. Over time, finding new pharmacological approaches to protect against these cardiorenal events (the “cardiorenal continuum”) has become the fundamental objective of research aimed at these patients.

Until a few years ago, treatment guidelines recommended a glucocentric approach to T2D,

but the appearance of new therapeutic agents such as sodium-glucose cotransporter 2 inhibitors (SGLT2i) or glucagon-like peptide 1 receptor agonists (GLP-1 RA) has meant a radical change evolving to a more holistic approach in which the cardiac and renal protection of patients plays a paramount role in addition to glycemic/metabolic control [1].

SGLT2i are a modern drug class of glucose-lowering agents, with a particular mechanism of action independent of  $\beta$ -cell function and insulin secretion, whose use in patients with T2D has increased in the past few years. By inhibiting the SGLT2 receptor, these drugs increase glycosuria and natriuresis, promoting different metabolic benefits and limiting the risk of hypoglycemia in patients with diabetes [2]. Also, these drugs demonstrate the potential to be used at any stage of T2D, alone or in combination with any class of glucose-lowering agent. Moreover, these agents have been proven to exert direct nephroprotective and cardioprotective effects [3] with important effects beyond their glucose-regulating role.

These benefits have led to the study of SGLT2i in patients with different cardiorenal disease phenotypes. Evidence from EMPA-REG OUT-COME, CANVAS Program, DECLARE-TIMI 58, VERTIS-CV, CREDENCE, and more recently DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DAPA-CKD show that the beneficial effects of SGLT2i are observed across all stages of

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J. Escalada (✉)  
Department of Endocrinology and Nutrition,  
Clínica Universidad de Navarra, Pamplona, Spain  
e-mail: fescalada@unav.es

J. Escalada  
CIBER Fisiopatología de la Obesidad y Nutrición  
(CIBEROBN), Instituto de Salud Carlos III, Madrid,  
Spain

the cardiorenal continuum, ranging from patients with diabetes and multiple risk factors to those with established cardiovascular/renal disease and even independently of T2D status [4, 5].

The benefits observed in these clinical trials have been confirmed in real-life studies in which SGLT2i have been associated with significantly lower risks of all-cause mortality, hospitalization for HF, and major kidney events compared with other glucose-lowering drugs. In addition, this current understanding of the pathophysiological pathways of SGLT2i places this class of drugs in an individualized patient-centered approach and allows clinicians to intervene in different stages of the cardiorenal continuum.

This supplement summarizes all the evidence of this therapeutic change and reviews the role of these drugs from prevention to management of patients who have already developed complications, such as patients with HF and chronic kidney disease.

## PREVENTION OF CARDIORENAL COMPLICATIONS

There is no doubt that prevention and treatment in the early stages of T2D are more cost-effective than managing more advanced disease [6]. In light of the favorable results obtained with SGLT2i, both in primary and secondary prevention, the fact that patients with T2D and comorbidities can be better treated and have options to avoid or delay these complications should be considered. Thus, assessing every patient's cardiovascular and renal risk status has become mandatory to individualize therapy according to the clinical status.

## ROLE OF SGLT2i IN HEART FAILURE

In patients with T2D, HF has been reported to be the most frequent primary cardiovascular disease manifestation. Until recently, no HF therapies directed at glucose metabolism were available, but recent data on the use of SGLT2i in patients with HF (DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and the

SOLOIST-WHF trial) have changed this paradigm showing that they are timely targeting various mechanisms underpinning the HF pathogenesis that go beyond the metabolic control of diabetes. The available published data suggests that SGLT2i can prevent, delay, and reduce the risk of HF, improve quality of life, and increase survival across the different stages of the cardiovascular continuum. Based on this clinical evidence, several guidelines have introduced SGLT2i as a first-line HF treatment.

## SGLT2i FOR THE TREATMENT OF RENAL COMPLICATIONS

Extensive data are now available regarding the renal effects of SGLT2i (such as the DAPA-CKD or CREDENCE clinical trials), demonstrating the renoprotective benefit of these drugs across different glomerular filtration rates and albuminuria values. Accordingly, the most relevant professional societies have updated their guidelines and recommendations regarding the use of these agents in people with chronic kidney disease.

Taking into account the aforementioned and given the solid and abundant scientific evidence that exists regarding SGLT2i, the authors of this special supplement have done an excellent task of synthesis. I would like to invite all those interested in the management of people with T2D to read the supplement, since its focus is those that are the true protagonists of our profession.

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