SGLT2 inhibitors in cardiovascular medicine

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Gliflozins are a relatively new class of drugs targeting and inhibiting sodium-glucose co-transporters (SGLTs). SGLT2 is the major cotransporter involved in glucose reabsorption in the kidney, and its inhibitors prevent the reabsorption of glucose in the kidney, increasing glycosuria and lowering blood glucose levels.^{1,2} Of the

numerous SGLT2 inhibitors available, empagliflozin, canagliflozin, and dapagliflozin have been approved and licenced by both the EMA and the FDA.

Recent evidence has shown that these drugs can have beneficial effects in patients with cardiovascular disorders.

Figure 1 Cartoon depicting the mechanism of action of SGLT2 inhibitors and their beneficial effects of on the cardiovascular system. AGE-RAGE, advanced glycation end products/receptor; ECC, excitation–contraction coupling; PCT, proximal convoluted tubule.

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Evidence from clinical trials

Two landmark clinical trials involving type 2 diabetes mellitus (T2DM) patients with an elevated risk of cardiovascular disease have shown that subjects treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo.³ Moreover, among HF patients with a reduced ejection fraction, the risk of worsening HF or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes.⁴ Another trial demonstrated that among patients receiving recommended therapy for HF, those treated with empagliflozin had a lower risk of cardiovascular death or HF hospitalization than those in the placebo group, independent from the presence of diabetes.² In addition, the effects of sotagliflozin, which also acts on intestinal SGLT1, have been recently tested in T2DM patients who had a recent episode of decompensated HF, revealing a protective effect of this less specific SGLT2 inhibitor on deaths from cardiovascular causes and hospitalizations and urgent visits for HF, without unanticipated increases in adverse events.⁵

Mechanisms underlying the beneficial effects of SGLT2 inhibition in cardiovascular outcomes

Numerous pathophysiological pathways contribute to the cardiovascular effects of SGLT-2 inhibition. Although SGLT2 inhibitors lower

glucose levels, the effects on cardiovascular and renal outcomes are not (only) dependent on glucose lowering (Figure 1).

The main mechanisms proposed to explain the beneficial effects on cardiovascular outcomes include improved cardiomyocyte calcium handling, reduction of blood pressure (most likely attributable to an ameliorated endothelial function), enhanced myocardial energetics, decreased inflammation, induction of autophagy and lysosomal degradation, and reduced epicardial fat.

Conflict of interest: none declared.

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