The Many Faces of SGLT2 Inhibitors : Are They Antidiabetic or Anti-CVDs?

Antidiabetic

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With the impressive benefits on cardiovascular (CV) mortality and hospitalization for heart failure in the EMPA-REG OUTCOME study and the CANVAS program, sodium-glucose cotransporter 2 (SGLT2) inhibitors has been the first class of the antihyperglycemic agents with proven CV benefit in type 2 diabetes with established atherosclerotic cardiovascular diseases (ASCVDs), followed by GLP-1 receptor agonists. Recently, the results of DECLARE-TIMI58 trial confirmed the benefit of SGLT2 inhibitors in reduction of the rate of hospitalization for heart failure, even in the patients with type 2 diabetes who were at high risk for CV events but did not have ASCVDs at baseline. All of the three major CV outcome trials of SGLT2 inhibitors showed consistent pattern of effect that SGLT2 inhibitors have a more robust and consistent effect on the prevention of heart failure and renal outcomes than on atherosclerotic CV events.

Although several clinical trials in patients without diabetes are ongoing, current evidence of CV benefit with SGLT2 inhibitors has been from the clinical trials conducted in patients with diabetes. Therefore, extrapolation of those results to the people without diabetes who have heart failure or are at high risk for developing heart failure should be cautious.

Just as the modest reduction in glucose level can not explain the CV benefit of SGLT2 inhibitors, any single factor including hemodynamic effects is not enough to explain the CV benefit of SGLT2 inhibitor. Importantly, as a compensation to the loss of glucose via glucosuria, SGLT2 inhibition causes a shift in whole body fuel metabolism resulting in increased free fatty acid and ketone levels. Ketone is a 'super fuel' for diabetic heart with metabolic inflexibility, in which inefficient fuel metabolism using free fatty acid is dominant due to insulin resistance. The shift in fuel metabolism by SGLT2 inhibition is also present but much attenuated in people without diabetes. Also, the benefit of such shift in fuel metabolism would be much smaller in people without insulin resistance or type 2 diabetes.