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Results confirm benefit of SGLT2 inhibitors on cardiovascular outcome in diabetic patients

Drugs that inhibit the sodium–glucose cotransporter 2 (SGLT2 inhibitors; gliflozins) decrease renal glucose reabsorption. The increase in urinary glucose excretion will reduce blood glucose levels and SGLT2 inhibitors were developed to improve glucose control in patients with type 2 diabetes. The randomized placebo-controlled cardiovascular outcome trial of the SGLT2 inhibitor empagliflozin (EMPA-REG OUTCOME), reported on in a previous issue of *ISH Hypertension News*, demonstrated a modest improvement in glucose control [1,2]. More important, however, the authors reported a lower rate of the primary composite cardiovascular endpoint (cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke), and of all-cause mortality in patients with type 2 diabetes. A recent publication by Neal and collaborators [3] now reports results that suggest that this benefit on cardiovascular outcome by SGLT2 inhibitors may be a drug class effect.

The CANVAS program integrated results from two studies with 10,142 patients with type 2 diabetes and high cardiovascular risk, randomized to receive the SGLT2 inhibitor canagliflozin or placebo, with a mean observation time of 3.6 years [3]. The two studies (CANVAS and CANVAS-R) had similar inclusion criteria and were intended to be analysed together, but CANVAS-R in addition assessed effects on albuminuria. The mean age was 63 years, the duration of diabetes 14 years, two thirds had a history of cardiovascular disease, and one fourth had microalbuminuria. Approximately 30% of the participants discontinued the assigned treatment during the course of the study, similar in both groups. Patients in the canagliflozin groups had on average about 0.6% lower haemoglobin A1c values, 4/1 mm Hg lower blood pressure, and lost 1.6 kg more in weight.

The primary outcome (a composite of cardiovascular mortality, non-fatal myocardial infarction, and non fatal stroke) occurred in 26.9 vs 31.5 patients per 1000 patient years, with a hazard ratio and 95% confidence interval in favour of active treatment of 0.86; 0.75 to 0.97. Active treatment also appeared to reduce the progression of renal dysfunction assessed as albuminuria (hazard ratio 0.73; 0.67 to 0.79), and the composite of deterioration of glomerular filtration rate, renal replacement therapy, and mortality from renal causes (hazard ratio 0.60; 0.47 to 0.77). Also heart failure hospitalizations were reduced. Somewhat unexpected, the risk of primarily distal amputation was higher in the group randomized to active treatment (hazard ratio 1.97; 1.41 to 2.75). As previously reported for SGLT2 inhibitors, adverse events with genital infections, volume depletion, and diuresis were more common in the group treated with canagliflozin.

The results of the CANVAS program suggest that the positive effects on cardiovascular outcome initially observed with empagliflozin [1] might be a general class effect of SGLT2 inhibitors. This is indirectly supported by a recently published observational analysis from the Nordic countries (Denmark, Norway, and Sweden) [4]. By use of individual patient level data from the Prescribed Drug Registers, Cause of Death Registers, and National Patient Registers, all patients with filled prescriptions for glucose lowering drugs between 2012 and 2015 were followed until the end of 2015. Matched SGLT2 inhibitor (94% dapagliflozin, 5% empagliflozin, and 1% canagliflozin) and other glucose lowering drug groups (1:3 propensity score matching) show a decreased risk for cardiovascular mortality (hazard ratio 0.53; 0.40 to 0.71) and major cardiovascular events (hazard ratio 0.78; 0.69 to 0.87) in favour of the SGLT2 inhibitor group.

These results taken together are important as they

suggest a class of glucose lowering drugs that can reduce cardiovascular morbidity and mortality in high-risk type 2 diabetic patients. However, the reductions in haemoglobin A1c were modest and it is unlikely that this change in glycaemic control could affect cardiovascular events within such a short period of time. The rapid effects of SGLT2 inhibitors on blood pressure, body weight (likely to reflect fluid loss and reduced tissue mass), and cardiovascular events suggest that hemodynamic effect contributes to the benefit observed with SGLT2 inhibitors. However, several mechanisms may be important for the beneficial effects on cardiovascular outcome [5-7]. SGLT2 inhibitors were developed to improve glucose control in diabetic patients. It will be interesting to see the results of ongoing studies, examining the effects of SGLT2 inhibitors on cardiovascular events in patients with cardiovascular disease but with no diabetes. These and other studies will eventually clarify if SGLT2 inhibitors should be considered glucose lowering drugs for diabetic patients with additional cardiovascular protective effects, cardiovascular (antihypertensive and/or diuretic) drugs with additional glucose lowering properties, or renal protective drugs with additional cardiovascular and glucose lowering effects. The issue is not trivial, for patients, care providers, regulatory authorities, and

for the pharmaceutical industry.

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Hot Off the Press



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Increased salt consumption induces body water conservation and decreases fluid intake

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This particular article made [international headlines](#) in May when the New York Times and other media outlets highlighted how the results could change our understanding of the body's handling of sodium ¹. Current dogma is that increased salt intake leads to increased thirst which stimulates fluid intake. However there had been prior studies which have questioned this relationship ². This study, and other related ones from the same study cohort, are quite comprehensive and could be the subject of much larger and more comprehensive summaries. I will restrict my summary to the major highlights of the study.

The primary goal of this study was to examine the relationship between salt intake and urine volume and the authors took a very innovative approach.

The authors took advantage of two simulated Mars missions being conducted by the European Space Agency and the