

Commentary:
SGLT2 inhibitors: hypotheses on the
mechanism of cardiovascular protection.

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and

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Diabetes is an important cardiovascular risk factor, but until recently there has been a disconnect between diabetic management and reduction of cardiovascular mortality and morbidity. Indeed, such was the mixed impact of previous generations of anti-hyperglycaemics that the US and European drug regulatory bodies mandated cardiovascular outcome studies for all future therapeutic interventions. It is ironic that this move has unveiled the unexpected but welcomed benefit of a new generation of diabetic management therapies that include the SGLT2 inhibitors. Much has already been written regarding the reduction of cardiovascular death in patients with, or at high risk of developing coronary artery disease and much speculation regarding the mechanism of cardioprotection in respect to blood pressure reduction, diuresis and weight loss¹. However, it is also worth speculating that these drugs have additional, potentially pleiotropic effects that underlie their cardioprotective outcomes.

SGLT2 inhibitors: a class benefit

With two large clinical outcome studies (Empagliflozin/ EMPA-REG OUTCOME² and Canagliflozin/ CANVAS³) in addition to supporting registry data from the retrospective CVD-REAL study⁴, it seems increasingly likely that the cardiovascular benefit of SGLT2 inhibition is a class effect. Mortality curves separate extremely quickly – within the first 2-3 months of treatment initiation, an observation that appears to favour a direct, cytoprotective mechanism of action against the toxic effect of elevated glucose in stressed cells. Indeed, in the high-risk patient cohort examined in the EMPA-REG study, patients were just as likely to suffer an acute myocardial or cerebral ischaemic event on an SGLT2 inhibitor, but they had a better chance of surviving that event – an observation supportive of a cellular protective hypothesis in the setting of an acute injury.

Potential cytoprotective mechanisms

There is emerging evidence of at least four disparate pleiotropic effects of SGLT2 inhibitors that extend beyond their efficacy as oral anti-hyperglycaemics, impacting upon tissues (brain and heart) that have negligible native SGLT2 expression.

1) The interaction between SGLT1/SMIT and gp91^{phox} NADPH oxidase

Reactive oxygen species (ROS) play a highly regulated role in normal physiological signalling and are involved in cellular adaptations to cellular stress (for example, gp91^{phox} NADPH oxidase-linked ischaemic conditioning⁵). However, excess ROS production leads to pathological states such as heart failure and exacerbation of ischaemic cell death as occurs in ischaemia/reperfusion injury and heart failure.⁶ In the heart, SGLT1/SMIT has been linked gp91^{phox} NADPH oxidase activity⁷, and demonstrated as a cause of myocardial injury. Clinical SGLT2 inhibitors such as Empagliflozin are highly selective towards SGLT2, but others, such as Canagliflozin, have more mixed SGLT2/SGLT1 inhibitory action; SGLT1 inhibition abrogates the excess ROS generation precipitated by pathophysiologically-relevant high glucose in experimental models⁷, and thus raises the hypothesis that SGLT2 inhibitors, either directly through mixed SGLT2/SGLT1 inhibition, or indirectly through improved glycaemic control at the time of the ischaemic insult, may reduce injury through attenuation of oxidant stress in ischaemic tissue.

2) Inhibition of the sodium hydrogen exchanger (NHE)

Recent data from Zuurbier's group demonstrates that Empagliflozin, at a clinically relevant concentration, attenuates myocyte sodium accumulation associated with raised extracellular glucose via NHE inhibition. The subsequent attenuation of cytosolic calcium accumulation and increased mitochondrial calcium⁸ is beneficial in heart failure.⁹ Moreover, NHE inhibition is known to be cardioprotective in the context of ischaemia/reperfusion injury: in animal studies, NHE inhibition has been found to be highly effective at reducing myocardial injury. These data informed early clinical trials studying acute NHE-1 inhibition in the context of ACS and CABG. However, these studies (ESCAMI and GUARDIAN) were largely neutral, thought to be due to failure of the inhibitors to reach the ischaemic myocardium prior to revascularisation; in animal studies, these drugs were highly cardioprotective only when administered prior to the onset of injurious ischaemia.¹⁰ While it is not known whether other SGLT2 inhibitors share this NHE inhibitory potential, patients in the EMPA-REG study would already have been exposed to Empagliflozin-mediated NHE inhibition prior to the ischaemic insult, raising an interesting, testable hypothesis to explain the observed reduction of fatal myocardial and cerebral ischaemia through NHE inhibition.

3) Inhibition of SGLT-induced intracellular sodium and calcium accumulation

In a similar vein to (1) and (2) above, a "glucotoxicity" model of exacerbated cellular injury has been suggested based upon neuronal and myocardial SGLT1 activity. Increased extracellular glucose promotes sodium and glucose transport into cells, and in the context of acute ischaemia/ reperfusion injury – as occurs in myocardial infarction or stroke – the combination of elevated extracellular glucose and vulnerable, post-ischaemic cells leads to toxic accumulation of sodium and therefore also of calcium, which in turn leads to opening of the mitochondrial permeability transition pore and thus to cell death.¹¹ That SGLT1 expression is also increased following ischaemia and in heart failure, SGLT1 may therefore play an important role in exacerbating cellular injury. While highly selective clinical SGLT2 inhibitors will have minimal impact upon SGLT1 activity, we hypothesise that improved glucose control with missed SGLT1/SGLT2 inhibitors may themselves be sufficient to mitigate against SGLT1-mediated glucotoxicity in acutely injured cells.

4) Glucagon and metabolic substrate switching towards ketones

Change of myocardial energy utilisation and metabolic substrate switching may not be unique to SGLT2 inhibitors, but these drugs do lead to marked glycosuria, caloric loss and a mild ketogenesis in diabetic patients.¹² Glucagon release by pancreatic α -cells is increased following SGLT2 inhibition, which may be beneficial in heart failure through its inotropic effects,¹³ but also increases availability of circulating ketones, thereby providing organs that are critically challenged by hypoxia or ischaemia are provided with an advantageous energy substrate in which to synthesise ATP with reduced oxygen consumption as compared to glucose or fat, as postulated by Ferrannini and others.^{14,15} Very little experimental data is currently available to support this hypothesis as an explanation for the advantageous outcomes in EMPA-REG and CANVAS, but it presents an intriguing avenue for further exploration.

Summary and conclusions

The recent outcome studies, EMPA-REG and CANVAS, present a dramatic step-change in our understanding of the management of diabetes and cardiovascular disease. Unexpected and welcome,

SGLT2 inhibition has been shown to have a beneficial cardiovascular outcome in patients with type 2 diabetes. While questions still remain, we are at an exciting juncture where anti-hyperglycaemic therapies may *finally* realise cardiovascular benefits in patients with type 2 diabetes. Oddly perhaps, we now need to undertake reverse translational medicine – i.e from bed-side to bench - and start to work out how these exciting findings are manifest

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