Beneficial effects of sodium glucose co-transporter 2 inhibitors (SGLT2i) on heart failure and cardiovascular death in patients with type 2 diabetes might be due to their off-target effects on cardiac metabolism

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Sodium/glucose co-transporter 2 inhibitors (SGLT2i) lower blood glucose by inhibiting the reabsorption of glucose in the proximal renal tubules. There are several licensed SGLT2i. One of them, empagliflozin, was evaluated in the EMPA-REG OUTCOME trial. This prospective, randomised, double-blind, placebo-controlled, survival study included 7020 patients with type 2 diabetes mellitus (T2DM) and followed them for a median period of 3.1 years. The EMPA-REG OUTCOME trial showed that the use of either 10 or 25 mg/d of empagliflozin (cumulative results presentation because there were no significant differences between the two doses) on top of standard therapy produced relative risk reductions in the primary endpoint (cumulative incidence of death from cardiovascular disease (CVD), nonfatal myocardial infarction (MI) or nonfatal stroke) by 14%, total mortality by 32%, of CVD mortality by 38% and hospitalisation for heart failure (HF) by 35% compared with placebo; all reductions were highly statistically significant. The main side effect was an increased rate of genital infection.

Following a review of a few cases, the European Medical Agency recommended an update of all SGLT2i Summary of Product Characteristics to include diabetic ketoacidosis as a rare (1/1000 patients) adverse reaction.

The mechanisms driving the effects of empagliflozin on HF and CVD death are not clear. Potential mechanisms include osmotic diuresis, modulation of the cardiorenal axis that reduced plasma volume and less sodium retention, reduction in arterial stiffness, reduced left ventricular afterload, fall in body weight and blood pressure (BP), without increases in sympathetic nervous activity, delay in renal function impairment, reduction in hyperglycaemia with linked reduction in insulin levels and reductions in serum uric acid (SUA) levels. However, even all those collectively may not be enough to explain the substantial clinical benefits of empagliflozin manifested early (within the first 3 months of the study) in the EMPA-REG trial.

Recently, two papers tried to explain the possible mechanism of empagliflozin clinical benefits focusing on its effect on heart metabolism or “energetics”; this hypothesis, together with all the off-target effects mentioned above, might be an explanation for the beneficial outcomes of empagliflozin in the EMPA-REG trial.

Several years ago, it was suggested that people with T2DM or insulin resistance have an impaired myocardial metabolism with decreased utilisation of glucose and increased myocardial free fatty acid (FFA) uptake and oxidation, resulting in a mismatch between blood/metabolite supply and cardiac metabolic needs. It has also been suggested that if myocardial dysfunction is no longer considered as the simple oxygen/metabolite demand/supply unbalance, but as an energetic disorder, this will motivate the development of drugs aiming at this specific metabolic disorder rather than just treating the risk factors and the symptoms of the ischaemic and/or failing diabetic heart. It has been suggested that a therapeutic approach aiming at an improvement of cardiac metabolism, through
manipulation of glucose and FFA may improve the risk of MI and HF.\[10\] This topic was forgotten until now.\[6,7\]

The hypothesis that the clinical benefits of empagliflozin might be partially due to “energetic” causes was presented in the two recent studies mentioned above.\[6,7\] These suggest that because of persistent hyperketonaemia (both fasting and postprandial plasma β-hydroxybutyrate concentrations are increased two- to three-fold in patients on SGLT2i),\[6,7\] β-hydroxybutyrate is freely and avidly taken up by the heart (and other organs like the kidney) and is oxidised in preference to FFA (also increased), resulting in a more competent oxidation of the cardiac mitochondria and in increasing free energy production by ATP hydrolysis.\[6,7\] This improves the transduction of oxygen consumption into work efficiency at the mitochondrial level, further boosted by the haemoconcentration seen in patients on SGLT2i, probably due to its diuretic effect.\[6,7\] This creates a synergy of increased oxygen supply combined with a metabolic substrate change to a more efficient “fuel.”\[6,7\] Thus, even small to moderate beneficial changes in energetics (better demand/supply and oxygen/metabolite ratios) and a more effective fuel consumption by the heart in every heartbeat for billions of heartbeats over the years translate into better cardiac perfusion and better cardiac pump capacity, manifested at a clinical level as a substantial improvement in CVD and HF outcomes.\[6,7\] The above suggests that a side effect (ketonaemia) of SGLT2i use which is present in most, if not all, of the patients with T2DM treated with SGLT2i, is an off-target cardiac metabolic effect of the drug. Together with other on- and off-target effects mentioned above, this effect may be related to the beneficial clinical outcomes seen in the EMPA-REG trial.\[2,6,7\]

The findings of EMPA-REG trial are of great significance, because HF is one of the most common initial manifestations of CVD in T2DM.\[11\] The CALIBER (from the UK) programme included 1,921,260 individuals, of whom 34,198 had T2DM on standard hypoglycaemic therapy.\[11\] There were 113,638 first CVD events during a mean follow-up period of 5.5 years.\[11\] HF (and peripheral arterial disease) was the most common initial manifestations of CVD in T2DM, even more common than MI.\[11\]

If previously known HF is taken into consideration, this increases dramatically the total prevalence of HF among patients with T2DM.\[12\] A study from the Netherlands showed that nearly one-third of T2DM subjects over 60 years of age had unknown HF previously; 6% with reduced ejection fraction (HFrEF) and 26% with preserved ejection fraction (HFpEF), $p < 0.001$. Thus, among T2DM patients with HF, the majority (81%) had HFrEF, while the minority (19%) had HFpEF.\[12\] The results were similar from the Shinkaen Database (2004–2011) which included 17,517 naïve patients.\[13\] A total of 1525 patients were diagnosed with symptomatic HF, 1121 patients (74%) exhibited HFpEF and 404 patients (26%) HFrEF.\[13\]

The ratio of the two forms of HF is important, because patients with HFpEF have a poor prognosis, and no treatment has been shown to improve outcomes.\[14\] In contrast, the treatment of HFrEF evolved during the last 20 years and improved patient (even those with T2DM) survival and quality of life.\[15–17\] However, the treatment options for HFpEF remained limited\[18\] and usually not effective.\[19\] Thus, if there is a drug with an off-target property to improve quality of life (hospitalisation for HF) and survival (HF, total, and CVD mortality), we have a groundbreaking finding.

The EMPA-REG trial did not report how many patients had HFpEF and HFrEF.\[2\] However, given that reliable data from previous studies and various countries\[11–13\] suggest that HFpEF is highly prevalent in T2DM subjects, we can hypothesise that most HF patients in that trial had HFrEF. All these numbers make the results of the EMPA-REG trial\[2\] even more impressive and useful. Data suggest that 10% of the EMPA-REG trial patients have HF, a complication of T2DM, presumably the majority with HFpEF which has poor prognosis and no generally accepted therapy. The use of a hypoglycaemic drug (empagliflozin) substantially decreased the incidence of hospitalisation for HF by 35%, beneficially affected sudden cardiac death, CVD fatal and non-fatal events and all-cause mortality.\[2,20\] These are impressive, and potentially guideline-changing, findings.\[2,20\] If these results are related to the specific SGLT2i compound or are drug class effects needs to be confirmed in prospective, randomised, controlled survival trials.

All the above effects of empagliflozin were probably not mediated by changes in the lipid profile because this drug seems to slightly increase low-density lipoprotein cholesterol (LDL-C) levels although high density lipoprotein cholesterol (HDL-C) levels are also increased.\[2\] However, the percentage of small dense low-density lipoprotein cholesterol particles (sdLDL) may be decreased thus compensating for the small rise in total LDL-C.\[21\] This is because SGLT2i modestly decreases triglyceride (TG) levels and increases HDL-C levels; these are markers that reflect a fall in sdLDL levels.\[22\] Moreover, both postprandial TG and fasting TGs levels may be predictors of CVD risk.\[23–27\] However, lipids probably do not play a major role in shaping CVD morbidity and mortality during SGLT2i therapy.

A GLP-1 RA with a SGLT2i might be more effective in reducing CVD-related morbidity and mortality than either drug alone.\[28\] This is because SGLT2i reduces total and CVD mortality as well as HF hospitalisations, and GLP-1 RA reduces total and CVD mortality as well as non-fatal MI.\[28\] The suggestion for drug combination leads to the idea of combining both of these two newer antidiabetic agents (GLP1 RA and SGLT2i) with a potent statin, which further reduces total and CVD morbidity and mortality,
with different mechanisms than the hypolipidaemic drugs mentioned above.\[29,30\]

In conclusion, the SGLT2 inhibitor empagliflozin exhibited significant morbidity and mortality results in the EMPA-REG trial.\[2\] It is unlikely that these benefits could be attributed to its mild hypoglycaemic effects (HbA1c reduction ranged by 0.54–0.60% at 12 weeks and 0.24–0.36% at the end of the study).\[2,7\] It is possible that off-target effects are responsible for these surprising results. The obvious off-target effects such as osmotic diuresis, modulation of the cardio-renal axis, reduction in plasma volume, avoidance of sodium retention, reduction in arterial stiffness, reduced left ventricular afterload, reduction in body weight and BP, delay in renal function impairment and reductions in SUA levels do not seem enough to explain the surprisingly beneficial results. Furthermore, the event-related benefits seem to occur early in the EMPA-REG trial. The recently presented “metabolic” theory (shift from FFA to ketone consumption by the heart in the presence of haemoconcentration) is promising.

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