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What have we learned from DAPA-HF?

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Take Home Messages

- After 4 large safety trials of sodium-glucose co-transporter 2 (SGLT2) inhibitors in type 2 diabetes showed unexpected benefits in preventing new-onset heart failure, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) was the first randomized controlled trial to test SGLT2 inhibitors in a population with established heart failure with reduced ejection fraction (HFrEF), with or without diabetes.
- In DAPA-HF, Dapaglifozin significantly reduced the primary composite outcome of worsening heart failure or cardiovascular death in a contemporary heart failure population, with benefits seen irrespective of diabetes
- These findings inform the ongoing debate regarding the mechanism by which SGLT2 inhibitors are cardio- and renoprotective, but to change practice would ideally require corroboration by ongoing trials in HF to establish a consistent class effect.

Introduction

The Dapaglifozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial [1] is the first randomized control-ed trial designed to assess the benefits of sodium-glucose cotransporter 2 (SGLT2) inhibitors in heart failure with reduced ejection fraction (HFrEF), regardless of the presence or absence of type 2 diabetes, and comes less than a month after the recently revised 2019 European Society of Cardiology / European Association for the Study of Diabetes (ESC/EASD) guideline [2]. It carries substantial implications for the heart failure community.

Before DAPA-HF

SGLT2 inhibitors were originally intended as drugs for diabetes mellitus: they block glucose reabsorption in the proximal renal tubule, resulting in glucosuria, natriuresis, and falls in afferent glomerular pressures, HbA1c, and body weight (3). Before DAPA-HF, four cardiovascular outcome trials with SGLT2 inhibitors had been published (4–9). These studies were designed primarily to assess cardiovascular safety in patients with type 2 diabet-es with insufficient glycaemic control at high cardiovascular risk. Such safety studies are a regulatory requirement since the thiazolidinediones, in particular Rosiglitazone, were shown to increase heart failure (HF) events (10,11). However, SGLT2 inhibitors were consistently associated with unexpected benefits with respect to lowering HF hospitalisations.

There were some differences in definitions of terms across the four safety studies (**Table 1**). Unlike the later studies, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients - Removing Excess Glucose (EMPA-REG OUTCOME) enrolled exclusively patients with established atherosclerotic cardiovascular disease.

About the author

Dr Mark Peterzan is an ST5 trainee on the South London rotation. He recently completed a DPhil investigating creatine kinase kinetics in the hearts of patients with severe valvular heart disease and in athletic remodelling at the Oxford Centre for Clinical Magnetic Resonance Research (John Radcliffe Hospital, Oxford), and plans to train in imaging and heart failure.

The EMPA-REG OUTCOME trial randomized 7020 patients to Empaglifozin 10 mg once daily (od), 25 mg od, or placebo, with a median observation time of 3.1 years, and showed reductions in all-cause mortality of 32% ($p<0.0001$) and HF hospitalisation of 35% ($p<0.002$) (12). Post hoc analyses showed that these benefits were irrespective of the presence of HF at baseline, which comprised 10% of the study cohort (13).

The Canagliflozin Cardiovascular Assessment Study (CANVAS) Program randomized 10,142 participants to Canaglifozin 100-300 mg od or placebo, with a median follow-up of 2.4 years, and showed reductions in the primary outcome (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) of 14% (odds ratio (OR) 0.86, 95% confidence interval (CI) 0.75-0.97) and in HF hospitalisation of 33% (OR 0.67, 95% CI 0.52-0.87) (7). The benefit on the primary outcome was irrespective of a history of HF, which comprised 14% of the study cohort, but was increased in those using diuretics ($p<0.001$). Patients with New York Heart Association (NYHA) class IV HF were excluded. The absolute risk reduction of the composite of cardiovascular death or HF hospitalisation was greater in those patients with a history of HF (14). A retrospective analysis stratified by left ventricular ejection fraction (LVEF) obtained as part of routine clinical care during an incident HF event found that Canagliflozin significantly reduced fatal or hospitalised HF events in HFrEF (LVEF<50%, hazard ratio (HR) 0.69, 95% CI 0.48-1.00, HF with unknown EF (HR 0.54, 95% CI 0.32-0.89) but not in HFpEF (LVEF≥50%, HR 0.83, 95% CI 0.55-1.25) (15). This analysis however was limited by the lack of pre-enrolment LVEF and incomplete data.

The Dapagliflozin Effect on Cardiovascular Events-Thrombolysis In Myocardial Infarction (DECLARE-TIMI 58) trial randomized 17,160 patients to Dapaglifozin 10 mg od or placebo, with a median follow-up of 4.2 years, showed no increase or decrease in major adverse cardiac events (MACE defined as cardiovascular death, nonfatal myocardial infarction, ischaemic stroke) but a fall in cardiovascular death or HF hospitalisation driven by a fall in the latter (HR 0.73, 95% CI 0.61-0.88) (8). The benefit on hospitalisation for HF was irrespective of baseline HF status (Supplemental Figure 5 in Ref (8); 10% of the cohort had HF at baseline). Unlike the other trials, patients with estimated creatinine clearance 30-59 ml/min were excluded. A retrospective analysis stratified by LVEF at baseline found that Dapaglifozin reduced cardiovascular death or HF hospitalisation to a greater extent in patients with HFrEF (LVEF <45%, HR 0.62, 95% CI 0.45-0.86) than in patients with HF without known reduced EF (LVEF ≥45% or unknown LVEF, HR 0.88, 95% CI 0.76-1.02; $p=0.046$ for interaction) (16). There were similar interactions indicating greater benefit in HF patients with LVEF <45% for HF hospitalisation, cardiovascular death and all-cause mortality. However, these observations are limited: most patients had estimated creatinine clearances ≥60 ml/min, LVEF values were available in only a third of patients, and no maximum time window for the LVEF measurement before enrolment was specified.

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial randomized 4401 patients to Canaglifozin 100-300 mg od or placebo, with a median follow-up of 2.6 years, and showed reductions in the primary composite renal outcome of 30%, and in the secondary outcomes cardiovascular death, nonfatal MI or stroke (HR 0.80, 95% CI 0.67-0.95) and HF hospitalisation (HR 0.61, 95% CI 0.47-0.80) (9). Fifteen per cent of the cohort had HF at baseline.

In summary, the findings from these four trials indicated a consistent benefit with respect to lowering HF hospitalisation. This was despite trial regimen discontinuation rates of 25% (EMPA-REG OUTCOME), 30% (CANVAS), 23% (DECLARE-TIMI 58), and 27% (CREDENCE). Genital infections were more common with all the SGLT2 inhibitors, whilst diabetic ketoacidosis was more common with Dapagliflozin and amputation of toes, feet or legs more common with Canagliflozin. The benefit on HF hospitalisation was increased in those with lower estimated glomerular filtration rates (eGFRs) (17). In the context of the low (10-15%) baseline HF rates, this points mainly to prevention of new clinical HF. While the mechanisms of action for this benefit were not clear (see below), they were likely to diverge from conventionally understood atherothrombotic risk modulation, as benefits on atherothrombotic events (myocardial infarction, stroke) were not observed in any one trial considered alone. (A meta-analysis of EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58 found that SGLT2 inhibitors reduced MACE in patients with established atherosclerotic disease (HR 0.86, 95% CI 0.80-0.93) but not in those with

multiple risk factors only (HR 1.00, 95% CI 0.87-1.16) (17). In patients with atherosclerotic cardiovascular disease, this composite was driven by falls in myocardial infarction (HR 0.85, 95% CI 0.76-0.95) and cardiovascular death (HR 0.80, 95% CI 0.71-0.91), with no effect on stroke.) Given this signal regarding HF events over atherothrombotic events, it was appropriate to assess the benefit of this class of drugs specifically in a population with established HF, regardless of the presence of type 2 diabetes.

DAPA-HF

DAPA-HF randomized 4744 patients with or without type 2 diabetes to Dapaglifozin 10 mg od or placebo with a median follow-up of 18.2 months (1). Eligibility criteria were age ≥18, LVEF ≤40% and NYHA II-IV symptoms, and N-Terminal-pro brain natriuretic peptide (NT-proBNP) ≥600 pg/ml (≥400 if hospitalised for HF in the previous year, and ≥900 if in atrial fibrillation or flutter). Exclusion criteria were recent treatment or unacceptable side effects with an SGLT2 inhibitor, type 1 diabetes, symptoms of hypotension or systolic blood pressure (BP) <95 mmHg, and eGFR <30 ml/min. At baseline, 42% had known type 2 diabetes and an additional 3% received a new diagnosis of diabetes. Mean age was 66±11; the main cause of HF was ischaemic in 56%, 68% were in NYHA II, mean HR was 72±12, mean systolic BP 122 mmHg, mean LVEF 31±7% and median NT-proBNP 1400 pg/ml. Eighty three percent were using ACE-I or ARB, 96% beta-blocker, 71% mineralocorticoid receptor antagonist (MRA), and 11% sacubitril-valsartan. Thirty eight percent had atrial fibrillation, 26% implantable cardioverter defbrillator (ICD) and 7% cardiac resynchronization therapy (CRT). During the trial, the study regimen was discontinued in 11% of patients.

The primary outcome, a composite of worsening HF (unplanned hospitalisation or an urgent visit resulting in intravenous therapy) or cardiovascular death, was reduced in the Dapaglifozin group (HR 0.74, 95% CI 0.65-0.85). Each component of this outcome was significantly reduced – hospitalisation for HF or urgent HF visit (HR 0.70, 95% CI 0.59-0.83), cardiovascular death (HR 0.82, 95 % CI 0.69-0.98) – and all-cause death (HR 0.83, 95% CI 0.71-0.97). More patients in the Dapaglifozin group had a ≥5-point improvement in the Kansas City Cardiomyopathy Questionnaire symptom score (OR 1.15, 95% CI 1.08-1.23) and fewer had significant deterioration (OR 0.84, 95% CI 0.78-0.90). There was no excess in any serious adverse event in the Dapaglifozin group.

The observed benefits were consistent irrespective of the presence of type 2 diabetes, supporting the hypothesis that the mechanism of benefit is independent of glucose lowering and for the first time potentially extending the role of the SGLT2 inhibitor class to patients without type 2 diabetes. Considering the primary outcome with respect to other subgroups (age above or below 65 years, sex, race, geographic region, LVEF above or below the median, NT-proBNP above or below the median, ischaemic or non-ischaemic aetiology of HF, body mass index above or below 30 kg/m2, eGFR above or below 60 ml/min), there was generally consistent benefit. There was a signal for less benefit in NYHA III-IV versus II, but this was not supported by the consistent benefit across subgroups when considering other indicators of more advanced disease (NT-proBNP, LVEF, worse renal function).

Author-noted limitations include the low proportion of black patients (<5%), few patients > age 85 years, and the low proportion of sacubitril-valsartan use (11%). To this we might add the lower proportion of women (23%), the baseline heart rate (72) and systolic BP indicating room for dose uptitration (baseline doses were not reported), and the lower proportion of severely symptomatic patients. Positive factors worth highlighting include the eGFR threshold of 30 ml/min (the prior Dapaglifozin study set 60 ml/min), the high rate of baseline MRA use, consistency of benefit across subgroups, and the size of benefit given the background HF therapies already employed.

How do SGLT2 inhibitors reduce HF hospitalisation? What are the possible beneficial mechanisms?

Several mechanisms have been suggested to mediate the cardiorenal benefits of SGLT2 inhibitors (reviewed (3,18–24)). These drugs block glucose reabsorption in the proximal renal tubule, resulting in glucosuria, natriuresis, and falls in afferent glomerular pressures, HbA1c, body weight, plasma volume, blood pressure, and serum uric acid. In DAPA-HF there were placebo-adjusted effects on HbA1c of -0.24%, on systolic BP of -1.3 mmHg, on haematocrit of +2.4%, on body weight of -0.87 kg, on NT-proBNP of -303 pg/ml, and on serum creatinine of +0.02 mg/dl.

Renoprotection

Benefits of SGLT2 inhibitors on MACE were observed only in those with established atherosclerotic cardiovascular disease and were only detectable on meta-analysis of three trials (17). In contrast, no heterogeneity between groups with and without established atherosclerotic disease was observed with respect to reduced HF hospitalisation (HR 0.70 for both groups) and reduced adverse renal outcomes (HR 0.55, 95% CI 0.48-0.64). Patients with worse baseline renal function were at higher risk of HF hospitalization (17). Together, these observations suggest that the beneficial effects of SGLT2 inhibitors on HF hospitalisation and renoprotection might share a common mechanism, as renoprotection and natriuresis would both be expected to reduce HF hospitalisation.

Glucose lowering and increased haematocrit

The hypothesis that glucose lowering might contribute to benefit has been further undermined by: the consistency of benefit irrespective of baseline diabetes status in DAPA-HF, the increased benefit in patients with worse renal function (where the glucosuric effect is weakened) (17), and the known modest effect of more-intensive glycaemic control on MACE (HR 0.91, 95 % CI 0.84-0.99) and the neutral effect on hospitalised/fatal HF (HR 1.00 95 % CI 0.86-1.16) as compared with less-intensive control (25). The hypothesis that haematocrit increases underlie the benefit is undermined by the lack of differential benefit in ischaemic HF versus non-ischaemic HF, and the known lack of benefit derived from erythropoietin-mimetics in systolic HF (26).

Natriuresis

Unlike loop diuretics, the natriuretic effect of SGLT2 inhibitors reduces afferent arteriolar pressures and intraglomerular hypertension. This may contribute to the renoprotective effect of the class. Furthermore, SGLT2 inhibitors result in falls in plasma and interstitial volume, while loop diuretics tend to reduce plasma volume preferentially. The significance of these effects is still not well understood (3). Although the natriuretic effects (on top of background diuretic therapy) could well indicate reduce LV wall stress (reduced preload and afterload) and LV mass index (await the EMPA-HEART Cardiolink-6 Trial, NCT02998970, A Randomized Trial Evaluating The Effect Of Empagliflozin On Left Ventricular Structure, Function And Biomarkers In People With Type 2 Diabetes And Coronary Heart Disease), the effect on HF outcomes is as large as that from current neurohormonal antagonists, and dis-proportionately larger than that seen in HF populations with natriuresis (from other diuretic therapy) alone. Furthermore, if the beneficial effect were solely driven by natriuresis, one would not expect to see such modest falls in NT-proBNP in DAPA-HF, nor the differential benefits in patients with low versus preserved LVEF in retrospective analyses of CANVAS and DECLARE-TIMI 58 (15,16). In addition there was no significant placebo-adjusted fall in mean NT-proBNP observed over 12 weeks in another randomized controlled trial, published in the same week as DAPA-HF (27). This trial randomized 263 patients with HFrEF (LVEF ≤40%, NYHA class II-III, eGFR ≥30 ml/min and NT-proBNP ≥400 pg/ml (≥600 in atrial fibrillation)) to Dapaglifozin 10 mg od or placebo and excluded decompensated HF. At baseline, mean age was 61.3, 73% were male, 40% African-American, 62% had type 2 diabetes, 40% had atrial fibrillation, median BMI was 30.6. Mean LVEF was 26%, NYHA class II was present in 66%, 86% were on loop diuretics; 62% had ICD and 35% CRT; median NT-proBNP was 1136 pg/ml. However, Dapaglifozin-treated patients were more likely to have a ≥20% decrease in NT-proBNP at 12 weeks (OR 1.90, 95 % CI 1.09-3.31) and more likely to have a ≥5-point improvement in KCCQ-CS score (OR 2.4, 95 % CI 1.3-4.2). This is also inconsistent with the known observation that use of higher doses of loop diuretics in HFrEF is associated with worse HF and renal outcomes, a finding likely related to ≥1 of the following: increased disease severity, perceived worsening disease status, diuretic resistance, secondary renin-angiotensin system activation and/or hypokalaemia (28). Thus other mechanisms are also likely to contribute.

NHE-1 inhibition

A related proposed mechanism of benefit is that SGLT2 inhibitors bind and directly inhibit the cardiomyocyte sodium-hydrogen exchanger-1 (NHE-1) (29,30). Overactivity of NHE-1 is seen in diabetes mellitus and HF and is implicated (in the heart) in cardiomyocyte cytosolic Na^+ and Ca^{2+} excess (and intramitochondrial Ca^{2+} deficiency), insulin resistance, hypertrophic signalling, ischaemia-reperfusion intolerance and fibrosis, and (in the kidney, along with NHE-3) in glomerular hyperfiltration, sodium retention, mesangial proliferation and resistance to natriuretic peptides.

Noradrenaline, angiotensin, aldosterone, insulin and certain adipokines all stimulate NHE-1 and -3 activity, while SGLT-2 inhibitors inhibit NHE-3 activity in the kidney and NHE-1 activity in the heart and vasculature (29). Thus, NHE-1 inhibition would be expected to have beneficial effects in HF irrespective of the presence of diabetes mellitus, and one would expect increased benefit in hyperinsulinaemic states (diabetes, obesity), and reduced benefit in the setting of concomitant mineralocorticoid antagonist use. If this hypothesis is proven, Packer argues that reconceptualising SGLT2 inhibitors as NHE-1 inhibitors could improve uptake by HF clinicians (30).

Metabolic modulation

Metabolic modulation with improved myocardial energetics is a further proposed mechanism (31,32). SGLT2-induced glucosuria results in reduced insulin/glucagon ratios, increased peripheral lipolysis and thus increases in hepatic ketogenesis and circulating free fatty acids and ketone bodies (33,34). Myocardial metabolism of the ketone body β-hydroxybutyrate expands the acetyl-CoA pool, competing with the oxidation of glucose and fatty acids, with the potential to increase oxygen efficiency. This is in the context of myocardial insulin resistance which predates and is a key metabolic signature of nonischaemic heart failure, including in nondiabetics (35,36), reduced fractional oxidation of fatty acids (37), and reduced capacity for fatty acid oxidation at the transcriptomic level in heart failure (38).

Unfortunately this hypothesised depiction of increased availability to the myocardium of a ketone body 'superfuel' is probably an oversimplification. Ketone body oxidation is already increased in the failing heart (39), yet it is unknown whether this is secondary also to reduced ketone body clearance, and whether this is desirable (40). Many metabolites including ketone bodies themselves have direct and pleiotropic signalling roles which may impact on hypertrophic signalling (41). Acute β-hydroxybutyrate infusion reduced systemic and pulmonary vascular resistances, increased echocardiographically-assessed cardiac output (stroke volume and heart rate) and myocardial oxygen consumption without altering external efficiency (external work/oxygen consumption) in HFrEF patients (42), but whether these responses were attributable to myocardial contractility and/or vasodilation is uncertain, as invasive pressure-volume loops were not recorded, and whether they operate longer term with intermittent (fasting-state) hyperketonaemia is unknown. Increased oxidation of acetyl-CoA derived from ketone bodies and free fatty acids could exacerbate the failing heart's ability to oxidise glucose, the substrate with the highest Phosphate:Oxygen ratio, a negative consequence not rescued by hyperketonaemia (43). An unbiased metabolomic approach in 25 patients with type 2 diabetes and cardiovascular disease (LVEF 49 ± 13%) before and after 1 month of Empaglifozin indicated increases in degradation of branched-chain and ketogenic amino acids and ketone bodies and unchanged levels of pyruvate, lactate, free fatty acids and long-chain acylcarnitines (44). However, no 'gold-standard' analysis of metabolic fluxes before and after SGLT2 inhibition has been performed (45).

In sum, we should not consider these hypotheses in competition with each other, nor should we be surprised that multiple mechanisms have been identified. Other mechanisms not further discussed here include modulation of cardiomyocyte survival signalling, fibroblast phenotype and activity, epicardial adipose tissue mass (reduced), and pro-inflammatory adipokine signalling (reduced). It is more plausible that an effect-size as large as seen in the SGLT2 inhibitor trials is mediated by multiple biological mechanisms rather than a few.

Conclusions

DAPA-HF represents a crucial step toward the re-conceptualisation of the SGLT2 inhibitor class as a heart failure drug rather than a glucose-lowering drug for type 2 diabetes. Should its results be substantiated as a class action by ongoing trials, efforts will accelerate to understand the biological mechanisms of benefit and explore its indications more broadly. Thus DAPA-HF should be viewed optimistically by clinicians and scientists in cardiology, nephrology, diabetes and obesity. The state of knowledge is summarised in Table 2.

Disclosures

None.

Table 1. Definitions of insufficient glycaemic control and high cardiovascular risk in four cardiovascular outcome trials of SGLT2 inhibitors before DAPA-HF

Definition of insufficient glycaemic control			
EMPA-REG OUTCOME (4)	**CANVAS (6)**	**DECLARE-TIMI 58 (8)**	**CREDENCE (9)**
HbA1c 7.0-9.0% (drug-naive) or 7.0-10.0% (on background therapy)	HbA1c 7.0-10.5%	HbA1c 6.5-12.0%	HbA1c 6.5-12.0%
Definition of high cardiovascular risk			
EMPA-REG OUTCOME (4)	**CANVAS (6)**	**DECLARE-TIMI 58 (8)**	**CREDENCE (9)**
≥1 of: 1) history of myocardial infarction >2 months before informed consent; 2) ≥2-vessel CAD or left main disease, defined as ≥50% stenosis on angiography, previous revascularisation ≥2 months before, or the combination of 1-vessel revascularisation and ≥50% stenosis in another major coronary artery; 3) non-revascularised single vessel CAD with either a positive non-invasive stress test for ischaemia or a hospital discharge for unstable angina within the last 12 months; 4) unstable angina >2 months prior with evidence of CAD; 5) history of stroke >2 months prior; (6) occlusive peripheral artery disease	1) Age ≥30 years with prior symptomatic coronary, cerebrovascular or peripheral artery disease, or 2) age ≥50 years with ≥2 of: duration of diabetes mellitus ≥10 years, systolic BP >140 mmHg while on ≥1 anti-hypertensive agent, current smoker, microalbuminuria (urinary ACR 30-300 mg/g) and or macroalbuminuria (urinary ACR >300 mg/g), or HDL <1 mmol/L.	1) Age ≥40 years with clinically evident coronary, cerebrovascular or peripheral artery disease or 2) age ≥55 years (men) or ≥60 years (women) with ≥1 of: hypertension, LDL >3.36 mmol/L or on lipid-lowing therapy for hyperlipidaemia, or current smoking.	Age ≥30 years with macroalbuminuric CKD (GFR 30-89 ml/min and urinary ACR >300-5000 mg/g) and on stable maximum tolerated dose of ACE-I or ARB for ≥4 weeks.

ACE-i angiotensin converting enzyme-inhibitor, ACR albumin creatinine ratio, ARB angiotensin receptor blocker, BP blood pressure, CAD coronary artery disease, CANVAS The Canagliflozin Cardiovascular Assessment Study, CKD chronic kidney disease, CREDENCE The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation, DECLARE-TIMI 58 The Dapagliflozin Effect on Cardiovascular Events-Thrombolysis In Myocardial Infarction, EMPA-REG OUTCOME Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients - Removing Excess Glucose, GFR glomerular filtration rate, HDL high density lipoprotein, LDL low density lipoprotein.

Table 2. Summary: what have we learned from DAPA-HF?

What we knew before DAPA-HF

- In patients with type 2 diabetes and prior MI, SGLT2 inhibitors reduce atherothrombotic, HF and renal events, largely through mechanisms independent of glucose-lowering.
- In patients with type 2 diabetes without established atherosclerotic cardiovascular disease but with multiple risk factors, SGLT2 inhibitors reduce HF and renal events. The weight of evidence is against a MACE-lowering effect, but the existing meta-analysis (17) did not incorporate the CREDENCE trial, used investigator-reported diagnoses rather than objectively determined measures, and used study-level rather than individual patient-level data.
- HF and renal outcomes, unlike MACE, appear to be particularly sensitive to SGLT2 inhibitor therapy in the studied populations (type 2 diabetes and high risk).
- SGLT2 inhibitor therapy is recommended (Class IA) as first-line therapy in patients with type 2 diabetes mellitus and high cardiovascular risk (2).

What we know now

- In patients with symptomatic HFrEF (LVEF ≤40% and NT-proBNP ≥600 pg/ml), the SGLT2 inhibitor Dapaglifozin is beneficial irrespective of the presence of type 2 diabetes.

What we still don't know

- Whether SGLT2 inhibitors are helpful in type 2 diabetes with recent MI (<2 months).
- Whether SGLT2 inhibitors are helpful in patients with estimated creatinine clearances <30 ml/min.
- Whether reduction of HF and renal outcomes by SGLT2 inhibitors will be cost-effective in patients at lower risk than those already studied.
- Whether SGLT2 inhibitors are helpful in patients with acutely decompensated HF or HFpEF.
- Whether other SGLT2 inhibitors are helpful in HFrEF.
- Which biomarkers best predict response / non-response to SGLT2 inhibition in HF.
- Whether and how SGLT2 inhibitors directly modulate cardiomyocyte survival and hypertrophic signalling.
- Whether and how SGLT2 inhibitors can be used safely in patients with type 1 diabetes.

Ongoing trials

- HFrEF: EMPEROR-Reduced (Empaglifozin, NCT03057977) and SOLOIST-WHF (Sotaglifozin; NCT03521934).
- HFpEF: EMPEROR-Preserved (NCT03057951) and DELIVER (Dapaglifozin, NCT03619213).
- CKD: DAPA-CKD (Dapaglifozin, NCT03036150) and EMPA-Kidney (Empaglifozin, NCT03594110).
- Type 2 diabetes with multiple risk factors and moderate renal impairment: SCORED (Sotaglifozin, NCT03315143).
- Type 2 diabetes with atherosclerotic cardiovascular disease: VERTIS CV (Ertuglifozin, NCT01986881).

DAPA-CKD A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease, DELIVER, Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure, EMPA-Kidney The Study of Heart and Kidney Protection With Empagliflozin, EMPEROR-Preserved EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction, EMPEROR-Reduced EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction, HFpEF heart failure with preserved ejection fraction, HFrEF heart failure with reduced ejection fraction, LVEF left ventricular ejection fraction, MACE major adverse cardiovascular events defined as cardiovascular death, nonfatal myocardial infarction, ischaemic stroke, MI myocardial infarction, NT-pro BNP N terminal-pro brain natriuretic peptide, SCORED Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk, SGLT2 sodium-glucose cotransporter 2, SOLOIST-WH Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure, VERTIS CV Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease.

References

1. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019;381:1995-2008.

2. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J Published Online First: 31 August 2019. doi:10.1093/eurheartj/ ehz486

3. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia 2018;61:2108–17.

4. Zinman B, Inzucchi SE, Lachin JM, et al. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME™). Cardiovasc Diabetol 2014;13:102.

5. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.

6. Neal B, Perkovic V, Matthews DR, et al. Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R): A randomized, placebo-controlled trial. Diabetes, Obes Metab 2017;19: 387–93.

7. Neal B, Perkovic V, Mahaffey KW, et al. CANVAS Programme Collaborative Group. Canagliflozin and Cardio-vascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017; 377:644–57.

8. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–57.

9. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–306.

10. Komajda M, McMurray JJV, Beck-Nielsen H, et al. Heart failure events with rosiglitazone in type 2 diabetes: Data from the RECORD clinical trial. Eur Heart J 2010;31:824–31.

11. Hernandez A V., Usmani A, Rajamanickam A, et al. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: A meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. Am J Cardiovasc Drugs 2011;11:115–28.

12. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015;373:2117–28.

13. Fitchett D, Zinman B, Wanner C, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: Results of the EMPA-REG OUTCOME trial. Eur Heart J 2016;37:1526–34.

14. Radholm K, Figtree G, Perkovic V, et al. Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation Published Online First: 2018.

15. Figtree GA, Rådholm K, Barrett TD, et al. Effects of Canagliflozin on Heart Failure Outcomes Associated With Preserved and Reduced Ejection Fraction in Type 2 Diabetes Mellitus. Circulation 2019;139:2591–3.

16. Kato ET, Silverman MG, Mosenzon O, et al. Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. Circulation 2019;139:2528–36.

17. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31–9.

18. Inzucchi SE, Zinman B, Wanner C, et al. SGLT-2 inhibitors and cardiovascular risk: Proposed pathways and review of ongoing outcome trials. Diabetes Vasc Dis Res 2015;12:90–100.

19. Staels B. Cardiovascular Protection by Sodium Glucose Cotransporter 2 Inhibitors: Potential Mechanisms. Am J Cardiol 2017;120:S28–36.

20. Butler J, Hamo CE, Filippatos G, et al. The potential role and rationale for treatment of heart failure with sodium-glucose co-transporter 2 inhibitors. Eur J Heart Fail 2017;19:1390–400.

21. DeFronzo RA, Norton L, Abdul-Ghani M. Renal, metabolic and cardiovascular considerations of SGLT2 inhibition. Nat Rev Nephrol 2017;13:11–26.

22. Sattar N, McLaren J, Kristensen SL, et al. SGLT2 Inhibition and cardiovascular events: why did EMPA-REG Outcomes surprise and what were the likely mechanisms? Diabetologia 2016;59:1333–9.

23. Maack C, Lehrke M, Backs J, et al. Heart failure and diabetes: Metabolic alterations and therapeutic interventions: A state-of-The-Art review from the Translational Research Committee of the Heart Failure Association-European Society of Cardiology. Eur Heart J 2018;39:4243–54.

24. Bertero E, Prates Roma L, Ameri P, et al. Cardiac effects of SGLT2 inhibitors: the sodium hypothesis. Cardiovasc Res 2018;114:12–8.

25. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes Action to Control Cardiovascular Risk in Diabetes ADVANCE Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation UKPDS UK Prospective D. Diabetologia 2009;52:2288–98.

26. Swedberg K, Young JB, Anand IS, et al. Treatment of Anemia with Darbepoetin Alfa in Systolic Heart Failure. N Engl J Med 2013;368:1210–9.

27. Nassif ME, Windsor S, Tang F, et al. Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction: The DEFINE-HF Trial. Circulation 2019;140(18):1463-1476.

28. Damman K, Kjekshus J, Wikstrand J, et al. Loop diuretics, renal function and clinical outcome in patients with heart failure and reduced ejection fraction. Eur J Heart Fail 2016;18:328–36.

29. Packer M. Activation and Inhibition of Sodium-Hydrogen Exchanger Is a Mechanism That Links the Pathophysiology and Treatment of Diabetes Mellitus with That of Heart Failure. Circulation 2017;136:1548–59.

30. Packer M. Reconceptualization of the Molecular Mechanism by Which Sodium-Glucose Cotransporter 2 Inhibitors Reduce the Risk of Heart Failure Events. Circulation 2019; 140:443–5.

31. Verma S, Rawat S, Ho KL, et al. Empagliflozin Increases Cardiac Energy Production in Diabetes. JACC Basic to Transl Sci 2018;3:575–87.

32. Crawford PA. Refueling the Failing Heart. JACC Basic to Transl Sci 2018;3:588–90.

33. Ferrannini E, Mark M, Mayoux E. CV Protection in the EMPA-REG OUTCOME Trial: A 'Thrifty Substrate' Hypothesis. Diabetes Care 2016;39:1108–14.

34. Mudaliar S, Alloju S, Henry RR. Can a Shift in Fuel Energetics Explain the Beneficial Cardiorenal Outcomes in the EMPA-REG OUTCOME Study? A Unifying Hypothesis. Diabetes Care 2016;39:1115–22.

35. Doehner W, Frenneaux M, Anker SD. Metabolic impairment in heart failure: The myocardial and systemic perspective. J Am Coll Cardiol 2014;64:1388–400.

36. Witteles RM, Fowler MB. Insulin-Resistant Cardiomyopathy: Clinical Evidence, Mechanisms, and Treatment Options. J Am Coll Cardiol 2008;51:93–102.

37. Neglia D, De Caterina A, Marraccini P, et al. Impaired myocardial metabolic reserve and substrate selection flexibility during stress in patients with idiopathic dilated cardiomyopathy. Am J Physiol Hear Circ Physiol 2007;293:H3270–8.
38. Sihag S, Cresci S, Li AY, et al. PGC-1 alpha and ERR alpha target gene downregulation is a signature of the failing human heart. J Mol Cell Cardiol 2009;46:201–12.
39. Bedi KC, Snyder NW, Brandimarto J, et al. Evidence for Intramyocardial Disruption of Lipid Metabolism and Increased Myocardial Ketone Utilization in Advanced Human Heart Failure. Circulation 2016;133:706–16.
40. Lopaschuk GD, Verma S. Empagliflozin's Fuel Hypothesis: Not so Soon. Cell Metab 2016;24:200–2.
41. Puchalska P, Crawford PA. Multi-dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics. Cell Metab 2017;25:262–84.