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Cardiac, renal, and metabolic effects of sodium-glucose co-transporter-2 inhibitors: a position paper from the European Society of Cardiology ad-hoc task force on sodium-glucose co-transporter-2 inhibitors

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ABSTRACT

In 2015, the first large-scale placebo-controlled trial designed to assess cardiovascular safety of glucose-lowering with sodium-glucose co-transporter-2 (SGLT-2) inhibition in type 2 diabetes mellitus raised hypotheses that the class could favourably modify not only risk of atherosclerotic cardiovascular disease, but also hospitalisation for heart failure, and the development or worsening of nephropathy. By the start of 2021, results from ten large SGLT-2 inhibitor placebo-controlled clinical outcome trials randomizing ~71,000 individuals have confirmed that SGLT-2 inhibitors can provide clinical benefits for each of these types of outcome in a range of different populations. The cardiovascular and renal benefits of SGLT-2 inhibitors appear to be larger than their comparatively modest effect on glycaemic control or glycosuria alone would predict, with three trials recently reporting that clinical benefits extend to individuals without diabetes mellitus who are at risk due to established heart failure with reduced ejection fraction, or albuminuric chronic kidney disease. This ESC position paper summarizes reported results from these ten large clinical outcome trials considering separately each of the different types of cardiorenal benefit, summarises key molecular and pathophysiological mechanisms, and provides a synopsis of metabolic effects and safety. We also describe two ongoing placebo-controlled trials among individuals with heart failure with preserved ejection fraction and one among individuals with chronic kidney disease.

Keywords: sodium-glucose co-transporter 2 inhibitors, heart failure, cardiovascular outcomes, chronic kidney disease; randomized trials

INTRODUCTION

Sodium glucose co-transporter (SGLT) inhibition's molecular mechanism

The foundations for inhibition of SGLTs were built almost a century ago when the "glucose threshold" was described. This threshold is the concentration of glucose in the kidney tubule above which glucose appears in the urine, and once exceeded, the urine glucose concentration is positively associated with the blood glucose concentration (1). It was recognized that this threshold could be reduced either genetically (e.g. in familial renal glycosuria in which affected individuals have detectable glucose in their urine despite normal blood glucose concentrations) or pharmacologically (e.g. with phlorizin, an extract from apple tree bark which mimics familial renal glycosuria (2, 3)). Following the cloning of the genes for SGLT-1 and SGLT-2, their distribution and function were appreciated and phlorizin characterized as a non-specific SGLT-2 inhibitor. Selective SGLT-2 inhibitors were identified in the 1990s and rapidly pursued as a potential glucose-lowering therapy for type 2 diabetes mellitus (DM). (4)

SGLT-1 is a low-capacity high-affinity transporter located primarily in the gastrointestinal tract (where it is responsible for the absorption of dietary glucose) and also in the late renal proximal tubule (where in health it reabsorbs ~3% of urinary glucose). By contrast, SGLT-2 is a high-capacity low-affinity transporter located primarily in the early renal proximal tubule and is responsible for reabsorbing ~97% of urinary glucose in healthy individuals. Other SGLTs exist but their function is unclear. Inhibition of SGLT-2 therefore has the larger effect on the glucose threshold, although SGLT-1 and dual SGLT-1/2 inhibitors (e.g. sotagliflozin) have also been developed with the aim of increasing glucose-lowering efficacy because SGLT-1 has significant reserve capacity to reabsorb glucose when SGLT-2 is not active (5). In reality, all SGLT-2 inhibitors also inhibit SGLT-1, but they differ in their selectivity for SGLT-2 over SGLT-1: ~20:1 for sotagliflozin (6), and from ~250:1 for canagliflozin to ~2500:1 for empagliflozin (7).

SGLT-2 inhibitors' development history

SGLT-2 inhibitors were initially developed for their effects on glycaemia: dapagliflozin was the first SGLT-2 inhibitor to be approved for this indication in Europe (8, 9). Although the effects on glycosylated haemoglobin (HbA1c) were modest, typically reducing it by 0.5-1.0% on the absolute scale, larger trials were initiated in order to assess their cardiovascular safety, as mandated by the FDA (10). These trials not only demonstrated that the SGLT-2 inhibitors were non-inferior to placebo with respect to cardiovascular outcomes, but actually were significantly superior (11-13). This led to major revisions to existing guidelines with a shift in focus to SGLT-2 inhibition's potential to modify disease risk, and not merely to improve glycaemic control. The realisation from these randomized data that SGLT-2 inhibition was a potentially effective treatment for heart failure and offered renoprotection triggered a series of dedicated trials in different heart failure and chronic kidney disease (CKD) populations.

European Society of Cardiology (ESC) guidelines and position statements

In 2019, the ESC published guidelines on the management of diabetes, prediabetes and cardiovascular diseases (14). At this time, recommendations for their use were based on results from four large placebo-controlled SGLT-2 inhibitor clinical outcome trials in individuals with type 2 DM, including three trials which selected patients for their high cardiovascular risk (EMPA-REG OUTCOME (11), the CANVAS program (12), and DECLARE-TIMI58 (13)), and one for albuminuric diabetic kidney disease (CREDENCE (15)). Subsequently, following the publication of the main results from DAPA-HF (16) - the first clinical outcome trial to report effects of SGLT-2 inhibition in a population selected for heart failure with reduced ejection fraction (HFrEF; EF≤40%) with or without DM - the Heart Failure Association of the ESC published a 2020 updated position paper on SGLT-2 inhibitors in heart failure (17). Since these two ESC publications, a further five placebo-controlled clinical outcome trials of SGLT-2 inhibitors have published their main results: one trial among individuals with type 2 DM and prior atherosclerotic cardiovascular disease

(VERTIS CV (18)); two trials among patients with heart failure (EMPEROR-REDUCED in HFrEF (19) and SOLOIST-WHF in individuals with recent admission for heart failure, irrespective of ejection fraction (20)); and two which studied patients with CKD (DAPA-CKD (21) and SCORED (22)). These placebo-controlled trials provide additional information about the effects of SGLT2 inhibitors on cardiorenal outcomes, with two of these newer trials including individuals without DM so that, overall, two trials in HFrEF populations and one in CKD now provide data in individuals without DM: DAPA-HF (16), EMPEROR-REDUCED (19) & DAPA-CKD (21). This ESC position paper aims to provide a summary of the effects of SGLT-2 inhibitors using reports from these ten large randomized clinical outcome trials (Table 1). We consider each of the three main types of cardiorenal clinical outcomes separately (i.e. heart failure, atherosclerotic disease and renal outcomes) in the different studied populations (i.e. patient groups with heart failure, type 2 DM at high atherosclerotic cardiovascular risk, and CKD), highlight key mechanisms, and summarise what is currently known about the safety of SGLT2 inhibitors.

EFFECTS ON HEART FAILURE

The EMPA-REG OUTCOME trial randomized individuals with prior atherosclerotic cardiovascular disease and type 2 DM and as the first large clinical outcome SGLT-2 inhibitor trials to report results (11), provided the initial evidence that SGLT-2 inhibition reduced hospitalization due to heart failure. Compared to placebo, allocation to empagliflozin reduced the risk of heart failure hospitalization by 35% (126/4687 vs 95/2333: hazard ratio [HR]=0.65, 95% confidence interval 0.50-0.85) (11), with similar benefits in individuals with or without a history of heart failure at recruitment (23). Reductions in the risk of cardiovascular mortality were also observed, so the effect on the composite of cardiovascular death or hospitalization for heart failure was a 34% relative risk reduction (HR=0.66, 0.55-0.79: Figure 1).

Subsequent trials in populations with type 2 DM which studied those at risk of atherosclerotic cardiovascular disease (DECLARE-TIMI-58 & the CANVAS Program), replicated these findings (Figure 1) (12, 13, 24), with the relative benefits consistent irrespective of ejection fraction at admission (25). Somewhat in contrast, VERTIS CV found ertugliflozin to be non-inferior to placebo with respect to its key secondary outcome of cardiovascular death or hospitalization for heart failure, but the trial results did not meet the criteria for superiority (HR=0.88, 0.75-1.03) (18). There was, however, a 30% reduction in the risk of hospitalization for heart failure (139/5499 vs 99/2747: HR=0.70, 0.54-0.90) (18), consistent with the effects of the other SGLT-2 inhibitors on this outcome (24). These benefits appeared similar across most baseline subgroups, with a possibility of larger effects identified among participants with reduced kidney function (i.e. estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2), albuminuria, or among those prescribed diuretics (26). Among individuals with CKD, and despite substantial attenuation of glycosuria induced by SGLT-2 inhibitors at lower levels of kidney function (15, 21, 27-30), the relative benefits of canagliflozin on hospitalization for heart failure in the CREDENCE trial in diabetic CKD (mean eGFR 56 mL/min/1.73m^2: Table 1) were similar to aggregated results from the trials recruiting individuals at high cardiovascular risk with type 2 DM (24). Similar findings on heart failure from the SCORED trial conducted in patients with type 2 DM and CKD (median eGFR 45 mL/min/1.73m^2) and among patients with albuminuric CKD in DAPA-CKD (mean eGFR 43 mL/min/1.73m^2) confirm such benefits among patients with reduced eGFR (21, 22), with limited numbers of heart failure precluding reliable conclusions among individuals with CKD without DM (31).

DAPA-HF was the first of the dedicated trials of SGLT-2 inhibition among patients with well-characterised heart failure to report its findings (Table 1). Individuals with HFrEF were randomized to dapagliflozin versus matching placebo, on top of optimal medical therapy (~95% were prescribed renin angiotensin system [RAS] blockade or sacubitril/valsartan, 71% mineralocorticoid receptor antagonists [MRA], and 96% beta-blockers) (16). Of the 4744

randomized, 2761 (58%) were free of type 2 DM at enrolment. Compared to placebo, dapagliflozin reduced the risk of the primary composite outcome of cardiovascular death, heart failure hospitalization or an urgent heart failure visit requiring intravenous therapy by 26% (386/2373 vs 502/2371: HR=0.74, 0.65-0.85) (16). Beneficial effects of dapagliflozin were observed for each of the components of this composite (Figure 1 also provides results for assessments of time to first cardiovascular death or hospitalization for heart failure, excluding urgent visits), and also improved heart failure symptoms, reduced NT-proBNP, and overall mortality (16). Furthermore, the relative benefits on the primary composite outcome were consistent across multiple pre-specified subgroups. In particular, there was direct evidence of benefit in individuals with and without type 2 DM, among those with ischaemic and non-ischaemic heart failure aetiologies, and among those with an ejection fraction above or below the recruited population median (16). Concomitant therapy, including angiotensin receptor-neprilysin inhibitor and MRA use, also did not modify these benefits when assessed in a series of post-hoc subgroup analyses (32-34). Dapagliflozin is now approved for the treatment of symptomatic chronic HFrEF (35).

The EMPEROR-REDUCED trial subsequently reinforced the findings of DAPA-HF. Allocation to empagliflozin reduced risk of the primary composite outcome of cardiovascular death and heart failure hospitalization by a quarter (HR=0.75, 0.65-0.86: Figure 1) and the total number of heart failure hospitalizations by 30% (388/1863 vs 553/1867: HR=0.70, 0.58-0.85) (19). Although there was no significant reduction in cardiovascular or in overall mortality, the mortality results for EMPEROR-REDUCED were consistent with those of DAPA-HF (36). Again, there was direct evidence of benefit both in individuals with and without type 2 DM and similar sized benefits were observed in individuals with ischaemic and non-ischaemic heart failure (19).

The most recently heart failure trial is SOLOIST-WHF, which tested the dual SGLT-1/-2 inhibitor sotagliflozin. The original intention was to randomize 4000 participants with type 2

DM, irrespective of ejection fraction, who had been hospitalized recently for worsening heart failure. However, enrolment was terminated prematurely for financial reasons and the COVID-19 pandemic after randomization of 1222 participants (Table 1). About four-fifths of the population (966/1222, 79%) had an ejection fraction <50%. Despite its early termination and <1 year of median follow-up, compared to placebo, allocation to sotagliflozin reduced the risk of the revised primary composite of cardiovascular death or total hospitalizations/urgent visits for heart failure by one-third (245/608 vs 355/614: HR=0.67, 0.52-0.85) (Figure 1 provides time to first cardiovascular death or hospitalization for heart failure results). Benefits were observed irrespective of ejection fraction at recruitment, including those with an ejection fraction ≥50% (20). Details on the safety of SGLT-2 inhibitors are discussed below, but an excess of adverse events for diarrhoea (6.1% vs 3.4%), hypotension (6.0% vs 4.6%) and hypoglycaemia (4.3% vs 2.8%) among those allocated sotagliflozin was observed (20). Excesses of these adverse events have generally not been a feature of the trials of other SGLT-2 inhibitors, and are perhaps consequences of additional effects of inhibition of gastrointestinal and renal SGLT-1 (7).

Trials assessing the effects of SGLT-2 inhibitors in individuals with heart failure with preserved ejection fraction (HFpEF) are ongoing: DELIVER and EMPEROR-PRESERVED results are expected in 2021/2022. Both trials have been recruiting individuals with preserved or mid-range left ventricular ejection fraction (i.e. >40%) (37) with individuals with and without type 2 DM eligible (see Table 1 for more details) (38, 39).

Multiple mechanisms explaining the clinical effects of SGLT-2 inhibition on heart failure are proposed (Figure 2) (19, 24, 40-53) but remain incompletely understood. Randomized analyses using the accumulated bioresources from the completed trials may help elucidate possible mechanisms of action for SGLT2 inhibitors. One attractive hypothesis is that they enhance control of interstitial fluid accumulation without causing excessive intravascular volume contraction (42). Combined natriuresis and osmotic diuresis contracts both

intravascular and extracellular volume, contributing to reductions in systemic blood pressure, arterial stiffness and wall stress, and therefore cardiac preload and afterload (43-47). However, randomized data show that clinical benefits (on a relative scale) are largely independent of glucose lowering, exist in individuals who experience attenuated effects on glycosuria (i.e. individuals without DM or low eGFR) (36), and are independent of recent fluid overload (54). It has also been suggested that increased glucagon levels yield inotropic and chronotropic effects, and increased hydroxybutyrate levels shift cardiac metabolism from glucose to energy-efficient ketones (48, 49). Direct cardiac mechanisms have also been hypothesized based on indirect evidence of increased myocardial expression of sodium-hydrogen exchange transporters in heart failure among individuals with DM, which may elevate myocyte cytoplasmic sodium levels, and consequently enhance calcium influx (42). Such a process may be reversed by inhibition of some cardiac sodium-hydrogen exchange transporters by SGLT-2 inhibitors (50-53).

EFFECTS ON ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

As introduced above, the primary purpose of the large SGLT-2 inhibitor trials in people with type 2 DM at high atherosclerotic cardiovascular risk (11-13, 18) was to test whether SGLT-2 inhibition was non-inferior to placebo with respect to cardiovascular safety (10). Allocation to empagliflozin 10 or 25 mg once daily versus placebo on top of usual care in the EMPA-REG OUTCOME trial reduced the risk of its primary composite outcome of cardiovascular death, myocardial infarction or stroke (i.e. major atherosclerotic/adverse cardiovascular events, MACE) by 14% (HR=0.86, 0.74-0.99: non-inferiority $p<0.001$; superiority $p=0.04$, thus demonstrating both non-inferiority and superiority with respect to safety (11). Non-inferiority for the MACE outcome for the tested SGLT-2 inhibitor versus placebo was subsequently confirmed in the CANVAS Program, DECLARE-TIMI58 and VERTIS CV (Figure 3). Although, of these trials, only the CANVAS Program formally replicated the superiority for MACE observed in EMPA-REG OUTCOME (11-13, 18), the relative benefits on MACE across the four trials are consistent with each other, and when aggregated in meta-analysis with the

CREDENCE trial there was a modest 10% reduction in the risk of MACE (aggregated HR=0.90, 95% confidence interval 0.85-0.95 [between trial heterogeneity test p=0.27]) (24). Results for the MACE outcome in DAPA-CKD and SCORED are consistent with a similar sized relative risk reduction (21, 22), which suggests that the relative benefits on MACE are at least as large in the individuals with CKD as those benefits identified in individuals with type 2 DM at high atherosclerotic cardiovascular risk.

The totality of the trial evidence therefore indicates the relative benefits of SGLT-2 inhibitors on heart failure outcomes (which are consistent across all the trial populations studied to date) are larger than on MACE outcomes. For example, the published meta-analysis of the available results from the four trials in people with type 2 DM populations at high atherosclerotic cardiovascular risk CREDENCE estimated that the risk of hospitalization for heart failure was reduced by 32% compared to placebo (aggregated RR=0.68, 0.61-0.76), which is substantially greater than the observed 10% reduction in risk of MACE (HR=0.90, 0.85-0.95). These modest benefits on MACE observed in populations with type 2 DM or CKD were driven primarily by reduced risk of cardiovascular death and myocardial infarction. The meta-analysis found, compared to placebo, that SGLT-2 inhibition reduced cardiovascular death risk by 15% (HR=0.85, 0.78-0.93) and myocardial infarction by 9% (HR=0.91, 0.84-0.99), with no clear effect on stroke (HR=0.96, 0.87-1.07) (24). We have not been able to identify published reports of the effects of MACE in heart failure populations. The more modest effects of SGLT-2 inhibition on atherothrombotic risk may represent opposing mechanisms. Reductions in blood pressure, HbA1c and adiposity with improved cardiac function might be partially offset by the increase in circulating low-density lipoprotein cholesterol concentration, resulting from greater lipolysis of triglyceride-rich lipoproteins with SGLT-2 inhibition (55). More plausibly, the natriuretic, osmotic diuretic and renoprotective effects of SGLT-2 inhibition may simply be more effective at targeting heart failure pathophysiology.

Following the publication of DECLARE-TIMI 58 results (13), it was hypothesized that relative reductions in MACE risk might be larger among individuals with prior atherosclerotic cardiovascular disease than individuals without (56). However, with the availability of more data from subsequent trials, the evidence of any effect modification by pre-existing disease is less convincing (24). Nevertheless, given the trials' results on different types of cardiovascular disease, together with the exploratory analyses from EMPA-REG OUTCOME (57), it seems plausible that any cardiovascular deaths which included chronic heart failure as a key mechanism may be more likely to be prevented with SGLT-2 inhibition than deaths which are more purely atherothrombotic in origin or from stroke. Testing such hypotheses may be possible once all the trials have completed and more cardiovascular deaths are available for analysis.

EFFECTS ON KIDNEY DISEASE

The prevalence of CKD in adults may be as high as ~1 in 10 individuals in developed countries, where diabetic nephropathy is frequently the commonest primary cause (58). CKD also often co-exists with heart failure due to a combination of shared risk factors and integrated pathophysiology (59). Structural heart disease is present in about one-half of individuals with CKD once their eGFR falls below 30 mL/min/1.73m^2 (60). Management of CKD therefore necessarily includes modification of risk of both progression to end-stage kidney disease (ESKD) and cardiovascular complications (59, 61), with the recommended standard of care for many individuals with CKD including blockade of the RAS system (particularly once albuminuria is evident (62)), and appropriate statin-based therapy (63).

In individuals with type 2 DM, SGLT-2 inhibitors cause a modest and reversible reduction in eGFR followed by a substantial decrease in the subsequent rate of chronic eGFR decline (15, 64). In post-hoc analyses of EMPA-REG OUTCOME, there was evidence of a reduction in a kidney disease progression which was driven by reductions in the risk of a doubling of serum creatinine. The other trials in populations at high cardiovascular risk with type 2 DM

trials subsequently reinforced this finding on kidney disease progression outcomes (Figure 4) (24). The CREDENCE trial then confirmed these renal benefits on ESKD in individuals with diabetic kidney disease. CREDENCE was stopped early for efficacy because the primary cardiorenal composite outcome (a sustained doubling of creatinine, ESKD, or death from renal or cardiovascular causes) was reduced by 30% (245/2202 vs 340/2199: HR=0.70, 0.59-0.82). Importantly, there were reductions in the risk of kidney disease progression (see Figure 4) and in the risk of clinical renal components of this outcome: the composite of initiation of maintenance dialysis, kidney transplantation or renal death was reduced by 28% (78/2202 vs 105/2199: HR=0.72, 0.54-0.97) (15).

The main renoprotective mechanism of SGLT-2 inhibition is considered to be through modulation of tubuloglomerular feedback through decreased proximal tubular sodium resorption and subsequent reductions in intraglomerular hypertension through glomerular afferent arteriolar vasoconstriction (64, 65). Intraglomerular hypertension, of which albuminuria is a marker, has been suggested as a final common pathway for kidney disease progression shared by many forms of CKD by virtue of reduced nephron numbers inducing hyperfiltration in remaining glomeruli (66). DAPA-CKD recruited a population composed of a variety of albuminuric causes of CKD, importantly including individuals with or without type 2 DM (Table 1) (31). DAPA-CKD was also stopped early due to efficacy, having observed a 39% reduction in its primary cardiorenal composite outcome of a sustained 50% decline in eGFR, ESKD, or death from renal or cardiovascular causes (197/2152 vs 312/2152: HR=0.61, 0.51-0.72). Importantly, these relative cardiorenal benefits appeared similar across all of the subtypes of studied patients, and the trial provided direct evidence of efficacy on this primary outcome in both those with or without type 2 DM (21). There was also a clear reduction in risk of kidney disease progression (Figure 4), and fewer initiations of maintenance dialysis, both overall and among those with DM considered in isolation. DAPA-CKD therefore reinforces the findings on albuminuric diabetic kidney disease from CREDENCE (15). DAPA-CKD also raised a strong hypothesis that renal benefits may exist in some non-diabetic

proteinuric causes of CKD, including glomerulonephritis not treated with immunosuppression (31). Confirmation of the DAPA-CKD results and their extension to a more diverse group of patients remains important. There were 128 primary outcomes from the 1398 participants without DM at randomization, including only 51 participants who started maintenance dialysis and 7 who received a kidney transplant (too few to directly confirm whether clinical renal benefits extend to individuals without DM) (31). Generalizability was also reduced by the exclusion of polycystic kidney disease and some immunological causes of kidney disease, and the recruitment of a population with particularly high levels of albuminuria (an average of at about 1 g/day).

Establishing definitively whether or not albuminuria is a pre-requisite for renal benefits of SGLT-2 inhibitors is an important question to address as: (i) the majority of individuals with CKD do not have albuminuria (perhaps as many as three-quarters of those with advanced CKD); and (ii) if mechanistic theories about intraglomerular hypertension are correct, renal benefits may be substantially attenuated in the absence of albuminuria. The SCORED trial recruited individuals with type 2 DM and an eGFR between 25 and 60 mL/min/1.73m^2 irrespective of levels of albuminuria (Table 1). Like SOLOIST-WHF, SCORED was stopped after a median of 16 months' follow-up due to withdrawn funding (and concerns about potential effects of the COVID-19 pandemic). Although the point estimates of effect for its kidney disease progression outcome are consistent with the results from other trials, there were only 89 such outcomes precluding any conclusive findings (22). Hypothesis generating analyses from the completed SGLT-2 inhibitor trials in people with type 2 DM at high atherosclerotic cardiovascular risk suggest there may be renal benefits in individuals without albuminuria (67), and eGFR slope-based analyses from EMPEROR-REDUCED and DAPA-HF raise the possibility that renoprotection afforded by SGLT-2 inhibitors may extend to non-albuminuric non-diabetic CKD (19, 29, 30). However, there are insufficient data on ESKD in all these trials to assess effects in non-albuminuric CKD definitively. The ongoing EMPA-KIDNEY trial has the widest eligibility criteria of the four SGLT-2 inhibitor trials recruited from

CKD populations (Table 1). EMPA-KIDNEY will help assess more precisely which individuals with non-diabetic causes of albuminuric CKD obtain renal benefits from SGLT-2 inhibition, and test whether the renal benefits consistently identified in trial populations studied to date extend to those without albuminuria or those not taking RAS inhibitors (66).

Acute kidney injury (AKI) was a theoretical concern of SGLT-2 inhibition due to the initial acute eGFR "dip" upon their commencement, and the potential to replicate the AKI hazard which emerged when combining two inhibitors of the RAS system (68). However, the acute eGFR dip is reversible even after long-term treatment (64), and does not modify cardiac or renal benefits (69). Furthermore, SGLT-2 inhibition appears to reduce the risk of adverse events attributed to AKI (by about 25% (67)) with a protective effect evident in the trials conducted in people with type 2 DM at high atherosclerotic cardiovascular risk (18, 67), heart failure (16, 20, 29) and proteinuric CKD alike (15, 21, 22). The trials have not reported of an excess hazard of AKI with SGLT-2 inhibitors in subtypes of studied patient at particular risk of volume contraction (including individuals with HFrEF and CKD in EMPEROR-REDUCED, among whom ~90% were on RAS blockade and diuretics, and two-thirds also treated with a mineralocorticoid receptor antagonist (29)). One potential protective mechanism of SGLT-2 inhibition may be reduced risk of ischaemic-reperfusion injury or renal tubular hypoxia from the lowered metabolic demand from inhibited sodium-glucose co-transport (70). Conceivably, a reduction in AKI risk may also translate into benefits on CKD progression, providing a mechanistic explanation for beneficial effect of SGLT-2 inhibition on eGFR slopes in individuals with heart failure (19, 29, 30, 71).

Patients with CKD are at increased risk of hyperkalaemia due to their low eGFR and medical therapies. However, combining an SGLT-2 inhibitor with RAS blockade does not have the same potential as dual RAS blockade to cause hyperkalaemia (68), thereby simplifying treatment monitoring even at reduced levels of kidney function. There were no changes in potassium in biochemical assessments in the CANVAS trial across a range of eGFRs (72).

Similarly in the CKD trials, CREDENCE and DAPA-CKD reported no significant difference in adverse events for hyperkalaemia (CREDENCE: canagliflozin 29.7 versus placebo 36.9 events per 1000 patient-years (15); and DAPA-CKD: 6 [0.3%] events of serious hyperkalaemia among those allocated dapagliflozin versus 12 [0.6%] among those allocated placebo) (21). Data from HFrEF populations are similarly reassuring, with no effect of SGLT-2 inhibitors on laboratory measurements of potassium or clinical events of hyperkalaemia overall, or among those co-prescribed MRA (34, 73). DAPA-HF subanalyses generated a hypothesis that SGLT-2 inhibition may even reduce risk of severe hyperkalaemia among MRA users (34). This hypothesis was not confirmed in EMPEROR-REDUCED, but intriguingly allocation to empagliflozin led to fewer discontinuation of MRA, and actually, also to fewer initiation of MRAs (73).

EFFECTS ON METABOLISM AND OTHER SAFETY OUTCOMES

Weight, ketosis and ketoacidosis

It was noted early in their development that SGLT-2 inhibitors did not simply lower blood glucose (and consequently HbA1c), but they had broader metabolic effects. Glycosuria leads to increased plasma glucagon and hence a reduction in the insulin:glucagon ratio which in turn increases hepatic glucose production in part by glycogenolysis (74, 75). Depletion of liver glycogen creates a fasting-like state and glucose utilisation in the peripheries is reduced to spare it for the brain's glucose-dependent metabolism; instead, the liver generates ketones as an alternative energy source (49).

The loss of energy-rich glucose in the urine recapitulates the state of uncontrolled DM which presents with weight loss and glycosuria. Randomized trials consistently show a dose-dependent reduction in weight which can be as large as 3 kg over 6 months of treatment (76). Whereas the early weight loss may be due to intra- and extra-vascular volume depletion (43), loss of adipose tissue does occur with longer-term treatment (77). However, despite a consistent daily urinary loss of 60-80 g glucose with longer-term treatment, weight

appears to stabilise after about 6 months suggesting that other compensatory mechanisms (e.g. increased appetite) establish a new energy balance (78). Weight loss also occurs in individuals with little glycosuria with SGLT-2 inhibition (i.e. those with reduced kidney function) suggesting other pathways mediating the weight loss are yet to be defined (27).

In addition to inducing a state of ketosis, SGLT-2 inhibitors also reduce renal ammoniagenesis because ATP accumulates in the kidney (as it is not consumed by the sodium/potassium ATPase which would otherwise generate the sodium gradient necessary for SGLT-2 function). This inhibits other ATP-generating processes such ammoniagenesis. This – in combination with ketosis – leads to urinary loss of bicarbonate which, combined with ketosis, may lower the threshold required to induce ketoacidosis in the presence of an additional insult (e.g. fasting or infection) (79). It is important to be aware that glycosuria and these mechanisms can mean that ketoacidosis in individuals taking SGLT-2 inhibitors may be accompanied by relatively normal blood glucose concentrations (so-called “euglycaemic ketoacidosis”). Ketoacidosis risk is approximately doubled among those randomized to SGLT-2 inhibition in the large randomized trials (80), however ketoacidosis remains rare in type 2 DM so this represents a small absolute excess. No cases of ketoacidosis (or indeed severe hypoglycaemia) have been reported in trial participants without DM (16, 19, 21). Nevertheless, it is advisable that SGLT-2 inhibition is used with caution in individuals prone to ketoacidosis and that it is discontinued at times of fasting or physiological stress (e.g. peri-operatively).

Since individuals with type 1 DM have no endogenous insulin production, they are at much higher (at least 10-fold) risk of ketoacidosis. They may however experience the same cardiorenal benefits as individuals with type 2 DM, so concerns around ketoacidosis have led to dedicated placebo-controlled trials exploring this with participants provided with ketone monitoring equipment. Among 1402 participants with type 1 DM, allocation to sotagliflozin reduced insulin requirements and reduced %HbA1c by 0.46% ($p<0.001$), increasing the

proportion achieving HbA1c <7.0% (15.2% versus 28.6%; p<0.001) over 24 weeks, but at the expense of an excess of ketoacidosis (3.0% versus 0.6%) (81). Similarly, the EASE trials of empagliflozin in 1707 individuals with type 1 DM showed modest reductions in HbA1c versus placebo (0.28%, 0.54% and 0.53% for empagliflozin 2.5, 10 and 25 mg respectively). Ketoacidosis was more common in individuals allocated to empagliflozin 10 or 25 mg daily (3.3% and 4.3% respectively) than placebo (1.2%) but was similar to placebo among those allocated 2.5 mg daily (0.8%) (82). Use of certain SGLT-2 inhibitors in type 1 DM have been granted by European regulators with lower doses and under specialist supervision (35, 83).

Effects on severe hypoglycaemia

The risk of severe hypoglycaemia caused by SGLT-2 inhibition is small (11-13, 15-22) and appears to be largely limited to individuals who are on insulin or insulin secretagogues. Mechanistically, hypoglycaemia would not be expected because of the compensatory effects of intact SGLT-1 activity and hepatic gluconeogenesis (84). Importantly, severe hypoglycaemia (usually defined as that requiring external assistance) has not been described among any participants without DM in the large trials (16, 21, 85).

Effects on genital and urinary tract infections

Mycotic genital infections (e.g. vulvovaginal candidiasis in women or candida balanitis in men) are common in individuals with DM, but there is a clear excess with SGLT-2 inhibitors. Although such infections rarely fulfil the regulatory definition of a “serious” adverse event (and subsequently are incompletely recorded in some of the large outcome trials focussed on here), the effect of SGLT-2 inhibition on these infections is large enough to have been apparent in the earlier smaller trials focussing on glycaemic control (8, 9, 86). Case reports of necrotizing fasciitis of the perineum (Fournier’s gangrene) attribute such devastating polymicrobial infections to SGLT-2 inhibitors (87), but the limited randomized data available do not show an excess so a causal association remains unproven (13, 18, 21, 36). The large amounts of glucose in the urine mean that urinary tract infections were an expected adverse

effect of SGLT-2 inhibitors and they are listed in the labels for all SGLT-2 inhibitors. However, the randomized data have not yet found definitive evidence that SGLT-2 inhibitors importantly increase risk of urinary tract infections: with nearly 5000 reported adverse events from the large trials (11-13, 15-22).

Effect on fracture and lower limb amputation

The CANVAS program, which tested canagliflozin in individuals with type 2 DM at high risk of atherosclerotic cardiovascular disease, raised two hypotheses about previously undescribed risks of SGLT-2 inhibitors. The trials identified a small excess of bone fractures (15.4 versus 11.9 events per 1000 patient-years; p=0.02 [uncorrected for multiplicity of hypotheses]), with the pre-specified outcome of low-trauma fracture constituting the commonest fracture (11.6 versus 9.2 events per 1000 patient-years; p=0.06) (12). Given the exploratory nature of this finding it is appropriate to consider it “hypothesis-generating” and to test it with the other available trial data: these do not confirm the finding (11-13, 15-22).

Similarly, the CANVAS program raised a hypothesis that SGLT-2 inhibitors might increase the risk of lower limb amputation (6.3 versus 3.4 events per 1000 patient-years; p<0.001) (12). Again, this hypothesis was not confirmed in other trials (11-13, 15-22), including those such as CREDENCE which also tested canagliflozin in a population at much higher baseline risk of amputation (15). Although *post hoc* biological rationales have been proposed for this effect of canagliflozin (88), chance findings still occur even in large trials and this remains a possible explanation for these results.

FUTURE DIRECTIONS AND CONCLUSIONS

The 2019 ESC guidelines on the management of diabetes, prediabetes and cardiovascular diseases made a grade IA recommendation for empagliflozin, canagliflozin or dapagliflozin to be used to reduce risk of cardiovascular events in individuals with type 2 DM if either they have established, or are at high/very high risk of, atherosclerotic cardiovascular disease (see

guidelines for risk definitions (14)). Table 2 and our graphical abstract provide up-to-date position statements developed from our task force review. The totality of the large-scale randomized trial evidence now indicates relative benefits of SGLT-2 inhibitors on heart failure outcomes are larger than on major atherosclerotic outcomes, with no clear effect on stroke. Effects on heart failure hospitalization are consistent across the different tested SGLT-2 inhibitors and studied populations. In individuals with HFrEF, both dapagliflozin and empagliflozin have similar benefits on cardiovascular death or hospitalization for heart failure, irrespective of DM status (36). The general consistency of findings suggest that any differences between individual SGLT-2 inhibitors are not creating large differences in clinical efficacy. As such, the beneficial effects of SGLT-2 inhibition on heart failure hospitalization appear likely to be a class effect**.** The ESC heart failure guidelines are currently being updated, with publication expected in 2021. Two clinical outcome trials testing these two SGLT-2 inhibitors in HFpEF populations combining individuals with and without DM (DELIVER (38) & EMPEROR-PRESERVED (39)) have also completed recruitment with results expected in 2021/2022.

In individuals with albuminuric CKD, SGLT-2 inhibitors reduce risk of progression to ESKD with effects unmodified by kidney function (down to at least ~30 mL/min/1.73m^2). The consistency between the CREDENCE and DAPA-CKD results also provide preliminary support for renoprotection being a class effect, at least in people with type 2 DM. Canagliflozin and dapagliflozin are both indicated for this purpose in individuals with albuminuric diabetic nephropathy and type 2 DM (89), with dapagliflozin also indicated in those at risk of CKD progression (i.e. irrespective of DM status) (90). Precisely which non-diabetic causes of CKD that SGLT-2 inhibition favourably affects remains uncertain, as does whether renal benefits exist in non-albuminuric CKD. Results from EMPA-KIDNEY are expected in 2022 (66).

FIGURE LEGENDS

Figure 1: Effect of SGLT−2 inhibition on CARDIOVASCULAR DEATH or HOSPITALIZATION FOR HEART FAILURE, by population

For hospitalisation for heart failure or cardiovascular death, results are based on time to first event analyses and exclude urgent visits for heart failure, wherever possible. EMPA−REG OUTCOME excluded stroke from the outcome of cardiovascular death. For SOLOISTWHF, the hazard ratio and 95% confidence interval for the time to first cardiovascular death or hospitalization for heart failure were available, but not the number of events (NA=not available). Event rates for hospitalization for heart failure or cardiovascular death estimated from number of events and follow−up duration for SCORED.

Figure 2: KEY FAVOURABLE EFFECTS OF SGLT-2 INHIBITION ON CARDIORENAL PATHOPHYSIOLOGY

Abbreviations: SGLT-2=sodium-glucose coptransporter-2; NHE=sodium-hydrogen exchanger; O_2=oxygen; CKD=chronic kidney disease; AKI=acute kidney injury

Figure 3: Effect of SGLT−2 inhibition on MAJOR ATHEROSCLEROTIC CARDIOVASCULAR EVENTS, by population

Major atherosclerotic cardiovascular events (MACE) is a composite outcome including cardiovascular death, myocardial infarction or stroke. MACE results from heart failure population trials are unavailable. Rate of MACE was calculated from number of events and other information for SCORED. The following trials also included unstable angina in the composite: EMPA−REG OUTCOME & CREDENCE. VERTIS CV used a non−inferiority population.

Figure 4: Effect of SGLT−2 inhibition on KIDNEY DISEASE PROGRESSION, by population

Kidney Disease Progression was generally defined as death from renal causes, commencement of renal replacement therapy, or a % decline in eGFR/doubling of creatinine from baseline. The following trials used a 40% decline in eGFR: EMPEROR−REDUCED, CANVAS Program, DECLARE−TIMI58. The following trials used a 50% decline in eGFR: DAPA−HF, DAPA−CKD, SCORED. The following trials used a doubling of creatinine: EMPA−REG OUTCOME, VERTIS CV, CREDENCE. Results for kidney disease progression unavailable for SOLOIST−WHF. EMPA−REG OUTCOME population restricted to those that received at least one dose of study treatment.

Table 1: Large placebo-controlled SGLT-2 inhibitor clinical outcome trials, by population

Population Trial (reference) (drug & daily dose)	Size	Median follow-up, years	Proportion with type 2 diabetes	Average (SD) eGFR, mL/min/1.73m^2	Key eligibility criteria	Primary outcome(s)	Selected secondary outcomes	Completion status
Ia. Heart failure (reduced ejection fraction) population								
DAPA-HF (16) (dapagliflozin 10mg)	4744	1.5	42%	Mean: 66 (19)	• Symptomatic chronic HF (class II-IV) with LVEF ≤40% • NT-proBNP ≥600 pg/mL • eGFR ≥30 • Appropriate doses of medical therapy and use of medical devices	• CV death or worsening HF (hospitalization or an urgent visit for intravenous therapy)	• CV death or hospitalization for HF • Total number of hospitalization for HF • Sustained ≥50% decline in eGFR, sustained eGFR <15, ESKD, or renal death • Death from any cause	Reported
EMPEROR-REDUCED (19) (empagliflozin 10mg)	3730	1.3	50%	Mean: 62 (22)	• Class II-IV chronic HF with LVEF ≤40% • NT-proBNP above a certain threshold (stratified by LVEF) • Appropriate doses of medical therapy and use of medical devices	• CV death or hospitalization for worsening HF	• Total number of hospitalization for HF • Rate of eGFR decline • Death from any cause	Reported
Ib. Heart failure (preserved or mixed ejection fraction) population								
SOLOIST-WHF (20) (sotagliflozin 200-400mg)	1222	0.8	100%	Median: 50	• Type 2 DM • Hospitalized for heart failure requiring intravenous therapy • eGFR ≥30 • No recent coronary event	• CV death or total number of worsening HF events (hospitalization or an urgent visit)	• Total number of worsening HF events (hospitalization or an urgent visit) • Change in eGFR • Death from any cause	Reported
DELIVER (38) (dapagliflozin 10mg)	About 6100	Ongoing	Individuals with & without DM eligible	Unknown	• Symptomatic chronic HF (class II-IV) with LVEF >40% & structural heart disease • Elevated NT-proBNP • eGFR ≥25	• CV death or worsening HF (hospitalization or an urgent visit)	• Total number of worsening HF events (hospitalization or an urgent visit) • Death from any cause	Expected in 2021
EMPEROR-PRESERVED (39) (empagliflozin 10mg)	5988	Ongoing	Individuals with & without DM eligible	Unknown	• Symptomatic chronic HF (class II-IV) with LVEF >40% & structural heart disease • NT-proBNP >300 pg/mL (or >900 if in AF) • eGFR ≥20	• CV death or hospitalization for HF	• eGFR slope • ESKD • All-cause hospitalization • Death from any cause	Expected in 2021
II. High cardiovascular risk + type 2 DM population								

EMPA-REG OUTCOME (11) (empagliflozin 10mg or 25mg)	7020	3.1	100%	Mean: 74 (21)	• Type 2 DM • History of coronary, cerebral or peripheral vascular disease • eGFR ≥30	• CV death, non-fatal myocardial infarction or non-fatal stroke	• Hospitalization for HF • Incident or worsening nephropathy: macroalbuminuria, a doubling of the serum creatinine (accompanied by an eGFR of ≤45), ESKD or renal death	Reported
CANVAS Program (12) (canagliflozin 100-300mg)	10142	2.4	100%	Mean: 76 (20)	• Type 2 DM • History of coronary, cerebral or peripheral vascular disease OR age >50y with at least 2 CV risk factors • eGFR ≥30	• CV death, non-fatal myocardial infarction or non-fatal stroke	• CV death or hospitalization for HF • 30% increase in albuminuria with change in category • Death from any cause	Reported
DECLARE-TIMI58 (13) (dapagliflozin 10mg)	17160	4.2	100%	Mean: 85 (16)	• Type 2 DM • Age 40y + history of coronary, cerebral or peripheral vascular disease OR age ≥55y in men/≥60y in women with at least 1 CV risk factors • Creatinine clearance ≥60 mL/min	Co-primaries • CV death, myocardial infarction or ischaemic stroke • CV death or hospitalization for worsening HF	• Sustained ≥40% decline in eGFR (to <60), ESKD, or death from kidney or CV causes • Death from any cause	Reported
VERTIS CV (18) (ertugliflozin 5 or 15 mg)	8246	3.0	100%	Mean: 76 (21)	• Type 2 DM • History of coronary, cerebral or peripheral vascular disease • eGFR ≥30	• CV death, non-fatal myocardial infarction or non-fatal stroke	• Hospitalization for HF • Doubling of the serum creatinine, ESKD, or renal death	Reported
III. Chronic kidney disease population								
CREDENCE (15) (canagliflozin 100mg)	4401	2.6	100%	Mean: 56 (18)	• Type 2 DM • eGFR 30-90 • uACR 300-5000 mg/g • Stable maximally tolerated RAS blockade	• Sustained doubling of creatinine, sustained eGFR <15, ESKD, or death from renal or CV causes	• Hospitalization for HF • CV death, non-fatal myocardial infarction or non-fatal stroke • Death from any cause	Reported
DAPA-CKD (21) (dapagliflozin 10mg)	4304	2.4	68%	Mean: 43 (12)	• eGFR 25-75 • uACR 200-5000 mg/g • Stable maximally tolerated RAS blockade, unless documented intolerance	• Sustained ≥50% decline in eGFR, sustained eGFR <15, ESKD, or death from renal or CV causes	• Hospitalization for HF • Death from any cause	Reported

SCORED (22) (sotagliflozin 200-400mg)	10584	1.3	100%	Median: 45	• Type 2 DM • eGFR 25-60 • At least 1 CV risk factor	• CV death or total number of worsening HF events (hospitalization or an urgent visit)	• CV death, non-fatal myocardial infarction or non-fatal stroke • Sustained ≥50% decline in eGFR, sustained eGFR <15, or ESKD • Death from any cause	Reported
EMPA-KIDNEY (66) (empagliflozin 10mg)	About 6600	Ongoing	About 45%	Mean: About 37	• eGFR 20-45, or eGFR 45-90 with uACR ≥200 mg/g • Clinically appropriate doses of RAS blockade, unless not tolerated	• Sustained ≥40% decline in eGFR, sustained eGFR <10, ESKD, or death from renal or CV causes	• CV death or hospitalization for HF • All-cause hospitalization • Death from any cause	Expected mid-2022

Footnote: AF=atrial fibrillation; CKD=chronic kidney disease; CV=cardiovascular; DM=diabetes mellitus; eGFR=estimate glomerular filtration rate (mL/min/1.73m^2); ESKD=end-stage kidney disease (i.e. maintenance dialysis or receipt of kidney transplant); HF=heart failure; LVEF=left ventricular ejection fraction; RAS=renin angiotensin system; uACR=urinary albumin:creatinine ratio

Table 2: Position statements on the cardiac and renal effects of sodium-glucose co-transporter-2 inhibitors

Heart failure populations
In individuals with heart failure with reduced ejection fraction (with or without type 2 diabetes mellitus [DM]), risk of cardiovascular (CV) death or hospitalization for heart failure is reduced by dapagliflozin or empagliflozin (16, 19)
In individuals with type 2 DM recently hospitalized for heart failure†, the risk of CV death or hospitalization for heart failure is reduced by sotagliflozin (20)
Type 2 DM at high/very high CV risk populations*
In individuals with type 2 DM at high/very high risk of CV disease, risk of major atherosclerotic CV events is reduced by empagliflozin and canagliflozin (11, 12), and risk of cardiovascular death and all-cause mortality is reduced by empagliflozin (11).
In individuals with type 2 DM at high/very high risk of CV disease, risk of CV death or hospitalization for heart failure is reduced by empagliflozin, canagliflozin, or dapagliflozin, and risk of hospitalization for heart failure is reduced by empagliflozin, canagliflozin, dapagliflozin or ertugliflozin (11-13, 18)
In individuals with type 2 DM, risk of kidney disease progression (i.e. clinically significant sustained reductions in kidney function) is reduced by empagliflozin, canagliflozin or dapagliflozin (13, 64, 67, 91)
Chronic kidney disease (CKD) populations
In individuals with type 2 DM and proteinuric diabetic kidney disease, progression to end-stage kidney disease is reduced by canagliflozin or dapagliflozin (15, 31)
In individuals with proteinuric CKD, with or without type 2 DM, the risk of kidney disease progression is reduced by dapagliflozin (21)
In individuals with type 2 DM and CKD, the risk of CV death or hospitalization for heart failure is reduced by canagliflozin, dapagliflozin or sotagliflozin (15, 21, 22)

* CV risk classification according to 2019 ESC guidelines on diabetes, prediabetes and CV disease (14). † information on those with ejection fraction ≥50% is limited to 256 participants from SOLOIST-WHF.

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