European Society of Cardiology/Heart Failure Association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is common in patients with heart failure (HF) and associated with considerable morbidity and mortality. Significant advances have recently occurred in the treatment of T2DM, with evidence of several new glucose-lowering medications showing either neutral or beneficial cardiovascular effects. However, some of these agents have safety characteristics with strong practical implications in HF (i.e. dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RA), and sodium-glucose contransporter-2 (SGLT-2) inhibitors).

Regarding safety of DPP-4 inhibitors, saxagliptin, is not recommended in HF because of a greater risk of HF hospitalisation. There is no compelling evidence of excess HF risk with the other DPP-4 inhibitors. GLP-1 RAs have an overall neutral effect on HF outcomes. However, a signal of harm suggested in two small trials of liraglutide in patients with reduced ejection fraction, indicates that their role remains to be defined in established HF. SGLT-2 inhibitors (empagliflozin, canagliflozin and dapagliflozin) have shown a consistent reduction in the risk of HF hospitalisation regardless of baseline cardiovascular risk or history of HF. Accordingly, SGLT-2 inhibitors could be recommended to prevent HF hospitalisation in patients with T2DM and established cardiovascular disease or with multiple risk factors. The recently completed trial with dapagliflozin, has shown a significant reduction in cardiovascular mortality and HF events in patients with HF and reduced ejection fraction, with or without T2DM. Several ongoing trials will assess whether the results observed with dapagliflozin could be extended to other SGLT-2 inhibitors in the treatment of HF, with either preserved or reduced ejection fraction, regardless of the presence of T2DM. This position paper aims to summarise relevant clinical trial evidence concerning the role and safety of new glucose-lowering therapies in patients with HF.

Key words: heart failure, type 2 diabetes mellitus, cardiovascular risk, hospitalisation, sodium glucose cotransporter 2 inhibitor, glucagon-like peptide-1 receptor agonist, dipeptidyl peptidase-4 inhibitor, clinical trial

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is common (~20-40%) in patients with heart failure (HF) [1], and is associated with worse symptoms and quality of life, a greater burden of HF hospitalization, and higher mortality rates compared to patients without T2DM [2-7]. Increased levels of glycosylated haemoglobin A_{1c} (HbA_{1c}) have been associated with increased morbidity and mortality in patients with T2DM and HF not receiving treatment with glucose-lowering drugs [8, 9]. However, once treatment of T2DM has been initiated, this relationship may no longer be linear. Most data suggests that mortality risk in patients with HF is lowest with moderate glycaemic control (i.e. HbA_{1c} levels 7.0-7.9%) [10-14]. Therefore, the 2016 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of HF stipulate that adequate glycaemic control should be achieved gradually and leniently, with agents shown to be safe and effective [15]. A holistic approach to T2DM management in HF should also include blood pressure, body weight, and lipid control, while avoiding hypoglycaemia, which is associated with a greater risk of death [16] and may be a cause of increased mortality in diabetic patients with HF on insulin therapy [17]. However, this may be challenging in clinical practice, as older age, frailty and multiple comorbidities, including coronary artery disease (CAD), and chronic kidney disease (CKD) [6, 18], increase the vulnerability to adverse drug effects in many patients with T2DM and HF.

New glucose-lowering medications (i.e. dipeptidyl peptidase 4 (DPP-4) inhibitors [19], glucagon like peptide-1 receptor agonists (GLP-1 RA) [20], and sodium glucose cotransporter type-2 (SGLT-2) inhibitors [21]) may have effects beyond glycaemic control pertinent to cardiovascular (CV) risk reduction in T2DM. **Figure 1** provides a summary of several proposed pleiotropic mechanisms that extend the benefits of new glucose lowering medications beyond glycaemic control to include positive metabolic, renal, vascular and haemodynamic effects [22]. At present, the exact mechanism(s) underlying favourable CV effects of these medications in humans are unclear and are under assessment in several mechanistic studies. However, the results from large CV outcome trials (CVOTs) have shown a comprehensive CV risk reduction with some of the new glucose-lowering agents, in particular with GLP-1 RA and SGLT-2 inhibitors, in patients with T2DM and established CV disease or with multiple risk factors. However, clinically relevant issues have been raised about the effectiveness and safety of these medications relevant for HF outcomes. Therefore, the purpose of this position paper is to summarize clinical trial data on the role and safety of these new evidence-based therapies for the treatment of T2DM in patients with HF.

HEART FAILURE OUTCOMES IN CARDIOVASCULAR OUTCOME TRIALS WITH NEW GLUCOSE-LOWERING MEDICATIONS

Since 2008 and 2012, Food and Drug Administration (FDA) and the European Medicines Agency (EMA), respectively, have required that CVOTs investigating novel glucose-lowering medications are designed to evaluate CV safety. To minimize potential confounding by differences in glycaemic control between the treatment groups, CVOTs promoted a concept of "glycaemic equipoise" (i.e. maintenance of similar glycaemic levels during the trial) between the treatment arms. In the majority of CVOTs, primary outcome has been a composite of the three major adverse CV events (3-point MACE) comprising CV death, non-fatal myocardial infarction (MI) and non-fatal stroke. Two trials also included hospitalisation for unstable angina (4-point MACE) [23, 24], and one trial had two co-primary outcomes (the 3-point MACE and a composite of CV mortality and HF hospitalisation) [25]. Most patients had a history of long-standing T2DM and established atherosclerotic CV disease (or alternatively were at high CV risk) and, therefore, the evidence derived from these trials is most compelling for secondary prevention of CV events. Despite the undisputed relevance of HF in patients with T2DM, none of these trials included HF events as a component of the primary outcome. However, hospitalisation for HF was a prespecified secondary outcome in all trials, and a co-primary composite outcome in one of the trials with SGLT-2 inhibitors [25]. Until recently, the generalisation of trial results to individuals with HF was hampered by the relatively modest number of patients with a history of HF enrolled, ranging 9-28% (**Tables 1, 2 and 3**) and limited characterisation of HF in terms of left ventricular (LV) ejection fraction (LVEF), aetiology, functional class or biomarker levels, either at baseline, or during the follow-up, with a possible exception, to some extent, of DECLARE-TIMI 58 trial (Dapagliflozin Effect on Cardiovascular Events –Thrombolysis in Myocardial Infarction 58) [25]. However, recently completed DAPA-HF (Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) has shown a significant reduction in CV mortality and HF events with dapagliflozin vs. placebo among patients with HF and reduced ejection fraction (HFrEF), regardless of T2DM status, suggesting that these medications could be beneficial in the treatment of HF [26]. Furthermore, observational and registry data suggest similar efficacy and safety characteristics of the new glucose-lowering drugs in "real-world" setting (compared with CVOTs) [27, 28], but current data is still limited.

DIPEPTIDYL PEPTIDASE-4 INHIBITORS

The CVOTs with DPP-4 inhibitors (saxagliptin, alogliptin, sitagliptin, and linagliptin) have demonstrated non-inferiority to placebo in respect to primary 3-point MACE, but they have not shown superiority. A summary of CVOT results with DPP-4 inhibitors are presented in **Figure 2**. Despite a consistently neutral effect on the primary composite outcome, the rates of HF hospitalisation were different among the DPP-4 inhibitors. (**Table 1**). In the SAVOR-TIMI 53 trial (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus - Thrombolysis In Myocardial Infarction 53) [29], a statistically significant increase of 27% in hospitalisation for HF was observed in patients randomised to saxagliptin vs. placebo (3.5% vs 2.8%; hazard ratio (HR), 1.27; 95% confidence interval (CI), 1.07-1.53) [30]. The EXAMINE trial (Examination of Cardiovascular Outcomes vs. Standard of Care in Patients with Type 2 Diabetes and Acute Coronary Syndrome) demonstrated a nonsignificant trend towards increased risk of HF hospitalisation with alogliptin vs. placebo (3.1% vs. 2.9%; HR, 1.07; 95% CI 0.79-1.46) [31]. In the TECOS (Trial Evaluating Cardiovascular Outcome with Sitagliptin), sitagliptin demonstrated no effect on the risk of HF hospitalisation compared to placebo (3.1% vs. 3.1%, HR, 1.00; 95% CI 0.84-1.20) [23]. In the most recent trial investigating this class of agents, CARMELINA (Effect of Linagliptin vs. Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk), there was no significant effect of linagliptin vs. placebo treatment on the risk of HF hospitalisation (2.8% vs. 3.0%; HR, 0.90; 95% CI, 0.74-1.08) [32], as well as other HF outcomes, including CV death or HF hospitalisation (HR, 0.94; 95% CI, 0.82–1.08), or recurrent HF hospitalisation events (326 versus 359 events, respectively; rate ratio, 0.94; 95% CI, 0.75–1.20) [33].

Whether DPP-4 inhibitors increase the risk of HF in general, or exhibit within-class differences, is not completely understood. A post hoc analysis of SAVOR-TIMI 53 has suggested a higher risk with saxagliptin in patients with a history of HF, renal dysfunction (estimated glomerular filtration rate eGFR <60 ml/min [34]) and higher baseline levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) [30]. However, this was not observed with alogliptin in a post hoc analysis of EXAMINE, in which the risk of HF hospitalisation was unaffected by the above-mentioned factors [31]. Notably, the higher incidence of HF hospitalization has not resulted in excess all-cause or CV mortality in the group treated with either saxagliptin in SAVOR-TIMI 53, or alogliptin in EXAMINE [29, 35]. In a prespecified sub-analysis of CARMELINA, linagliptin was safe for HF outcomes in patients with or without prior HF,

irrespective of LVEF, and across a spectrum of renal impairment [33]. In the smaller VIVIDD study (Effects of Vildagliptin on Ventricular Function in Patients with Type 2 Diabetes Mellitus and Heart Failure), vildagliptin had no significant effect on LVEF, BNP levels, or HF status in patients with HF and reduced ejection fraction (HFrEF) [36]. However, treatment with vildagliptin resulted in an increase in LV volumes and more deaths compared with placebo (8.6% vs. 3.2%), albeit with no consistent pattern and not reaching statistical significance [36]. The clinical significance of these findings remains to be determined.

Several meta-analyses of these trials have indicated either a higher risk of HF in patients with established CV disease [37], or a higher HF risk associated with saxagliptin, but not with other DPP-4 inhibitors [38]. A recently presented CAROLINA trial (Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes) demonstrated no difference in the 3-point MACE outcome and no increase in the risk of HF hospitalisation (3.7% vs 3.1%; HR, 1.21; P = 0.176) between linagliptin and an active comparator, glimepiride, but patients treated with glimepiride experienced more hypoglycaemia compared with those receiving linagliptin (NCT01243424, [39]).

GLUCAGON LIKE PEPTIDE-1 RECEPTOR AGONISTS

Six CVOTs have assessed the CV safety profile of the subcutaneous GLP-1 RA class of agents (lixisenatide, liraglutide, semaglutide, exenatide, albiglutide and dulaglutide) and one trial has evaluated the first orally active form of the GLP-1 RA, oral semaglutide [40], **Table 2**. Two of these CVOTs, ELIXA (Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome) [41] and EXSCEL (Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes) [42], found that lixisenatide and exenatide, respectively, had a neutral effect on the primary composite outcome. There was no effect of lixisenatide (4.2% vs. 4.0%; HR 0.96, 95%CI 0.75-1.23) or exenatide (3.0% vs. 3.1%, HR, 0.94; 95% CI, 0.78−1.13) vs. placebo on the risk of HF hospitalisation [41, 42]. Conversely, CVOTs with liraglutide, semaglutide and albiglutide have shown a reduction in CV outcomes compared with placebo. A summary of CVOT outcomes with GLP-1 RA is shown in **Figure 2**.

In LEADER (Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes), liraglutide treatment led to a decrease of 13% in the risk of primary endpoint MACE, as well as significantly lower risks of CV mortality, all-cause mortality and microvascular events compared to placebo [43]. There was a nonsignificant 13% reduction in the risk of HF hospitalisation, (4.7% vs. 5.3%; HR, 0.87; 95% CI,

0.73 - 1.05) [43]. In SUSTAIN-6 (Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes), subcutaneous semaglutide led to a 26% lower risk of the primary endpoint MACE, mainly driven by a reduction in the rate of stroke [44]. The relative risk of HF hospitalisation was unaffected by semaglutide treatment (3.6% vs. 3.3%; HR, 1.11; 95%, 0.77 - 2.78) [44]. Recently, PIONEER 6 trial (Peptide Innovation for Early Diabetes Treatment) explored CV safety of the first oral GLP-1 RA compared with placebo. The trial demonstrated no excess in the risk of 3-point MACE (2.9% vs. 3.7%; HR, 0.79, 95% CI, 0.57 – 1.11) and no increase in HF hospitalisation (1.3% vs. 1.5%; HR 0.86, 95% CI, 0.48 – 1.55) with oral semaglutide compared with placebo [40]. Furthermore, the results of PIONEER 7 (Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes: a multicentre, open-label, randomised, phase 3a trial) suggest that flexible dose-adjusted oral semaglutide can provide superior glycaemic control and weight loss compared with sitagliptin, with safety characteristics similar to subcutaneous GLP-1 RAs [45]. These results open a possibility to further explore oral GLP-1 RA as an alternative to the injectable form of these medications.

Recently, in HARMONY Outcomes (Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease) there was a 22% lower risk of the primary composite outcome with albiglutide compared with placebo, driven by a significant reduction in the rate of MI [46]. Also, a trend was observed towards a lower risk of the composite outcome of CV death or hospital admission for HF with albiglutide compared with placebo (4.0% vs. 5.0%; HR, 0.85, 95% CI, 0.70–1.04) [46]. In addition, the REWIND trial (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) demonstrated a 12% risk reduction for the 3-point MACE with the long-acting dulaglutide vs. placebo (12.0% vs. 13.4%; HR, 0.88, 95% CI, 0.79-0.99), primarily due to a significant reduction in the risk of non-fatal stroke [47]. Again, there was no difference between the two treatment arms with respect to HF events (4.3% vs. 4.6%; HR 0.93, 95% CI 0.77 – 1.12) [47].

A metanalysis of the four trials with a GLP-1 RA has suggested that these medications can reduce the rate of 3-point MACE, albeit to a varying degree for individual drugs [20]. The discrepant responses may be related to differences in molecular structure and pharmacokinetic properties (long-acting vs. short-acting) of different GLP-1 RA, or, perhaps, to a heterogeneity in patient risk profiles, and study design of particular CVOTs [48]. Improvement in CV outcomes emerged late (after 12 to 18 months) in the setting of modest glucose-lowering effects and mainly due to a reduction in vascular

events (either stroke or MI) suggesting that non-hemodynamic mechanisms beyond glycaemic control, possibly related to anti-atherosclerotic effects, underpin the benefits of GLP-1 RA (**Figure 1**).

Thus far, GLP-1 RA have shown a neutral effect on the risk of HF hospitalization, with a favourable trend observed with liraglutide, albiglutide and oral semaglutide. An observed increase in heart rate (by a mean of ~3-9 beats/minute) may conceivably be partly accountable for the lack of an effect on HF [49, 50]. In the recent LIVE study (Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes), liraglutide had a neutral effect on LVEF in patients with chronic stable HFrEF (with or without T2DM), but led to an increase in heart rate and more adverse CV events compared with placebo [51]. A similar signal has come from the FIGHT trial (Functional Impact of GLP-1 for Heart Failure Treatment) in which a trend towards higher risk of death and rehospitalisation for HF was observed with liraglutide compared with placebo in HFrEF patients (with or without T2DM) [52]. In a small randomized trial, no significant effect was documented with albiglutide on cardiac function or myocardial glucose utilisation in patients with symptomatic HFrEF, but there was a modest increase in peak oxygen consumption, the importance of which remains to be determined [53]. The suggested safety signal with some of the GLP-1 RA in patients with HFrEF merits further investigation.

SODIUM GLUCOSE COTRANSPORTER TYPE-2 INHIBITORS

Sodium-glucose cotransporter type-2 (SGLT-2) inhibitors (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin) have a unique glucose-lowering effect via inhibiting glucose reabsorption in the proximal renal tubule [54]. Due to the favourable outcomes in recent trials, SGLT2 inhibitors are assumed to have cardioprotective properties, via several mechanisms, as reviewed [22, 55-57]. Beneficial effects of SGLT-2 inhibition on CV outcomes have been shown in the recent landmark CVOTs with empagliflozin, canagliflozin and dapagliflozin (**Table 3**), while ertugliflozin is being assessed in an ongoing VERTIS trial (NCT01986881). Notably, SGLT-2 inhibitors are the first class of glucose lowering medications that have demonstrated a positive effect on risk reduction for HF hospitalization (**Figure 2**). In the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients Removing Excess Glucose), empagliflozin treatment in patients with T2DM and established CV disease has resulted in a significant 14% relative risk reduction for the primary composite outcome, driven by a 38% risk reduction in CV mortality (3.7% vs. 5.9%; HR, 0.62; 95% CI, 0.49–0.77) [58]. The trial also reported a 35% risk reduction of hospitalisation for HF

(2.7% vs. 4.1%, HR, 0.65; 95% CI, 0.5-0.85) and a 32% lower all-cause mortality with empagliflozin compared with placebo (5.7% vs. 8.3%; HR, 0.68; 95%, 0.57-0.82) [58]. In a sub-analysis of HF outcomes in this trial, empagliflozin reduced the composite risk of HF hospitalisation or CV death (5.7% vs. 8.5%; HR, 0.66; 95% CI; 0.55-0.79), as well as its individual components compared to placebo [59]. In addition, empagliflozin also reduced HF-related hospitalisation and mortality (2.8% vs. 4.5%; HR; 0.61; 95% CI, 0.47 – 0.79) [59] and reduced the need for introduction of loop diuretics, which is in concert with the observed lower incidence of HF hospitalisation [59, 60]. The beneficial effect of empagliflozin on HF hospitalisation was consistent across pre-defined subgroups, including patients with and without a history of HF (HRs, 0.75, 95% CI 0.48 - 1.19 and 0.59; 95% CI, 0.43 - 0.82, respectively) [59]. The favourable effects on HF events occurred within the first 6 months after treatment initiation with an even earlier divergence of the Kaplan-Meier curves, suggesting improvement in haemodynamic status and reduced congestion as putative mechanisms (**Figure 1**). Of note, compared with placebo, empagliflozin had no effect on the risk of MI, but there was a numerical increase in the risk of stroke (HR, 1.18; 95% CI, 0.89-1.56) [58]. A subsequent sub-analysis showed that this difference could be explained by events occurring >90 days after the last dose of the drug, whereas there was no difference in events occurring on-treatment or within 90 days after the last dose (HR, 1.08; 95% CI, 0.81-1.45; P=0.60) [61]. Subsequent CVOTs with other SGLT-2 inhibitors have not shown an increase in risk of stroke.

The CANVAS Program (Canagliflozin Cardiovascular Assessment Study), comprised the CANVAS and CANVAS-R trials enrolling T2DM patients with established atherosclerotic CV disease (66%), or at high CV risk (34%) [62]. Treatment with canagliflozin resulted in a significant 14% relative risk reduction in the primary composite outcome compared with placebo, with the individual components demonstrating a statistically non-significant trend towards benefit. This study also showed a substantial 33% reduction in the risk of HF hospitalisation (5.5% vs. 8.7%; HR, 0.67; 95% CI, 0.52-0.87), although this finding was not considered statistically significant based on the prespecified sequence of hypothesis testing [62]. An ancillary analysis of CANVAS trial with a retrospective review of medical records to obtain data on LVEF at the time of HF hospitalisation demonstrated that the prevailing phenotype of HF was HFrEF, defined as admission LVEF <50% (122 cases of 276 HF events), followed by HFpEF, defined as LVEF ≥50% (101 cases of 276 HF events), while the rest had HF event with unknown LVEF [63]. Patients with HFpEF were more likely to be female, hypertensive and to have high

body mass index or microvascular disease in comparison with patients with HFrEF. Importantly, canagliflozin reduced the risk of all HF events, with no distinct difference in effects on HFrEF versus HFpEF events [63].

Further support of the therapeutic benefit with canagliflozin comes from CREDENCE trial (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation), showing a 34% relative risk reduction in cardiorenal outcomes compared with placebo in patients with T2DM and kidney dysfunction (albuminuria and eGFR 30 to <90 mL/min/1.73 m^2) already on optimal doses of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [64]. Importantly, this trial has confirmed a robust attenuation in the composite risk of CV death or HF hospitalisation (HR 0.69; 95% CI, 0.57-0.83), including a significant risk reduction for HF hospitalisation. On that basis, SGLT-2 inhibition may be a novel approach to improve cardiorenal protection and reduce the risk of HF hospitalisation among high-risk patients with T2DM and mild-to-moderate CKD.

Recently DECLARE TIMI-58 trial assessed the effects of dapagliflozin vs. placebo on CV outcomes in the predominantly (59%) primary prevention population of T2DM patients. Despite a neutral effect on the 3-point MACE outcome, dapagliflozin was superior compared with placebo in reducing a composite of CV death or HF hospitalization (4.7% vs. 5.8%, HR, 0.83; 95% CI, 0.73 – 0.95) [65]. This effect was due to a significant 27% risk reduction for HF hospitalisation (HR 0.73, 95% CI, 0.61 – 0.88), whereas the risk of CV death was unaffected [65]. Further insights into the effects of dapagliflozin according to baseline HF status (with or without a history of HF) and LVEF came from a sub-analysis of DECLARE-TIMI 58 trial, demonstrating consistent reduction in the risk of HF hospitalisation in all patients, regardless of baseline HF status or LVEF [66]. However, the largest risk reduction in HF hospitalisation was observed in patients with HFrEF (3.9% in patients with baseline LVEF <45%), in whom dapagliflozin also attenuated all-cause and CV mortality [66]. By contrast, in non-HFrEF patients (either without known HF or without known reduced LVEF), HF risk reduction was lower compared with HFrEF patients and there was no effect on mortality. Yet another sub-analysis of the same trial has demonstrated a reduction in hospitalisation irrespective of baseline CV risk profile (established CV disease or multiple risk factors), albeit individuals with prior MI derived the greatest benefit, including a reduction in the risk of 3-point MACE with dapagliflozin [67].

Several haemodynamic and metabolic mechanisms (not mutually exclusive) have been proposed to explain the salutary CV effects of SGLT-2 inhibitors (**Figure 1**) [22], but they await

confirmation from clinical trials. In a recent exploratory analysis of EMPA-REG OUTCOME, changes in markers of plasma volume (haematocrit and haemoglobin) had the largest impact on relative risk reduction of CV death (51.8% and 48.9%, respectively) [68]. These changes were likely haemodynamic in origin, reflecting a sustained effect on plasma volume contraction owing to increased diuresis and natriuresis with SGLT-2 inhibitors. SGLT-2 inhibitors exert renal protection [58, 62, 65], which could also contribute to CV protection. Furthermore, in a mechanistic experimental study, empagliflozin has been associated with an improvement in myocardial diastolic stiffness in isolated human cardiomyocytes, most likely due to enhanced phosphorylation of myofilament regulatory proteins [69].

A subanalysis of a small number of patients from EMPA-REG OUTCOME has shown early and significant reduction in LV mass index and improvement in diastolic function without changes in LV systolic function or volumes with empagliflozin compared with placebo [70]. Most recently, EMPA-HEART Cardiolink-6 study has shown a reduction in LV mass index on cardiac magnetic resonance following 6 months of empagliflozin treatment (compared with placebo) among diabetic patients with stable CAD, normal LVEF and without a history of HF [71]. Although intriguing, these concepts require further confirmation from larger studies [56]. The results of DAPA-HF suggest that SGLT-2 inhibitors may indeed benefit the treatment of HF, as discussed below.

A SUGGESTED APPROACH TO GLUCOSE-LOWERING THERAPY IN PATIENTS WITH TYPE 2 DIABETES AND HEART FAILURE

Recent CVOTs provide a perspective on the role and safety profile of new glucose-lowering medications for the treatment of T2DM in patients with HF.

There is currently insufficient evidence on the safety profile of DPP-4 inhibitors in patients with established HF. Based on the available data, saxagliptin, and, possibly, vildagliptin should not be used in those patients, while caution is recommended with alogliptin. There is no evidence of adverse HF outcomes with linagliptin, or sitagliptin.

In the general population of T2DM patients, DPP-4 inhibitors are well tolerated, weight-neutral and associated with a low risk of hypoglycaemia (**Figure 3**). The recommended doses, dose modifications and important precautions relevant for DPP-4 inhibitors use are presented in **Figure 3**.

GLP-1 RA demonstrated a neutral effect on the risk of HF, and a trend towards a lower risk was observed with liraglutide, albiglutide and oral semaglutide. However, a signal of harm detected in

smaller trials of GLP-1 RA in patients with HFrEF warrants caution. Therefore, this concerning safety issue needs further investigation prior to defining the role of GLP-1 RA for T2DM treatment in patients with established HF.

The risk of hypoglycaemia is not increased with GLP-1 RA monotherapy but may be aggravated in combined treatment with other glucose-lowering drugs, in particular insulin or insulin secretagogues. The therapy with GLP-1 RA increases postprandial satiety that may have favourable effect on weight loss. The most frequent side-effects of subcutaneous GLP-1 RA include (transient) gastrointestinal intolerance, and increased frequency of gall bladder disease [72]. Gastrointestinal intolerance is also the most frequent side-effect of oral semaglutide [40]. There may be an increased risk of acute pancreatitis, whereas a higher risk of C-cell hyperplasia/medullary thyroid carcinoma has not been confirmed in human studies [72]. The recommended doses, dose modifications, and precautions relevant for GLP-1 RA use in general population of patients with T2DM are presented in **Figure 3.**

The three CVOTs with SGLT-2 inhibitors have consistently demonstrated that treatment with these agents is associated with lower risk of HF hospitalisation in patients with T2DM and established atherosclerotic CV disease or with multiple risk factors, with the strongest effects in individuals with established CV disease. These results were corroborated by a recent meta-analysis of these CVOTs, demonstrating a significant 23% risk reduction for CV death or HF hospitalisation (HR, 0.77; 95% CI 0.71–0.84), as well as a reduction in HF hospitalisation by 31% (HR, 0.69; 95% 0.61–0.79) with SGLT-2 inhibitors [73]. Importantly, these findings were consistent regardless of CV disease burden, or a prior history of HF, suggesting that SGLT-2 inhibitors may have a beneficial effect on HF prevention in a broad spectrum of T2DM patients [73].

This beneficial effect has already been acknowledged for empagliflozin in the 2016 ESC Guidelines for the diagnosis and treatment of HF [15] and in the Guidelines for cardiovascular prevention [74], which have recommended its use in patients with T2DM to delay the onset of HF. In line with emerging clinical trial data, the 2019 expert consensus report from the ESC Heart Failure Association has extended this recommendation to all three SGLT-2 inhibitors [75]. Likewise, the 2018 ADA/EASD Consensus statement has positioned SGLT-2 inhibitors as the preferred treatment of T2DM in patients with known HF or at risk of HF [76]. Accordingly, SGLT-2 inhibitors have been recommended as an add-on therapy in patients who have not achieved adequate glucose control with metformin (or in whom metformin is contraindicated/not tolerated) [76]. In patients with HF receiving dual or multiple

glucose-lowering medications, not including SGLT-2 inhibitors, a switch to an SGLT-2 inhibitor has been recommended [76]. A similar recommendation has been issued from the American College of Cardiology [77], however in the absence of prospective data in patients with prevalent HF.

Clinical trials specifically investigating a potential benefit of this class of drugs in patients with prevalent HF, independent of the presence of T2DM, are currently ongoing (**Table 4**). The first completed among those trials, DAPA-HF reported a significant risk reduction in the primary endpoint comprising CV mortality/HF hospitalisation/urgent HF visit (HR, 0.74; 95% CI, 0.65 – 0.85) in patients with HFrEF (LVEF ≤40% and elevated natriuretic peptides) [26]. Primary composite outcome was consistently reduced in patients with T2DM (HR 0.75; 95% CI, 0.63 – 0.90) and in those without T2DM (HR 0.73; 95% CI, 0.60 – 0.88). Both components of the primary outcome (CV mortality and HF events) were significantly reduced with dapagliflozin treatment (by 18% and 30%, respectively) and there were no interactions with respect to demographic/clinical characteristics or HF treatment [26]. Further information is awaited from trials with other SGLT-2 inhibitors, including patients with either HFrEF or HFpEF, with or without T2DM (**Table 4**).

In addition, a clinical trial with sotagliflozin, a unique, dual SGLT-2 and 1 inhibitor is underway to investigate CV mortality and HF hospitalisation in patients recently hospitalised for worsening HF (NCT03521934). Inhibition of both SGLT-2- and 1 may increase glycosuria beyond the effect observed with SGLT-2 inhibitors and to reduce intestinal glucose absorption. However, unlike SGLT-2, SGLT-1 is also expressed in various other organs, including the heart, where it may have an effect on glucose uptake. There is currently a paucity of data to indicate whether these effects could have incremental therapeutic value in patients with T2DM [78].

SGLT-2 inhibitors are associated with a low risk of hypoglycaemia and can be safely and effectively combined with other glucose-lowering drugs in order to achieve optimal glucose control [79]. However, adverse effects need to be considered. The most frequently observed adverse events are genital mycotic infections, usually mild and non-recurring after treatment [58, 62, 65]. Rarely, “euglycaemic” ketoacidosis may occur (characterised by lower than typical blood glucose levels), possibly caused by increased glucagon release and decreased renal ketone body excretion in the face of enhanced glycosuria in insulin deficient patients (i.e. patients receiving insulin therapy) [80]. Although ketoacidosis has not been more frequently observed in EMPA-REG OUTCOME or CANVAS trials, it occurred more frequently with dapagliflozin in DECLARE TIMI 58 (HR, 2.18; 95% CI, 1.10 – 4.30) [65].

Hospitalisation for an acute illness or surgery may exacerbate the risk of ketoacidosis, and it may be prudent to temporarily discontinue SGLT-2 inhibitors under those circumstances [81, 82]. Reinitiating SGLT-2 inhibitors following the episode of ketoacidosis is not recommended because of an increased risk of recurrence [81, 82]. In addition, safety analyses of CANVAS Program have suggested a greater risk of bone fractures and lower limb amputations with canagliflozin. The most prominent increase in the absolute risk was observed among patients with previous amputations or peripheral arterial disease, possibly explained by volume depletion and greater vulnerability to ischaemic complications [62]. By contrast, no significant increase in the risk of lower-limb amputations, or fractures was observed with canagliflozin in CREDENCE. Of note, in DAPA-HF, among the high-risk HFrEF patients with or without T2DM, no significant excess in serious adverse events was noted with dapagliflozin vs. placebo (including fractures, amputations or ketoacidosis in patients with T2DM) [26].

The three SGLT-2 inhibitors (empagliflozin, canagliflozin or dapagliflozin) can be considered patients with eGFR ≥30 mL/min/1.73 m^2 [83]. They are not recommended/should be discontinued in patients with severe CKD; i.e. eGFR <30 mL/min/1.73 m^2 (**Figure 5**). Considering a predilection for worsening renal function in patients with HF, an emphasis should be given on regular eGFR monitoring in patients treated with SGLT-2 inhibitors.

Dosing and precautions pertinent to SGLT-2 inhibitor therapy in the general population of patients with T2DM are presented in **Figure 5.**

SAFETY ASPECTS OF COMBINING NEW AND TRADITIONAL GLUCOSE-LOWERING MEDICATIONS

Although metformin has not been evaluated in a randomized trial in HF population, a substantial body of observational data indicates that it is safe and associated with a reduction in all-cause mortality and rehospitalisation for HF, compared with sulphonylureas or insulin [84-88]. These benefits extend to patients with advanced HFrEF [84], as well as to patients with moderate renal or hepatic dysfunction [88, 89], in whom aggravated risk of lactic acidosis with metformin has not been confirmed [88]. Severe CKD (eGFR <30 mL/min/1.73 m^2) remains a contraindication for metformin use, and dose adjustment is advised in patients with eGFR <45 mL/min/1.73 m^2. A favourable impact on CV outcomes, coupled with a low risk of hypoglycaemia, a neutral effect on body weight, and low cost, have led to the current

recommendation that metformin should be considered in T2DM in HF patients with stable eGFR >30 mL/min/1.73 m^2 [83]. It is also the preferred choice in the combined treatment with SGLT-2 inhibitors, intending to achieve both optimal glycaemic control and risk reduction of HF hospitalization [72].

Earlier clinical trials with thiazolidinediones (pioglitazone, rosiglitazone) have consistently demonstrated an increased risk of HF compared with placebo [90-92]. Furthermore, a meta-analysis including 20 191 patients from 7 trials reported a significantly higher risk of HF with thiazolidinediones [93].

The possible underlying mechanisms include increased renal fluid reabsorption and increased vascular permeability leading to oedema formation and weight gain [94]. Hence, thiazolidinediones are contraindicated in patients with HF, or at high risk of developing HF, and there is insufficient data to indicate that this risk is mitigated by the combined treatment with novel glucose lowering agents.

Similar to metformin, sulfonylureas (gliclazide, glimepiride, glipizide, and glibenclamide [95]) and glinides (repaglinide and nateglinide) have not been prospectively evaluated for CV safety. Data on HF outcomes are sparse and difficult to generalize to all sulphonylureas/glinides. A recent propensity score-matched analysis of 130,000 patients (6% with a history of HF), has suggested a greater risk of HF hospitalisation or CV death with sulfonylureas compared with metformin [96]. A recent cohort study of almost 500,000 patients reported a higher all-cause mortality in patients receiving sulphonylurea monotherapy or a combination therapy with insulin, whereas the risk was not increased when sulphonylureas were combined with metformin, thiazolidinediones or DPP-4 inhibitors [97]. There is limited data to indicate a heterogeneity in CV benefits of the new glucose-lowering drugs in combination with sulphonylureas or glinides, but a dose adjustment of the letter drugs may be needed to avoid the risk of hypoglycaemia. As the risk of hypoglycaemia with sulphonylureas tends to escalate with declining renal function, these medications are not recommended in patients with severe CKD (eGFR <30 mL/min/1.73 m^2) [72, 98, 99].

Insulin therapy is widely used in patients with T2DM, but only a few studies have investigated its association with HF. Data from the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) have suggested a higher risk of HF and worse outcomes in patients receiving insulin compared to those treated with oral glucose-lowering agents [100]. Conversely, in the UKPDS (UK Prospective Diabetes Study) there was no difference in the incidence of HF between patients

receiving insulin and those receiving sulphonylurea [101]. In the ORIGIN trial (Outcome Reduction With Initial Glargine Intervention), among 12,537 patients with different levels of dysglycaemia (impaired glucose tolerance, impaired fasting glucose, or T2DM) and CV risk factors, randomized to basal insulin glargine or placebo, there were no differences in CV outcomes, including HF hospitalisation [102]. In the recent CVOTs with SGLT-2 inhibitors, about 40-50% of patients were already treated with insulin and subgroup analyses of all trials have demonstrated no interaction with CV outcomes in patients with or without insulin. However, insulin therapy may increase the risk of hypoglycaemia, and dose-adjustment is necessary in individuals treated concomitantly with new glucose-lowering agents. In addition, insulin has an intrinsic anti-natriuretic effect [103], unaffected by insulin resistance in other tissues [104]. Although fluid retention is usually mild, it may contribute to weight gain, and lead to worsening HF. Of note, data from an observational cohort including patients with HFrEF and advanced HF, suggest that insulin therapy has been associated with significantly higher one-year mortality [105].

Although available data suggests mostly neutral effect of insulin on the risk of HF, further research is required to address risks and benefits of different insulin regimens in patients with HF.

Although all new glucose-lowering agents carry a low risk of hypoglycaemia when used as a monotherapy or in combination with metformin, this risk may be potentiated when combined with insulin or insulin secretagogues (i.e. sulphonylurea, glinides). Current recommendations from the ADA and EASD stipulate dose-adjustment or even discontinuation of some of antihyperglycemic agents to prevent hypoglycaemia when initiating a new glucose-lowering medication in patients already receiving insulin and/or insulin secretagogues [76]. In addition, decompensated HF, worsening renal function, infection and other critical conditions, may exacerbate the risk of hypoglycaemia. Hence, a multidisciplinary team management (cardiologists, diabetologists, and HF nurses) should be considered in patients receiving complex glucose-lowering regiments (two or more drugs). Even in T2DM patients principally managed by the cardiologists, periodic consultation with a diabetologist would be important. Future long-term follow-up studies with concomitant assessment of adherence should consider the potential risks of polypharmacy, in terms of adverse reactions, and drug to drug interactions, especially among vulnerable patients with HF and T2DM, such as the elderly, frail and associated multi-comorbid conditions.

CONCLUSIONS

Over the last decade, management of T2DM has evolved from optimising glycaemic control with the primary aim of preventing the development or progression of microvascular complications (retinopathy, nephropathy and neuropathy), to using new glucose-lowering medications for improving CV outcomes, including prevention of HF hospitalisation. Recent CVOTs have shown a heterogeneity with respect to risk of HF among the classes of new glucose-lowering drugs. Specifically, important safety concerns have been raised regarding the risk of HF hospitalization with some of these classes of agents. Accordingly, a DPP-4 inhibitor, saxagliptin should not be prescribed to patients with HF, whilst caution is advised with alogliptin and vildagliptin. Although sitagliptin and linagliptin do not increase HF risk, they have no clear effect on CV outcomes, so their use needs to be compared with benefits demonstrated with other classes, including several of the GLP-1 RA and SGLT-2 inhibitors. Based on published CVOTs, GLP-1 RA have demonstrated a neutral effect on HF risk in the general population of T2DM patients with established CV disease or with multiple risk factors. In addition, their beneficial effects on weight and prevention of atherosclerotic events (MI and stroke) deserve consideration in T2DM patients deemed to have high CV risk. However, a signal of harm with liraglutide suggested by two small randomised trials of patients with reduced LVEF, indicates that the role GLP-1 RA remains to be defined in individuals with established HF. The three SGLT-2 inhibitors (empagliflozin, canagliflozin and dapagliflozin) have consistently demonstrated a substantial reduction in the risk of HF hospitalisation across the spectrum of CV risk and regardless of a history of HF. On that basis, SGLT-2 inhibitors could be recommended to prevent HF hospitalisation in patients with T2DM and high CV risk. Importantly, this class of medications has a favourable safety profile, with low risk of hypoglycaemia and beneficial effect on weight control, while serious adverse events (e.g. ketoacidosis, bone fracture or limb amputations) occur infrequently and could be avoided by appropriate patient selection and monitoring. Despite encouraging results with dapagliflozin, it remains to be determined in ongoing clinical trials whether SGLT-2 inhibitors could be used for the treatment of HF, with or without reduced LVEF, and whether their beneficial CV effects could be extended to HF patients without T2DM.

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Figure legend

Figure 1. Proposed mechanisms of pleiotropic effects of new glucose-lowering medications.

DPP-4 i – Dipeptidyl peptidase-4 inhibitor; FFA – free fatty acid; GI – gastrointestinal motility; GLP-1 RA – glucagon-like protein-1 receptor agonist; SGLT-2 i – sodium-glucose cotransporter inhibitor

Figure 2. Summary of clinical trial results with new glucose-lowering medications in patients with type 2 diabetes mellitus

*In the co-primary efficacy analyses, dapagliflozin did not reduce the risk of 3-point MACE (hazard ratio, 0.93; 95% confidence interval, 0.84 to 1.03; P=0.17) but did result in a lower risk of cardiovascular death or hospitalization for heart failure (hazard ratio, 0.83; 95% CI, 0.73 to 0.95; P=0.005).

Figure 3. DPP-4 inhibitors: dosing, dose-adjustment and precautions

Figure 4. GLP-1 RA: dosing, dose-adjustment and precautions

Figure 5. SGLT-2 inhibitors: dosing, dose adjustment and precautions

Table 1. Risk of HF hospitalisation in CV outcome trials with DPP-4 inhibitors

Medication	Trial	Patients, n	Patient characteristics	HbA_{1c} (mean)	History of HF, n (%)	Follow-up (mean or median)	HF hospitalisation (HR, 95% CI)*	P-value
Saxagliptin	SAVOR-TIMI 53 [29, 30]	16,492	Established CVD; multiple CV risk factors	8.0%	2,105 (13%)	2.1 years	1.27 (1.07-1.51)	0.007
Alogliptin	EXAMINE [31]	5,380	Recent acute coronary syndrome	8.0%	1,533 (28%)	1.5 years	1.07 (0.79 - 1.46)	0.66
Sitagliptin	TECOS [23]	14,671	Established CVD	7.2%	2,643 (18%)	3 years	1.00 (0.83 - 1.20)	0.98
Linagliptin	CARMELINA [32]	6,991	High CV and renal risk	~7.9%	1,876 (27%)	2.2 years	0.90 (0.74 -1.08)	0.26

HF – Heart failure; HR – hazard ratio; CI – confidence interval; CVD – cardiovascular disease; CV - cardiovascular

*treatment vs. placebo

Figure 2. Summary of clinical trial results with new glucose-lowering medications

Table 2. Risk of HF hospitalisation in CV outcome trials with GLP-1 RA

Medication	Trial	Patients, n	Patient characteristics	HbA_{1c} (mean)	History of HF, n (%)	Follow-up (mean or median)	HF hospitalisation (HR, 95% CI)*	P-value
Lixisenatide	ELIXA [41]	6,068	Recent acute coronary syndrome	~7.7%	1,358 (22%)	2.1 years	0.96 (0.75 – 1.23)	0.75
Liraglutide	LEADER [43]	9,340	Age ≥50 years and established CVD; Age ≥60 years and CV risk factors	8.7%	1,667 (18%)	3.8 years	0.87 (0.73 – 1.05)	0.14
Semaglutide (subcutaneous)	SUSTAIN-6 [44].	3,297	Age ≥50 years and established CVD; Age ≥60 years and CV risk factors	8.7%	777 (24%)	2.1 years	1.11 (0.77 – 1.61)	0.57
Semaglutide (oral)	PIONEER-6 [40]	3,183	Age ≥50 years and established CVD; Age ≥60 years and CV risk factors	8.2%	388 (12%)	1.3 years	0.86 (0.48 – 1.55)	---
Exenatide	EXSCEL [42]	14,752	Established CVD (73%) CV risk factors (37%)	8.0%	2389 (16%)	3.2 years	0.94 (0.78 – 1.13)	---

Albiglutide	HARMONY Outcome [46]	9,463	Established CVD	~8.7%	1,922 (20%)	1.5 years	0.85 (0.70 – 1.04)**	0.11
Dulaglutide	REWIND [47]	9,901	Established CVD (31.5%) CV risk factors (68.5%)	~7.3%	853 (8.6%)	5.4 years	0.93 (0.77 – 1.12)†	0.46

HF – Heart failure; HR – hazard ratio; CI – confidence interval; CVD – cardiovascular disease; CV - cardiovascular

*treatment vs. placebo

**A composite of CV death or HF hospitalisation

†HF hospitalisation or urgent HF visit

Table 3. Risk of HF hospitalisation in CV outcome trials with SGLT-2 inhibitors

Medication	Trial	Patients, n	Patient characteristics	HbA_{1c} (mean)	History of HF	Follow-up (mean or median)	HF hospitalisation (HR, 95% CI)*	P-value
Empagliflozin	EMPA-REG OUTCOME [58]	7,020	Established CVD	8.1%	10%	3.1 years	0.65 (0.50-0.85)	0.002
Canagliflozin	CANVAS Program [62]	10,142	Established CVD (66%); CV risk factors (34%)	8.2%	14%	3.2 years	0.67 (0.52–0.87)	---
Canagliflozin	CREDENCE [64]	4,401	Albuminuric chronic kidney disease**	8.3%	~15%	2.62 years	0.61 (0.47–0.80)	<0.001
Dapagliflozin	DECLARE TIMI-58 [65]	17,160	Established CVD (41%) CV risk factors (59%)	8.3%	10%	4.2 years	0.73 (0.61-0.88)	---
Dapagliflozin	DAPA-HF [26]	4,744	Symptomatic HF (NYHA II-IV), NT-proBNP ≥ 600 pg/mL (or ≥400 pg/mL if hospitalised for HF within the previous 12 months; if AF/AFL ≥900 pg/mL).	A history of T2DM: 42%	100%	1.5 years	0.70 (0.59 - 0.83)	---

HF – Heart failure; HR – hazard ratio; CI – confidence interval; CVD – cardiovascular disease; CV – cardiovascular

*treatment vs. placebo

**Estimated glomerular filtration rate: 30 to <90 ml/min/1.73 m^2 and albuminuria: albumin-to-creatinine ratio >300 to 5000 mg/g

Table 4. Selected ongoing randomized clinical trials of SGLT2 inhibitors in patients with heart failure

Clinical trial	Brief description of the trial
EMPAGLIFLOZIN	
EMPA-RESPONSE-AHF (NCT03200860)	Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure • Study population: acute decompenzated heart failure • Estimated enrolment: *n*=80. • Treatment: empagliflozin vs. Placebo • Primary outcome: Change in NTproBNP. Secondary outcome: All Cause Mortality or HF readmission
EMPEROR-Reduced (NCT03057977)	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction • Study population: HFrEF, with or without T2DM. • Estimated enrolment: *n*=2850. • Treatment: empagliflozin vs. placebo on top of guideline-based medical therapy. • Primary outcome: CV death or HF hospitalization (time frame: up to 38 months).
EMPEROR-Preserved (NCT03057951)	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction • Study population: HFpEF, with or without T2DM. • Estimated enrolment: *n*=6000. • Treatment: empagliflozin vs. placebo on top of guideline-based medical therapy. • Primary outcome: CV death or HF hospitalization (time frame: up to 38 months).
Empire HF (NCT03198585)	Empagliflozin in Heart Failure Patients With Reduced Ejection Fraction • Study population: HFrEF, with or without T2DM. • Estimated enrolment: *n*=189. • Treatment: empagliflozin vs. placebo on top of guideline-based medical therapy. • Primary outcome: change in plasma concentrations of NT-proBNP (time frame: 90 days) as a measure of treatment impact on HF.
EMPERIAL-Reduced (NCT03448419)	Empagliflozin in Patients With HFrEF: aiming to assess how far patients can walk in 6 minutes and their symptoms • Study population: HFrEF (LVEF <40%), with or without T2DM. • Estimated enrolment: *n*=300. • Treatment: empagliflozin vs. placebo on top of guideline-based medical therapy. • Primary outcome: change from baseline to week 12 in exercise capacity as measured by the distance walked in 6 minutes in standardised conditions
EMPERIAL-Preserved (NCT03448406	Empagliflozin in Patients With HFpEF: aiming to assess how far patients can walk in 6 minutes and their symptoms • Study population: HFrEF (LVEF ≥40%), with or without T2DM. • Estimated enrolment: *n*=300. • Treatment: empagliflozin vs. placebo on top of guideline-based medical therapy. • Primary outcome: change from baseline to week 12 in exercise capacity as measured by the distance walked in 6 minutes in standardised conditions
CANAGLIFLOZIN	
Canagliflozin (NCT02920918)	Treatment of Diabetes in Patients With Systolic Heart Failure

	• Study population: HFrEF with T2DM. • Estimated enrolment: *n*=88. • Treatment: canagliflozin vs. sitagliptin. • Primary outcome: change in aerobic exercise capacity and ventilator efficiency (time frame: baseline and 12 weeks).
DAPAGLIFLOZIN	
DEFINE-HF **(NCT02653482)**	Dapagliflozin Effect on Symptoms and Biomarkers in Diabetic Patients With Heart Failure • Study population: HFrEF with T2DM. • Estimated enrolment: *n*=250. • Treatment: dapagliflozin vs. placebo. • Primary outcome: change in plasma concentrations of NT-proBNP (time frame: 12 weeks) as a measure • of treatment impact on HF
DELIVER **(NCT03619213)**	Dapagliflozin evaluation to improve the lives of patients with preserved ejection fraction heart failure • Study population: HFpEF • Estimated enrolment: n=4,700 • Treatment: dapagliflozin vs. placebo • Primary outcome: Composite of CV death, hospitalisation for HF or urgent HF visit. Secondary outcome: hospitalisations for HF and CV death, worsened NYHA class
DETERMINE–reduced **(NCT03877237)**	Dapagliflozin Effect on Exercise Capacity Using a 6-minute Walk Test in Patients With Heart Failure With Reduced Ejection Fraction • Study population: HFrEF, EF $\leq$ 40%; NYHA Class II-IV • Estimated enrolment: n= 300 • Treatment: dapagliflozin vs. placebo. • Primary outcome: change from baseline in 6-minute walking distance at week 16
DETERMINE–preserved **(NCT03877224)**	Dapagliflozin Effect on Exercise Capacity Using a 6-minute Walk Test in Patients With Heart Failure With Preserved Ejection Fraction • Study population: HFpEF, EF > 40%; NYHA Class II-IV • Estimated enrolment: n= 400 • Treatment: dapagliflozin vs. placebo: change from baseline in 6-minute walking distance at week 16
PRESERVED-HF **(NCT03030235)**	Dapagliflozin Effect on Symptoms and Biomarkers in patients HFpEF • Study population: HFpEF with T2DM or pre-diabetes. • Estimated enrolment: *n*=320. • Treatment: dapagliflozin vs. placebo. • Primary outcome: change in plasma concentrations of NT-proBNP (time frame: baseline to week 6 and • 12) as a measure of treatment impact on HF.
SOLOIST-WHF Trial **(NCT03521934)**	Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure • Study population: a) T2DM, HF and LVEF <50% after admission for worsening HF; b) T2DM, HF, regardless of LVEF after admission for worsening HF • Estimated enrolment: *n*=4,000. • Treatment: sotagliflozin vs. placebo. • Primary outcome: time to first occurrence of either CV death or hospitalisation for HF in patients with LVEF <50%, as well as in the total patient population (regardless of LVEF)