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REVIEW

Clinical aspects of heart failure in individuals with diabetes

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Abstract

Heart failure (HF) is an important comorbidity in individuals with diabetes. Most commonly, the condition is secondary to ischaemia and hypertension. Diabetic cardiomyopathy is becoming increasingly recognised as a cause of HF and blood glucose control plays a pivotal role in the prevention and treatment of HF. Since the US Food and Drug Administration regulatory guidance in 2008, new glucose-lowering agents are evaluated routinely by cardiovascular outcome trials. These trials offer a wealth of knowledge and allow better understanding of the risks and benefits of contemporary diabetes medications. In this review, we will focus on the risks of HF with emerging glucose-lowering therapies and the safety of these medications in patients with established HF. We will summarise the guidance that is available for the treatment algorithm of diabetes in those with HF and highlight future areas of research.

Keywords Diabetes · Heart failure · Medical management · Review

Abbreviations

CANVAS	Canagliflozin Cardiovascular Assessment Study
CVD	Cardiovascular disease
CVO	Cardiovascular outcome
DECLARE-TIMI 58	Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58
DPP-4	Dipeptidyl peptidase-4
EMPA-REG OUTCOME	Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
FDA	Food and Drug Administration
GLP-1	Glucagon-like peptide 1
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HHF	Hospitalisation for heart failure
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
NT-proBNP	N-terminal-pro-B-type-natriuretic peptide
NYHA	New York Heart Association
REWIND	Researching Cardiovascular Events with a Weekly Incretin in Diabetes
SAVOR-TIMI 53	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53
SGLT2	Sodium–glucose cotransporter 2
TECOS	Trial Evaluating Cardiovascular Outcomes with Sitagliptin

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Introduction

Diabetes is a predictor of morbidity and mortality in individuals with heart failure (HF) and is associated with worse prognosis. HF in individuals with diabetes is often secondary to ischaemic cardiomyopathy and hypertension. Furthermore, diabetic cardiomyopathy is becoming a recognised cause of HF. Clinically, affected individuals initially have diastolic dysfunction, progressing to severe diastolic HF with preserved ejection fraction (HFpEF) and then to systolic dysfunction (HF with

CVO trials of glucose-lowering agents

CANVAS Program Canagliflozin Cardiovascular Assessment Study (CANVAS) plus CANVAS-Renal (CANVAS-R)

CARMELINA Cardiovascular and Renal Microvascular Outcome study with Linagliptin

CAROLINA Cardiovascular Outcome trial of Linagliptin versus Glimepiride in Type 2 Diabetes

DECLARE-TIMI 58 Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58

ELIXA Evaluation of Lixisenatide in Acute Coronary Syndrome

EMPA-REG OUTCOME Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients

EXAMINE Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care

EXSCEL Exenatide Study of Cardiovascular Event Lowering

Harmony Outcomes A Long Term, Randomised, Double Blind, Placebo-Controlled Study to Determine the Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Patients with Type 2 Diabetes Mellitus

LEADER Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results

ORIGIN Outcome Reduction With Initial Glargine Intervention

PROactive PROspective Pioglitazone Clinical Trial in Macrovascular Events

RECORD Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes

REWIND Researching Cardiovascular Events with a Weekly Incretin in Diabetes

SAVOR-TIMI 53 Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53

SUSTAIN-6 Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes

TECOS Trial Evaluating Cardiovascular Outcomes with Sitagliptin

VIVIDD Vildagliptin in Ventricular Dysfunction Diabetes

reduced ejection fraction [HFrEF]) [1]. Observational data suggest that hyperglycaemia is associated with HF development. Thus, such data may also suggest that improving glycaemic control plays an important role in prevention of diabetic cardiomyopathy [2, 3].

The rate of developing HF is two- to fivefold higher in diabetic vs non-diabetic individuals [4]. A heightened awareness of potential HF is needed when evaluating those at high risk. In a recent study using electronic medical records, individuals with diabetes of longer duration (>6 years), advanced age, renal disease, poor glycaemic control, ischaemic heart disease, obesity and elevated diastolic blood pressure (BP) were identified as having highest risks for HF [5]. It has also been suggested that overall glycaemic burden, and not simply HbA_{1c} at the time of diagnosis, is a better predictor of HF risk [5]. Left ventricular diastolic dysfunction in asymptomatic, normotensive individuals with diabetes can be as prevalent as 75% [6]. Diabetes is associated with increased risk of cardiovascular death and hospitalisation for HF (HHF) in individuals with HFpEF and HFrEF [7]. Those with both HF and diabetes have more severe New York Heart Association (NYHA) class symptoms when compared with non-diabetic individuals with similar left ventricular ejection fraction [8].

The evolving medications and data for glucose-lowering agents can make the regimen decision increasingly complex. In this review, we describe the risks of HF with emerging glucose-lowering therapies, as well as safe use of medications in patients with established HF. We examine guidance available supporting the treatment algorithm for diabetes in individuals with HF and highlight future areas of research.

The goal of glycaemic control in HF

The reduction in microvascular disease (neuropathy, retinopathy and nephropathy) with improved glycaemic control is well established, but this therapeutic benefit is not as well established with macrovascular disease (coronary artery disease, peripheral vascular disease and stroke) [9]. The UK Prospective Diabetes Study (UKPDS) was a prospective

observational study, demonstrating a 16% reduction in HF risk for every 1% decrease in HbA_{1c} [3]. Although improved control has been associated with lower HF risk, tight control (HbA_{1c}<7% [53 mmol/mol]) has been associated with higher mortality rate in individuals with moderate-to-severe HFrEF [10]. Thus, glycaemic control appears to have a U-shaped curve relative to mortality rate. A retrospective study of veterans with HF and diabetes demonstrated that the lowest mortality rate was with HbA_{1c} between 7.1% and 7.8% (54–62 mmol/mol) [11].

Medical management of diabetes: risk of developing HF

Prior to the 2008 US Food and Drug Administration (FDA)-issued guidance for industry, 'Diabetes mellitus — evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes', glucose-lowering agents were approved based solely on improvements in glycaemic control. The guidance aimed to establish that there would be no unacceptable increase in cardiovascular risk (specifically, ischaemic events) prior to the approval of new medications [12]. Now, with dedicated cardiovascular outcome (CVO) trials (see Table 1 for a summary of the results of these trials), clinicians may consider individual patient factors and individualise therapeutic regimens. Here, we discuss the risk of developing HF or increased risk of HHF for commonly used glucose-lowering agents.

Medications with neutral effects on risk of HF

Metformin Metformin is weight-neutral, does not increase the risk of hypoglycaemia and can also improve lipid profile. In addition, there is no suggested increase in risk of HF with use of this drug. The limited side-effects with use of this medication and its effectiveness in glucose-lowering has made it a first-line therapy, as outlined in the joint Consensus statement released by the American Association of Clinical Endocrinologists and American College of Endocrinology [13].

Sulfonylureas and insulin Use of insulin or sulfonylureas is associated with modest weight gain and hypoglycaemia. Initiating basal insulin in patients with diabetes has not demonstrated an increased risk of HF [14]. On the other hand, the safety data on sulfonylureas are based on observational studies, with conflicting results. There is a theoretical concern that increased insulin levels and weight gain might lead to an increased risk of HF. Compared with metformin, sulfonylureas may be associated with a higher mortality rate [15] and some studies suggest an increased risk for congestive HF [16, 17]. This potentially unfavourable profile has led to sulfonylureas being placed towards the bottom of treatment algorithms [13]. The Cardiovascular Outcome trial of Linagliptin versus Glimepiride in Type 2 Diabetes (CAROLINA) trial is currently evaluating the cardiovascular impact of linagliptin (a dipeptidyl peptidase-4 [DPP-4] inhibitor) vs glimepiride (a sulfonylurea) in patients with diabetes who are at high cardiovascular risk (CinicalTrials.gov registration no. NCT01243424). Results from this study may provide important additional information on the cardiovascular safety of sulfonylureas.

Glucagon-like peptide 1 receptor agonists Glucagon-like peptide 1 (GLP-1) receptor agonists delay gastric emptying, reduce appetite, improve satiety and lead to weight loss. The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) study was the first CVO trial for GLP-1 receptor agonists [18]. In this study, diabetic individuals who had a prior myocardial infarction (MI) or who were hospitalised for unstable angina within the previous 180 days (baseline HF rate, 22.4%) were randomised to lixisenatide or placebo. There was no difference in the primary endpoint of major adverse cardiovascular events (MACE), which includes cardiovascular mortality, MI and stroke. In comparison, in a subsequent CVO trial in this class, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER), individuals with high cardiovascular risk (baseline HF rate, 17.8%) were randomised to liraglutide or placebo [18]. The primary endpoint of MACE occurred in significantly fewer participants in the liraglutide arm, primarily driven by a decrease in cardiovascular mortality. These findings directly led to expanded US FDA labelling for liraglutide, stating that it can be used for reducing MACE in adults with type 2 diabetes and established cardiovascular disease (CVD) [19].

Similar results were seen in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) [20], in which participants with established CVD or at high risk for CVD (baseline HF rate, 23.6%) were randomised to receive semaglutide or placebo; in this study, the primary endpoint of MACE was decreased in the treatment arm, primarily driven by a decrease in non-fatal stroke and MI. The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) randomised diabetic individuals with increased cardiovascular risk (baseline HF rate, 16.2%) to exenatide or placebo and found no difference in the primary endpoint of MACE [21]. These trials also demonstrated that lixisenatide [22], liraglutide [18], semaglutide [20] and exenatide [23] all had a neutral effect on HHF, which was a pre-specified secondary endpoint for each study.

CVO data for albiglutide was also recently published [24]. In diabetic individuals with CVD (baseline HF rate, 20%) who were randomised to albiglutide or placebo, there was a significant reduction in the primary endpoint of MACE with

Table 1 Findings from CVO trials

Medication	Trial	Year	3-Point MACE	HHF
SGLT2 inhibitors				
Empagliflozin	EMPA-REG OUTCOME [26]	2015	Rate: 37.4 with empagliflozin vs 43.9 with placebo per 1000 patient-years (HR 0.86 [95% CI 0.74, 0.99])	Rate: 9.4 with empagliflozin vs 14.5 with placebo per 1000 patient-years (HR 0.65 [95% CI 0.50, 0.85])
Canagliflozin	CANVAS [30, 66]/ CANVAS-R [30, 67]	2017	Rate: 26.9 with canagliflozin vs 31.5 with placebo per 1000 patient-years (HR 0.86 [95% CI 0.75, 0.97])	Rate: 5.5 with canagliflozin vs 9.0 with placebo per 1000 patient-years (HR 0.67 [95% CI 0.52, 0.77])
Dapagliflozin	DECLARE-TIMI 58 [32]	2018	Rate: 22.6 with dapagliflozin vs 24.2 with placebo per 1000 patient-years (HR 0.93 [95% CI 0.84, 1.03])	Rate: 6.2 with dapagliflozin vs 8.5 with placebo per 1000 patient-years (HR 0.73 [95% CI 0.61, 0.88])
GLP-1 receptor agonists				
Lixisenatide	ELIXA [22]	2015	13.4% with lixisenatide vs 13.2% with placebo (HR 1.02 [95% CI 0.89, 1.17])	4.0% with lixisenatide vs 4.2% with placebo (HR 0.96 [95% CI 0.75, 1.23])
Liraglutide	LEADER [18]	2016	13.0% with liraglutide vs 14.9% with placebo (HR 0.87 [95% CI 0.78, 0.97])	4.7% with liraglutide vs 5.3% with placebo (HR 0.87 [95% CI 0.73, 1.05])
Semaglutide	SUSTAIN-6 [20]	2016	6.6% with semaglutide vs 8.9% with placebo (HR 0.74 [95% CI 0.58, 0.95])	3.6% with semaglutide vs 3.3% with placebo (HR 1.11 [95% CI 0.77, 1.61])
Exenatide	EXSCEL [23]	2017	11.4% with exenatide vs 12.2% with placebo (HR 0.91 [95% CI 0.83, 1.00])	3% with exenatide vs 3.1% with placebo (HR 0.94 [95% CI 0.78, 1.13])
Albiglutide	Harmony Outcomes [24]	2018	7% with albiglutide vs 9% with placebo (HR 0.78 [95% CI 0.68, 0.90])	4% with albiglutide vs 5% with placebo[a] (HR 0.85 [95% CI 0.70, 1.04])
DPP-4 inhibitors				
Saxagliptin	SAVOR-TIMI 53 [38]	2013	7.3% with saxagliptin vs 7.2% with placebo (HR 1.00 [95% CI 0.89, 1.12])	3.5% with saxagliptin vs 2.8% with placebo (HR 1.27 [95% CI 1.07, 1.51])
Alogliptin	EXAMINE [53]	2013	11.3% with alogliptin vs 11.8% with placebo (HR 0.96; upper limit of 95% CI ≤1.16)	3.1% with alogliptin vs 2.9% with placebo (HR 1.07 [95% CI 0.79, 1.46])
Sitagliptin	TECOS [41]	2015	11.4% with sitagliptin vs 11.6% with placebo (HR 0.99 [95% CI 0.89, 1.08])	3.1% with sitagliptin vs 3.1% with placebo (HR 1.00 [95% CI 0.83, 1.20])
Linagliptin	CARMELINA [44]	2018	12.4% with linagliptin vs 12.1% with placebo (HR 1.02 [95% CI 0.98, 1.17])	6.0% with linagliptin vs 6.5% with placebo (HR 0.90 [95% CI 0.74, 1.08])

[a] Data are for composite of death from cardiovascular causes or HHF

CANVAS-R, CANVAS-Renal; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study with Linagliptin; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes

albiglutide, driven by a reduction in MI. Similar to other trials of drugs in this class, a neutral effect on the secondary composite endpoint of death from cardiovascular causes and HHF was demonstrated.

Recently, the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial on dulaglutide was published. REWIND evaluated a limited number of participants with established CVD at baseline. Results demonstrate a reduction in MACE in those treated with dulaglutide. Thus, data continue to support significant cardiovascular benefit with this medication class [25].

Medications that may reduce risk of developing HF

Sodium–glucose cotransporter 2 inhibitors Sodium–glucose cotransporter 2 (SGLT2) inhibitors are associated with weight loss and both systolic and diastolic BP reduction. Empagliflozin was first-in-class to have published CVO data;

the Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study [26] included participants with established CVD (baseline HF rate, 10.1%) who were randomised to empagliflozin or placebo. There was a significant decrease in the primary endpoint of MACE with empagliflozin use, driven by a decrease in cardiovascular death. This led to approval of an indication for empagliflozin by the US FDA in 2016, to reduce the risk of cardiovascular death in adults with type 2 diabetes and CVD [27]. Although not a primary endpoint in EMPA-REG OUTCOME, a significant decrease in the rate of HHF was also seen in the empagliflozin arm. Findings were consistent across subgroups, regardless of dose, age, race and eGFR [28].

Similarly, in the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, canagliflozin reduced rates of HHF in participants at high cardiovascular risk (baseline HF rate, 14.4%), although a reduction in cardiovascular mortality was not demonstrated [29, 30]. The association between SGLT2 inhibitors and improved rates of HHF is further supported by a multinational study with data from real-world practice [31] and the recently published Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) study [32]. DECLARE-TIMI 58 included diabetic participants at high cardiovascular risk (baseline HF rate, 10%), but differed from previous studies by involving a larger population without known atherosclerotic CVD [32]. Although dapagliflozin was non-inferior vs placebo in its effects on MACE, the results did support improved HHF rates.

Indeed, although specific trials have differed in detail, overall effects have been largely consistent and suggest a class effect on HHF rate [32]. There are multiple proposed mechanisms to explain the benefit of SGLT2 inhibitors on HF. Benefits were seen early on in the EMPA-REG Outcome study, suggesting this effect may actually be independent of glycaemic control. A suggested mechanism involves the role of SGLT2-mediated glucose uptake and its interaction with the Na^+–H^+ exchanger; this exchanger is responsible for the majority of sodium reuptake in the kidney, which is increased in HF and may play a role in diuretic resistance [33, 34]. Other proposed mechanisms include decreased plasma volume, increased natriuresis, weight loss and improved haemodynamics.

Medications that may increase risk of developing HF

Thiazolidinediones Thiazolidinediones increase insulin sensitivity in peripheral tissues but are associated with fluid retention, subcutaneous fat accumulation and increased bone fractures. In the PROspective Pioglitazone Clinical Trial In Macrovascular Events (PROactive), despite excluding individuals with NYHA class II HF or above, pioglitazone demonstrated increased rates of HHF compared with placebo [35]. The Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) trial demonstrated comparable results, with an increased rate of HHF with rosiglitazone [36]. Therefore, thiazolidinediones can only be recommended for use with significant caution in those at risk of developing HF.

DPP-4 inhibitors DPP-4 inhibitors result in increased fasting and postprandial GLP-1 levels and are better tolerated than GLP-1 receptor agonists (less nausea) but lack the benefit of weight loss. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53), evaluating participants with diabetes and established or high risk for CVD (12.8% with prior history of HF), had unexpected results [37, 38]; although there was no difference in the primary endpoint of MACE, surprisingly, increased rates of HHF were demonstrated. This was most notable in those with a previous history of HF, eGFR <60 ml min^{-1} (1.73 $m)^{-2}$ and elevated N-terminal-pro-B-type-natriuretic peptide (NT-proBNP) at baseline. Similarly, in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study, in which individuals with diabetes and acute coronary syndrome in the previous 15–90 days (27.9% with prior HF) were randomised to alogliptin or placebo [39], there was no difference in the primary endpoint of MACE but alogliptin increased the rate of HHF although this increase was not statistically significant. Those with increased HHF were older, with longer duration of diabetes, and had reduced eGFR (~55 ml min^{-1} [1.73 $m]^{-2}$), previous coronary artery bypass, peripheral vascular disease and a personal history of HF [40]. In contrast, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) enrolled individuals with type 2 diabetes and established CVD (HF rate, 18.3%) [41] and the results were neutral for the primary endpoint of cardiovascular death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina, and also for the secondary endpoint of HHF. In addition, some post-marketing studies have suggested no increased risk of congestive HF among patients with diabetes using incretin-based therapies [42, 43].

In 2017, the FDA placed an HF warning on all agents in this class. Nonetheless, it could be suggested that this has not been truly established, especially when considering the most recent data published for linagliptin in the Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELINA), demonstrating no increased risk of HHF in a population at particularly high risk of HF (with coronary artery disease [CAD] or chronic kidney disease [CKD]), with 26.8% of the patients having known HF [44].

Medical management of diabetes: implications for individuals with HF

Medications with neutral effects in individuals with HF

Metformin Metformin is now considered safe to use in certain patients with HF and may be associated with improved clinical outcomes [45, 46]. So far there has been no RCTs evaluating metformin's use in HF, so these conclusions are based on observational data. Initial reports of lactic acidosis with other biguanides led to similar concerns about metformin. Previously, the US FDA had placed an absolute contraindication against its use in HF, which was later removed (2006), although caution on use in acute and advanced HF remains [47].

Guidance specifically for the treatment of type 2 diabetes in those with HF continues to recommend metformin as first-line therapy [48, 49]. The 2018 update to the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) 2015 publication, 'Management of Hyperglycemia in Type 2 Diabetes' [50], advises the initial assessment of cardiovascular status and offers a separate algorithm for metformin treatment of type 2 diabetic individuals with HF. Metformin remains a first-line therapy as long as moderate renal function is maintained (eGFR >30 ml min^{-1} $[1.73\ m]^{-2}$) [50].

GLP-1 receptor agonists Although GLP-1 receptor agonists have not been associated with an increased rate of HHF in diabetes in the large clinical trials published so far, concern has been raised in smaller studies with different patient populations, specifically in those with HF. In an evaluation of individuals with HFrEF after recent hospitalisation, liraglutide demonstrated a neutral effect on time-to-death, time-to-rehospitalisation for HF and NT-proBNP levels [51]. When further evaluated in individuals with stable HFrEF, liraglutide significantly increased heart rate (7 beats/min) compared with placebo and increased rates of serious cardiac events (ventricular tachycardia, atrial fibrillation, acute coronary syndrome and worsening of congestive HF) [52]. These later results raise concern regarding the net benefit of liraglutide in HFrEF patients. Currently, data are lacking to determine whether this is a class effect. The unique US FDA indication for liraglutide acknowledges that there is clear benefit for individuals with established CVD but further research needs to evaluate safety in those with HFrEF. GLP-1 receptor agonists remain recommended as a second-line therapy in those with known CVD, and in those with HF if an SGLT2 inhibitor is not appropriate [50].

Medications that may reduce risk of developing HF

SGLT2 inhibitors SGLT2 inhibitors have shown a significant reduction in HHF, but these findings come from studies that were not designed to evaluate benefits in people with HF. EMPA-REG OUTCOME and the CANVAS Program only included a small population of participants with HF at baseline (10% and 14%, respectively) [26, 29, 30]. Sub-analyses of those with HF in EMPA-REG OUTCOME continued to show a benefit of decreased HHF with empagliflozin [28]. In 2018, the ADA/EASD recommended SGLT2 inhibitors as second-line therapy for diabetes in individuals with HF, with preference given to empagliflozin based on the CVD benefits shown in EMPA-REG OUTCOME, as long as the patient has adequate renal function (eGFR >45 ml min^{-1} $[1.73\ m]^{-2}$) [50].

Given the potentially increased use of SGLT2 inhibitors in HF patients, this class of drugs must be further studied in this population. Currently, large RCTs of SGLT2 inhibitors are enrolling participants with HF, although diabetes is not a mandatory inclusion criterion. Two of these will evaluate empagliflozin vs placebo, with the primary endpoints of cardiovascular death and HHF, in individuals with either HFrEF (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction [EMPEROR-Reduced]; ClinicalTrials.gov registration no. NCT03057977) or HFpEF (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction [EMPEROR-Preserved]; ClinicalTrials.gov registration no. NCT03057951). A third study will assess dapagliflozin vs placebo in individuals with HFrEF, with the primary endpoints of cardiovascular death and HHF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure [DAPA-HF]; ClinicalTrials.gov registration no. NCT03036124).

Medications that may increase risk of developing HF

DPP-4 inhibitors DPP-4 inhibitors have become popular as they can be taken orally and are better tolerated than GLP-1 agents. Concerns of worsening HF with this class were based on trials in individuals with stable diabetes but limited numbers had established HF [38, 41, 44, 53]. Publicly available data in the US FDA Adverse Event Reporting System was reviewed with the aim of evaluating the association between HF and DPP-4 inhibitors [54]. An increased association with saxagliptin was found with this class of drugs, as previously suggested in SAVOR-TIMI 53. Interestingly, there was an increase in HF with sitagliptin, which conflicts with the TECOS findings [41].

There are currently no specific guidelines on how to manage patients at high risk for HF who are already being treated with DPP-4 inhibitors. Published CVO trials may underestimate the risk of DPP-4 inhibitors in established HF, although this has been poorly studied. The Vildagliptin in Ventricular Dysfunction Diabetes (VIVIDD) study was designed to evaluate the effects of DPP-4 inhibitors in individuals with left

ventricular dysfunction [55]. Increased left ventricular volumes were demonstrated with DPP-4 inhibitor use, although the clinical significance of this finding is unknown. Until further studies evaluate use of DPP-4 inhibitors in this designated population, clinicians need to be cautious in prescribing these drugs to patients at high risk for HF and should consider avoiding their use in those with known HF.

Thiazolidinediones, sulfonylureas and insulin There have been no RCTs evaluating the effects of thiazolidinediones, sulfonylureas or insulin in diabetic individuals with HF. Thiazolidinediones are contraindicated in NYHA class III–IV HF and should be used with caution in those at risk for HF. Sulfonylureas and insulin are often considered third-line therapies for type 2 diabetes. Sulfonylureas have an unclear safety profile in HF. Individuals with HFrEF who are taking insulin have a significantly worse prognosis than those not on insulin [56], although it is not known whether this is a marker of advanced disease state or a causal relationship.

Pharmacological management of HF in diabetic individuals

No specific restrictions exist on the use of medications for treating HF in diabetic individuals. Angiotensin converting enzyme (ACE) inhibitors have demonstrated mortality benefit in type 2 diabetes [57]. There are less data on angiotensin receptor blockers (ARBs) specifically in diabetic individuals, but these have been proven to delay the first HHF in diabetes [58]. Expert opinion recommends starting at low doses of ARBs and titrating upwards, with frequent monitoring of electrolytes and renal function, given risks such as hyperkalaemia [59].

Concern has been expressed regarding blunting of hypoglycaemic symptoms with use of β-blockers. Nonetheless, their mortality benefit in diabetes is clear and, therefore, this class is recommended [57]. In addition, carvedilol may have a favourable effect on insulin resistance; however, metoprolol has been shown to increase HbA_{1c} [60]. So far, there is no specific guidance regarding which β-blocker to use in a hierarchical fashion.

Both spironolactone and eplerenone have been shown to significantly decrease morbidity and mortality in individuals with HFrEF [61, 62]. Data on the impact of mineralocorticoid receptor blockade on glycaemic control are conflicting, but their safety is largely accepted in diabetic patients with HF [63]. Given risk of hyperkalaemia with these drugs, clinicians should monitor renal function and electrolytes.

Sacubitril/valsartan (LCZ696) has demonstrated superiority to enalapril in reducing the risk of death and HHF [64] and has been shown to improve glycaemic control; participants in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial who received sacubitril/valsartan displayed a greater reduction in HbA_{1c} [65].

Conclusion

Therapies for diabetes were initially approved only on the basis of blood glucose control. Now, through CVO trials, we have knowledge on novel therapies and a better understanding of how to individualise treatment in populations at high risk for HF (see Fig. 1 for a summary of HF outcomes with select glucose-lowering therapies). Metformin remains the first-line therapy in individuals with diabetes with and without HF, with second-line options including SGLT2 inhibitors. GLP-1 receptor agonists provide another second-line option but require further focused HF trials to establish safety. Caution must be

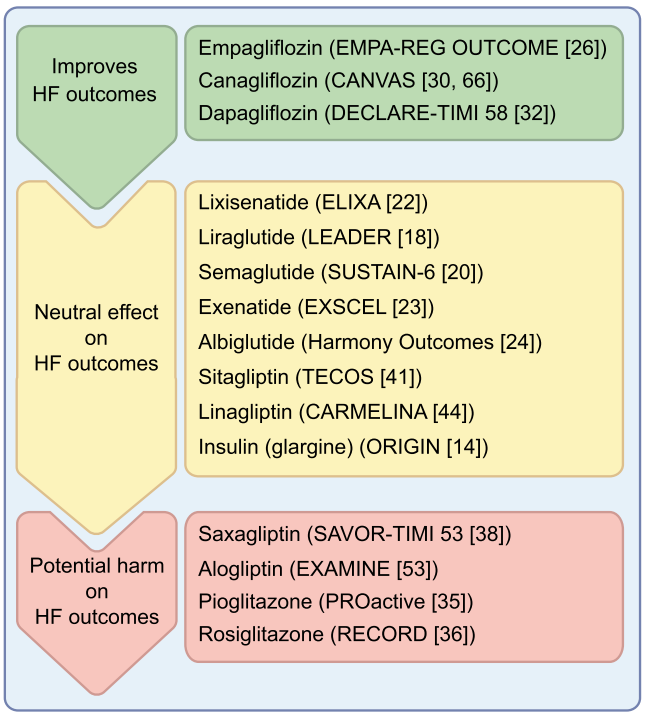

Fig. 1 HF outcomes with select glucose-lowering therapies. Note that although sitagliptin was found in CVO trials to have a neutral effect on heart failure, a later review of adverse event reporting data indicated that it may increase heart failure. CARMELINA, Cardiovascular and Renal Microvascular Outcome Study with Linagliptin; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; ORIGIN, Outcome Reduction With Initial Glargine Intervention; PROactive, PROspective Pioglitazone Clinical Trial In Macrovascular Events; RECORD, Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes. This figure is available as a downloadable slide

used with DPP-4 inhibitors in those at risk for HF due to an increased risk of HF outcomes with some drugs in this class, although whether this is a class effect is still debated. Meanwhile, thiazolidinediones remain contraindicated in those with NYHA class III–IV HF. Further studies will add to the complexity of treatment algorithms for diabetic patients with HF. More robust population studies of HF subgroups are needed in well-designed clinical trials for further treatment stratification. New data will support development of more individualised guidelines for management of diabetic individuals at risk for, or already with, HF and will permit evidence-based decisions when devising treatment regimens for these patients.

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