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INVITED COMMENTARY

Treating Diabetes in Patients with Heart Failure: Moving from Risk to Benefit

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Abstract Over the past two decades, therapeutics for diabetes have evolved from drugs with known heart failure risk to classes with potential benefit for patients with heart failure. As many as 25 to 35 % of patients with heart failure carry a diagnosis of type 2 diabetes mellitus. Therefore, newer drug classes including dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 (GIP-1) agonists, and sodium-glucose cotransporter 2 (SGLT-2) inhibitors are being examined for cardiovascular safety as well as their effects on left ventricular function, quality of life, and other measures of disease progression. The purpose of this review is to summarize the existing evidence on these classes of anti-diabetic agents in patients with heart failure.

Keywords Diabetes · Heart failure · Insulin resistance · Dipeptidyl peptidase 4 inhibitor · Glucagon-like peptide 1 agonist · Sodium-glucose cotransporter 2 inhibitor

Introduction

The clinical and pathophysiological intersection between heart failure (HF) and diabetes mellitus (DM) is complex. DM is present in as many as 25–35 % of patients with HF, irrespective of ejection fraction [1]. Furthermore, diabetes is a strong and independent predictor of the development of heart failure and its progression [2]. In patients with asymptomatic left ventricular dysfunction, DM is a risk factor for HF symptoms and hospitalization [3]. After myocardial infarction, diabetic individuals form less collaterals when compared to their counterparts without diabetes. This increased risk is true for heart failure with either preserved or reduced ejection fraction [4].

The heart is dependent on synthesis of adenosine triphosphate (ATP). As the heart fails, ATP synthesis becomes increasingly dependent on glucose (Fig. 1). In advanced heart failure, the myocardium becomes insulin-resistant [5–7]. Insulin resistance is a prognostic factor that independently predicts reduced survival even in non-diabetic patients [8]. Hyperglycemia may be associated with neurohormonal activation, inflammatory cytokines, reactive oxygen species, and oxidative stress, leading to endothelial dysfunction and hemodynamic impairment [8]. Furthermore, hyperglycemia leads to elevated free fatty acid levels that may cause myocardial lipid accumulation. Some have suggested that there is a disease-specific diabetic cardiomyopathy, which is independent of other cardiac risk factors [9–11]. Therefore, the pathogenesis of heart failure in diabetes is multifactorial, with contributions from coronary artery disease, hypertension, diabetic cardiomyopathy, and extracellular fluid volume expansion [12].

Several studies including the United Kingdom Prospective Diabetes Study have showed that poor glycemic control is associated with an increased risk of heart failure [13]. However, meta-analyses of randomized controlled trials including the Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Action in Diabetes and Vascular Disease (ADVANCE), and the Veteran Affairs Diabetes Trial (VADT) failed to show that intensive glycemic control reduces the risk of hospital admissions for heart failure [14]. Nevertheless, therapeutics for diabetes may have some

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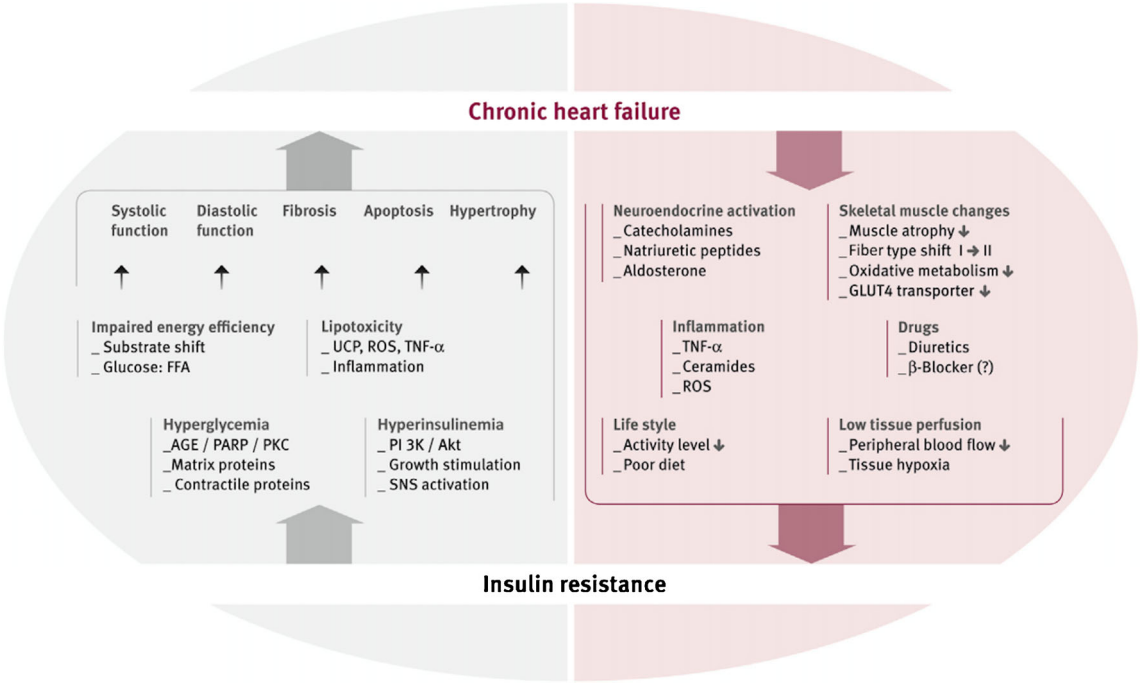

Fig. 1 Chronic heart failure is associated with neuroendocrine activation, inflammation, and low tissue perfusion which then can trigger insulin resistance. Subsequently, insulin resistance elicits a number of neurochemical signals including reactive oxygen species and impaired efficiency of free fatty acids which leads to impaired systolic and diastolic function and cardiac remodeling. *FFA* free fatty acid, *AGE* advanced glycation end product, *PARP* poly(ADP-ribose) polymerase, *PKC* protein kinase C, *UCP* uncoupling protein, *ROS* reactive oxygen species, *TNF* tumor necrosis factor, *SNS* sympathetic nervous system, *GLUT4* glucose transporter 4, *PI 3K* phosphoinositide 3-kinase (reproduced with permission from Doehner et al. [8])

cardiovascular benefits. The purpose of this review is to summarize the existing evidence on newer classes of anti-diabetic agents in patients with heart failure.

Older Landscape of Diabetes Therapy

Older therapies for diabetes have been associated with heart failure risk. The thiazolidinediones (TZDs) were first approved for use in type 2 diabetes in the 1990s. This class of medications that works by agonism of the peroxisome proliferator-activated receptor (PPAR)-gamma was known to be associated with an increased risk of heart failure at the time of FDA approval [15, 16]. PPAR-gamma activation of the renal collecting duct leads to fluid retention and thus edema and heart failure [17, 18]. Patients with New York Heart Association (NYHA) functional class III or IV heart failure were excluded from the trials. Subsequent randomized trials reported increases in the relative risk of heart failure with pioglitazone (PROactive), rosiglitazone (DREAM), and others [18–21]. The AleCardio trial focused on aleglitazar and cardiovascular outcomes after acute coronary syndrome in patients with type 2 diabetes [22–24]. The trial was terminated early as treatment with aleglitazar led to increased heart failure admissions and doubling in edema rates as well as increased rates of renal dysfunction [22].

In 2003, the American Heart Association and the American Diabetes Association issued a consensus statement warning against the use of TZDs in patients with NYHA class III and IV heart failure. In patients with no or mild symptoms, the drug should be used cautiously and initiated at low doses with monitoring for the development of weight gain, edema, or new-onset heart failure [25].

There have also been concerns raised for patients with heart failure and DM taking metformin, especially those with concomitant renal dysfunction. In the setting of worsening HF, overdiuresis, and alteration of renal blood flow, the risk for lactic acidosis is thought to be higher. However, multiple studies have suggested the contrary. Eurich et al. [26] demonstrated reduced mortality in patients with DM treated with metformin who developed heart failure compared to those who were not treated with metformin. Similarly, in a large study of more than 16,000 Medicare beneficiaries treated with metformin, heart failure readmissions were reduced by 13 %, mortality rates were lower, and there were no excess admissions for metabolic acidosis [27, 28]. This was validated in another systematic review of 34,000 patients where metformin was associated with reduced mortality in patients with heart failure and a small reduction in all-cause hospitalizations [29].

Dipeptidyl Peptidase 4 Inhibitors

Dipeptidyl peptidase 4 (DPP-4) inhibitors block the degradation of glucagon-like peptide 1 (GLP-1), gastric inhibitory peptide (GIP) and a variety of other peptides involved in glucose-dependent stimulation of insulin secretion [4]. Of these, GLP-1 is the most widely studied. DPP-4 is an important driver of myocardial damage, although the mechanisms are unclear. DPP-4 has three major functions which include adenosine deaminase binding, peptidase activity, and extracellular matrix binding [30]. DPP-4 also cleaves and inactivates cardioactive peptides including B-type natriuretic peptide (BNP), neuropeptide Y, stromal cell-derived factor 1, and GLP-1 [31]. Therefore, DPP-4 inhibitors may be effective in the setting of myocardial infarction and heart failure by potentiating the vascular and renal effects of natriuretic peptides [32]. By preventing cleavage of these peptides, DPP-4 inhibition may interfere with sodium reabsorption and increase the natriuretic response [33].

In animal models of diabetes where DPP-4 is genetically cleaved, mutant mice and rats survive longer than matched controls following myocardial infarction [31, 34]. Treatment of wild-type mice with sitagliptin, a DPP-4 inhibitor, mimicked these protective findings [31]. Interestingly, though, in diabetic, high fat-fed mice, administration of a highly selective DPP-4 inhibitor led to impairment of cardiac function, modest cardiac hypertrophy, and dysregulation of genes and proteins controlling inflammation and cardiac fibrosis [35]. These laboratory data may help to explain both the clinical benefits and cardiovascular risks associated with DPP-4 inhibition in patients with diabetes and set the stage for human studies.

The Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus (SAVOR-TIMI 53) trial was a multicenter, randomized placebo-controlled trial to evaluate the safety and efficacy of saxagliptin in patients with a history of, or at risk for, cardiovascular events. The primary composite endpoint included cardiovascular death, non-fatal myocardial infarction, and non-fatal ischemic stroke, and secondary endpoints included hospitalization for heart failure [36]. Compared to placebo, saxagliptin had no significant effect on the primary endpoint but was associated with an increased risk of heart failure hospitalization (3.5 versus 2.8 %, hazard ratio (HR) 1.27, $p = 0.007$). A post hoc analysis sought to focus specifically on heart failure outcomes [37]. At 12 months, 1.9 % of the patients treated with saxagliptin were hospitalized compared to 1.3 % in the placebo group (HR 1.46, $p = 0.002$); however, there was no significant difference in hospitalization rates beyond 1 year. Patients at greatest risk for hospitalization for HF had previous HF, elevated baseline *N*-terminal pro-B-type natriuretic peptide (NT-proBNP), and estimated glomerular filtration rate ≤60 ml/min [37].

The Alogliptin after Acute Coronary Syndrome in patients with Type 2 Diabetes (EXAMINE) trial enrolled patients with an acute coronary syndrome within 15–90 days of randomization [38]. The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. Similar to the SAVOR-TIMI 53 trial, the rates of major adverse cardiovascular events were not increased with the DPP-4 inhibitor alogliptin compared to placebo. In a post hoc analysis, alogliptin had no effect on the composite of cardiovascular death and hospital admission for heart failure (HR 1.00, 95 % confidence interval (CI) 0.82–1.21) and the results did not differ by baseline BNP concentration [39]. Heart failure hospitalization occurred in 85 patients (3.1 %) taking alogliptin and in 79 patients (2.9 %) taking placebo. However, there did appear to be a significantly increased risk of hospitalization in those without heart failure at baseline, and the risk of HF hospitalization increased proportionally with an increasing quartile of BNP [39].

More recently, Green and colleagues studied the effect of sitagliptin on long-term cardiovascular events in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study [40, 41]. Over 14,000 patients were randomized to sitagliptin or placebo and followed for a median of 3 years. The time to hospital admission for heart failure was a pre-specified secondary endpoint. Notably, patients were excluded if they had been treated with prior incretin-based therapy or a TZD in the preceding 3 months. Hospitalization for HF was reported in 3.1 % of both groups, and there was no significant difference in all-cause mortality [40]. Other studies have shown that sitagliptin treatment, even in patients without diabetes, is associated with significant recovery of ischemic myocardium, as demonstrated by dobutamine stress echocardiography [42].

Vildagliptin may exert differential myocardial effects compared to other DPP-4 inhibitors. In rats treated with isoproterenol, vildagliptin lowered LV end-diastolic pressures and attenuated cardiomyocyte hypertrophy and perivascular fibrosis [43]. The Vildagliptin in Ventricular Dysfunction Diabetes (VIVIDD) study was designed to evaluate the effect of DPP-4 inhibition on left ventricular ejection fraction (LVEF) in patients with type 2 diabetes and NYHA class I–III heart failure [12, 41, 44]. Patients were randomized to receive vildagliptin 50 mg twice daily or placebo in addition to standard glucose-lowering and heart failure therapy. After 52 weeks, there were no significant differences in LVEF or heart failure hospitalization (18 % of the vildagliptin group versus 17.6 % of the placebo group), but increases in LV systolic and end-diastolic volume were seen in the vildagliptin group. BNP levels decreased in both groups, but to a greater extent in the vildagliptin group (ratio of 0.72 compared to baseline versus 0.86 compared to baseline in the placebo group) [12].

The results of the SAVOR-TIMI 53, EXAMINE, TECOS, and VIVIDD trials suggest that there may be in-class differences between the DPP-4 inhibitors or that differences in

patient populations are responsible for the results. Son and Kim [44] performed a meta-analysis of these trials, excluding VIVIDD, and showed that the risk of heart failure hospitalization was not increased. This finding was confirmed in an Italian cohort study of 282,000 unselected patients with diabetes treated with anti-diabetic drugs that compared DPP-4 inhibitors to any other anti-diabetic treatment and found no increased risk of HF hospitalization (odds ratio (OR) 1.00, 95 % CI 0.94–1.07) [45]. However, another meta-analysis of 50 trials with DPP-4 inhibitors showed a statistically significant increase in heart failure events (relative risk (RR) 1.16, 95 % CI 1.01–1.33, $p=0.04$) [46]. The weight of the analysis was dominated by the SAVOR-TIMI 53, EXAMINE, and VIVIDD trials [46].

Other agents in this class are currently being studied. The CAROLINA and CARMELINA trials will enroll a total of 14,000 patients to study the efficacy and cardiovascular safety of linagliptin versus glimepiride (CAROLINA) or placebo (CARMELINA) in patients with type 2 diabetes, who are at increased risk of cardiovascular events. These studies should help to define further the risk-benefit ratio of DPP-4 inhibitors in patients with DM and heart failure.

Glucagon-Like Peptide 1 Agonists

Glucagon-like peptide 1 (GLP-1) agonists stimulate glucose-dependent insulin release and enhance myocardial glucose uptake [47]. In patients with advanced heart failure, the myocardium becomes insulin-resistant, thus limiting glucose uptake. In this setting, GLP-1 augments glucose uptake by increasing insulin sensitivity. GLP-1 agonists have been shown to have cardioprotective effects in patients following myocardial infarction as well as in those with cardiomyopathy, which may be due to effects on oxidative stress and endothelial dysfunction. In addition, glucagon-like peptide has direct beneficial effects on the heart, vessels, and kidney through the type 1 glucagon-like peptide receptor (GLP-1R) [32]. Nikolaidis et al. [48] treated 16 dogs with dilated cardiomyopathy with a continuous GLP-1 infusion. Compared to saline-treated animals, dogs treated with the GLP-1 agonist showed improved left ventricular systolic function, increases in cardiac output, and decreases in heart rate and systemic vascular resistance [47, 48]. Similar studies in rats have shown improved LVEF and reverse ventricular remodeling with chronic GLP-1 agonist treatment [47]. In mouse models of diabetic cardiomyopathy, administration of exendin-4, a selective GLP-1R agonist, reduced left ventricular hypertrophy, attenuated oxidative stress, decreased LDH leakage, and improved survival [49, 50].

Promising animal studies paved the way for early clinical trials of GLP-1 agonists in human HF. Thrainsdottir et al. [51] performed a pilot study in six patients with type 2 diabetes and NYHA class II–III heart failure. A 3-day infusion of recombinant GLP-1 resulted in a non-significant trend towards improvement in LVEF as well as in glycemic state. A similar uncontrolled trial was performed by Sokos et al. [52] in 12 patients with NYHA class III or IV heart failure and reduced LVEF. In this proof-of-concept study, a 5-week infusion of GLP-1 in addition to standard HF therapy improved LVEF, submaximal and maximal exercise capacity, and quality of life [52]. Benefits were seen in both diabetic and non-diabetic patients. Contrary to these results, Halbirk et al. [53] demonstrated no benefit of short-term GLP-1 agonist therapy on non-invasive measures of systolic or diastolic function or BNP levels in patients with ischemic cardiomyopathy. However, Nathanson et al. [54, 55] showed improved hemodynamics as measured with a pulmonary artery catheter including decreases in pulmonary capillary wedge pressure, pulmonary artery pressure, and right arterial pressure and increased cardiac output in patients with diabetes and HF treated with an exenatide infusion. Circulating atrial natriuretic peptide levels also decreased in the exenatide group [55].

Liraglutide, another member of this class, was studied in 90 patients with type 2 diabetes and non-ST elevation myocardial infarction [56]. Patients were randomized to receive liraglutide (0.6 mg for 2 days and 1.2 mg for 2 days, followed by 1.8 mg for 3 days) or placebo for 1 week. At 3 months, the placebo-corrected change in LVEF between the two groups was +4.7 % (95 % CI +0.7 to +9.2 %, $p=0.009$), and inflammation and oxidative stress improved significantly with liraglutide. More recently, the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) study sought to determine the safety and efficacy of liraglutide in a high-risk heart failure population [57]. Three-hundred patients with heart failure, reduced EF, and recent HF hospitalization despite optimal medical therapy were randomized to receive liraglutide (target dose 1.8 mg daily) or placebo via a daily subcutaneous injection for 6 months. The primary endpoint included time to death, heart failure hospitalization, and proportional change in NT-proBNP. Secondary endpoints included quality of life, 6-min walk, and change in cardiac structure and function by echocardiogram. Preliminary data shows that liraglutide did not improve post-hospitalization clinical stability or any of the secondary outcomes [58]. Although not statistically significant, the composite of death or heart failure hospitalization as well as renal function metrics numerically favored the placebo group. Among patients with diabetes (60 % of the study population), a mild reduction in weight and improved glucose control was observed. In a large controlled trial of lixisenatide in patients with diabetes and acute coronary syndromes, GLP-1 agonist therapy did not significantly alter the rate of major cardiovascular events or other serious adverse events, including HF hospitalization (HR 0.96, 95 % CI 0.75–1.23) [59].

Other studies with liraglutide are ongoing, including an active-controlled trial comparing the effect of liraglutide plus

metformin to glimepiride plus metformin on left ventricular function. The Effect of Liraglutide on Left Ventricular Function in Chronic Heart Failure Patients With and Without Type 2 Diabetes Mellitus (LIVE) study has completed recruitment and is administering liraglutide (target dose 1.8 mg daily) or placebo to patients with NYHA class I–III heart failure and LVEF ≤45 %. The primary outcome is the change in LVEF from baseline to week 24 [47, 60]. More recently, albiglutide was studied in patients with NYHA Class II or III heart failure. Compared with placebo, albiglutide did not improve LVEF, 6-minute walk test or myocardial glucose use [61].

Sodium-Glucose Cotransporter 2 Inhibitors

The newest class of diabetes therapeutics, the sodium-glucose cotransporter 2 (SGLT-2) inhibitors, has generated great enthusiasm in the overall population of adults with diabetes and raise the possibility of efficacy in patients with HF (Table 1). These agents inhibit proteins that use the sodium gradient generated by the Na/K pump to move glucose against its concentration gradient in the proximal tubules. SGLT-2, in particular, mediates more than 90 % of glucose reabsorption in the kidney. Inhibitors of SGLT-2, therefore, prevent the majority of glucose reabsorption without off-target effects [62]. In patients with diabetes, these agents have also been shown to reduce body weight and blood pressure [62]. In heart failure, inhibitors of SGLT-2 increase hematocrit by approximately 3 %, suggestive of volume contraction. The first available SGLT-2 inhibitors in the USA included canagliflozin and dapagliflozin, with empagliflozin approved more recently.

In 2013, the FDA approved canagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes [63, 64]. Additional benefits include less hypoglycemia, weight loss, and blood pressure reduction. Also, in placebo-controlled trials, canagliflozin reduced uric acid levels by 14 % [65]. Uric acid levels have been shown to be independent predictors of morbidity and mortality in patients with heart failure [66–70]. Whether reduction in uric acid levels with SGLT-2 inhibitors will translate into clinical benefits in HF remains unknown. However, uric acid-lowering therapy with high-dose allopurinol had no effect on clinical outcomes, exercise capacity, quality of life, or LVEF in high-risk HF patients with reduced ejection fraction [70].

The cardiovascular effects of empagliflozin were studied in the EMPA-REG OUTCOME trial, in which 7020 patients with type 2 diabetes at high cardiovascular risk were randomly assigned to receive empagliflozin (10 or 25 mg) or placebo once daily. After a median follow-up of 3.1 years, the risk of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke was reduced by 24 % in the empagliflozin group, and all-cause mortality was reduced by 32 % ($p<0.001$). With respect to heart failure, treatment with empagliflozin reduced heart failure hospitalizations by 35 % (HR 0.65, 95 % CI 0.50–0.85, $p=0.0002$), although the number of events was relatively small (2.7 % of empagliflozin patients versus 4.1 % of placebo) [71].

Studies are currently underway to determine if the benefits observed in the EMPA-REG OUTCOME trial are specific to empagliflozin or can be generalized to the SGLT-2 inhibitor

Table 1 Summary of existing and ongoing trials in sodium-glucose cotransporter 2 (SGLT-2) inhibitors

Trial	Agent	Number	Entry criteria	Follow-up	Findings/outcomes
EMPA-REG OUTCOME [71]	Empagliflozin	7020	T2DM at high cardiovascular risk, HbA1c 7.0–10 %, BMI ≤45	3.1 years	Significantly lower rates of death from cardiovascular causes, hospitalization for HF, and all-cause mortality
REFORM [72]	Dapagliflozin	58	T2DM, NYHA class I–II HF with LVSD, furosemide 80 mg daily or less, stable HF symptoms, and therapy for 3 months	1 year	Primary outcomes: change in LV end-systolic and diastolic volume and ejection fraction Secondary outcomes: fluid status assessed by bioimpedance, 6-min walk test, QOL measures, BNP levels, and diuretic requirements
DEFINE-HF [73]	Dapagliflozin	250	T2DM, HbA1c 6.5–10 %, NYHA class II–III HF with LVEF ≤40 %, BNP ≥150 pg/ml, or NT-proBNP ≥900 pg/ml	12 weeks	Primary outcomes: reduction in NT-proBNP, heart disease-specific QOL Secondary outcomes: 6-min walk test, HbA1c, weight, and systolic blood pressure
DECLARE-TIMI 58 [74]	Dapagliflozin	17,276	40 years or older, T2DM, high risk for cardiovascular events	6 years	Primary outcome: time to composite endpoint of CV death, MI, or ischemic stroke Secondary outcomes: hospitalization for HF and all-cause mortality

BMI body mass index, *BNP* B-type natriuretic peptide, *CV* cardiovascular, *HF* heart failure, *HbA1c*, hemoglobin A1c, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *LVSD* left ventricular systolic dysfunction, *MI* myocardial infarction, *NT-proBNP N*-terminal pro-B-type natriuretic peptide, *NYHA* New York Heart Association, *QOL* quality of life, *T2DM* type 2 diabetes mellitus

class. The REFORM study will examine the safety and efficacy of dapagliflozin in patients with NYHA class I–II heart failure and diabetes [72]. The primary endpoint is change in LV mass index and ejection fraction at 1 year as measured by cardiac MRI. Secondary endpoints include fluid status assessed by bioimpedance, 6-min walk test, and quality of life. BNP levels and diuretic requirements will also be tracked. A larger study, DEFINE-HF, will randomize 250 patients with type 2 diabetes, NYHA class II–III heart failure, and LVEF ≤40 % to 12 weeks of treatment with dapagliflozin (10 mg once daily) or placebo [73]. Disease-specific biomarkers (BNP and NT-proBNP), symptoms, health status, and quality of life will be assessed. Similar to the EMPA-REG OUTCOME trials, the DECLARE-TIMI 58 trial aims to enroll over 17,000 patients with diabetes at high risk for cardiovascular events into a safety and efficacy study [74]. The primary outcome is the composite endpoint of cardiovascular death, myocardial infarction, or ischemic stroke.

Conclusions

Over the past two decades, therapeutics for diabetes have evolved from drugs with known heart failure risks to classes with potential benefit for patients with heart failure. With an increasing focus on cardiovascular safety, the US Food and Drug Administration has required pharmaceutical companies to conduct large prospective post-marketing studies of new diabetes agents. As knowledge of the molecular underpinnings of diabetes and heart failure grows, there is increasing hope of developing rational drug targets with the goal of reducing myocardial insulin resistance and oxidative stress. The newest class of medications, the SGLT-2 inhibitors, raises the exciting possibility of improved outcomes in heart failure. Further studies are ongoing to determine whether these agents will improve disease-specific symptoms, quality of life, ejection fraction, and other important clinical endpoints.

Compliance with Ethical Standards

Conflict of Interest Ersilia M. DeFilippis and Michael M. Givertz declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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