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Review Article

MANAGEMENT OF HEART FAILURE IN PATIENTS WITH DIABETES MELLITUS: A REVIEW

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ABSTRACT

Heart failure is a common comorbidity in diabetes and patients with both conditions have particularly poor prognosis. The coexistence of type 2 diabetes mellitus (T2DM) and heart failure (HF) either with reduced (HFrEF) or preserved (HFpEF) is frequent (30 -40% of patients) and associated with higher risk of HF hospitalizations, all-cause and cardiovascular (CV) mortality. The most important causes of HF in T2DM are coronary artery disease, arterial hypertension and a direct detrimental effect of T2DM on the myocardium. T2DM is often unrecognized in HF patients, and vice versa, which emphasizes the importance of an active search for both disorders in the clinical practice. There are no specific limitations to HF treatment in T2DM. Concerning T2DM treatment in HF patients, most guidelines currently recommend metformin as the first-line choice. Sulphonylureas and insulin have been the traditional second- and third-line therapies although their safety in HF is equivocal. Neither glucagon-like preptide-1 (GLP-1) receptor agonists, nor dipeptidyl peptidase-4(DPP4) inhibitors reduce the risk for HF hospitalization. Indeed, a DPP4 inhibitor, saxagliptin, has been associated with a higher risk of HF hospitalization. Thiazolidinedione (pioglitazone and Rosiglitazone) are contraindicated in patients with (or at risk of) HF. In recent trials, sodium–glucose co-transporter-2 (SGLT2) inhibitors, empagliflozin and canagliflozin, have both have shown a significant reduction in HF hospitalization in patients with established CV disease or at risk of CV disease. This review articles summarizes the epidemiology and current understanding of the mechanisms underlying the intersection between T2DM and HF. It further presents contemporary treatment options for patients with established T2DM and HF, and summarizes recent evidence of HF prevention with drugs used to treat T2DM.

Keywords: Type 2 Diabetes mellitus, Heart failure, Heart failure management, Glucose lowering agents, and cardiovascular events.

INTRODUCTION

Heart failure is a clinical syndrome characterized by symptoms and signs caused by structural or functional abnormalities of the heart. Typical symptoms are breathlessness, ankle swelling, and fatigue. Typical signs are increased jugular venous pressure, third heart sound, peripheral edema, and pulmonary crackles, however, the condition can be present in the absence of these findings. It is important to address the underlying cause of heart failure, because the specific etiology determines the choice of treatment. Common causes of heart failure are ischemic heart disease, dilated cardiomyopathy, valvular lesions, atrial fibrillation, and hypertension. The toxic impact of chemotherapy and high levels of alcohol consumption can also lead to systolic left ventricular failure [1, 2]. Diabetes accelerates atherosclerosis and often leads to hypertension but it is still debated whether diabetes causes a specific cardiomyopathy. The coexistence of heart failure (HF) and type 2 diabetes mellitus (T2DM) is common and has a strong impact on clinical management and prognosis. T2DM is associated with worse clinical status and increased all-cause and cardiovascular (CV) mortality in both patients with HF with reduced (HFrEF) and preserved ejection fraction (HFpEF), compared to HF patients without T2DM [3]. Conversely, HFrEF is an independent predictor of fatal and non-fatal clinical outcomes in patients with T2DM [4, 5]. The major causes of HF in T2DM include coronary artery disease (CAD) and hypertension, but also, a possible direct detrimental effect of T2DM on the myocardium [6].

EPIDEMIOLOGY

Prevalence of type 2 diabetes mellitus and heart failure in general populations:

The prevalence of T2DM, which encompasses 90–95% of diabetic individuals, has globally increased from 4.7% in 1980 to 8.5% in 2014[7]. The overall prevalence of HF is 11.8% (range 4.7–13.3%) in the general populations [8].

Prevalence of heart failure in patients with type 2 diabetes mellitus:

In the general population, the prevalence of HF in people with T2DM was 12% as shown in table 1 [9]. In this study, HF was more common in patients with T2DM aged >70 years (i.e. 16% and 22%of men and women, respectively). In the Kaiser Permanente population, patients with T2DM aged <75 years had an approximately three-fold higher prevalence of HF compared to those without T2DM [10]. In those aged 75–84 years, T2DM was associated with a doubling of risk for HF. In these relatively old studies, HF phenotype (i.e. HFrEF or HFpEF) or biomarker status was not reported. In clinical trials of T2DM patients, the prevalence of HF at baseline has varied between approximately 10% and 30%.

Trials	Prevalence of HF at baseline	References
1. Glucose Lowering Trials:		
ACCORD	4.3%	[11]
2. DPP4 inhibitors Trials:		
TECOS	18%	[12]
EXAMINE	28%	[13]
3. SGLT2 inhibitors Trials:		
EMPA-REG outcome	10%	[14]
CANVAS	14-15%	[15]
4. GLP-1 Receptors agonist trials:		
LEADER	14%	[16]
ELIXA	22%	[17]
EXSCEL	16%	[18]

Table 1: Prevalence of heart failure in selected trials of type 2 antidiabetic drugs

DPP4=dipeptidyl peptidase-4. GLP-1=glucagon-like peptide-1. HF= heart failure. SGLT2= sodium–glucose co-transporter type 2.

Prevalence of type 2 diabetes mellitus in patients with heart failure:

In the general population, HF is associated with a higher prevalence of T2DM compared to patients without HF as shown in table 2[9]. Approximately 25% of patients with HF in England and Denmark also had T2DM. Despite younger age and less obesity, a significantly higher prevalence of T2DM (57%) was observed in a population-based cohort of Southeast Asian HF patients compared to Caucasian patients (24%) [19]. The reasons for the wide regional variation in T2DM prevalence in HF patients warrant further international studies with shared study design and standardized data collection. In clinical trials of chronic HF patients, the prevalence of T2DM was around 30%, irrespective of HF phenotype (i.e. HFrEF and HFpEF) [20]. The highest prevalence of T2DM was seen in trials of acute HF (around 40%). In registries of hospitalized HF patients in North America and Europe, the prevalence of T2DM around 40–45% [21] and a slight increase in the prevalence was reported in North America over time [21].

Trials	Prevalence of Type 2 Diabetes mellitus.	References
1. Trials of HFrEF:		
SHIFT	30%	[22]
SENIOR	26%	[23]
MERIT-HF	25%	[24]
2. Trials of HFpEF:		
1-preserve	27%	[25]
PEP-CHF	21%	[26]
3. Trials of Acute HF:		
EVEREST	39%	[27]
TRUE-AHF	39%	[28]

Table 2: Prevalence of Type 2 Diabetes mellitus in selected trials of heart failure

HF=heart failure. HFpEF= heart failure with preserved ejection fraction. HFrEF=heart failure with reduced ejection fraction. T2DM= type 2 diabetes mellitus.

Incidence of new type 2 diabetes mellitus in patients with heart failure:

In patients with HF, data from observational and clinical trials demonstrate an increased risk for new-onset T2DM compared to patients without HF. In a Danish nationwide cohort study, 8% of HF patients developed T2DM over3 years, and the severity of HF was associated with a stepwise increased risk of developing T2DM [29]. HF treatment with Angiotensin-converting enzyme (ACE) inhibitors was shown to lower the incidence of T2DM in HFrEF patients. Registry data corroborate that the use of renin–Angiotensin system inhibitors is associated with attenuated risk for T2DM in HF patients receiving loop diuretics [29].

Incidence of heart failure in patients with type 2 diabetes mellitus:

Recently, a population-based study of 1.9 million patients with T2DM without overt CV disease, followed for 5.5 years, demonstrated that incident HF was observed more frequently(14.1%) than vascular events, including myocardial infarction (MI) or stroke[30]. T2DM is an independent risk factor for the development of HF [10]. In a retrospective cohort followed for up to 72months, patients with T2DM were more likely to develop HF than patients without T2DM [31]. In elderly patients with T2DM, the incidence of HF was two-fold higher compared to patients without T2DM [32]. In the UKPDS 35 trial including newly diagnosed diabetic patients, HF incidence steeply increased with the severity of dysglycaemia ranging from 2.3 to 11.9/1000 person-years for patients with glycated hemoglobin (HbA1c) <6% and HbA1c >10%, respectively[33]. In the ARIC study, higher HbA1c levels in T2DM patients were associated with significantly more incident HF cases than in patients with T2DM and lower HbA1c levels [34].The incidence of HF in T2DM patients compared to those without T2DM is even higher in patients with established CAD, in which each 1% increase in HbA1c level was associated with a 36% increased risk for HF hospitalization [35].

TYPE 2 DIABETES MELLITUS, CLINICAL STATUS AND OUTCOMES IN PATIENTS WITH HEART FAILURE

Clinical presentation, quality of life and functional status of patients with type 2 diabetes mellitus and heart failure:

Patients with T2DM and both HFrEF and HFpEF have worse NYHA functional class and more HF-related symptoms and signs than patients without T2DM, despite having similar ejection fraction [36]. In the SOLVD-Prevention trial of patients with asymptomatic left ventricular systolic dysfunction, patients with T2DM were more likely to progress to symptomatic HF than those without T2DM, although the increased risk appeared to be confined to patients with HF secondary to CAD [37]. Most trials also demonstrated worse quality of life in patients with T2DM and concurrent HF (both HFrEF and HFpEF), as compared to patients without T2DM [[38].

Type 2 diabetes mellitus and mortality in patients with heart failure:

In all population-based studies, T2DM was associated with increased all-cause mortality in HF patients and no differentiation between HFrEF and HFpEF was performed [39]. T2DM was associated with an excess risk for CV death that was similar to the risk of all-cause mortality. T2DM increased mid-to-long-term mortality following hospitalization for HF. The presence of T2DM was independently associated with increased 1-year all-cause mortality.

Type 2 diabetes mellitus and causes of death in patients with heart failure:

In the CHARM trial, patients with T2DM and both HFrEF and HFpEF were more likely to die of all subtypes of CV death [i.e. death due to HF, sudden cardiac death (SCD), death due to MI and death due to stroke[3]. The patients with T2DM and HFrEF were more likely to die of CV as well as all-cause mortality compared with patients without T2DM[38]. In the BEST trial, T2DM was an independent risk factor for death from pump failure [40]. Aside from CV death, results from the Emerging Risk Factors Collaboration, including 820 900 people, demonstrate that T2DM is independently associated with increased risk of death from several cancers (i.e. liver, pancreas, ovary, colorectum, lung, bladder, and breast), renal and liver disease, pneumonia and other infectious diseases, mental and nervous system disorders, non-hepatic digestive diseases, external causes, and chronic obstructive pulmonary disease [41]. The increased risk of mortality with T2DM in HF patients is seen in both those of ischemic and non-ischemic aetiology is uncertain. The increased mortality risk of T2DM was seen in both women and men, but the effect was slightly greater in women [42].

Does glycated hemoglobin predict mortality in patients with heart failure and type 2 diabetes mellitus?

The high HbA1c was associated with increased all-cause and CV mortality in patients with T2DM and both HFrEF and HFpEF [43]. A 1% increase in HbA1c was associated with an increased HR of 1.1 for CV mortality [43]. In patients from US study of HF clinics, a U-shaped relationship with regard to increased all-cause mortality was found [37]. Patients with either very low or very high HbA1c were at greatest risk. A similar

U-shaped curve was found in a single-centre study from Scotland [44]. In one single-centre observational study of 123 young patients with advanced HF and T2DM, patients with a HbA1c of <7% had higher rates of all-cause mortality[45]. The high HbA1c levels in T2DM and HF are consistently associated with higher mortality.

Pre-diabetes and undiagnosed type 2 diabetes mellitus and risk of mortality in heart failure:

Patients with pre-diabetes were at increased risk of mortality. Patients with undiagnosed T2DM were also at higher risk of mortality than subjects without T2DM, but the risk was not as high as in patients with previously known T2DM. The pre-diabetes and undiagnosed T2DM were both associated with greater rates of HF hospitalization, CV and all-cause mortality than those without T2DM[25].

Type 2 diabetes mellitus, myocardial infarction and stroke in patients with heart failure:

The only trial to investigate the association between T2DM and risk of MI and stroke in HF patients was the CHARM trial demonstrating that the presence of T2DM increased the risk for MI and stroke irrespective of HF phenotype (i.e. HFrEF or HFpEF)[3].

Risk for HF hospitalization in patients with type 2 diabetes mellitus without previous history of heart failure:

In the ARIC registry, representing a cohort of 14 079 people in the community without known HF; T2DM was the most powerful risk factor for incident HF hospitalization [46]. In a large meta-analysis of patients with T2DM but without HF, predictors of incident HF included insulin use, HbA1c and fasting glucose [47].

Mortality in type 2 diabetes mellitus patients with heart failure:

In Patients with T2DM, the development of HF is associated with markedly higher mortality. Patients with T2DM who developed HF had a 10 to 12 time greater mortality than those who did not develop HF [48]. In addition, they are also at a 2.45-fold greater risk of CV death compared with patients with T2DM but without HF [49].

Unrecognized heart failure in patients with type 2 diabetes mellitus and unrecognized type 2 diabetes mellitus in patients with heart failure:

The significant proportion of patients aged ≥ 60 years (27.7%) may have unrecognized HF (22.9% and 4.8%, HFpEF and HFrEF, respectively) based on the ESC diagnostic criteria [50, 51]. On the other hand, pre-diabetes and undiagnosed T2DM are common in patients with HF. In the PARADIGM-HF trial, 13% of patients with HFrEF had undiagnosedT2DM and 25% had pre-diabetes [38]. The T2DM patients, screening for HF might be currently based on clinical characteristics (i.e. age, history of CAD, exercise-related shortness of breath, body mass index, laterally displaced apex beat)that have been shown to reliably identify elderly subjects at risk of HF that may require further assessment (e.g. echocardiography)[50].

PATHOPHYSIOLOGICAL ASPECTS OF MYOCARDIAL DYSFUNCTION IN TYPE2 DIABETES MELLITUS

The most common co-existing conditions that cause HF in patients with T2DM are CAD and hypertension. It has also been hypothesized that T2DM-related processes can cause HF by directly affecting the structure and function of the heart [6]. The major drivers of myocardial dysfunction in T2DM are insulin resistance/hyperinsulinemia and impaired glucose tolerance, which may be effective years or even decades before overt T2DM develops [51]. Their detrimental effect is associated with numerous metabolic abnormalities such as advanced glycosylation end products (AGEs) deposition, lipotoxicity and microvascular rarefaction [6]. Harmful interrelations between these pathophysiological mechanisms may exert a potentiating effect, leading to several maladaptive responses and resulting in myocytes alteration [6]. Insulin resistance leads to increased free fatty acid release and is linked with HF-related neuroendocrine dysregulation [52]. It is also an important etiological factor in the development of left ventricular hypertrophy[53], as confirmed in the Framingham study, where left ventricular mass was significantly higher in female patients with T2DM compared to patients without T2DM[40]. Hyperglycemia also exerts extensive influences on CV changes in T2DM, and can directly cause cardiomyocyte contractile dysfunction, mitochondrial network fragmentation and an increase in protein kinase C activity [54-56]. Also, it causes activation of reactive oxygen species and the deposition of AGEs in both endothelial and smooth muscle cells, which predisposes to concentric left ventricular remodeling and raises left ventricular diastolic stiffness [54, 55]. High myocardial free fatty acid uptake results in the accumulation of triglyceride in the myocardium (i.e. lipotoxicity). Cardiac steatosis, confirmed by proton magnetic resonance spectroscopy, is the clinical equivalent of high myocardial triglyceride content and may present as left ventricular diastolic dysfunction.

Phenotypes of type 2 diabetes mellitus-related cardiomyopathy:

Left ventricular diastolic dysfunction and heart failure with preserved ejection fraction in type 2 diabetes mellitus:

Left ventricular diastolic dysfunction can be detected in 75% of T2DM patients and develops early in T2DM course, as confirmed by demographic characteristics of these patients, including younger age, normal blood pressure and optimal T2DM control[57, 58]. Furthermore, the degree of glucose dysregulation correlates with left ventricular diastolic dysfunction severity [59] and with increased risk of incident HF and CV mortality in T2DM [60, 61]. Almost half of HF patients with T2DM have HFpEF, which is more frequent in older, hypertensive and female patients with T2DM and is difficult to diagnose because the symptoms are often mild, appear upon physical activity, and could be frequently misdiagnosed as chronic obstructive pulmonary disease [62]. HFpEF is usually associated with mild T2DM complications in the early stages of T2DM, whilst HFrEF is associated with more severe T2DM complications [63]. This suggests that severity and duration of hyperglycemia are important for the development of left ventricular dysfunction.

Heart failure with reduced ejection fraction in type 2diabetes mellitus:

The major cause of HFrEF in T2DM is CAD. T2DM is associated with a two-fold higher risk of CAD and ischemic stroke, and a two- to four-fold higher CAD- and stroke-related mortality [64]. CAD in T2DM is usually diffuse, multi-vessel and may lead to silent MI.

TREATMENT OF HEART FAILURE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

There are no specific constraints to HF treatment in T2DM patients as recommended by the 2016 ESC guidelines for the management of HF [1]. In clinical trials, all pharmacological and device therapies for HF were similarly effective whether or not patients had T2DM. Thus far, there were no clinical trials of HF treatment that included only patients with T2DM, and available evidence is derived from sub analyses of mixed populations. However, several HF drugs may exert metabolic effects that should be taken into account in T2DM patients.

Pharmacological therapy:

Angiotensin-converting enzyme inhibitors:

The ESC/EASD guidelines on diabetes, pre-diabetes, and CV diseases recommend Angiotensin-converting enzyme (ACE)-inhibitors in patients with HFrEF and T2DM, as they have been shown to improve symptoms and reduce morbidity and mortality [1]. The effectiveness of ACE-inhibitors in patients with both T2DM and HF or post-MI left ventricular systolic dysfunction was examined in a large meta-analysis of seven randomized clinical trials [65]. For the endpoint of all-cause mortality, ACE-inhibitors had a similar treatment benefit in subjects with and without T2DM. The only large ACE-inhibitor trial in HFrEF to provide detailed information on patients with T2DM was the ATLAS, which compared low-dose (2.5–5.0 mg daily) to high-dose (32.5–35.0 mg daily) Lisinopril[66, 67]. The greater relative benefit for the composite primary endpoint (all-cause mortality or HF hospitalization) of high-dose Lisinopril was similar in patients with and without T2DM. However, because patients with T2DM were at greater risk, the absolute benefit of high-dose Lisinopril was larger in patients with T2DM [67]. The occurrence of adverse effects with high-dose Lisinopril was similar in those with and without T2DM with respect to hypotension/dizziness (35% vs. 32%), renal dysfunction/Hyperkalemia (29% vs. 22%) and cough (12% vs. 10%)[67].

Angiotensin receptor blockers:

In the CHARM trial, a significant reduction in CV death, HF hospitalization and all-cause mortality was achieved with Candesartan in patients with HF and HFrEF, irrespectively of T2DM [3]. Also with Valsartan treatment led to a significant relative risk reduction in the co-primary composite endpoint (death or HF morbidity—mainly HF hospitalization) regardless of T2DM [68]. A subsequent trial showed that 150 mg daily of Losartan was superior to 50 mg daily in reducing the risk of death or HF hospitalization, supporting the similar findings of the ATLAS trial with the ACE-inhibitor Lisinopril. There is little information about the tolerability of Angiotensin receptor blockers (ARBs) in T2DM. The patients with T2DM had doubled the risk of developing Hyperkalemia on Candesartan compared to those without T2DM [69]. T2DM confers a higher risk

of diabetic nephropathy and chronic kidney disease [70]. Specifically, diabetic nephropathy is characterized by increased renal sodium retention [71, 72] and a higher risk of Hyperkalemia [73]. When ACE-inhibitors or ARBs are administered to diabetic patients, as these drugs may interfere with renal potassium excretion, Hence, monitoring of serum electrolytes and creatinine is recommended when starting ACE-inhibitors or ARBs.

Beta-blockers:

The beta-blockers reduce mortality and hospitalization and improve symptoms in moderate to severe HF, irrespectively of T2DM [74, 75]. Beta-blockers recommended in HF and T2DM include metoprolol succinate [24], bisoprolol [24], and carvedilol [76]. The MERIT-HF trial reported similar efficacy and safety of metoprolol succinate in patients with and without T2DM. Adverse events were more often observed in T2DM patients, but were less likely to occur if those patients were treated with metoprolol succinate than with placebo. The beta-blockers could alter awareness of hypoglycemia by decreasing palpitations and tremor and prolong recovery from hypoglycemia by blocking 2 receptors, which partly control glucose production in the liver. In summary, beta-blockers in patients with T2DM and HF lead to significant improvements in morbidity and mortality that are consistent with results in patients without T2DM. These treatment benefits of beta-blockers in diabetic patients far outweigh the theoretical risks related to hypoglycemia and minor changes in HbA1c and serum lipids. These benefits strongly support beta-blocker treatment in patients with concurrent T2DM and HF.

Mineralocorticoid receptor antagonists:

The mortality benefit of spironolactone in the RALES trial and eplerenone in the EMPHASIS-HF trial was consistent in T2DMand non-T2DM patients with HFrEF [77, 78]. Importantly, eplerenone seems to have no effect on new-onset T2DM in patients with HF, suggesting a neutral metabolic profile [79]. Caution is necessary when these medications are used in patients with impaired renal function and in those with serum potassium levels of ≥ 5.0 mmol/L. Monitoring of kidney function and potassium is mandatory since nephropathy is frequent in T2DM. Addition of an ARB (or renin inhibitor) to a combination of ACE-inhibitor and mineralocorticoid receptor antagonists is prohibited because of the increased risk of renal dysfunction and Hyperkalemia and the lack of additional benefit [80].

Sacubitril/Valsartan:

In the PARADIGM-HF trial, sacubitril/Valsartan was superior to the ACE-inhibitor Enalapril in reducing the risks of death and HF hospitalization in patients with HFrEF [20]. A T2DM subgroup analysis has shown that the effect of sacubitril/Valsartan compared with Enalapril for the primary endpoint was similar in patients with and without T2DM [38]. In the post hoc analysis, treatment with sacubitril/Valsartan was associated with a greater HbA1c reduction and a lower rate of initiation of insulin or other drugs for T2DM compared to Enalapril [81].

Nitrates and Hydralazine:

The A-HeFT trial examined the efficacy for the reduction in all-cause mortality, hospitalization and quality of life of a fixed dose combination of isosorbide dinitrate and Hydralazine hydrochloride in African Americans with HF [82]. A very large proportion (41%) of patients in the study had T2DM.

Ivabradine:

In a large trial involving 6558 patients with HF (30% with T2DM), ivabradine demonstrated a significant reduction in the composite end point of CV death or HF hospitalization, with no difference between T2DM and non-T2DM patients [83].

Diuretics:

Diuretics are usually required to treat the symptoms and signs of fluid overload in patients with HF. There are no clinical trials examining their efficacy in patients with both T2DM and HF. Theoretically thiazide diuretics can lead to increased insulin resistance and subsequent worsening of glycemic control.

Devices and surgery:

Implantable cardioverter-defibrillators:

There is a higher risk of death due to worsening HF patients with T2DM and HF are at increased risk of malignant ventricular arrhythmias and sudden cardiac death (SCD). Patients with T2DM experienced a significantly higher rate of sudden cardiac death compared to patients without T2DM and the increased risk of sudden cardiac death was observed irrespective of HF phenotype (i.e. HFrEF and HFpEF). Observational data also demonstrate an increased risk of SCD in the presence of T2DM in HF of both ischaemic and non-ischaemic aetiology [84]. Device therapies, implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy with ICD (CRT-D) offer a possibility to reduce overall mortality with effective prevention of SCD, and data from clinical trials support this notion in patients with and without T2DM.

Cardiac resynchronization therapy:

The effectiveness of CRT to reduce the risk of all-cause death and HF hospitalization was evaluated in two clinical trials(COMPANION167 and CARE-HF168) that randomized patients with moderate to severely symptomatic HF (NYHA class III or IV) to either optimal medical therapy or optimal medical therapy plus CRT. In relation to T2DM status, both COMPANION (41% of T2DM patients), and CARE-HF (29% of T2DM patients) demonstrated similar effectiveness of CRT for the reduction in mortality and HF hospitalization [85, 86]. Patients with T2DM did not experience a higher rate of complications related to device implantation, including infection [87]. There were similar CRT-related improvements in left ventricular volumes and ejection fraction in those with and without T2DM.

Coronary arteries bypass grafting:

Coronary artery disease is the leading cause of premature mortality in patients with T2DM, which stresses the importance of an early detection (e.g. stress echocardiography, coronary angiography) based on the estimated CV risk, and a timely treatment of CAD [88, 89]. Patients suitable for surgery were randomized to coronary artery bypass graft (CABG) plus medical therapy or medical therapy alone. The patients with two or three-vessel CAD, including a left anterior descending stenosis, are suitable for surgery.

Cardiac transplantation:

Cardiac transplantation in T2DM with macrovascular complications and end-stage HF may impose several challenging issues, including renal dysfunction, peripheral vascular disease, increased risk of infection

and the need for prednisolone-based immunosuppression. T2DM was an independent risk factor for reduced 10-year survival in a large registry of 22385 transplant patients [90]. However, with modern immunosuppression regimens allowing more rapid tapering of steroid doses and steroid-free immunosuppression, cardiac transplantation in T2DM (in the absence of majorT2DM complications) should be considered on a case-by-case basis.

Exercise prescription:

The effects of exercise training in patient with mild to moderately severe HF, reduction in the primary composite outcome of all-cause mortality or all-cause hospitalization. The trial enrolled 32% of patients with T2DM and there was no interaction between T2DM status and the effect of exercise on clinical outcomes.

Type 2 antidiabetic drugs and the risk of heart failure:

Drugs that increase heart failure hospitalizations:

T2DM drugs might increase the risk for HF [91-93]. Drugs that are now known to increase the risk for HF are Thiazolidinedione (TZDs), dipeptidyl peptidase-4 (DPP4) inhibitor, saxagliptin [94, 95]. The patients randomized to TZDs, Rosiglitazone and pioglitazone, respectively, had more HF events than those on placebo. Patients at greatest risk were those with a history of HF an estimated glomerular filtration rate (eGFR) ≤60 mL/min, or elevated baseline levels of N-terminal pro B-type natriuretic peptide [94]. On that basis, pioglitazone, Rosiglitazone and saxagliptin are contraindicated in patients with HF or at risk of HF. Not all DPP4 inhibitors are associated with higher rates of [94].

Study	Antidiabetic drugs	comparators	Results	References
DPP4 inhibitors				
SAVOR-TIMI	Saxagliptin	Placebo	Increase in HF hospitalization	[94, 95]
EXAMINE	Alogliptin	Placebo	No statistically significant increase in HF hospitalization	[96]
TECOS	Sitagliptin	Placebo	No effect on HF hospitalization	[97]
GLP-1 receptor agonists				
ELIXA	Lixisenatide	Placebo	No effect on HF hospitalization.	[17]
LEADER	Liraglutide	Placebo	No effect on HF hospitalization.	[16]
SUSTAIN-6	Semaglutide	Placebo	No effect on HF hospitalization.	[98]
EXSCEL	Exenatide	Placebo	No effect on HF hospitalization.	[18]
SGLT2 inhibitors				
EMPA-REG OUTCOME	Empagliflozin	Placebo	Reduced HF hospitalization.	[14]
CANVAS	Canagliflozin	Placebo	Reduced HF hospitalization.	[15]

Table 3: Heart failure outcomes in published large cardiovascular outcome trials in patients with type 2 Diabetes mellitus

DPP4 = Dipeptidyl peptidase-4. GLP-1 =Glucagon-like peptide-1. HF = heart failure. SGLT2 = sodium–glucose co-transporter type 2.

Drugs that might increase the risk for heart failure:

The insulin causes sodium and water retention, may increase the risk for the development of HF. In large observational studies, insulin is associated with higher mortality rates than metformin [4]. There have been similar concerns with sulphonylureas which, as insulin secretagogues, have also been associated with higher death rates than metformin [4]. Currently, sulphonylureas and insulin could be used in T2DM patients with HF (usually as a second- or third-line treatment), although their safety in HF is still inconclusive.

Antidiabetic drugs that might be safe in heart failure:

The metformin might be safe and efficacious in patients with T2DM and HF. Metformin was associated with lower mortality and HF hospitalization rates than other T2DM drugs (primarily insulin and sulphonylureas). There are no RCTs of metformin in patients with T2DM and HF. Metformin could be recommended as first-line treatment for patients with T2DM and HF who have preserved or moderately reduced renal function (i.e. eGFR >30 mL/min). Glucagon-like peptide 1 (GLP-1) receptor agonists have been the subject of many large placebo-controlled trials in patients with T2DM and CV disease or at high risk of CV disease [98]. In these trials, GLP-1 receptor agonists had a neutral effect on the risk for HF hospitalization. Similarly, no signal for a higher risk for HF hospitalization was seen with acarbose (placebo) in patients with insulin resistance and CAD [99].

Prevention of heart failure by type 2antidiabetic drugs:

Two large RCTs that assessed CV safety of the sodium–glucose co-transporter type 2 (SGLT2) inhibitors, empagliflozin and canagliflozin; have shown a significant reduction in HF hospitalization with both drugs [100]. The primary out come in both trials was the three-point major adverse CV event (i.e. CV death, non-fatal MI or non-fatal stroke) and HF hospitalization was a secondary outcome. In established CV disease and eGFR>30 mL/min/1.73m2, there was a major reduction in HF hospitalization with empagliflozin compared with placebo. Canagliflozin was associated with a significantly higher risk of lower-limb amputations and possibly a higher risk of fractures compared with placebo.

Class of antidiabetic drugs	Evidence
1. SGLT2 inhibitors: (E.g. empagliflozin, Canagliflozin)	No RCTs in HF. Large RCTs in patients with HF with a without T2DM are underway.
2. Metformin:	No RCTs in HF. Metformin is associated with lower mortality than sulfonylurea or insulin [91]. Beneficial /risk ration unknown.
3. GLP-1 receptor Antagonists: (e.g. Liraglutide, albiglutide)	No RCTs in HF patients with HF. Liraglutide - two small RCTs reported no effect on LV function [92]. Beneficial /risk ration unknown.
4. Sulphonylureas:	No RCTs in HF. Observational data suggest an increased mortality risk with sulphonylureas compared with metformin [91].
5. Insulin:	No RCTs in HF. In observational studies in HF, Insulin was associated with higher mortality rates than metformin [91]. Benefit/risk ratio unknown.
6. DPP4 inhibitors:	No RCTs in HF (saxagliptin is contraindicated in HF [95]. Benefit/risk ratio unknown.

Table 4: Summary of evidences for type 2 antidiabetic drugs in patients with prevalent heart failure DPP4 = dipeptidyl peptidase-4. GLP-1 = glucagon-like peptide-1. HF = Heart failure. LV= Left ventricular. RCT = Randomized clinical trials. SGLT2 = sodium–glucose co-transporter type 2. T2DM = type 2 diabetes mellitus.

Treatment of heart failure with type 2 antidiabetic drugs:

Randomized clinical trials with SGLT2inhibitors:

While two drugs (i.e. empagliflozin and canagliflozin) have a favorable effect on HF hospitalization, no T2DM drug has yet been investigated as a treatment for HF. In 2017, three large RCTs with SGLT2 inhibitors (i.e. empagliflozin and dapagliflozin) have started, which will enroll HF patients either with or without T2DM.

Two trials will assess safety and efficacy of empagliflozin vs. placebo on top of guideline-based medical therapy for the reduction in primary outcome (CV death or HF hospitalization) both in patients with HFrEF and HFpEF. Among secondary outcomes, the two trials will assess all-cause mortality, and renal effects of empagliflozin vs. placebo in patients with HF. The third trial will assess safety and efficacy of dapagliflozin vs. placebo for the reduction in CV death or HF hospitalization in patients with HFrEF. The results of these trials will shed more light on potential beneficial CV and renal effects of SGLT2 inhibitors in HF patients, including those without T2DM.

Randomized clinical trials with GLP-1receptor agonists:

In the LIVE trial, in patients with stable HFrEF, with and without T2DM, there were no significant changes in left ventricular ejection fraction between patients randomized on liraglutide or placebo [92]. In a placebo-controlled FIGHT trial, of patients with HFrEF, with and without T2DM (41%), liraglutide was not associated with an improvement in the composite primary endpoint of death, rehospitalization and NT-proBNP change [93]. These observations have raised some concern regarding the safety of liraglutide in HFrEF patients that warrants further research.

CONCLUSION

Type 2 diabetes mellitus and HF are both common and frequently co-exist. The causes of HF in T2DM are numerous, but CAD and hypertension are likely the most important contributors to concurrent T2DM and HF, whereas a direct effect of T2DM on the myocardium (e.g. 'diabetic cardiomyopathy') might also play a role. Evidence from recent large-scale clinical trials and registries indicates a significantly higher risk of adverse outcomes in patients with HF and T2DM, including a higher risk for hospitalization and rehospitalization for HF, as well as increased all-cause and CV mortality, independent of HF aetiology or phenotype (i.e. HFrEF and HFpEF). HF treatment with medications and devices (e.g. ICD, CRT-D) is similarly effective in patients with and without T2DM. There has been uncertainty about the safety of older T2DM drugs such as insulin and sulphonylureas in patients with T2DM and HF but there are no RCTs to allow firm conclusions. In patients with T2DM without HF, some drugs have been shown to increase the risk of HF hospitalizations (i.e. Rosiglitazone, pioglitazone and saxagliptin) and, consequently, these medications are contraindicated in patients T2DM with prior HF or at risk of HF. Large clinical trials investigating CV safety of newer antidiabetic drugs in patients with CV disease or at high CV risk have demonstrated that GLP-1 receptor agonists and a DPP4 inhibitor, Sitagliptin, have a neutral effect on the risk of HF hospitalizations. In addition, SGLT2 inhibitors, empagliflozin and canagliflozin demonstrated a significant reduction in the risk of HF hospitalizations in patients with T2DM. SGLT2 inhibitors are currently being investigated as a potential addition to the optimal medical treatment of HF, not only in patients with, but also in those without T2DM.

Abbreviations:

T2DM: Type 2 diabetes mellitus.

HFrEF: Heart failure with reduced ejection fraction.

HFpEF: Heart failure with preserved ejection fraction.

CV: Cardiovascular.

HF: Heart failure.

CAD: Coronary artery disease.

ACE: Angiotensin converting enzyme inhibitors.

SCD: Sudden cardiac death.

ICD: Implantable cardioverter defibrillators.

CRT: Cardiac resynchronization therapy.

Conflicts of Interest:

There authors have no Conflicts of interest to declare.

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