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Type-2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology

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Abstract

The coexistence of type 2 diabetes mellitus (T2DM) and heart failure (HF), either with reduced (HFrEF) or preserved ejection fraction (HFpEF), is frequent (30-40% of patients) and associated with a higher risk of HF hospitalization, 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. Subanalyses of trials addressing HF treatment in the general population have shown that all HF therapies are similarly effective regardless of 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 (GLP1) 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. Thiazolidinediones (pioglitazone and rosiglitazone) are contraindicated in patients with (or at risk of) HF. In recent trials, sodium glucose cotransporter-2 (SGLT2) inhibitors, empagliflozin and canagliflozin, have both shown a significant reduction in HF hospitalization in patients with established CV disease or at risk of CV disease. Several ongoing trials should provide an insight into the effectiveness of SGLT2 inhibitors in patients with HFrEF and HFpEF in the absence of T2DM.

Key words: heart failure, type 2 diabetes, heart failure hospitalization, heart failure treatment, glucose lowering agents

Introduction

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 (1). Conversely, HFrEF is an independent predictor of fatal and non-fatal clinical outcomes in patients with T2DM (2, 3). 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 (4). This position paper provides advice and education pertinent to the clinical management of patients with T2DM and HF. The document 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.

Epidemiology

Prevalence of T2DM and HF 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 (5), albeit diagnostic criteria have changed over that period (6, 7). Contemporary data suggest a stable overall HF prevalence of 11.8% (range 4.7-13.3%) in the general population (8) .

The prevalence of HF in patients with T2DM

In the Reykjavik study in the general population, the prevalence of HF in people with T2DM was 12% (9). In this study, HF was more common in patients with T2DM >70 years (i.e. 16% and 22% of men and women, respectively). In the Kaiser Permanente population, patients with T2DM <75 years had an approximately 3-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% (**Table 1**).

The prevalence of T2DM in patients with HF

In the general population, HF is associated with a higher prevalence of T2DM compared to patients without HF (**Table 2**), but marked regional differences have been observed both in Europe and in rest of the world. In studies conducted in Iceland (9) and Italy (11), T2DM prevalence was 4 and 3 times higher, respectively, whereas in Italy, T2DM prevalence was almost doubled in HF subjects (**Table 2**). Approximately 25% of patients with HF in England (12) and Denmark (13) 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%) (14). The reasons for the wide regional variation in T2DM prevalence in HF patients warrants 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) (**Table 3**). 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 is around 40-45% (15-18), and a slight increase in the prevalence was reported in the North America over time (15, 18). In the Swedish HF Registry, Swed-HF, (68% from hospitals and 32% from primary care) T2DM was more prevalent in HF patients with CAD compared to those without (30% versus 19%, respectively) (19).

The incidence of new T2DM in patients with HF

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 Kaiser

Permanente study, the incidence of T2DM was significantly higher in patients with than without HF (i.e. 13.6/1000 versus 9.2/1000) over a 5 year follow-up (10). In a Danish nation-wide cohort study, 8% of HF patients developed T2DM over 3 years, and the severity of HF was associated with a stepwise increased risk of developing T2DM (20). Similar incidence of T2DM was reported in clinical trials of HF patients, as demonstrated by the CHARM program, in which 7.8% of patients developed T2DM over 2.8 years (21, 22). In the EMPHASIS trial including HFrEF patients, the incidence of T2DM was 3.7% over a median follow-up of 21 months (23). Notably, HF treatment with angiotensin converting enzyme (ACE) inhibitors was shown to lower the incidence of T2DM in HFrEF patients; in a substudy of the SOLVD trial, 6% of patients in the enalapril arm developed T2DM over a mean follow-up of 2.9 years as opposed to 22% in the placebo arm (24). Registry data corroborate that the use of renin-angiotensin system inhibitors is associated with attenuated risk for T2DM in HF patients receiving loop diuretics (20). Clinical trials also demonstrated that the severity of HF, as indicated by a higher New York Heart Association (NYHA) class, increases the likelihood of developing T2DM (11, 25).

The incidence of HF in patients with T2DM

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 (26). T2DM is an independent risk factor for the development of HF (10). In a retrospective cohort followed for up to 72 months, patients with T2DM were more likely to develop HF than patients without T2DM (incidence rate 30.9 versus 12.4/1,000 person-years, rate ratio 2.5) (27). In elderly patients with T2DM, the incidence of HF was 2-fold higher compared to patients without T2DM (121 vs. 62 cases/1000 patient-years) (28). In UKPDS 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 HbA1c <6% and HbA1c >10%,

respectively (29). Similarly, in the observational studies, NHANES (30) and ARIC (31), the incidence of HF in patients with T2DM was higher than in those without T2DM, with the corresponding hazard ratios (HRs) of 1.85 and 3.54. Indeed, 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 (31). 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 (32, 33). Patients with pre-diabetes in the ARIC study also had more HF than those without pre-diabetes (34).

T2DM, clinical status and outcomes in patients with HF

Clinical presentation, quality of life and functional status of patients with T2DM and HF

Patients with T2DM and both HFrEF (1, 35-37) and HFpEF (1) have worse NYHA functional class and more HF-related symptoms and signs than patients without T2DM, despite having similar ejection fraction (36, 37). In the SOLVD-Prevention trial of patients with asymptomatic left ventricular systolic dysfunction (LVSD), 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 (38).

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 (36, 39). Patients with T2DM and HFrEF also have shorter 6-minute walk distances and decreased peak oxygen uptake in comparison to non-diabetics (21, 36, 40).

T2DM and mortality in patients with HF

In all population-based studies, T2DM was associated with increased all-cause mortality in HF patients, albeit substantial regional differences were reported across Europe, and no differentiation between HFrEF and HFpEF was performed (**Table 4**).

In Sweden, there was a moderately higher risk (HR, 1.60) (19) and in the Netherlands a significantly higher risk of death (HR, 3.19) (41) attributed to T2DM. Additionally, in the Rotterdam study, T2DM was associated with an excess risk for CV death (HR, 3.25) that was similar to the risk of all-cause mortality (41). Likewise, all studies of the effect of T2DM on mortality in HF outpatients have found a higher mortality risk attributable to T2DM (**Table 4**).

Concerning patients hospitalized for HF, data on the association between T2DM and in-hospital mortality are divergent. In the OPTIMIZE, ADHERE and Get With the Guidelines-HF registries in the United States, T2DM was not associated with a higher in-hospital mortality (42-45). Conversely, in the ALARM registry (six European countries, Mexico and Australia), and in the ESC-HF-Long Term Registry, T2DM was independently associated with a higher risk of in-hospital mortality (17, 46). There is a suggestion from some cohorts (42, 47) that short term mortality in HF patients post discharge may be similar or slightly lower in those with T2DM. However, with longer-term follow-up, an association between T2DM and worse outcomes in HF patients becomes evident. For example, in the EVEREST trial in which patients were followed for 9.9 months after a HF hospitalization, T2DM conferred a slightly higher mortality (48). Also, in patients from Scotland, T2DM increased mid-to-long term mortality following hospitalization for HF (47). Likewise, in the ESC-HF Long Term Registry, the presence of T2DM was independently associated with increased 1-year all-cause mortality (17, 49).

Clinical trial results are somewhat conflicting regarding the risk of all-cause and CV mortality attributed to T2DM in HF patients, but most clinical trials reported an increased risk of death in patients with concurrent T2DM and HF. In HFrEF, 7 out of 11 trials demonstrated an association between T2DM and increased all-cause mortality, with the reported HRs between 1.3 and 2.0 (mostly around 1.5) (**Table 5**). Also 3 HFrEF trials reported increased CV death, with HRs between 1.5 and 1.8 (1, 50, 51). Concerning HFpEF, all trials reported increased all-cause mortality (HRs, 1.5

to 1.8) and 2 out of 4 trials also reported an increased risk of CV mortality in patients with T2DM compared to patients without T2DM, with HRs 1.6 to 1.9 (**Table 5**). In the CHARM trial, T2DM was an independent risk factor for both all-cause mortality and CV mortality even after adjustment for 32 co-variates (1). Additionally, in the same study, T2DM had a greater association with higher all-cause and CV mortality in patients with HFpEF than HFrEF (1).

A recent meta-analysis of 31 registries and 12 clinical trials with 381,725 patients with acute and chronic HF, with a median follow-up of 3 years confirms that T2DM is independently associated with a higher risk of all-cause death (random-effects HR, 1.28), CV death (HR, 1.34), hospitalization (HR, 1.35), and the combined end point of all-cause death or hospitalization (HR, 1.41), and the observed long term risk appears greater in patients with chronic than in those with acute HF (52).

T2DM and causes of death in patients with HF

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, death due to MI and death due to stroke) (1). The PARADIGM study also reported that patients with T2DM and HFrEF were more likely to die of CV as well as all-cause mortality compared with patients without T2DM (36). In the BEST trial, T2DM was an independent risk factor for death from pump failure (53).

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, nonhepatic digestive diseases, external causes, and chronic obstructive pulmonary disease (54). The study found that a 50-year-old with T2DM died, on average, 6 years earlier than an individual without T2DM, with about 40% of the difference in survival attributable to excess nonvascular deaths (54).

Is the higher risk of T2DM only seen in HF secondary to CAD?

Whether or not the increased risk of mortality with T2DM in HF patients is seen in both those of ischemic and non-ischemic etiology is uncertain. The majority of the available data suggests that T2DM is associated with higher risk of mortality in both patients of ischemic and non-ischemic aetiology (**Table 6**). In a population-based Danish study, which followed patients for 6.8 years, patients with T2DM and HF had higher mortality whether or not they had CAD (55). The higher risk appeared early and persisted throughout follow-up. In the CHARM trial, patients with both HFrEF and HFpEF had higher mortality attributed to T2DM whether or not they had CAD (1). In the DIAMOND trial, T2DM was associated with a higher risk of mortality in both ischemic and non-ischemic HF (56). These consistent findings conflict with 2 smaller population-based studies in the United States (57) and France (58) and one Spanish single-center study (59) of patients hospitalized with HF which suggested that DM was only associated with higher mortality in those with non-ischemic etiology. In 3 early clinical trials (SOLVD (60), BEST (53), and DIG (61)) the risk appeared to be confined to those with an ischemic etiology.

Is the higher risk of mortality with T2DM and HF seen in both women and men?

An early report from the Framingham study reported that the mortality risk related to T2DM was confined to women and not to men (62). In 2 population-based studies from Scotland and Sweden, the increased mortality risk of T2DM was seen in both women and men, but the effect was slightly greater in women (47, 55). Likewise, in the recent ESC-HF Long Term Registry and in the CHARM trial, T2DM was a risk factor for mortality in both men and women (1, 49).

Does HbA1c predict mortality in patients with HF and T2DM?

In the CHARM trial, high HbA1c was associated with increased all-cause and CV mortality in patients with T2DM and both HFrEF and HFpEF (63). A 1% increase in HbA1c was associated with an increased HR of 1.1 for CV mortality (63). In patients from a US study of HF clinics, a U-shaped relationship with regards to increased all-

cause mortality was found (38). Patients with either very low or very high HbA1c were at greatest risk. A similar U-shaped curve was found in a single-center study from Scotland (64). In one single center observational study of 123 young patients with advanced HF and T2DM, patients with a HbA1c of <7% had higher rates of all-cause mortality (65). In the GISSI-HF study, including 6935 chronic HF patients, the presence of T2DM and higher HbA1c levels were independent predictors of all-cause mortality (HRs, 1.43 and 1.21, respectively) and the composite outcome of mortality and CV hospitalization (HRs, 1.21 and 1.14) (66).

In summary, high HbA1c levels in T2DM and HF are consistently associated with higher mortality. Conversely, low HbA1c levels can be associated with good outcomes (at least in a clinical trial cohort), but can be associated with worse outcomes (in population-based studies and those with very advanced HF).

Pre-diabetes and undiagnosed T2DM and risk of mortality in HF

In the PARADIGM-HF trial, patients with pre-diabetes were at increased risk of mortality (36). 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. In the CHARM, pre-diabetes and undiagnosed T2DM were both associated with greater rates of HF hospitalization, CV and all-cause mortality than those without T2DM (67). However, not all studies have reported an increased mortality risk with pre-diabetes. In a study of 970 non-diabetic patients with HF, an increased 1-year mortality risk was found only in patients with HbA1c >6.7% and reduced left ventricular ejection fraction (LVEF) ≤45%, but not in those with HFpEF (68). Also, in the GISSI-HF study of unselected HF patients, pre-diabetes was not an independent predictor of increased mortality (66). The reasons behind these discrepancies might be attributed to differences in patient characteristics and warrant further assessment.

T2DM and risk for HF hospitalization

Several clinical trials documented that patients with T2DM and HFrEF were more likely than patients without T2DM to be hospitalized for HF (1, 36, 37, 53, 69). In the CHARM trial, rates of hospitalization for HF in patients with T2DM were greater for those with HFpEF than HFrEF and patients with HFpEF and T2DM were almost 2.5 times more likely to be hospitalized for HF than those without T2DM (1). In I-PRESERVE, patients with T2DM and HFpEF were also more likely to be hospitalized with HF (39).

Readmission after a hospitalization for HF

Registry data indicate that patients with T2DM had more all-cause re-hospitalizations than those without T2DM (42, 70, 71). In a population-based study in Scotland, T2DM was a predictor of readmission for HF (with the increased risk greatest in younger women) (47). In the ESC-HF Long Term Registry, T2DM was independently associated with re-hospitalizations for HF (17). Likewise, in the EVEREST trial, T2DM was associated with greater rates of HF re-hospitalization (HR, 1.19) (48).

In addition, as demonstrate by the OPTIMIZE and Get With The Guidelines Registries in the United States, patients with HF and T2DM experience slightly longer hospitalizations than patients without T2DM (42-44).

T2DM, myocardial infarction and stroke in patients with HF

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) (1).

Risk for HF hospitalization in patients with T2DM without a previous history of HF

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 (70). In a large meta-analysis of patients with T2DM but without HF, predictors of incident HF include insulin use, HbA1c and fasting glucose (72).

Mortality in T2DM patients with HF

In the CV outcomes trials of new therapies for T2DM, the development of HF is associated with markedly higher mortality (especially in RECORD (73) and SAVOR-TIMI (74)). Patients with T2DM who developed HF had a 10 to 12 times greater mortality than those who did not develop HF (3)(75). In addition, they are also at a 2.45-fold greater risk of CV death compared with patients with T2DM but without HF (76).

Unrecognized HF in patients with T2DM and unrecognized T2DM in patients with HF

Observational evidence indicates that a 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 (77, 78). On the other hand, pre-diabetes and undiagnosed T2DM are common in patients with HF. In the PARADIGM trial, 13% of patients with HFrEF had undiagnosed T2DM and 25% had pre-diabetes (36). Likewise, 11% of "non-T2DM" patients with HFrEF in the RESOLVD trial had undiagnosed T2DM (79). In the CHARM study, undiagnosed T2DM was common in both HFrEF and HFpEF (67). In the ESC-HF-Long Term Registry, even higher proportion of HF patients (19.1%) had undiagnosed T2DM (49).

Considering prognostic implications of concurrent T2DM and HF, these findings stress the importance of developing screening strategies for unrecognized HF among T2DM patients and *vice versa*. Since evidence is sparse of strategies for HF screening (78), in 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) (80). Such a strategy may be used to prevent complications and possibly improve outcomes, particularly in subjects with HFrEF (81). Conversely, since undiagnosed T2DM is common among patients with HF, it is prudent to screen

patients without known T2DM in accordance with current recommendations using the 8-hour fasting plasma glucose, 2-hour glucose tolerance test or HbA1c levels (equally appropriate) (82).

Pathophysiological aspects of myocardial dysfunction in T2DM

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 (4). 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 (83). Their detrimental effect is associated with numerous metabolic abnormalities such as advanced glycosylation end products (AGEs) deposition, lipotoxicity and microvascular rarefication (4). Harmful interrelations between these pathophysiologic mechanisms may exert a potentiating effect, leading to several maladaptive responses and resulting in myocyte alteration (4). Insulin resistance leads to increased free fatty acids release and is linked with HF-related neuroendocrine dysregulation (84). It is also an important etiological factor in the development of left ventricular (LV) hypertrophy (85), as confirmed in the Framingham study, where LV mass was significantly higher in female patients with T2DM compared to patients without T2DM (86). 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 (87-89). Also, it causes activation of reactive oxygen species and the deposition of AGEs in both endothelial and smooth muscle cells, which predisposes to concentric LV remodeling and raises LV diastolic stiffness (87, 88). 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 LV diastolic dysfunction (LVDD) (90).

Diabetic cardiomyopathy

In 1954, Lundbæk was the first to propose the existence of a specific diabetic heart muscle disease without involvement of CAD or hypertension (91). Two decades later, Rubler described diabetic-related post-mortem findings in 4 patients with T2DM, glomerulosclerosis and HFrEF with normal epicardial coronary arteries (92). There is no definition of diabetic cardiomyopathy, which makes studies of epidemiology, pathophysiology, natural history and associated clinical outcomes challenging. The most commonly accepted definition refers to a myocardial dysfunction which occurs in the absence of all other CV disease (82, 93).

Phenotypes of T2DM-related cardiomyopathy

Left ventricular diastolic dysfunction and HFpEF in T2DM

LVDD 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 (94, 95). Furthermore, the degree of glucose dysregulation correlates with LVDD severity (96), and with increased risk of incident HF and CV mortality in T2DM (97-99). 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 (100).

HFpEF is usually associated with mild T2DM complications in the early stages of T2DM, whilst HFrEF is associated with more severe T2DM complications (101). This suggests that severity and duration of hyperglycemia are important for the development of LV dysfunction.

HFrEF in T2DM

The major cause of HFrEF in T2DM is CAD. T2DM is associated with a 2-fold higher risk of CAD and ischemic stroke, and a 2 to 4-fold higher CAD- and stroke-related mortality (102-104). CAD in T2DM is usually diffuse, multi-vessel and may lead to silent MI.

Treatment of HF in patients with T2DM

There are no specific constraints to HF treatment in T2DM patients as recommended by the ESC/HFA 2016 Guidelines for the management of HF (78). 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 subanalyses of mixed populations. However, several HF drugs may exert metabolic effects that should be taken into account in T2DM patients.

Pharmacological therapy

ACE-Inhibitors

The ESC/EASD Guidelines on diabetes, pre-diabetes, and CV diseases recommend ACE-inhibitors in patients with HFrEF and T2DM, as they have been shown to improve symptoms and reduce morbidity and mortality (78). The effectiveness of ACE-inhibitors in patients with both T2DM and HF, or post-MI LVSD was examined in a large meta-analysis of seven RCTs (105). For the end-point of all-cause mortality, ACE-inhibitors had a similar treatment benefit in subjects with and without T2DM (HR, 0.84 and 0.85, respectively).

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 (106, 107). 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 (107). The occurrence of adverse effects with high-dose lisinopril was similar in those with and without T2DM with respect to hypotension/dizziness (35% versus 32%, respectively), renal dysfunction/hyperkalemia (29% versus 22%) and cough (12% versus 10%) (107).

Angiotensin Receptor Blockers

In the CHARM trial, a significant reduction of CV death, HF hospitalization and all-cause mortality was achieved with candesartan in patients with HF and HFrEF, irrespectively of T2DM (1). Also, in the Val-HeFT, valsartan treatment led to a significant relative risk reduction in the co-primary composite end-point (death or HF morbidity - mainly HF hospitalization) regardless of T2DM (108). A subsequent trial, HEAAL (109), 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. The treatment effect was again not different in the subgroup of patients with T2DM compared to those without T2DM (HR, 0.96; interaction p=0.35).

There is little information about the tolerability of ARBs in T2DM. In the overall CHARM program, patients with T2DM had double the risk of developing hyperkalemia on candesartan compared to those without T2DM (110).

T2DM confers a higher risk of diabetic nephropathy and chronic kidney disease (111). Specifically, diabetic nephropathy is characterized by increased renal sodium retention (112, 113), and a higher risk of hyperkalemia (114). This caveat deserves consideration 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 or escalating the dose of ACE-inhibitors or ARBs.

β-blockers

Subgroup analyses of large HF trials show that beta-blockers reduce mortality and hospitalization and improve symptoms in moderate to severe HF, irrespectively of T2DM (115)(69, 116). Beta-blockers recommended in HF and T2DM include metoprolol succinate (MERIT-HF) (69), bisoprolol (CIBIS II) (115) and carvedilol (COPERNICUS and COMET) (117, 118). The MERIT-HF reported similar efficacy and safety of metoprolol succinate in patients with and without T2DM (69). 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. In a meta-analysis of 6 trials, beta-blocker therapy reduced all-cause mortality in patients with T2DM (HR, 0.84) similarly to those without T2DM (HR, 0.72) (119). An analysis of 3 trials (CIBIS II, MERIT-HF and COPERNICUS) reported a relative risk reduction for mortality of 0.77 in patients with T2DM and 0.65 in patients without T2DM (105). A third meta-analysis that focused on 7 trials using carvedilol, including a post-MI trial, revealed a similar, significant reduction in the risk for mortality with carvedilol in patients with and without T2DM (28% and 37%, respectively, interaction p=0.25) (120).

Hypoglycemia is a concern in patients with T2DM treated with insulin or sulfonylureas. Theoretically, β-blockers could alter awareness of hypoglycemia by decreasing palpitations and tremor and prolong recovery from hypoglycemia by blocking β_2 receptors, which partly control glucose production in the liver. However, among patients with T2DM in MERIT-HF only three (0.6%) in the placebo group and four (0.8%) in the metoprolol succinate group had an adverse event related to hypoglycaemia (in each case in patients taking insulin) (69).

In summary, β-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 β-blockers in diabetic patients far outweigh the theoretical risks related to hypoglycaemia and minor changes in HbA1c and serum lipids. These benefits strongly support β-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 T2DM and non-T2DM patients with HFrEF (121, 122). Importantly, eplerenone seems to have no effect on new-onset T2DM in patients with HF, suggesting a neutral metabolic profile (123). 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 (124).

Sacubitril/valsartan

In the PARADIGM-HF trial, sacubitril/valsartan was superior to ACE-inhibitor, enalapril, in reducing the risks of death and HF hospitalization (primary endpoint) in patients with HFrEF (50). 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 (HR, 0.83 and 0.77; respectively, interaction p value=0.40) (36). 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 (125).

Nitrates and hydralazine

The A-HEFT 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 (126). A very large proportion (41%) of patients in the study had T2DM. The treatment effect on mortality was similar in patients with and without T2DM (HRs, 0.56 and 0.59, respectively).

Ivabradine

In a large trial involving 6558 patients with HF (30% with T2DM), ivabradine demonstrated a significant reduction in composite end-point of CV death or HF hospitalization, with no difference between T2DM and non-T2DM patients (HRs, 0.81 and 0.83, respectively) (127).

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 glycaemic control.

Devices and surgery

Implantable cardioverter defibrillators

In addition to 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). In the CHARM trial, patients with T2DM experienced a significantly higher rate of SCD compared to patients without T2DM (40 versus 25.9 events/1000 patient years of follow-up), and the increased risk of SCD was observed irrespective of HF phenotype (i.e. HFrEF and HFpEF) (1). Observational data also demonstrate an increased risk of SCD in the presence of T2DM in HF of both ischemic and non-

ischemic etiology (128). 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.

The SCD-HeFT trial included patients with both non-ischemic and ischemic HFrEF who were randomized to placebo, amiodarone, or an ICD (129). The study included approximately 30% of patients with T2DM in every treatment arm. ICD treatment led to a significant relative risk reduction in death and in subgroup analysis, there were no interactions with T2DM. The HRs for the primary endpoint of all-cause mortality in ICD group were 0.95 for patients with T2DM and 0.67 for those without T2DM and in amiodarone group 1.2 for patients with T2DM, and for 1.0 for those without T2DM. In the DANISH trial, patients with non-ischaemic cardiomyopathies were randomized to ICD and optimal medical therapy or optimal medical therapy alone (130). Approximately 19% of patients had T2DM. In prespecified subgroup analysis, there was no significant difference in treatment effect in patients with and without T2DM (HRs, 0.92 and 0.85, respectively, interaction p value=0.60).

Cardiac resynchronization therapy

The effectiveness of CRT to reduce the risk of all-cause death and HF hospitalization was evaluated in 2 clinical trials (the COMPANION (131) and CARE-HF (132)) 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. Additionally, two trials (MADIT-CRT (133) and RAFT (134)), randomized patients with mild to moderate HF symptoms to optimal medical therapy plus ICD, or optimal medical therapy plus CRT-D, for the primary endpoint (death or HF hospitalization). 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 (135, 136).

In MADIT-CRT, CRT-D treatment, compared with optimal medical therapy plus ICD, led to a similar reduction in the risk of all-cause death or HF hospitalization in patients with and without T2DM (adjusted HRs 0.56 and 0.67, respectively) (133, 137). Also, subgroup analysis of the RAFT trial showed that the benefit of CRT-D was similar in patients with and without T2DM (134). Patients with T2DM did not experience a higher rate of complications related to device implantation, including infection (134). There were similar CRT-related improvements in LV volumes and ejection fraction in those with and without T2DM.

Coronary artery bypass grafting

CAD 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 (138, 139).

The STICH trial addressed the broader role of surgical revascularization in patients with HFrEF and less severe CAD (140). Patients suitable for surgery were randomized to coronary artery bypass graft (CABG) plus medical therapy or medical therapy alone. In the subanalysis of the STICH trial, there was no significant difference between patients with (40%) and without T2DM with respect to the primary outcome of all-cause mortality (141). This trial therefore extends the indication for CABG to 'STICH-like' patients with two- or three vessel CAD, including a left anterior descending stenosis, who are otherwise suitable for surgery. The benefits are similar whether or not a patient has T2DM.

Exercise prescription

Recently, a single large trial, the HF-ACTION (35), investigated the effects of exercise training in patients with mild to moderately severe HF symptoms. In an adjusted analysis, exercise training led to an 11% (p=0.03) 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.

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 of prednisolone-based immunosuppression. T2DM was an independent risk factor for reduced 10-year survival in a large registry of 22,385 transplant patients (142). However, with modern immunosuppression regimens allowing more rapid tapering of steroid doses and steroid-free immunosuppression, cardiac transplantation in T2DM (in the absence of major T2DM complications) should be considered on a case-by-case basis.

T2DM drugs and the risk of HF

Drugs that increase HF hospitalizations

Over the last 15 years there has been concern that some of T2DM drugs might increase the risk for HF (**Table 7**). Drugs that are now known to increase the risk for HF are thiazolidinediones (TZDs) and a dipeptidyl peptidase-4 (DPP4) inhibitor, saxagliptin (74, 143). In the RECORD (73) and the PROACTIVE trials (144), patients randomized to TZDs, rosiglitazone and pioglitazone, respectively, had more HF events than those on placebo. In the SAVOR-TIMI 33 trial (saxagliptin versus placebo), saxagliptin significantly increased the risk for HF hospitalizations (HR, 1.27, P=0.007) (74). 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 (NT-proBNP) (74). In both RECORD and SAVOR-TIMI trials, patients who developed HF had a high rate of subsequent death. 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 HF (**Table 8**). In the EXAMINE trial of alogliptin versus placebo in patients who had had an acute coronary syndrome, there was not a statistically significant increase in the risk of HF hospitalizations in patients randomised to alogliptin (145, 146). Likewise, sitagliptin in the TECOS trial had no signal of excess rates of HF (147, 148). Two ongoing trials, CAROLINA (CV Outcome Study of Linagliptin Versus Glimepiride in Patients With T2DM; NCT01243424), and CARMELINA (linagliptin versus placebo in patients with T2DM at high vascular risk; NCT01897532), will allow further clarification on the role DPP4 inhibitors in patients with T2DM and HF.

T2DM drugs that might increase the risk for HF

Over many years there has been suspicion that insulin (which 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 (2). There have been similar concerns with sulphonylureas which, as insulin secretagogues, have also associated with higher death rates than metformin (2). These studies, although large, are non-randomized and therefore inconclusive. In the only randomized trial of insulin versus placebo (ORIGIN - 12,537 people with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or T2DM [i.e. not in patients with HF]), insulin was not associated with higher rates of HF hospitalization than placebo (149). Remarkably, despite the use of insulin and sulphonylureas for decades there are no other placebo-controlled randomized trials.

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.

T2DM drugs that might be safe in HF

It has been proposed that metformin might be safe and efficacious in patients with T2DM and HF. This was based on large observational studies where metformin was associated with lower mortality and HF hospitalization rates than other T2DM drugs

(primarily insulin and sulphonylureas) (2). There are no randomized trials of metformin in patients with T2DM and HF. Whether or not metformin is efficacious or safe is inconclusive. Previous concerns that metformin may cause metabolic acidosis are no longer justified (2). Accordingly, metformin could be recommended as the 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 (GLP1) 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 (**Table 8**) (150-153). In these trials, GLP1 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 (versus placebo) in patients with insulin resistance and CAD (154). Bromocriptine has not been studied with respect to its effect on HF outcomes.

Prevention of HF by T2DM drugs

A significant breakthrough in contemporary cardiology was the finding that some T2DM drugs are associated with a lower risk of HF hospitalization in patients with CV disease or at high risk of CV disease (**Table 8**). Two large RTCs 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 (155, 156). The primary outcome in both trials was the 3-point major adverse CV event (i.e. CV death, nonfatal MI or nonfatal stroke) and HF hospitalization was a secondary outcome. In the EMPA-REG OUTCOME trial (n=7020), including patients with T2DM, established CV disease and eGFR >30 mL/min/1.73 m^2, there was a major reduction in HF hospitalization (HR, 0.65) with empagliflozin compared with placebo (155). The observed beneficial effect of empagliflozin became evident early (i.e. 2-3 months of treatment) and was observed across a range of prespecified subgroups, including patients with (10%) and without investigator-reported HF at baseline, that had a similar reduction in HF hospitalizations with empagliflozin

compared with placebo. No echocardiograms or natriuretic peptide measurements are available from this trial, so the detail of the beneficial effect on HF hospitalization is not available. Patients hospitalized for HF during the study had a high mortality, which was lower in patients receiving empagliflozin than placebo (13.5% versus 24.2%, respectively) (155). In the CANVAS trial, patients with T2DM (n=10,143) either with established CV disease or at high risk of CV disease, randomized to canagliflozin or placebo had a significantly lower risk of HF hospitalization (HR, 0.67) (156, 157). Empagliflozin in EMPA-REG Outcome, but not canagliflozin in CANVAS, reduced all-cause and CV mortality as well as HF hospitalization. In the EMPA-REG trial, the only major adverse event was an increased risk of genital tract infections, which were treatable, and infrequently recurred (155). In the CANVAS trial, treatment with canagliflozin was associated with a significantly higher risk of lower-limb amputations (6.3 vs. 3.4 per 1000 patient-years; HR, 1.97) and possibly a higher risk of fractures compared with placebo (157). Large RCTs of other new T2DM drugs have not shown a reduction in incident HF (**Table 8**).

Treatment of HF with T2DM drugs

Randomized clinical trials with SGLT2 inhibitors

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 (i.e. T2DM is not a mandatory inclusion criteria). Two trials will assess safety and efficacy of empagliflozin versus placebo on top of guideline-based medical therapy for the reduction in primary outcome (CV death or HF hospitalization) both in patients with HFrEF (EMPEROR-Reduced, NCT03057977) and HFpEF (EMPEROR-Preserved, NCT03057951) (**Table 9**). Among secondary outcomes, the two trials will assess all-cause mortality, and renal effects of empagliflozin versus placebo in patients with HF. The third trial, Dapa-HF (NCT03036124), will assess safety and efficacy of

dapagliflozin versus placebo for the reduction in CV death or HF hospitalization (or urgent HF visit) in patients with HFrEF. Secondary outcomes will include all-cause mortality and effects on renal function. The results of these trials will shed more light on the beneficial CV and renal effects of SGLT2 inhibitors in HF patients, including those without T2DM.

In addition, a number of ongoing smaller randomized trials are assessing the effect of SGLT2 inhibitors on CV outcomes, including various aspects of HF in patients with and without T2DM, as summarized in **Table 9**.

Randomized clinical trials with GLP1 receptor agonists

In the LIVE trial, in patients with stable HFrEF, with and without T2DM, there were no significant changes in LVEF between patients randomized on liraglutide or placebo (158). However, there was a significant increase in heart rate ($P<0.0001$) and more serious cardiac adverse events with liraglutide ($P=0.04$). In a placebo-controlled FIGHT trial, of patients with HFrEF, with and without T2DM (41%), liraglutide was not associated with an improvement in a composite primary end point of death, rehospitalization and NT-proBNP change (159). Prespecified subgroup analyses in patients with T2DM did not reveal any significant between-group differences. A small randomized, placebo-controlled trial of albiglutide in HFrEF showed no effect on LV function and 6-minute walk distance (160). These observations have raised some concern regarding the safety of liraglutide in HFrEF patients that warrant further research.

Conclusions

T2DM and HF are both common and frequently coexist. 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 etiology 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 sulphonlyureas in patients with T2DM and HF but there are no randomized controlled trials 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 saxaglitpin) 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 GLP1 receptor agonists and a DPP4 inhibitor, sitagliptin, have a neutral effect on the risk of HF hospitalisations. 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 beeing investigated as a potential addition to the optimal medical treatment of HF, not only in patients with, but also in those without T2DM.

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Tables

Table 1. Prevalence of HF in selected trials of T2DM drugs

Trial	Prevalence of HF at baseline
Glucose-lowering trials	
UKPDS (161)	NR (severe concurrent illness excluded)
ADVANCE (162, 163)	NR
ACCORD (164)	4.3%
VADT (165)	NR
DPP4 inhibitors trials	
SAVOR-TIMI 53 (74, 143)	13%
TECOS (147)	18%
EXAMINE (145)	28%
SGLT2 inhibitors trials	
EMPA-REG OUTCOME (155)	10%
CANVAS (157)	14-15%
GLP1 receptor agonists trials	

LEADER (152)	14%
ELIXA (153)	22%
EXSCEL (150)	16%

DPP4 - dipeptidyl peptidase-4; SGLT2 - sodium glucose cotransporter type-2; GLP1 - glucagon like peptide-1

Table 2. The prevalence of T2DM in patients with HF in the general population

Study	Year of publication	Age range (years)	Prevalence of T2DM in HF	Prevalence of T2DM without HF
England (12)	2001	>45	24%	3%
Rotterdam (41)	2001	55-94	18%	10%
Italy (11)	1997	>65	30%	13%
Reykavik (9)	2005	33-84	12%	3%
Copenhagen (13)	2005	mean age 69	25%	NA
USA, Olmsted county (57)	2006	mean age 77	20%	NA

NA - Not available (cohort of HF patients only)

Table 3. The prevalence of T2DM in selected trials of HF

Trial	Prevalence of T2DM
Trials of HFrEF	
PARADIGM (50)	35%
SHIFT (166)	30%
ECHO-CRT (51)	41%
HF-ACTION (35)	32%
SENIORS (167)	26%
SOLVD (168)	15%
MERIT-HF (69)	25%
CHARM-added (169)	29%
DIG-REF (170)	28%
Trials of HFpEF	

I-PRESERVE (39)	27%
PEP-CHF (171)	21%
DIG-PEF (172)	29%
CHARM-preserved (173)	28%
TOPCAT (174)	33%
Trials of acute HF	
EVEREST (48)	39%
TRUE-HF (175)	39%
ASCEND (176)	42.6%
RELAX-AHF (177)	47%

HFrEF - heart failure with reduced ejection fraction; HFpEF - heart failure with preserved ejection fraction.

Table 4. T2DM and mortality in HF in population studies, outpatient clinics and hospitalized patients

Country (region)	Year of publication	Type of study	Total number of patients	Number of patients with T2DM	Adjusted all-cause mortality risk of T2DM	Adjusted CV mortality risk of T2DM
Population-based studies						
ESC-HF-Long term Registry (17)	2017	Population-based	9428	3440	1.28 (1.07–1.54)	1.28 (0.99–1.66)
ESC-HF-Long term Registry (49)	2017	Population-based	6926	3422	1.77 (1.28–2.45)	NA
Swedish HF Registry (178)	2014	Population and specialist outpatient- based	36454	8809	1.60 (1.50-1.71)	NA
United States (Olmsted) (57)	2006	Population-based	665	128	1.48 (1.20-1.82)	NA
Netherlands (Rotterdam) (41)	2001	Population-based	5540	557	3.19 (1.80–5.65)	3·25 (1·53–6·93) (Sudden cardiac death 3·65 (1·28–10·4)
Outpatient clinics						
UK (128)	2013	Cardiology clinics	1091	280	2.08 (1.61 2.69)	NA

USA (179, 180)	2005	HF clinic	495	293	1.71 (1.16–2.51)	NA
Italy (181)	2003	Outpatient Registry 'BRING-UP'	2843	621	1.44 (1.16–1.78)	NA
Hospitalized patients						
Spain (71) (RICA Registry)	2014	Hospitalized multicenter registry	1082	490	1.54 (1.20–1.97)	NA
Spain INCAex (182)	2013	Hospitalized single center	1659	Not stated	1.35 (1.11 to 1.66)	NA
USA - MEDICARE (183)	1999	Hospitalization-based	170239	NA	Black: 1.11 (1.06–1.16) White: 1.22 (1.24–1.25)	NA

HR - Hazard Ratio; NA – not available

Table 5. T2DM and all-cause mortality in clinical trials with HF

Clinical trial	Year trial published	Treatment	Total number of patients	Number of patients with T2DM	Adjusted all-cause mortality risk of T2DM	Adjusted CV mortality risk of T2DM
HFrEF trials						
PARADIGM-HF (50)	2015	sacubitril/ valsartan	8399	2907	1.46 (1.26–1.70)	1.54 (1.30–1.83)
SHIFT (166)	2010	ivabradine	6505	1979	1.10 (0.96–1.25)	1.05 (0.91–1.20) Mortality due to HF 1.15 (0.88–1.49)
ECHO-CRT (51)	2013	CRT	809	328	2.08 (1.29, 3.36)	1.79 (1.06, 3.03) Mortality due to HF 2.45 (1.03, 5.78)
HF-ACTION (35)	2016	exercise	2331	748	0.97 (0.78, 1.2)	NA
SENIORS (167)	2010	nebivolol	2128	555	1.25 (0.99–1.58)	NA
SOLVD (184)	1996	enalapril	4223	647	1.29 (1.1–1.5)	NA
MERIT-HF (69)	2005	metoprolol	3991	985	1.08 (0.80-1.47)	NA

CHARM (1)	2008	candesartan	4576	1306	1.55	1.54
HFpEF trials						
DIG - preserved (172)	2010	digoxin	987		1.48 (1.10- 1.99)	NA
I-PRESERVE (185)	2017	irbesartan	4128	1134	1.59 (1.33–1.91)	1.59 (1.28–1.96)
CHARM (1, 186)	2008	candesartan	3023	857	1.84	1.93
TOPCAT (174)	2017	spironolactone	3385	1109	without microvascular complications: HR 1.51, 95% CI 1.14, 1.99; with microvascular complications: HR 1.35, 95% CI 1.04, 1.75	NA
Acute HF trials						
EVEREST (48, 187)	2013	tolvaptan	4133	1657	1.16 (1.00–1.34)	NA

HFrEF - heart failure with reduced ejection fraction; NA – not available; HFpEF - heart failure with preserved ejection fraction.

Table 6. T2DM and all-cause mortality in heart failure: ischemic versus non-ischemic etiology

Location	Year of publication	Type of study	Number of patients	Number of patients with T2DM	Adjusted all-cause mortality risk of T2DM ischemic vs. non-ischemic etiology	Adjusted CV mortality risk of T2DM ischemic vs. non- ischemic etiology
Population studies and HF clinics						
Denmark (55)	2009	Population-based cohort	2621	420	HF secondary to CAD: 1.45 (1.22–1.73) HF secondary to other etiologies 1.50 (1.22–1.84)	NA
Olmsted, USA (57)	2006	Population-based cohort study	665	128	HF secondary to CAD: 1.11 (0.81–1.51) HF secondary to other etiologies: 1.79 (1.33–2.41)	NA
France (58)	2004	HF clinic	1246	274	HF secondary to CAD 1.54 (1.13–2.09)	NA

					HF secondary to other etiologies: 0.65 (0.39–1.07)	
Clinical trials		**Drug**				
SOLVD (60, 184)	1996	enalapril	4223	647	HF secondary to CAD: 1.37 (1.21–1.55) HF secondary to other etiologies: 0.98(0.76–1.32)	NA
BEST (53)	2003	bucindolol	2708	964	HF secondary to CAD: 1.33 (1.12–1.58) HF secondary to other etiologies: 0.98 (0.74–1.30)	NA
DIG (188)	2004	digoxin	4277	NA	HF secondary to CAD: 1.43 (1.26–1.63) HF secondary to other etiologies: HR not stated	NA

CV - cardiovascular; CAD - coronary artery disease; NA – not available

Table 7. Summary of evidence for T2DM drugs in patients with prevalent HF

Class of drug	Evidence
SGLT-2 inhibitors (e.g. empagliflozin, canagliflozin)	No RCTs in HF Large RCTs in patients with HF with an without T2DM are underway
Metformin	No RCTs in HF In observational studies in HF metformin is associated with lower mortality rates than sulphonylureas or insulin (189). Benefit/ risk unknown
GLP-1 receptor antagonists (eg liraglutide, albiglutide)	No large RCTs liraglutide - 2 small RCTs reported no effect on i) LV function (158) ii) hierarchical composite of death/ HF hospitalization/ BNP change (159) Benefit/ risk unknown
Sulphonylureas	No RCTs in HF Data Equivocal. Some observational data suggest an increased mortality risk with sulphonylureas compared with metformin (189, 190).
Insulin	No RCTs in HF In observational studies in HF insulin was associated with higher mortality rates than metformin (189). Benefit/ risk unknown

DPP4 inhibitors	No RCTs in HF (saxagliptin contra-indicated in HF (74, 143)) Benefit/ risk unknown

SGLT2 - sodium glucose cotransporter type 2; RCT - randomized clinical trials; GLP1 - glucagon-like peptide 1; LV - left ventricular; DPP4 - dipeptidyl peptidase-4

Table 8. HF outcomes in published large cardiovascular outcome trials in patients withT2DM

Study	**SAVOR TIMI 53 (74, 143)**	**EXAMINE (145, 146)**	**TECOS (147, 148)**	
DPP4 inhibitor comparator	saxagliptin placebo	alogliptin placebo	sitagliptin placebo	
results	increase in HF hospitalization	no statistically significant increase in HF hospitalization	no effect on HF hospitalization	
Study	**ELIXA (150)**	**LEADER (152)**	**SUSTAIN 6 (151)**	**EXSCEL (150)**
GLP1 receptor agonists comparator	lixisenatide placebo	liraglutide placebo	semaglutide placebo	exenatide placebo
results	no effect on HF hospitalization	no effect on HF hospitalization	no effect on HF hospitalization	no effect on HF hospitalization
Study	**EMPA-REG OUTCOME (155)**	**CANVAS (157)**		
SGLT-2 inhibitor comparator	empaglifozin placebo	canagliflozin placebo		
results	reduced HF hospitalization	reduced HF hospitalization		

DPP4 - dipeptidyl peptidase-4; GLP1 - glucagon-like peptide 1; SGLT2 - sodium glucose cotransporter type 2

Table 9. Selected ongoing randomized clinical trials of SGLT2 inhibitors in patients with prevalent HF

Clinical trial	Brief description of the trial
EMPAGLIFLOZIN	
EMPEROR-Reduced (NCT03057977)	EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction. ▪ Study population: HFrEF, with and without T2DM. ▪ Estimated enrolment: n= 2850. ▪ Treatment: empagliflozin vs. placebo on top of guideline-based medical therapy. ▪ Primary outcome: CV death or HF hospitalisation (Time Frame: up to 38 months).
EMPEROR-Preserved (NCT03057951)	EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction ▪ Study population: HFpEF, with and without T2DM. ▪ Estimated enrolment: n= 4126. ▪ Treatment: empagliflozin vs. placebo on top of guideline-based medical therapy. ▪ Primary outcome: CV death or HF hospitalisation (Time Frame: up to 38 months).
Empire HF (NCT03198585)	Empagliflozin in HF Patients With Reduced Ejection Fraction ▪ Study population: HFrEF, with and without T2DM. ▪ Estimated enrolment: n=189. ▪ Treatment: empagliflozin vs. placebo on top of guideline-based medical therapy. ▪ Primary outcome: Change in plasma concentrations of NT-proBNP (Time Frame: 90 days) as a measure of treatment impact on HF
EMMY (NCT03087773)	Impact of EMpagliflozin on Cardiac Function and Biomarkers of Heart Failure in Patients With Acute MYocardial Infarction ▪ Study population: patients with acute MI with and without T2DM. ▪ Estimated enrolment: n=476. ▪ Treatment: empagliflozin vs. placebo. ▪ Primary outcome: change in plasma concentrations of NT-proBNP (Time Frame: 26 weeks) as a measure of treatment impact on HF
RECEDE-CHF	SGLT2 Inhibition in Combination With Diuretics in HF.

(NCT03226457)	▪ Study population: HFrEF with T2DM. ▪ Estimated enrolment: n=34. ▪ Treatment: empagliflozin vs. placebo. ▪ Primary outcome: the effect on the change in urine output from baseline (Time Frame: 6 weeks).
CANAGLIFLOZIN	
NCT02920918	Treatment of DM in patients with systolic HF ▪ Study population: HFrEF with T2DM. ▪ Estimated enrolment: n=88. ▪ Treatment: canagliflozin vs. sitagliptin. ▪ Primary outcome: change in aerobic exercise capacity and ventilator efficiency (Time Frame: baseline and 12 weeks)
DAPAGLIFLOZIN	
Dapa-HF (NCT03036124)	Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic HF. ▪ Study population: HFrEF with and without T2DM ▪ Estimated enrolment: n=4500. ▪ Treatment: dapagliflozin vs. placebo. ▪ Primary outcome: CV death or hospitalization for HF, or an urgent HF visit (Time Frame: from randomization up to approximately 3 years).
DEFINE-HF (NCT02653482)	Effects on symptoms and biomarkers of HF in patients HFrEF ▪ Study population: HFrEF with T2DM. ▪ Estimated enrolment: n=250. ▪ Treatment: dapagliflozin vs. placebo. ▪ Primary outcome: change in plasma concentrations of NT-proBNP (Time Frame: 12 weeks) as a measure of treatment impact on HF
PRESERVED-HF (NCT03030235)	Dapagliflozin Effect on Symptoms and Biomarkers in patients HFpEF ▪ Study population: HFpEF with T2DM or prediabetes. ▪ Estimated enrolment: n=320. ▪ Treatment: dapagliflozin vs. placebo. ▪ Primary outcome: change in plasma concentrations of NT-proBNP (Time Frame: Baseline to Week 6 and Week 12) as a

	measure of treatment impact on HF
REFORM (NCT02397421)	Safety and Effectiveness of SGLT-2 Inhibitors in Patients With Heart Failure and Diabetes ▪ Study population: HFrEF with T2DM. ▪ Estimated enrolment: n=56. ▪ Treatment: dapagliflozin vs. placebo. ▪ Primary outcome: changes in LV systolic and diastolic volumes in patients as determined by cardiac magnetic resonance imaging.

CV - cardiovascular, NT-proBNP - N-terminal pro B-type natriuretic; MI - myocardial infarction; SGLT2 - sodium glucose cotransporter type 2; LV - left ventricular

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