

DIABETES, CARDIOMYOPATHY, AND HEART FAILURE

Ahmet Afşin Oktay, MD, The Heart and Vascular Institute, Rush University Medical Center, Chicago, IL.
Ahmet_a_oktay@rush.edu
Timir K. Paul, MD, PhD, MPH, University of Tennessee Health Sciences Center at Nashville, Saint Thomas Heart Institute, Nashville, TN
Christian A. Koch, MD, PhD, University of Florida College of Medicine – Jacksonville, FL.
christian.koch65@gmail.com
Carl J. Lavie, MD, John Ochsner Heart and Vascular Institute, Ochsner Clinical School-The University of Queensland School of Medicine, New Orleans, LA. clavie@ochsner.org

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ABSTRACT

Heart failure (HF) is an underappreciated complication of diabetes. HF occurs in individuals with diabetes at higher rates, even in the absence of other HF risk factors such as coronary artery disease and hypertension. Comorbid ischemic heart disease and cardiovascular risk factors significantly contribute to the etiology of cardiomyopathy and HF in patients with diabetes. In addition, long-standing diabetes can independently cause subclinical alteration in cardiac structure and function, eventually leading to the development and progression of HF. A complex interplay between numerous mechanisms underlies the pathophysiologic links between diabetes and HF. Patients with concurrent diabetes and HF have impaired quality of life and a poor prognosis with a high risk of hospitalization and mortality. Despite the solid epidemiologic link between poor glycemic control and HF risk, the effects of intensified glycemic control in preventing HF remain controversial. Large-scale cardiovascular outcome trials published since 2015 have confirmed the efficacy and safety of sodiumglucose co-transporter-2 inhibitors (SGLT2) inhibitors in preventing HF among patients with type 2 diabetes mellitus. In addition, several dedicated major clinical trials confirmed the cardiovascular benefits of SGLT2 inhibitors in patients with established HF, regardless of left ventricular ejection fraction or diabetes status. Furthermore, high-quality data from these clinical trials transformed SGLT2 inhibitors from glucose-lowering agents to HF drugs. This chapter outlines the complex relationship between HF and diabetes, focusing on the epidemiology, pathophysiology, and prognostic implications. Additionally, we review the current knowledge on identifying subclinical cardiac remodeling, predicting HF risk, and preventing HF in diabetes. We also summarize the recent evidence and guideline recommendations for the pharmacological treatment of patients with coexisting HF and diabetes.

INTRODUCTION

Diabetes is a risk factor for cardiomyopathy and heart failure (HF) independent of traditional cardiovascular (CV) disease (CVD) risk factors such as hypertension and coronary artery disease (CAD) (1–4). The universal definition of HF recognizes patients with diabetes as "at risk for HF" (Stage A). Asymptomatic individuals with at least one of the following: 1) evidence of structural heart disease, 2) abnormal cardiac function, or 3) elevated cardiac natriuretic peptide or troponins are considered to have "pre-HF" (stage B). According to this classification, HF (stage C) is defined as a clinical syndrome with signs or symptoms of HF caused by an abnormality in cardiac structure and function and corroborated by elevated natriuretic peptide or objective evidence of cardiogenic congestion (pulmonary or systemic) (3,5).

The prevalence of diabetes is approximately 10.2% in the U.S. population, and HF affects 9 to 22% of patients with diabetes (6–10). In clinical trials of antidiabetic agents, HF was present in 4 to 30% of participants with diabetes (11). On the other hand, the prevalence of pre-diabetes or diabetes was 30 to 40% among individuals enrolled in HF trials (12,13).

Longstanding diabetes alters cardiac structure and function, resulting from the direct effects of abnormal myocardial metabolism and insulin resistance (IR) even without atherosclerotic CAD (14). The pathophysiologic link between diabetes and HF is complex and multifactorial, involving various abnormal biochemical pathways including but not limited to abnormal calcium signaling, deranged glucose/fatty metabolism, and inflammatory pathways acid contributing to myocardial fibrosis, stiffness, and hypertrophy (7,15,16). A complex interaction of these mechanisms can cause asymptomatic diastolic and systolic dysfunction, eventually leading to the clinical syndrome of HF. Conversely, HF is also associated with a higher prevalence of diabetes and is considered a predictor of future risk of type 2 diabetes mellitus (T2DM) (17).

Left ventricular (LV) dysfunction in patients with diabetes may present with three different HF phenotypes, such as HF with preserved LV ejection fraction (LVEF \geq 50%; HFpEF), HF with mildly-reduced LVEF (HFmrEF; LVEF 40-49%), and HF with reduced LVEF (HFrEF; LVEF \leq 40%) (3). Diagnosing HFpEF and HFmrEF is often challenging since the symptomatology of HF may overlap with other comorbidities such as obesity, lung disease, and chronic kidney disease (CKD). Therefore, the guidelines usually recommend incorporating additional objective diagnostic criteria such as

elevated natriuretic peptides or imaging evidence of either structural heart disease or diastolic dysfunction (18).

The coexistence of diabetes and HF is a poor prognostic factor, posing a greater risk of HF hospitalization, all-cause mortality, and CVD mortality. For instance, epidemiologic studies indicated a 50-90% higher risk of CVD mortality in patients with HF and diabetes, regardless of HF phenotype (12,19). HF patients without DM are at increased risk of developing glycemic abnormalities. In addition, newly diagnosed pre-diabetes was associated with a significantly higher risk of all-cause and CV mortality in HF patients. These findings underscore the importance of screening for pre-diabetes or diabetes among patients with HF (17,20,21). Moreover, early assessment with echocardiography can be helpful for the detection of subclinical structural abnormalities and myocardial dysfunction in asymptomatic patients with diabetes.

The pathophysiology of diabetes-related HF is complex, and despite significant advances over the past decades, many areas are still poorly understood. Since 2015, several landmark clinical trials on sodiumglucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP1-RA) have revolutionized our understanding of CVD risk reduction in patients with T2DM and have led to a paradigm shift in the clinical practice recommendations for the management of T2DM (22). Incredible evidence from the CVD outcome trials (CVOTs) has confirmed the significant improvement in HF outcomes with SGLT2 inhibitors in patients with or without diabetes. These findings increased medical communities' awareness and interest in the links between diabetes and HF.

The American Diabetes Association (ADA) now recommends using SGLT2 inhibitors as first-line agents in T2DM patients with a high risk of or

established HF (23). In addition, several dedicated major randomized clinical trials (RCTs) confirmed the CVD benefits of SGLT2 inhibitors in patients with established HF, regardless of LVEF or diabetes status. Moreover, these RCTs transformed SGLT2 inhibitors from glucose-lowering agents to HF drugs. The 2022 American College of Cardiology (ACC) Foundation / American Heart Association (AHA) / Heart Failure Society of America (HFSA) guideline for the management of HF recommended the use of SGLT2 inhibitors for the treatment of HF, regardless of LVEF (3).

This chapter outlines the complex relationship between HF and diabetes, focusing on the epidemiology, pathophysiology, and prognostic implications. Additionally, we review the current knowledge on identifying subclinical cardiac remodeling, predicting HF risk, and preventing HF in diabetes. We also summarize the recent evidence and guideline recommendations for the pharmacological treatment of patients with coexisting HF and diabetes.

EPIDEMIOLOGY OF DIABETES AND HF

There is a bidirectional link between diabetes and HF (24). Diabetes, either type 1 or type 2, is a strong risk factor for developing HF (25–27). In addition, HF may contribute to the pathogenesis of IR and T2DM (28). The shared underlying risk factors and the overlap of the pathophysiological mechanisms play a critical role in the frequent coexistence of T2DM and HF.

Based on the data from the National Health and Nutrition Examination Survey (NHANES) from 2015 to 2018, the prevalence of HF is 2.3% in the US general adult population (29). The prevalence of HF in individuals with diabetes ranges between 9% and 22%, depending on the characteristics of the population studied (6,8,9). Diabetes is also highly prevalent among patients with HF. In major contemporary drug trials of HF, 32% to 43% of patients with chronic HF had coexisting diabetes (12,30,31). A report from a nationwide US registry (NHANES 2005-2016) demonstrated that, among patients with HF, the prevalence rates of diagnosed and undiagnosed T2DM were 34.7% and 12.8%, respectively (32).

HF is a common but often neglected complication of diabetes (33). HF and cardiomyopathy have a heterogeneous etiology in patients with diabetes (Figure 1 and Figure 2). The strong link between diabetes and CAD, hypertension, and renal disease plays a significant role in the development of cardiomyopathy and HF in patients with diabetes (34). Moreover, HF occurs in individuals with diabetes at higher rates, even in the absence of other HF risk factors (16,35).

Diabetic Cardiomyopathy

Diabetic cardiomyopathy, which lacks a standardized clinical definition, generally refers to diabetes-related myocardial dysfunction without other potential causes (36). A report by Lundbæk in 1954 described the concept of diabetes directly causing myocardial dysfunction (37). In 1972, a landmark study by Rubler et al. described diabetic cardiomyopathy as a new clinical entity by reporting the post-mortem results of 4 patients with diabetes-related HF and dilated cardiomyopathy without other apparent causes of myocardial dysfunction (14). The initial reports of diabetic cardiomyopathy referred to a dilated LV with eccentric hypertrophy and LV systolic dysfunction (HFrEF). Nevertheless, more recent clinical studies described HFpEF with concentric LV hypertrophy and LV diastolic dysfunction as a distinct phenotype of cardiomyopathy rather than being an intermediate form between risk factors and HFrEF (38). The transition from HFpEF to HFrEF does not appear to occur as commonly as it was once presumed.

Epidemiologic Evidence

Evidence from large-scale epidemiologic studies has confirmed the strong link between diabetes and HF. For instance. reports from the prospective Framingham Heart Study in the 1970s indicated that individuals with diabetes had 2-fold (in men) to 5-fold (in women) higher risk of developing HF than individuals without diabetes after adjustment for other risk factors (2,39). Similarly, contemporary cohort studies suggested that diabetes is independently associated with a 1.7 to 2.5-fold greater risk of HF (6,40).

A recent nationwide cohort study from Sweden including >679.000 patients with T2DM and >2 million matched control subjects demonstrated that a diagnosis of T2DM was associated with HF risk even if CVD risk factors, such as glycated hemoglobin, systolic blood pressure (BP), estimated glomerular filtration rate, and lipids were within a target range (41). The study also demonstrated that CVD complications have significantly declined over the past 20 years in individuals with and without T2DM. However, the decline in the rate of HF in patients with T2DM has plateaued over recent years. One potential explanation for this finding is the obesity epidemic, as adiposity plays a major role in the development of HF in patients with diabetes. For instance, a recent analysis of 2 US cohort studies demonstrated that overall obesity, abdominal obesity, and fat mass were strongly associated with a greater risk of HF in participants with diabetes. Interestingly, a similar independent association was absent in those without T2DM (42).

Ischemic heart disease is more frequently seen in HF patients with coexistent T2DM than those without T2DM (63% vs. 47%). Moreover, ~90% of the patients with T2DM and HF of non-ischemic etiology have at least one comorbidity that can contribute to HF development, such as hypertension, atrial fibrillation, valvular disease, or pulmonary disease (43).



Figure 1. Heart failure with reduced ejection fraction due to ischemic cardiomyopathy in a patient with uncontrolled type 2 diabetes. 57-year-old female patient with a history of uncontrolled type 2 diabetes (HbA1c = 12.0) and active tobacco abuse presented with a 2-day history of intermittent midsternal chest pain. (A) Her ECG on presentation demonstrated findings of acute/recent anteroseptal myocardial infarct and old/age indeterminate inferior myocardial infarct, and her serum troponin I was markedly elevated. (B and C) Her echocardiography revealed a dilated left ventricle with severely reduced systolic function, an ejection fraction of 20-25%, and akinetic anterior and inferior wall segments. Her coronary angiography, which was performed emergently, demonstrated subacute occlusion of the proximal segment of the anterior descending artery (arrow in image D) and chronic total occlusion of the middle segment of the right coronary artery (arrow in image E).



Figure 2. Heart failure with reduced ejection fraction due to non-ischemic cardiomyopathy in a patient with uncontrolled type 2 diabetes. 59-year-old male patient with a history of hypertension (medically managed), class I obesity, hyperlipidemia, moderate alcohol consumption, and undiagnosed type 2 diabetes (HbA1c = 13.5) presented with dyspnea on exertion, orthopnea, and leg edema and he was admitted with the diagnoses of acute decompensated heart failure. (A) His ECG on presentation demonstrated left ventricular hypertrophy with repolarization abnormalities. (B and C) His echocardiography revealed a dilated left ventricle with severely reduced systolic function and diffuse hypokinesis, an ejection fraction of 25-30%, and eccentric left ventricular hypertrophy. (D and E) His coronary angiography, performed for ischemic evaluation, demonstrated no evidence of significant

epicardial coronary artery disease. The patient's non-ischemic cardiomyopathy was attributed to a mixed presentation of alcoholic and diabetic cardiomyopathy and hypertensive heart disease.

Diabetes is an independent predictor of progression from preclinical HF (stage A and stage B) to clinic HF (stage C) (44). A population-based analysis on the found National Scottish Register that HF hospitalization risk was ~2-fold higher among patients with diabetes than those without diabetes (45). A prospective cohort study, including individuals from the southeastern U.S.. demonstrated that hypertension and diabetes were associated with the highest HF risk in white and black participants (46). The population-attributable risk of HF was highest for hypertension (31.8%), followed by diabetes (17%). A population-based case-control study also observed an attributable risk of HF at ~17% for diabetes, without any significant difference between HFpEF and HFrEF (47).

Epidemiologic studies have demonstrated a higher incidence of HF in men than in women with diabetes (27,40). This finding is consistent with the strong association between HF risk and male sex in the general population. However, interestingly, diabetes contributes to the future risk of HF more in women than in men, as supported by multiple epidemiologic studies (27,39). In a meta-analysis of 47 cohort studies including >12 million individuals, type 1 diabetes mellitus (T1DM) and T2DM were associated with a 47% and 9% greater excess risk of HF in women than men, respectively (48). The basis for the sex-specific disparity in HF risk attributable to diabetes remains unclear.

Prediabetes and HF Risk

Some epidemiologic studies have suggested that prediabetes may pose a risk for cardiomyopathy and HF(49). In a population-based cohort study, prediabetes was independently associated with HF with an odds ratio of 1.7 (9). A modest but significant

association exists between fasting plasma glucose levels and the risk of HF independent of an individual's diabetes status (50).

Glycemic Control and HF Risk

Glycemic exposure predicts HF risk in individuals with T1DM and T2DM (26,27,51). A population-based prospective case-control study from the Swedish National Diabetes Register evaluated the impact of glycemic control on the future risk of HF hospitalization over a mean follow-up of 7.9 years (26). Compared to a population-based control group without diabetes, patients with T1DM had a four times higher risk of HF hospitalization. Nevertheless, the risk markedly varied depending on glycemic control or comorbidities; hazard-ratio (HR) of 2.2 (1.5-3.0; p<0.0001) in patients with hemoglobin A1c (HbA1c) ≤6.9%, HR of 11.2 $(8\cdot4-14\cdot9; p<0\cdot0001)$ in patients with HbA1c ≥9.7%. Another report from the same dataset revealed that each 1% increase in HbA1c correlated with a 20% higher risk of HF in patients with myocardial infarction and T1DM (52). Among individuals with T2DM, the excess risk of HF attributable to glycemic control varies depending on the patient's age. For instance, poor glycemic control correlates more strongly with excess risk of HF among middle-aged adults (<55 years old). In contrast, the correlation between HbA1c and the risk of HF markedly attenuates with advanced age (27).

Age at Diagnosis of Diabetes and HF Risk

Diagnosis of diabetes at a younger age correlates with a higher risk of HF (45,53,54). A report by Rawshani et al. using the data from the Swedish National Diabetes Register demonstrated that compared to a control group without diabetes, individuals with onset of T1DM before age ten years had 12 times and those with onset during young adulthood (20 to 29 years) had five times increased risk of HF. Sattar et al., using the same registry data, evaluated the association between age at diagnosis and future HF risk among participants with T2DM (54). Their analysis revealed that adults diagnosed with T2DM before 41 years of age had a five times higher risk of HF than their counterparts without diabetes. Interestingly, T2DM diagnosis after the age of 80 years did not increase the risk of HF and was associated with a lower risk of all-cause and CV mortality. Consistently, an analysis from a US cohort demonstrated that every 5-year increase in the duration of DM was independently associated with a 17% rise in the risk of incident HF (55). As expected, the association between diabetes duration and HF risk was more prominent in patients with elevated HbA1c.

The explanations behind the association of duration and age at diabetes diagnosis and future HF risk are likely multifaceted, with a variation between T1DM and T2DM. The total glycemic load, defined as the cumulative exposure to the effects of hyperglycemia, is a predictor of complications of diabetes. The main components of the total glycemic load are the glycemic variability and the duration of diabetes determined by the age of diabetes onset, more prominently in T1DM (53). Individuals who develop T2DM at a younger age are more likely to have other comorbidities such as obesity, dyslipidemia, hypertension, nephropathy, smoking, and lower socioeconomic status when compared to their counterparts without diabetes. Furthermore, this comorbidity burden likely contributes to the relative excess risk of HF observed in patients diagnosed with T2DM at a relatively young age (54). These findings highlight the significance of delaying diabetes onset as one focus of HF prevention efforts (55).

The Relationship Between Diabetes and Comorbidities

Traditional modifiable CVD risk factors, such as hypertension, obesity, dyslipidemia, and cigarette smoking, are prevalent among individuals with diabetes. Hypertension affects 66% to 76% of adults with diabetes in the US (56). According to the 2020 National Diabetes Statistics Report, 45.8% of adults with diabetes are obese (body-mass-index [BMI] of 30 to 39.9 kg/m²), and 15.5% are morbidly obese (BMI of \geq 40 kg/m²) (10).

Coexisting CVD risk factors significantly contribute to the risk of HF in patients with diabetes. A large prospective cohort study, including >270,000 participants with T2DM in the Swedish National Diabetes Register, examined the relationship between five risk factors (elevated HbA1C, dyslipidemia, albuminuria, smoking, and high BP) and CVD outcomes after a median follow-up of 5.7 years (57), The analyses revealed that participants with T2DM who had no risk-factor variables outside the target ranges had a 45% higher risk of hospitalization for HF when compared to that of a control group without diabetes. However, the excess risk of hospitalization for HF was substantially higher (HR vs. control, 11.35; 95% CI, 7.16 to 18.01) when patients with T2DM had all five risk-factor variables outside the target range. These findings indicated the importance of controlling coexisting CV risk factors for preventing HF in diabetes.

Recent reports have indicated that comorbid mental disorders may increase HF risk in individuals with diabetes. A retrospective analysis of nationwide health claims data of Korean participants demonstrated an independent association between HF risk and the number of mental disorders in patients with diabetes (58).

HF as a Risk Factor for Diabetes

Patients with HF are at risk of developing incident DM over time. Data from clinical trials showed that the incidence of new-onset diabetes among patients with HF is 7 to 11% over a 3- to 5-year follow-up period (59,60). Even though the published data is sparse, some evidence has emerged over the past two decades supporting the possible independent role of HF as a risk factor for incident T2DM (61). Analyses of prospective cohort studies and clinical trial participants demonstrated that HF at baseline might predispose the future risk of new-onset diabetes (61–64). Significant predictors of incident diabetes among individuals with HF are elevated glucose and HbA1c, higher BMI and waist circumference, longer duration of HF, and higher functional class of HF (28,61–63).

IMPACT OF DIABETES ON CARDIAC STRUCTURE AND FUNCTION

The frequent coexistence of diabetes with other comorbidities, such as hypertension and obesity, makes it difficult to understand the relative contribution of each disease entity in cardiac remodeling and dysfunction in clinical practice (65). However, growing evidence has supported an independent association between diabetes and various alterations in cardiac structure and function. These asymptomatic subclinical alterations at earlier stages can be detrimental and increase the risk of developing HF and CVD morbidity and mortality in general (44). Recognizing these subclinical alterations is critical for the early identification of high-risk patients and preventing overt HF and diabetic cardiomyopathy.

Left Ventricular Hypertrophy

LV hypertrophy (LVH) is characterized by increased LV mass due to myocardial remodeling. LVH is usually caused by a complex interaction between several factors, including hypertension, diabetes, metabolic syndrome, obesity, gender, ethnicity, and genetic and neurohumoral factors (66). There are three distinct LV geometric abnormality patterns: concentric remodeling (normal LV mass with increased relative wall thickness), concentric LVH (increased LV mass and increased relative wall thickness), and eccentric LVH (increased LV mass and normal relative wall thickness) (Figure 3).





LVH has long been recognized as a target organ response and a strong independent risk factor for HF, CAD, stroke, and CVD mortality (66,67). LVH leads to LV diastolic dysfunction by reduced LV compliance, impaired diastolic filling, prolonged isovolumetric relaxation, and increased LV and left atrial filling pressures (16). The universal definition of HF recognizes asymptomatic LVH, LV systolic dysfunction, and LV diastolic dysfunction as "pre-HF" to emphasize the progressive nature of HF and the importance of HF prevention (5). LVH is common among adults with diabetes, with an estimated prevalence as high as 70% (68). A pooled analysis of 3 epidemiological cohort studies, including 2900 individuals with T2DM and no known CVD, demonstrated that 67% of the participants had at least one of the following echocardiographic abnormalities: LVH, left atrial enlargement, or diastolic dysfunction (44). Coexistent hypertension appears to be the main contributor to LVH in patients with diabetes (69). However, several studies have also demonstrated an independent association between diabetes and LVH. In the Framingham Heart Study, serum glucose, insulin levels, and IR were significantly linked to concentric LV remodeling, a finding that was more striking in women than in men (70,71). Results from a prospective cohort study with a 25-year follow-up period indicated that long-standing glycemic abnormalities have a cumulative effect on LV remodeling, and patients with early-onset diabetes tend to have a worse degree of LVH (72).

Diabetic cardiomyopathy may present with distinct LVH features (34). Thickened and stiff LV walls with normal LV volume usually characterize diabetic cardiomyopathy with HFpEF phenotype. Furthermore, at the cellular level, cardiomyocytes appear hypertrophied with normal sarcomere structure and increased collagen deposition in the interstitial space. Contrarily, diabetic cardiomyopathy with HFrEF phenotype usually manifests with eccentric LVH with dilated LV volume. At the cellular level. cardiomyocytes appear to have damage with loss of sarcomeres and replacement of some cardiomyocytes with interstitial fibrosis (38).

LV Diastolic Dysfunction

Diastolic dysfunction is common among otherwise asymptomatic individuals with diabetes, and its prevalence varies between 20% and 60% depending on the diagnostic criteria used and the population studied (73–75). Prospective cohort studies have confirmed that diabetes and poor glycemic control can independently contribute to the development of diastolic dysfunction (72). Even though diastolic dysfunction is often linked to LVH, it can occur in patients with diabetes, even in the absence of LVH (34).

Mild diastolic dysfunction (delayed myocardial relaxation) has a weak prognostic significance. However, the progression of diastolic dysfunction and increased LV filling pressure findings on echocardiography predispose to the future risk of HF and mortality in patients with diabetes (73,75). Moreover, among asymptomatic individuals with baseline diastolic dysfunction, diabetes is an independent predictor of progression to HFpEF or HFrEF (76).

LV Systolic Dysfunction

Traditionally, impaired LVEF is the primary marker of cardiomyopathy and systolic dysfunction. LVEF is a simple measure commonly used in the CV risk evaluation and management of CVD. However, LVEF does not capture the full spectrum of myocardial function (77). Global longitudinal strain (GLS) evaluated by speckle-tracking echocardiography is a robust technique that measures tissue deformation in a longitudinal direction (Figure 4). Reduced GLS is a marker of reduced contractility (75). GLS is more sensitive than conventional LVEF as a measure of systolic function and has an additional prognostic value (77,78). Therefore, it is now commonly used to detect subclinical LV systolic dysfunction.



Figure 4. Global longitudinal strain by speckle tracking echocardiography. Assessment of global longitudinal strain (GLS) in a healthy, asymptomatic individual with a GLS of -25%. The top row displays a regional strain map superimposed on the grayscale two-dimensional echocardiographic images in apical four-chamber (A4C), apical two-chamber (A2C), and apical three-chamber (A3C) views. The bottom left bullseye displays regional longitudinal strain for each segment of a 16-segment left ventricle model. Bright red denotes the most negative normal values of GLS. The bottom right bullseye shows the time (ms) between aortic valve opening and peak longitudinal strain, a measure of desynchrony, for each segment.

Impaired GLS is highly prevalent in asymptomatic, normotensive patients with diabetes and normal LVEF (67,79,80). Diabetes is associated with reduced GLS, even in adolescents and young adults with T1DM or T2DM (81,82). Moreover, an inverse correlation exists between HbA1C and GLS regardless of diabetes status, race, and sex (83). Not surprisingly, impaired GLS is a robust independent predictor of new-onset HF and mortality in patients with diabetes (67).

Diabetes can lead to clinical HF syndrome in individuals with asymptomatic LV systolic dysfunction. An RCT that included adults with asymptomatic LV systolic dysfunction demonstrated that diabetes increased the risk of HF development by 53% and

doubled the risk of HF hospitalization over a median follow-up of 3 years (84).

Better glycemic control in patients with diabetes can lead to improvements in LV systolic and diastolic function indices. In a prospective cohort study of subjects with uncontrolled T2DM, lowering of average HbA1c from 10.3% to 8.3% over 12 months was associated with a 21% increase in GLS and a 24% increase in septal e' velocity, a marker of myocardial relaxation (85).

PATHOPHYSIOLOGIC LINKS BETWEEN DIABETES AND HF

A complex interplay between numerous mechanisms underlies the pathophysiologic links between diabetes and HF. These pathophysiologic mechanisms include but are not limited to impaired cardiac insulin signaling, glucotoxicity, lipotoxicity, mitochondrial dysfunction, myocardial fibrosis, oxidative stress, impaired myocardial calcium handling, CV autonomic dysfunction, endocardial dysfunction, overactivation of the renin-angiotensin-aldosterone system (7) (Figure 5). The relative contribution of each pathophysiologic mechanism and their relationship with the phenotype of diabetic cardiomyopathy are still poorly understood. The pathophysiology of cardiomyopathy and HF vary depending on the type of diabetes (T1DM vs. T2DM) and type of HF (HFrEF vs. HFpEF) (86).



Figure 5. Pathophysiological mechanisms, subclinical abnormalities, and clinical manifestations of diabetic cardiomyopathy. AGEs, advanced glycation end-products; CMP, cardiomyopathy; EF, ejection fraction; HF, heart failure; LV, left ventricular; RAAS, renin-angiotensin-aldosterone system. *In patients with type-1 diabetes mellitus.

Alterations in Myocardial Energy Substrate

Under normal circumstances, the heart predominantly consumes free fatty acids (FFA; ~70%) and glucose (~30%) and can adapt its choice of fuels depending on their availability (15). In T2DM, cardiomyocyte substrate utilization shifts towards FFA, and glucose utilization decreases in response to IR. As a result, the heart becomes metabolically less flexible and almost

completely reliant on FFA. These alterations lead to inefficient energy metabolism since FFA oxidation requires more oxygen for energy production than glucose or ketone bodies (15,87). Moreover, the increased FFA uptake causes the accumulation of triglycerides in the cardiomyocytes and promotes lipotoxicity, mitochondrial dysfunction, oxidative stress, and apoptosis (34). A prospective study elegantly evaluated the impact of diabetes on lipid accumulation by analyzing endomyocardial biopsy samples from 158 adult heart transplant recipients (88). The investigators demonstrated that cardiomyocyte samples of transplanted healthy hearts begin to show evidence of lipid accumulation (triacylglycerol and ceramide) as early as three months after a transplant in diabetic recipients. In comparison, no lipid accumulation was present in cardiomyocyte samples of transplant recipients without diabetes. Not surprisingly, cardiomyocyte lipid accumulation was an independent predictor of early systolic and diastolic dysfunction in recipients with diabetes after 12 months of a transplant.

Hyperinsulinemia and Insulin Resistance

In broad terms, IR is defined as the inability of insulin to carry on its metabolic actions at the cellular level (34). IR is the central defect in the pathogenesis of metabolic syndrome and T2DM. Moreover, HF is a well-known insulin-resistant state, and HF risk and prognosis are markedly affected by IR (34,89).

IR increases lipolysis, hepatic lipogenesis, and hepatic gluconeogenesis. These changes lead to substrate overload and myocardial dysfunction through lipotoxicity and glucotoxicity (75). IR and related hyperinsulinemia can affect the signaling pathways involved in cardiomyocyte hypertrophy (38).

Oxidative Stress

Oxidative stress is the imbalance between the increased generation of reactive oxygen species and reduced antioxidant defense (75). Exposure to hyperglycemia induces oxidative stress by activating NADPH oxidase, promoting mitochondrial production of superoxides, and increasing the formation of advanced glycation end products (AGEs) due to nonenzymatic glycation and oxidation of proteins and lipids (34,87).

Oxidative stress contributes to increased cardiac remodeling, reduced cardiac contractility and relaxation, and impaired cardiomyocyte calcium handling (75). Moreover, oxidative stress contributes to myocardial dysfunction by causing protein and DNA damage, increasing myocardial inflammation, and impairing intracellular signaling pathways (34).

Endoplasmic Reticulum Stress and Impaired Calcium Handling

Myocardial intracellular calcium levels regulate myocardial contractility during a cardiac cycle. Alterations in the complex mechanism of calcium handling can impact myocardial contraction and relaxation (90). The endoplasmic reticulum has a major role in Ca²⁺ handling, lipid synthesis, and protein folding and modification (91). Moreover, cytosolic Ca²⁺ levels regulate cellular metabolism and cell signaling. Hyperglycemia and IR trigger endoplasmic reticulum stress, leading to unfolded proteins accumulating and impairing Ca²⁺ handling. In diabetic cardiomyopathy, impaired Ca²⁺ reuptake by the endoplasmic reticulum prolongs diastolic relaxation time (91). Studies on animal models have indicated that impaired cardiomyocyte Ca²⁺ handling plays a crucial role in the pathophysiology of diabetic cardiomyopathy (7,90).

Endothelial and Microvascular Dysfunction

Endothelial dysfunction, which disturbs endothelialcardiomyocyte communication and vascular function, is common in patients with diabetes and CVD (15). Diabetes induces the deposition of AGEs in the endothelial and smooth muscle cells of the myocardial microvasculature (92). Furthermore, the deposition of AGEs triggers vascular inflammation, which reduces endothelial nitric oxide production. Low myocardial nitric oxide bioavailability levels predispose to concentric LV remodeling and diastolic dysfunction (38). Diabetes has also been linked to capillary rarefaction and pericyte loss. Microcirculatory rarefaction can impair myocardial perfusion, reduce coronary flow reserve, lead to tissue hypoxia, increase myocardial stiffness, and decrease contractility (38,93).

Inflammation

Systemic inflammation is a central component of the association between obesity, diabetes, CAD, and HF (34). In individuals with obesity, the expanding adipose tissue recruits immune cells and causes overproduction of proinflammatory cytokines, leading to obesity-mediated chronic inflammation (94). Chronic low-grade inflammation predisposes to IR and T2DM and contributes to diabetes-related complications (94). Similarly, systemic inflammation is highly prevalent in patients with HF, contributing to the development, progression, and poor prognosis of HF regardless of LVEF (95). Animal model studies have shown a complex interaction between various inflammatory pathways cardiac implicated in inflammation and the development of diabetic cardiomyopathy (96,97). One potential link between HF and diabetes is S100A12, an inflammatory protein that increases with hyperglycemic stress. Α prospective cohort study including 1345 patients with T2DM demonstrated an independent association between increased A100A12 and risk of HF hospitalization (98).

Epicardial Adipose Tissue Expansion

Diabetes and obesity can independently contribute to the expansion and transformation of epicardial adipose tissue (86,99). Epicardial adipose tissue expansion has been associated with LV systolic and diastolic dysfunction in patients with T2DM (100). Epicardial fat volume correlates with myocardial fibrosis (101), vascular stiffness (102), and reduced coronary microcirculation (103). Epicardial adipose tissue expansion and transformation contribute to the alterations in the cardiac structure and function through several pathophysiological mechanisms such as proinflammatory effects of adipokines (i.e., leptin, tumor necrosis factor-a, interleukin-1b and interleukin-6) secreted from epicardial fat and oxidative stress induced by reactive oxygen species released from adipocytes (86,104).

Autoimmunity

Autoimmunity is implicated in the pathogenesis of CVD among patients with T1DM (38,105). A recent report from a prospective cohort study showed that participants with T1DM and uncontrolled glycemia (HbA1c \geq 9.0%) have a high prevalence of cardiac autoantibodies with an antibody profile similar to that seen in patients with chronic Chagas cardiomyopathy (106). Moreover, cardiac autoantibody positivity predicted elevated high-sensitivity C-reactive protein and the future risk of CVD events. Interestingly, cardiac autoimmunity was lower in participants with controlled T1DM (HbA1c <7.0%) compared to those with uncontrolled (HbA1c \geq 9.0%). The specific role of cardiac autoimmunity in the development and progression of diabetic cardiomyopathy remains to be further explored.

Overactivation of the Renin-Angiotensin-Aldosterone System

Overactivation of the renin-angiotensin-aldosterone system (RAAS) constitutes a robust pathophysiologic link between diabetes, obesity, hypertension, and HF (34). The typical features of RAAS overactivation are elevated serum angiotensin and aldosterone levels the upregulation of angiotensin and and mineralocorticoid receptors (91,107). There is a bidirectional relationship between RAAS activation and dysglycemia. Hyperglycemia and IR can activate the RAAS, and in return, RAAS induces systemic and cardiac IR and contributes to oxidative stress in cardiomyocytes by increasing the activity of NADPH oxidase (7).

Autonomic Dysfunction

Autonomic nervous system dysfunction is highly prevalent in patients with diabetes. CV autonomic neuropathy (CAN) differentially impacts the cardiac innervation's sympathetic and parasympathetic components, leading to sympathetic overactivation in the earlier stages (16). This imbalance is believed to contribute to the pathogenesis of CVD. CAN induces LV remodeling, LV systolic and diastolic dysfunction, and myocardial ischemia (108–110). CAN is usually asymptomatic at earlier stages, and at advanced stages, it may present with resting tachycardia, orthostatic hypotension, abnormal BP regulation, blunted heart rate response to exercise, and impaired heart rate variability (34,111).

Myocardial Fibrosis

Myocardial fibrosis, detected by histopathology or cardiac MRI, is a hallmark of diabetes-induced cardiac remodeling and related myocardial dysfunction. In patients with diabetes, the degree of myocardial fibrosis directly correlates with HbA1c levels (112). Diabetes-induced myocardial fibrosis is characterized by the remodeling of extracellular matrix with the deposition and crosslinking of stiff collagen. progressive elimination of muscular fibrils, perivascular fibrosis, basement membrane thickening, coronary microvascular sclerosis, and formation of microaneurysms (16). Myocardial fibrosis is often considered an end product of various pathophysiologic abnormalities such as hyperglycemia, hyperinsulinemia, oxidative stress, CAN, inflammation, and the overactivation of RAAS.

Apoptosis

Apoptosis, the process of programmed cell death, has been implicated in the development of diabetic cardiomyopathy and HF (113). Studies from animal models and human subjects have demonstrated a strong association between hyperglycemia and cardiomyocyte apoptosis (114,115). The primary drivers of cardiomyocyte apoptosis in diabetes are oxidative stress, endoplasmic reticulum stress, and dysregulation of autophagy, the lysosomal process that degrades and recycles cellular proteins and organelles (34,116).

PROGNOSTIC IMPLICATIONS OF DIABETES IN HF

Data from epidemiologic studies and clinical trials have consistently demonstrated that individuals with concurrent diabetes and HF have impaired quality of life, are at high risk of hospitalization and mortality, and have an overall poor prognosis (33,117). In addition, coexistent prediabetes also appears to increase the risk of morbidity and mortality in patients with HF as well (118).

A large meta-analysis including >380,000 subjects with acute and chronic HF from 43 registries and clinical trials revealed that diabetes was associated with a 28% increased risk of all-cause mortality and ~35% increased risk of both CV death and hospitalization (mostly from HF) over a three year follow up (119). Interestingly, the adverse impact of diabetes on the risk of hospitalization and mortality did not differ according to the LVEF group (≤35% vs. >35%) but was higher in patients with chronic HF than those with acute HF. Observational studies have suggested a U-shaped relationship between HbA1c and mortality in patients with coexisting HF and diabetes. Aguliar et al. reported that HbA1c of 7.1% to ≤7.8% was associated with the lowest risk of mortality when compared with the other quantiles of HbA1c in a cohort of ambulatory patients with HF who were receiving medical therapy for diabetes in the early 2000s (120).

Several potential mechanisms have been proposed to explain the prognostic impacts of diabetes in HF.

Diabetes is linked to multimorbidity, which significantly alters HF outcomes. Moreover, diabetes induces myocardial fibrosis, inflammation, and endothelial dysfunction, leading to higher LV pressures, poor functional status, and impaired exercise capacity in patients with HF (121-125). Diabetes predisposes neurohumoral overactivation and alterations of renal sodium handling, which may lead to congestion, cardiorenal syndrome. and impaired diuretic responsiveness (121). Also, hyperglycemia in patients with diabetes upregulates SGLT2, which leads to increased renal sodium absorption and volume expansion (121). Moreover, the increased burden of ischemic heart disease and other diabetes-related comorbidities, such as CKD, contribute to the detrimental effects of HF (126).

Data from the Swedish Heart Failure Registry demonstrated that the diabetes-associated mortality risk is more pronounced in individuals with HF of ischemic etiology than those with nonischemic etiology (43). The 2-year survival rate was less than 50% among those with HF, T2DM, and ischemic heart disease.

The presence of preexisting microvascular disease is an independent risk factor for the risk of future HF events in patients with T2DM (44). In addition, microvascular disease portends an increased risk of mortality and morbidity in patients with HF. A post hoc analysis of a large RCT

demonstrated a significant association between a history of microvascular complications and future risk of adverse events among study subjects with diabetes and HFpEF (127).

PREVENTION OF HF IN PATIENTS WITH DIABETES

The critical importance of HF prevention is underscored by HF staging, where risk factors such as hypertension and diabetes are classified as stage A (at risk for HF) (3). Because of the detrimental prognostic impact of clinical HF, the prevention of asymptomatic cardiac remodeling and dysfunction (pre-HF, stage B) and symptomatic HF (stage C) are among the primary goals of the management of patients with diabetes (128).

Prevention of HF by Preventing Diabetes

Preventing the onset of diabetes during young adulthood or middle age is an effective strategy for reducing HF risk later in life. An analysis of a large pooled US cohort evaluated the cumulative and relative impact of the absence of five modifiable HF factors (diabetes, hypertension, risk obesity. dyslipidemia, smoking) in middle age (45 to 55 years of age) (129). The data showed that the absence of diabetes in middle age strongly predicted HF-free survival, with a more than 60% lower risk of incident HF than those with diabetes. In addition, subjects without diabetes, hypertension, and obesity at ages 45 to 55 years, compared to those with all 3 of these risk factors, had an average >10 years longer HF-free survival and 13 years longer overall survival (129).

Prediction of HF Risk in Patients with DM

HF risk stratification is essential for prevention in patients with DM or prediabetes who do not have ASCVD. Even though echocardiography can detect cardiac remodeling in patients with diabetes, its use is not routinely recommended for asymptomatic individuals because of concerns about costeffectiveness (4). However, measuring natriuretic peptides or high-sensitivity cardiac troponin can help identify patients with pre-HF or those at risk of progression to HF. Therefore, patients with diabetes should have a measurement of natriuretic peptides or high-sensitivity cardiac troponin yearly to identify highrisk individuals and assist with HF prevention (4).

Several risk prediction tools and algorithms have been developed to predict incident HF in patients with dysglycemia. Pandey et al. described a simple biomarker-based risk score including high-sensitivity cardiac troponin T \geq 6 ng/l, high-sensitivity C-reactive protein ≥3 mg/l, N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥125 pg/ml, and LVH by ECG, with each abnormal parameter counting as 1 point. This risk score was tested in participants from 3 major US cohort studies. This risk score had good risk stratification for predicting 5-year incident HF risk in patients with both diabetes and prediabetes (130). More complex risk prediction tools (WATCH-DM and TRS-HF_{DM}) incorporating a more extensive list of clinical variables have also been developed. Validation studies on participants from different clinical trials demonstrated that these risk scores could stratify HF risk among patients with T2DM (131–133). However, prospective studies have not evaluated these risk scores, and their clinical utility remains uncertain.

Glycemic control, obesity management, and BP control are well-established therapeutic options to lower the risk of microvascular or macrovascular complications in patients with diabetes. The clinical implications of these therapeutic options in HF prevention will be reviewed here.

Impact of Blood Pressure Control on HF Prevention

Diabetes and hypertension commonly coexist because of the overlap of underlying risk factors and pathophysiological mechanisms (134,135). The coexistence of diabetes and hypertension synergistically contributes to the risk of microvascular and macrovascular complications and CVD. Therefore, BP control with lifestyle modifications and antihypertensive medications is a primary target for reducing the risk of complications due to coexisting diabetes and hypertension (134). The ACC/AHA guidelines recommend initiating an antihypertensive agent when patients with diabetes have an office BP of ≥140/90 mmHg. The recommended BP target is below 140/90 mmHg for low-risk patients and below 130/80 for individuals with established or high risk for atherosclerotic CVD (136).

BP lowering has strong benefits in preventing HF among individuals with diabetes (35). However, the magnitude of this benefit appears to be smaller in patients with diabetes than in those without diabetes. Large meta-analyses of RCTs of BP-lowering therapy demonstrated that every 10 mmHg reduction in systolic BP (SBP) was associated with a 16% to 25% lower risk of HF among individuals with diabetes and 25% to 43% risk reduction among those without diabetes (137,138). The landmark ACCORD BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) trial compared the impact of intensive (SBP goal <120 mmHg) versus standard BP control (SBP <140 mmHg) on major adverse CV events (MACE) in hypertensive patients with diabetes (139). In this trial, intensive BP control did not improve the risk of MACE or HF but increased the risk of adverse events. Therefore, the 2018 European Society of Cardiology (ESC)/European Society of Hypertension guidelines for the management of arterial hypertension recommended avoiding a target SBP <120 mmHg in patients with diabetes (140).

The antihypertensive drug classes with strong CV risk reduction in individuals with diabetes are thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and dihydropyridine calcium channel blockers. Therefore, any of these agents can be considered a first-line therapy for lowering BP in individuals with diabetes. Because of their renal protection benefits, an ACE inhibitor or an ARB should be a part of the initial therapy for those with albuminuria (136,141). It should be noted that beta-blockers are not among the first-line antihypertensive agents for patients with or

without diabetes. Because there is insufficient evidence on the mortality benefits of beta-blockers when used for the sole purpose of BP reduction in the absence of HF or CAD (136,141). The landmark Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) has been the largest trial designed to assess the relative efficacy of different antihypertensive agents in protection against CVD. The results of this trial demonstrated that chlorthalidone (a thiazide diuretic) was superior to lisinopril (an ACE inhibitor) and amlodipine (a calciumchannel blocker) in the prevention of HF among patients with or without diabetes (142,143). A subsequent large meta-analysis of RCTs revealed that diuretics and renin-angiotensin system blockers were independently superior to other antihypertensive agents in the prevention of HF among patients with diabetes (138).

Loop diuretics are considered to have a neutral effect on glycemic control in patients with diabetes. Evidence from posthoc analysis and meta-analysis of antihypertensive drug trials has shown a small but significant association between thiazide diuretic use and higher fasting plasma glucose (144). A metaanalysis of 26 RCTs demonstrated that thiazide diuretic use was associated with a 4.6 mg/dL higher fasting plasma glucose than non-thiazide agents or placebo in patients with hypertension (145). A possible link between thiazide diuretic use and new-onset diabetes in patients with hypertension was supported by some studies (146) but not all (147). Overall, the CV benefits of thiazide diuretics outweigh the risk of new-onset diabetes in non-diabetic individuals and the risk of uncontrolled glycemia in patients with diabetes (144). Therefore, neither hypertension nor HF management guidelines recommend avoidance of thiazide diuretics in patients with or at risk for diabetes.

The ACC/AHA guidelines recommend the use of steroidal mineralocorticoid receptor antagonists (MRA, i.e., spironolactone and eplerenone) as an add-

on therapy to the first-line antihypertensive agents in the treatment of resistant hypertension (136). Besides modest BP reduction, these agents can provide antifibrotic, anti-inflammatory, and anti-proteinuric benefits (148,149). The clinical CV benefits of these agents have been proven in patients with HFrEF. However, we lack large-scale RCTs demonstrating their CV benefits in primary prevention settings among patients with hypertension or diabetes. In a small RCT including 140 patients with T2DM and high CVD risk, adding high-dose eplerenone to standard treatment reduced LV mass and decreased NT-ProBNP and a circulating serum marker of myocardial fibrosis (150). Our knowledge of MRAs in patients with diabetes has expanded with two Phase III landmark RCTs evaluating the cardiorenal benefits of Fineranone, a recently discovered non-steroidal MRA with high affinity and specificity for the mineralocorticoid receptor (151). FIDELIO-DKD and FIGARO-DKD trials demonstrated that fineranone therapy on top of maximally tolerated RAAS inhibitor treatment was renally protective and reduced the risk of the primary endpoint of CVD outcomes in patients with T2DM and CKD (152,153). More specifically, fineranone therapy significantly reduced the risk of hospitalization for HF (HR; 0.71 [95% CI, 0.56-0.90]) in the FIGARO-DKD trial (153). Based on these results, the U.S. Food and Drug Administration (FDA) recently approved fineranone to reduce the risk of estimated glomerular filtration rate (eGFR) decline, end-stage renal disease, CVD death, non-fatal MI, and HF hospitalization in patients with CKD and T2DM (151).

Obesity Management and Lifestyle Modifications

Studies have consistently demonstrated that purposeful weight reduction, achieved via diet, exercise, or bariatric surgery, has favorable impacts on glycemic control, IR, BP, and lipid profiles and reduces the need for antidiabetics in obese individuals with T2DM (34,154,155). Moreover, weight reduction can delay the progression from prediabetes to T2DM (156). The ADA recommends lifestyle modification to achieve at least a 5% weight loss for all overweight or obese individuals with prediabetes or diabetes (157). Also, the guidelines emphasize the need for an individualized medical nutrition therapy program for individuals with diabetes to achieve treatment goals. The recommended exercise regimen for most individuals with T1DM and T2DM is at least 150 minutes of moderate to vigorous aerobic activity per week, spread over at least three days/week, and an additional 2-3 sessions/week of resistance exercise (157).

Despite the well-established favorable effects of weight loss in patients with diabetes, the role of lifestyle changes and weight loss in preventing HF among diabetic patients remains uncertain. A metaanalysis of 36 prospective cohort studies published before 2014 demonstrated that achieving recommended physical activity levels (150 minutes of moderate-intensity aerobic activity per week) was associated with reduced risk of incident HF (relative risk; 0.81 [0.76, 0.86]) in patients with diabetes (112).

The Look AHEAD (Action for Health in Diabetes) has been the largest RCT evaluating the CV effects of an intensive lifestyle intervention that promoted weight loss through decreased caloric intake and increased physical activity in overweight or obese participants with T2DM (154). The study subjects in the intensive lifestyle intervention group lost 8.6% of body weight at one year and, by the end of the 10-year follow-up, maintained a modest (6%) weight loss compared to 3.5% in the control group. Despite the achieved relative weight loss and improved physical fitness and HbA1c, the intensive lifestyle intervention did not reduce the risk of CVD mortality and morbidity, including HF risk, which was a secondary outcome. A post hoc analysis by Pandey et al. evaluated the impact of cardiorespiratory fitness and the degree of weight loss on the HF risk among the Look AHEAD trial participants with an extended follow-up period

(158). The investigators observed a 20% reduction in incident HF risk as a response to a 10% reduction in BMI over a 4-year follow-up. Moreover, a higher baseline and improvement of cardiorespiratory fitness over time predicted a lower risk of incident HF. Interestingly, subgroup analysis revealed a more significant correlation between baseline fitness and incident HFpEF than incident HFrEF. Future dedicated studies are needed to explore the HF risk reduction effects of more intense weight loss and exercise training interventions to promote sustained improvements in body weight and cardiorespiratory fitness in patients with T2DM (158).

Metabolic surgeries, when performed as a part of a comprehensive weight management strategy, are effective treatment options for achieving more significant and durable weight loss in individuals with severe obesity (159). Individuals with T2DM and severe obesity who undergo metabolic surgeries experience improvement in glycemic control and insulin sensitivity and may have remission of diabetes (159). Evidence from RCTs and observational studies has demonstrated that metabolic surgery, as compared to conventional lifestyle modifications and medical therapy, can reduce overall CV risk and improve the quality of life in individuals with T2DM and severe obesity (160-162). The impact of metabolic surgeries on incident HF risk has not yet been evaluated in large-scale RCTs. In a large nationwide prospective observational study of obese individuals without a known history of HF, metabolic surgery was associated with a >50% reduction in the risk of incident HF (163). Another retrospective cohort study from the Cleveland Clinic Health System in the U.S. demonstrated that metabolic surgery among patients with T2DM and obesity was associated with approximately 40% relative reduction of major adverse CV event risk and more than 60% relative reduction of incident HF risk over a median follow-up of 3.9 years (164).

Impact of Glycemic Control

In patients with T1DM and T2DM, intensive glycemic control significantly reduces the risk and severity of microvascular complications (34). However, despite the solid epidemiologic link between poor glycemic control and HF risk, the effects of intensified glycemic control in preventing HF remain controversial. Early clinical trials that established the CV benefits and risks of intensive glycemic control did not include HF as a primary endpoint. However, post hoc or secondary outcome analyses of prospective trials have shed light on the relationship between glycemic control and HF prevention.

In the UK Prospective Study of Diabetes (UKPDS) published more than 20 years ago, intensive glycemic control with metformin, sulfonylureas, or insulin was compared to conventional therapy in adults with recently diagnosed T2DM. A post hoc analysis of the main trial demonstrated that each 1% reduction in mean HbA1c was associated with a 16% decrease in incident HF (165). However, similar results were not replicated by subsequent large-scale RCTs such as the ACCORD (166,167), the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (168), and the VADT (Veterans Affair Diabetes Trial) (169) which failed to show any reduction in HF risk with intensive glucose control in patients with T2DM. Consistently, a meta-analysis of all these trials showed no overall effect of intensive glucose control on HF risk despite a modest (9%) reduction in the risk of major CV outcomes (170). These observations confirmed that blood-glucose-lowering and improvement of HbA1c are insufficient targets for preventing HF in patients with diabetes.

The treatment section below discusses the impact of specific antidiabetic agents on the prevention of HF in high-risk patients.

TREATMENT OF HF IN PATIENTS WITH DIABETES

The primary objectives in managing HF are to reduce mortality, prevent HF hospitalization, and improve patients' clinical status, quality of life, and functional capacity (18). The major components of managing HF are lifestyle changes, education and support for HF self-management, monitoring, control of the underlying causes and associated comorbidities, pharmacologic therapy, cardiac rehabilitation, device therapies, mechanical circulatory support, and cardiac transplantation (171). The major society guidelines for the management of patients with HF include the ACC/AHA/HFSA guidelines published in 2022 (3) and the European Society of Cardiology (ESC) guidelines published in 2021 (18).

The main components of lifestyle changes recommended for patients with HF are physical smoking cessation, restriction of or exercise. abstinence from alcohol consumption, dietary modifications, and avoidance of obesity (18). ACC/AHA/HFSA and ESC guidelines strongly recommend regular aerobic exercise and exercise training to improve functional capacity and symptoms in patients with HF who can participate. The ACC/AHA/HFSA guideline indicated that avoiding excessive dietary sodium intake is reasonable (class IIa) for patients with symptomatic HF to reduce congestive symptoms (3). However, because of a lack of affirmative evidence from clinical trials, the guidelines did not provide precise recommendations about the limit of daily sodium intake and whether it should vary depending on the type, stage, or severity of HF or comorbidities.

Diuretic Therapy in HF

Diuretics increase urinary sodium excretion and reduce physical signs and symptoms of congestion in HF patients by inhibiting sodium or chloride reabsorption in the renal tubules. Loop diuretics such as bumetanide, furosemide, and torsemide act in the loop of Henle, whereas thiazide diuretics such as hydrochlorothiazide, metolazone, chlorthalidone, and potassium-sparing diuretics such as spironolactone, eplerenone, and triamterene act in the distal position of the tubule (172). Loop diuretics, which produce a shorter and more intense diuresis than thiazides, are usually the preferred agents for achieving and maintaining euvolemia and reducing the risk of HF hospitalization in patients with HF. Large-scale RCTs have not evaluated the effects of the loop and thiazide diuretics on mortality and morbidity in patients with HF.

First-Line Pharmacological Treatment of HFrEF

Neurohumoral antagonists (RAAS inhibitors and betablockers) and SGLT2 inhibitors with proven morbidity and mortality benefits are the cornerstone of guidelinedirected medical therapy for patients with chronic HFrEF (173). The guidelines generally do not recommend specific therapeutic approaches in patients with diabetes compared to those without diabetes.

RAAS AND NEPRILYSIN INHIBITORS

The guidelines from AHA/ACC/HFSA (3) and ESC (18) recommend (Class I) the use of angiotensin receptor-neprilysin inhibitor (ARNI; sacubitril/valsartan) as a first-line therapy for patients with HFrEF (New York Heart Association [NYHA] Class ll or III). ACE inhibitors (Class recommendation) are recommended to reduce the risk of morbidity and mortality in patients with HFrEF when using ARNI is not feasible. ARBs are considered acceptable vasodilator treatment options (class I recommendation) as a first-line alternative to ACE inhibitors for patients intolerant of ACE inhibitors because of cough or angioedema and when using ARNI is not feasible.

Subgroup analysis or meta-analysis of major HF trials demonstrated that the effectiveness of RAAS and neprilysin inhibitors in HF does not vary based on patients' diabetes status. Therapy with ACE inhibitors, ARBs, or an ARNI reduces the risk of morbidity and mortality among HF patients without significant effect variation based on diabetes status (33,61,122,174). In addition, ARNI therapy provides a similar degree of natriuretic peptide improvement and cardiac reverse remodeling in patients with or without diabetes (175).

Post hoc analysis of RCTs revealed that ACE inhibitors and ARBs might reduce the risk of incident diabetes in patients with HFrEF (59,61,176). However, the data on the impact of these agents on glycemic control in patients with HF and preexisting diabetes remains limited. Neprilysin inhibition with sacubitril appears to have more favorable effects on glycemic control than ACE inhibitors (61). In the PARADIGM-HF trial, HFrEF patients enrolled in the enalapril and sacubitril-valsartan arms experienced an average of 0.16% and 0.26% HbA1c reduction after one year of treatment (177). In addition, sacubitril-valsartan use was associated with a 29% reduction in new insulin use compared to enalapril.

Diabetes confers a higher risk of diabetic nephropathy and CKD. Diabetic nephropathy can lead to increased renal sodium retention and a higher risk of hyperkalemia. Therefore, it is critical to monitor serum electrolytes and creatinine when starting or escalating the dose of RAAS inhibitors in patients with HF and diabetes (178). Of note, ARNI therapy may cause a higher rate of hypotension than ACE inhibitors or ARB (4).

BETA-BLOCKERS

Beta-blocker therapy is recommended (class I) for all patients with stable, symptomatic HFrEF (3,18). Betablocker therapy reduces the risk of death and hospitalization and improves LVEF and clinical status in patients with HFrEF. The ACC/AHA/HFSA guidelines recommend using one of the three betablockers with proven mortality benefits (e.g., metoprolol succinate, carvedilol, and bisoprolol).

Based on RCTs, the morbidity and mortality benefits of beta-blockers are similar in HFrEF patients with or without diabetes (174,179,180). A prospective cohort study from the UK suggested that increasing betablocker dose was associated with a more significant prognostic advantage in HF patients with diabetes than those without diabetes (181).

Data from some old observational studies and clinical trials raised concerns for a slight increase in the risk of new-onset diabetes associated with using propranolol, a first-generation non-selective beta-blocker, to treat hypertension (182,183). However, such an adverse effect concern is not present with newer-generation beta-blockers in HF populations (184). Compared to other beta-blockers, carvedilol use may even reduce HbA1c, fasting insulin levels, and risk of new-onset diabetes in patients with HFrEF (60,184).

Beta-blockers can potentially mask hypoglycemia symptoms by preventing palpitations and tremors and could prolong recovery from hypoglycemia by reducing glucose production in the liver (178). A post hoc analysis of the ACCORD trial demonstrated a significant association between beta-blocker use and severe hypoglycemia risk in patients with diabetes (185). However, a post hoc analysis of the MERIT-HF trial (Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure) did not show a similar association between beta-blocker use and hypoglycemia events in patients with HF and coexisting T2DM (186).

MINERALCORTICOID RECEPTOR INHIBITORS MRAs (i.e., spironolactone or eplerenone) are recommended for all patients with HFrEF (LVEF ≤35%) and NYHA class II to IV symptoms if eGFR is >30 ml/min/1.73 m² and serum potassium is <5 mEq/L (3,18). Similar to other RAAS inhibitors, the clinical benefits of MRAs have been consistent in HF patients with or without diabetes (187). Based on limited data, MRAs appear to have a neutral effect on glycemic parameters and diabetes risk in individuals with HFrEF (64,188). MRAs can cause hyperkalemia; therefore, monitoring electrolytes while initiating or maintaining MRA therapy is crucial.

SGLT2 INHIBITORS

SGLT2 inhibitors are recommended (class I) to reduce CVD mortality and HF hospitalization in patients with symptomatic HFrEF, irrespective of the presence of T2DM (3,18). Empagliflozin, Dapagliflozin, and Sotagliflozin are the SGLT2 inhibitors approved by the U.S. FDA to reduce CVD death and HF hospitalization in patients with HF across the range of LVEF (HFrEF, HFpEF, HFmrEF).

Dedicated landmark trials proved the CV benefits of SGLT2 inhibitors in patients with HFrEF, regardless of T2DM status (Table 1). The DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) (189) and EMPEROR-Reduced (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction) (190) trials enrolled symptomatic chronic HFrEF (LVEF ≤40%, NYHA class II to IV, and elevated natriuretic peptides) and were already on guideline-directed medical therapy. Patients with T1DM and advanced CKD were excluded. In these trials, compared to placebo, SGLT2 inhibitors reduced the composite of CVD death and HF hospitalization by ~25%. In addition, SGLT2 inhibitors slowed the progression of renal disease. The SGLT2 inhibitors' CV benefits are independent of their glucose-lowering effects (191). In addition, SGLT2 inhibitor therapy appears to improve the clinical stability and functional status of patients with HF. An analysis EMPEROR-Reduced trial from the

demonstrated that empagliflozin therapy was associated with improvement in the NYHA class and requirement of diuretic intensification when compared to placebo (192).

Sotagliflozin is a dual SGLT1/SGLT2 inhibitor that increases urinary glucose excretion by SGLT2 inhibition and delays intestinal glucose absorption by SGLT1 inhibition. The SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes And Worsening Heart Failure) trial evaluated the efficacy and safety of sotagliflozin in patients with T2DM who were hospitalized with HF (HFpEF and HFrEF) (190). In this trial, Sotagliflozin therapy initiated before or shortly after hospital discharge reduced the combined endpoint of CVD death, HF hospitalization, or urgent HF visits by 33%.

Despite the guideline recommendations and strong clinical trial evidence supporting their benefits, SGLT2 inhibitor therapy utilization among patients with HF remains low. A recent nationwide retrospective cohort study analyzed the STLT2 inhibitor prescription patterns among patients hospitalized with HFrEF between July 2021 and July 2022 (193). Only 20% of eligible patients in this cohort were prescribed SGLT2 inhibitors at discharge. Moreover, the utilization was low even among patients with multiple indications, such as comorbid CKD and T2DM.

Table 1. Trials of SGLT2 Inhibitors in Patients with HF						
Medication	Trial	Publication Year	Patient Characteristics	History of T2DM	Follow-up Period	Primary Outcome* (HR, 95% CI)
Empagliflozin	EMPEROR- REDUCED (190)	2020	Symptomatic stable HF (LVEF ≤40%)	50%	16 months	0.75 (0.65 – 0.86)
Empagliflozin	EMPEROR- PRESERVED (194)	2021	Symptomatic stable HF (LVEF > 40%)	49%	26 months	0.79 (0.69 – 0.90)
Dapagliflozin	DAPA-HF(189)	2019	Symptomatic stable HF (LVEF ≤40%)	42%	18 months	0.74 (0.0.65 - 0.85)
Dapagliflozin	DELIVER(118)	2022	Symptomatic stable HF (LVEF > 40%)	45%	2.3 years	0.82 (0.73 – 0.92)
Sotagliflozin	SOLOIST-WHF (195)	2021	Recently hospitalized HF (All LVEF groups)	100%	9 months	0.67 (0.52 – 0.85)

*Primary outcome was a composite of cardiovascular death or hospitalization for HF.



Device Therapies for HFrEF

Implantable cardioverter-defibrillator (ICD) is strongly recommended (Class I) for primary prevention of sudden cardiac death in patients with symptomatic HFrEF who have an LVEF ≤35% despite guidelinedirected medical therapy for >3 months (3,18). HFrEF patients with diabetes carry a significantly higher risk of sudden cardiac death than those without diabetes (122). This observation highlights the importance of considering ICD in appropriately selected cases with HFrEF and diabetes. Strong evidence from major ICD trials has confirmed the sudden cardiac death risk reduction benefits of ICDs in individuals with coexisting HFrEF and diabetes (196,197).

Cardiac resynchronization therapy (CRT) is a wellestablished therapeutic modality in patients with HFrEF and prolonged QRS duration. In appropriately selected cases, CRT with biventricular pacing can improve LV systolic function and reduce the risk of morbidity and mortality through its ability to reverse the remodeling of LV (198). In major CRT trials, HFrEF patients with and without diabetes experienced similar overall effectiveness of CRT for reducing mortality and HF hospitalization (199–201). However, observational studies suggested that the magnitude of LV reverse remodeling and improvement of systolic and diastolic function may be less pronounced in individuals with diabetes than in those without diabetes (198,202,203).

Treatment of HFpEF

Until recently, the management of patients with HFpEF and HFmrEF lacked specific therapies shown to improve morbidity and mortality definitively. Clinical trials of pharmacologic agents with proven benefits in HFrEF have predominantly revealed neutral results in populations with HFpEF (30,31,204).

The guidelines focus on aggressive management of risk factors and comorbidities, exercise training, and symptom management with diuretics when volume overload findings are present in patients with HFpEF (3). The landscape of medical management of HFpEF has dramatically changed with the data from clinical trials evaluating the safety and efficacy of SGLT2 inhibitor therapy in patients with HFpEF (Table 1). The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) enrolled 5988 symptomatic patients with HF with LVEF >40% and elevated natriuretic peptides (194). In this trial, compared to placebo, empagliflozin therapy reduced the primary composite outcome of CVD death or HF hospitalization by 21%, primarily driven by a 29% reduction in HF hospitalization. SGLT2 inhibitor therapy was beneficial regardless of the presence or absence of T2DM. Based on the results of the EMPEROR-Preserved trial. the 2022 ACC/AHA/HFSA guidelines recommended (class IIa) SGLT2 inhibitor therapy to reduce CV death and HF hospitalization in patients with HFpEF and HFmrEF (3). Since the publication of these guidelines, the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) trial was completed (118). This trial demonstrated similar benefits of dapagliflozin therapy in patients with HF and LVEF >40%. Data from the PRESERVED-HF trial, a relatively small-size multicentric RCT, evaluated the impact of dapagliflozin on the quality of life and symptoms in patients with HFpEF. In this trial, 12 of dapagliflozin treatment weeks significantly improved patient-reported physical limitations and symptoms and objectively measured exercise tolerance (205).

The 2022 ACC/AHA/HFSA guidelines indicate that based on a subgroup analysis of RCTs, ARBs, MRAs, and ARNI (in appropriately selected patients) might be

considered (Class IIb) in patients with HFpEF or HFmrEF to decrease hospitalizations (3).

PHARMACOLOGIC THERAPY OF T2DM IN PATIENTS WITH HF

Lifestyle therapy is essential to managing patients with diabetes and established or high risk for HF. We point the readers to documents from ADA and ACC/AHA for detailed review and recommendations on lifestyle therapy in this patient population (3,4,157).

In this chapter, we provide a focused review of the effects of glucose-lowering agents from a HF perspective. Glycemic control is essential in patients with diabetes who have additional CV risk factors or established CVD. The ADA Standards of Medical Care in Diabetes recommend a holistic, multifactorial, and patient-centered approach when choosing antidiabetic medications. As per the guidelines, antidiabetic therapy should be selected according to patient-

specific goals such as cardiorenal protection or achieving and maintaining glycemic and weight management goals. Moreover, considering comorbidities, such as HF and CKD, is essential when determining management goals (23,141).

SGLT2 Inhibitors

In light of the evidence from CVOTs showing the benefits of CVD risk reduction and renal protection, the ADA recommends using GLP1-RAs or SGLT2 inhibitors as first-line agents in T2DM patients with high-risk or established ASCVD (23). In addition, SGLT2 inhibitors are the preferred first-line antidiabetic in patients with known HF or CKD (eGFR <60 ml/min/1.73 m² or albuminuria). This approach is a change from before, as the guidelines no longer require first-line metformin therapy before initiating SGLT2 inhibitors or GLP1-RAs when the therapy is started with the goal of cardiorenal risk reduction in high-risk patients with T2DM. (Table 2).

Patients with T2DM		
Risk Profile	First-line Therapy	Second-line Therapy if A1C is Above the Target
ASCVD* Indicators of High Risk**	GLP1-RA with proven CVD benefit Or SGLT2 inhibitor with proven CVD benefit	GLP1-RA with proven CVD benefit Or SGLT2 inhibitor with proven CVD benefit
Heart Failure	SGLT2 inhibitor with proven HF benefit	Follow the algorithm for the achievement of glycemic and weight management goals.
CKD***	SGLT2 Inhibitor with proven CKD benefits	GLP1-RA with proven CVD benefit

Table 2. Pharmacologic Therapy with a Goal of Cardiorenal Risk Reduction in High-Risk

*ASCVD, atherosclerotic cardiovascular disease: Individuals with established cardiovascular disease such as myocardial infarction, stroke, revascularization procedure, amputation, or symptomatic/asymptomatic coronary artery disease. **Indicators of high risk: ≥55 years of age with two or more additional risk factors such as obesity,

hypertension, dyslipidemia, smoking, and albuminuria. ***CKD, chronic kidney disease: GFR <60 ml/min/1.73 m² or albuminuria (albumin-creatinine ratio ≥30 mg/g). GLP1-RA, glucagon-like peptide-1 receptor agonists; A1C, hemoglobin A1c, SGLT2, sodium-glucose co-transporter -2.

A wealth of high-quality data proves the HF benefits of SGLT2 inhibitors in patients with T2DM. Since the publication of EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial results in 2015, (206) several large-scale CVOTs have revolutionized our understanding of the prevention of CV events and HF in patients with T2DM (Table 1 and 3).

In the EMPA-REG OUTCOME, empagliflozin, in the CANVAS (Canagliflozin Cardiovascular Assessment Study), canagliflozin and in the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58), dapagliflozin significantly reduced incident HF events as a secondary end-point in patients with established or high risk for CVD (206-208). The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial, designed to assess renal outcomes of canagliflozin, also showed a reduction in hospitalization for HF (HR:0.69, p<0.001) (209). In the VERTIS-CV (Cardiovascular Outcomes Following Ertugliflozin Treatment in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease) trial, ertugliflozin was non-inferior to placebo in regards to major CVD events in 8264 patients with T2DM and established CVD. In this trial, Ertugliflozin reduced the risk of HF hospitalization (an exploratory secondary outcome) by 30% (hazard ratio 0.70 [95% CI, 0.54 to 0.90]) (210).

A meta-analysis of 6 RCTs (EMPAREG-OUTCOME, CANVAS, DECLARE-TIMI 58, and CREDENCE,

VERTIS-CV) explored the CV benefits of 4 SGLT2 inhibitors in a combined sample size of 46969 patients with T2DM. In this meta-analysis, SGLT2 inhibitor therapy was associated with a reduced risk of MACE (HR, 0.90; 95% CI, 0.85-0.95), kidney outcomes (HR, 0.62; 95% CI, 0.56-0.70), and a combined outcome of CVD death and HF hospitalization (HR, 0.78; 95% CI, 0.73-0.84) (118).

The SCORE trial (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) evaluated the CV benefits of sotagliflozin, a dual SGLT1/SGLT2 inhibitor, against placebo in 10584 patients with T2DM, CKD, and risk of CVD. In this trial, Sotagliflozin reduced the coprimary end-point of MACE (HR; 0.84 [95% CI, 0.72 to 0.99]) and secondary end-point of HF hospitalization (HR; 0.67 [0.55–0.82]) (210).

In Europe and Japan, SGLT-2 inhibitors are approved as adjunctive therapy for T1DM in patients with a BMI of at least 27 kg/m². This recommendation is primarily based on the assumption that CV and renal protective effects of SGLT2 inhibitors can be generalized to T1DM populations. However, we still lack large-scale RCTs assessing the cardiorenal benefits of SGLT2 inhibitors in T1DM (211). Considering the high risk of diabetic ketoacidosis and the lack of proven diabetic ketoacidosis risk mitigation strategies, the U.S. FDA denied the approval of SGLT2 inhibitors for T1DM in the U.S.

Table 3. Heart Failure Hospitalization Risk with SGLT-2 Inhibitors in Patients with T2DM						
Medication	Trial	Publication Year	Patient Characteristics	History of HF	Follow- up Period	HF hospitalization (HR, 95% CI)
Empagliflozin	EMPA-REG OUTCOME (206)	2015	Established CVD	10%	3.1 years	0.65 (0.50 - 0.85)
Empagliflozin	EMPA-KIDNEY (212)	2023	CKD with or without albuminuria*	Not reporte d	2 years	0.84 (0.67 – 1.07) ** [p=0.15]
Canagliflozin	CANVAS Program (207)	2017	CV risk factors (34%) Established CVD (66%)	14%	3.2 years	0.67 (0.52 - 0.87)
Canagliflozin	CREDENCE (209)	2019	CKD with albuminuria	15%	2.6 years	0.61 (0.47 - 0.80)
Dapagliflozin	DECLARE-TIMI 58(208)	2019	CV risk factors (59%) Established CVD (41%)	10%	4.2 years	0.73 (0.61 - 0.88)
Dapagliflozin	DAPA-CKD (213)	2020	CKD with albuminuria	11%	2.4 years	0.71 (0.55 – 0.92) **
Ertugliflozin	VERTIS-CV (210)	2020	Established CVD	24%	3.5 years	0.70 (0.54 - 0.90)
Sotagliflozin	SCORED (214)	2020	CKD with a high risk for CVD	31%	16 months	0.67 (0.55 – 0.82)

*Estimated eGFR of 20 to 45 ml/min/1.73 m², or eGFR of 45 to 90 ml/min/1.73 m² with a urinary albumin-tocreatinine ratio of \geq 200 mg/g. **Composite secondary outcome of cardiovascular death and heart failure hospitalization. CKD, chronic kidney disease; CVD, cardiovascular disease.

Glucagon-like Peptide-1 Receptor Agonists

As mentioned above, GLP1-RAs are among the firstline agents for glucose-lowering and cardiorenal risk reduction in T2DM patients with indicators of high-risk or established ASCVD (23). In addition, GLP1-RAs are recommended as second-line therapy in patients with CKD if SGLT2 inhibitor therapy is contraindicated or not tolerated or if the HbA1c remains above target despite using an SGLT2 inhibitor.

Landmark CVOTs have confirmed the favorable effects of GLP1-RAs on the risk of major CV events such as CV death, nonfatal myocardial infarction, or

nonfatal stroke in patients with T2DM. However, individual trials revealed mostly neutral results regarding the effect of GLP1-RAs on HF outcomes in patients with T2DM and at risk for HF (Table 4) (215,216). Efpeglenatide was the only GLP-RA that significantly reduced HF hospitalization as a secondary end-point in a major CVOT, including T2DM patients with a history of CVD or CKD (217). U.S. FDA has not yet approved this agent.

Some early small-size trials raised concerns for increased risk of hospitalization or arrhythmia in response to GLP1-RA treatment in patients HFrEF (218). However, A recent meta-analysis of 7 RCTs, including 54,092 ambulatory patients with T2DM, revealed that GLP1-RAs reduced the composite of HF hospitalization and CVD death (HR 0.84, 95% CI: 0.76-0.92.) in patients without a prior history of HF. However, compared to placebo, GLP1-RAs did not reduce the same outcome in patients with a previous history of HF (219). Based on available data, GLP1-RAs may potentially prevent HF in patients with no history of HF. However, GLP1-RAs do not appear to reduce HF-related events in patients with a history of HF and coexisting diabetes (218).

GLP1-RAs (i.e., liraglutide and semaglutide) have also been approved as a medical therapy for weight loss in non-diabetic individuals with overweight or obesity. And in a landmark trial, treatment with tirzepatide, a novel combined glucose-dependent insulinotropic polypeptide and GLP1-RA, led to substantial and sustained weight loss and improvement of cardiometabolic parameters in individuals with obesity (220). Several ongoing CVOTs are expected to shed light on the CV-related efficacy and safety of semaglutide or tirzepatide therapy in people with obesity or overweight but without diabetes.

STEP-HFpEF (Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects with

Obesity-related Heart Failure with Preserved Ejection Fraction) trial has been the first RCT demonstrating the benefits of weight loss with a GLP1-RA in nondiabetic patients with HFpEF and obesity (BMI ≥ 30 kg/m^2) (221). In this trial, semaglutide once-weekly therapy for one year led to 13.3% weight loss and was associated with significant reductions in HF-related symptoms and physical limitations. In addition, patients treated with semaglutide experienced significant improvement in 6-minute wall distance and reduction levels of natriuretic peptide and c-reactive protein. Interestingly, fewer serious adverse events were observed with semaglutide than placebo. This trial was not powered to evaluate mortality and HF hospitalization outcomes properly. Another ongoing trial is investigating the impact of semaglutide in patients with HFpEF, obesity, and T2DM.

Metformin

As per the recent guidelines, metformin remains the preferred initial pharmacologic agent for treating T2DM if the treatment goal is achieving and maintaining glycemic control and weight management (23). The efficacy and safety of metformin in patients with HF have not been evaluated in dedicated prospective CVOTs. Therefore, metformin is no longer considered the first-line agent for cardiorenal renal risk reduction in T2DM patients with established or increased risk of HF. However, metformin can be used for glucose lowering in patients with T2DM and stable HF if eGFR remains >30 ml/min/1.73 m². However, it should be avoided in hospitalized patients with HF (141).

Data from retrospective studies and post hoc analysis of prospective RCTs predominantly supported the benefits and safety of metformin in HF populations (222). A meta-analysis of 9 observational studies conducted in the 2000s and early 2010s showed reduced mortality and no change in safety outcomes with the use of metformin compared to sulfonylurea therapy (predominantly) in HF populations (223). It should be noted that the U.S. FDA removed HF from the contraindication list of metformin in 2006 since the lactic acidosis risk is rare, and the benefits of metformin use in patients with HF were supported by observational studies (61).

Table 4. Effect of Glucose-Lo	owering Drugs on Heart Fa	ailure Hospitalization Risk in			
Patients with T2DM					
Drug Class	Medication	HF Hospitalization			
SGLT-2 Inhibitors	Empagliflozin	35% reduced risk			
	Canagliflozin	33% reduced risk			
	Dapagliflozin	27% reduced risk			
	Ertugliflozin	30% reduced risk*			
Dual SGLT1/SGLT2 Inhibitor	Sotagliflozin	33% reduced risk			
GLP-1 Receptor Agonists	Liraglutide	Neutral effect			
	Lixisenatide	Neutral effect			
	Semaglutide	Neutral effect			
	Albiglutide	Neutral effect			
	Exenatide	Neutral effect			
	Efpeglenatide	39% reduced risk			
DPP-4 Inhibitors	Saxagliptin	27% increased risk			
	Alogliptin	Neutral effect**			
	Sitagliptin	Neutral effect			
	Vildagliptin	Neutral effect			
	Linagliptin	Neutral effect			
Thiazolidinediones	Rosiglitazone	Increased risk***			
	Pioglitazone	41% Increased risk			

*Exploratory secondary outcome (primary outcome of MACE was similar to placebo). **Possible increase in the risk of HF hospitalization in patients without a history of HF at baseline (HR 1.76, 1.07–2.90). *** Increased risk of HF hospitalization and HF-related death (HR 2.10, 1.35-3.27).

DPP4 Inhibitors

CV safety and HF outcomes of DPP4 inhibitors have been examined in several large-scale CVOTs (Table 4). In the Savor-TIMI-53 trial, there was no significant difference between Saxagliptin and placebo regarding the primary outcome of CV events. However, saxagliptin use was associated with a 27% relative increase in the risk of HF hospitalizations (224). In the EXAMINE (Cardiovascular Outcomes Study of Alogliptin in Patients With Type 2 Diabetes and Acute Coronary Syndrome) trial, alogliptin use showed a non-significant trend towards (3.9% vs. 3.3%, p = 0.22) increased risk of HF hospitalizations in the entire study population with a history of T2DM and recent acute coronary syndrome (225). However, the subgroup analysis showed an unexpected increase (2.2% vs. 1.3%, p = 0.026) in the risk of HF hospitalizations among subjects without a previous history of HF at baseline. Contrarily, a similar increase in the risk of HF hospitalization was not observed with other DPP4 inhibitors in dedicated CVOTs (226,227). The mechanism of increased HF hospitalization risk with saxagliptin and alogliptin remains unknown.

A recent retrospective comparative-effectiveness study using a US health insurance data set compared the CVD outcomes among patients with T2DM who were prescribed a DPP4 inhibitor vs. an SGLT2 inhibitor (193). In this cohort, the DPP4 inhibitor therapy group experienced a higher risk of MACE and hospitalization for HF than those initiated on an SGLT2 inhibitor.

DPP4 inhibitors have become less popular due to their cost and limited effectiveness in CV risk reduction compared to SGLT2 inhibitors and GLP1-RAs. Therefore, they are not among the preferred first- or second-line agents for managing T2DM in patients with HF. Based on available data, saxagliptin should be avoided in patients with known or at risk for HF. Moreover, HF risk is listed in the prescribing precautions of alogliptin.

Insulin

No solid evidence exists to suggest that, in T2DM, improving glycemic control with insulin lowers HF risk in at-risk patients or improves outcomes in those with established HF. Even though some observational studies suggested an increased risk of CV mortality and HF in T2DM patients treated with insulin (228), limited prospective trial data did not support such an association. The ORIGIN Trial (Outcome Reduction With Initial Glargine Intervention) was a CVOT that examined the early use of basal insulin (glargine) versus standard care in patients with T2DM or prediabetes and a high risk of CVD. The study found that insulin glargine was neutral with regards to CV outcomes and HF events (229).

Sulfonylureas

Sulfonylureas (i.e., glipizide, glyburide, and glimepiride) are widely used glucose-lowering agents that promote weight gain and fluid retention (4). No dedicated RCTs evaluated the efficacy and safety of sulfonylureas in patients with HF. Data from post hoc analysis of prospective trials and observational studies have suggested either no change or worsening of HF outcomes with the use of sulfonylureas in patients with or without known HF. A recent population-based cohort study including older diabetic patients hospitalized for HF between 2006 and 2014 demonstrated that sulfonylurea initiation was associated with increased risk of future HF hospitalization (HR: 1.22; 95% CI: 1.00-1.48; P = 0.050) and mortality (HR: 1.24; 95% CI: 1.00-1.52; P = 0.045) (193). Based on current evidence, SGLT2 inhibitors, GLP1-RAs, and metformin are strongly preferable; sulfonylurea use should be avoided in patients with established or high risk for HF (4, 141).

Thiazolidinediones

Thiazolidinediones (rosiglitazone and pioglitazone) have been effective oral antidiabetics in treating T2DM, significantly reducing HbA1c. However, they carry a risk of HF exacerbation and thus should be avoided in patients with established or at risk for HF. (Table 4). Therefore, thiazolidinediones should not be used in patients with pre-HF or clinical HF (4). European Medicines Agencies and the U.S. FDA restricted the use of rosiglitazone, citing concerns about increased HF exacerbation after the publication of the results of the RECORD trial (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) (230). Similarly, the PROactive study (PROspective pioglitAzone Clinical In macroVascular Events) showed Trial an improvement in MACE but an increased risk of HF events with pioglitazone therapy in high-risk patients with T2DM (231). The worsening HF outcomes with the treatment of thiazolidinediones have mainly been attributed to their effect on fluid retention. Some studies have raised concerns about the adverse impact of thiazolidinediones on myocardial metabolism and remodeling (61,222). Because of the availability of better options and their potential unfavorable side effect profile, the popularity of thiazolidinediones has significantly declined.

CONCLUSIONS

HF and cardiomyopathy have a heterogeneous etiology in patients with diabetes. Diabetes-related comorbidities, such as CAD and hypertension, contribute to the pathogenesis of HF in patients with diabetes. The pathophysiologic link between diabetes and HF is multifactorial, involving various abnormal biochemical pathways. A complex interaction of these mechanisms contributes to the development of asymptomatic diastolic and systolic dysfunction, eventually leading to the clinical syndrome of HF.

The coexistence of diabetes and HF is a poor prognostic factor, and it poses a higher risk of HF hospitalization, all-cause mortality, and CVD mortality. Therefore, the prevention of asymptomatic cardiac remodeling and progression into symptomatic HF are among the primary goals of the clinical management of patients with diabetes. BP lowering has substantial benefits in preventing HF among individuals with diabetes. Despite the well-established favorable effects of weight loss, the role of lifestyle changes and weight loss in preventing HF among diabetic patients remains uncertain. Observational data demonstrated a significant reduction in HF outcomes in response to metabolic surgeries among patients with diabetes and morbid obesity.

Guideline-directed medical therapy for HF has robust morbidity and mortality benefits in individuals with or without diabetes. Subgroup analysis or meta-analysis of major HF RCTs demonstrated that the effectiveness of HF therapies such as beta-blockers, RAAS inhibitors, ARNI, and MRAs do not vary based on patients' diabetes status, and these therapies lead to similar reductions in morbidity and mortality among HF patients with or without diabetes.

Since 2015, several landmark clinical trials of SGLT2 inhibitors and GLP1-RA have revolutionized our understanding of CVD risk reduction in patients with T2DM and have led to a paradigm shift in the clinical practice recommendations for managing T2DM. SGLT-2 inhibitors are the preferred agents in the glucose-lowering regimen independent of baseline HbA1c in T2DM patients with known or at risk for HF.

Several dedicated major clinical trials confirmed the CVD benefits of SGLT2 inhibitors in patients with established HF, regardless of LVEF or diabetes status. High-quality data from these clinical trials transformed SGLT2 inhibitors from a glucose-lowering agent to a HF drug. Moreover, SGLT2 inhibitors are the only medication class with U.S. FDA approval and strong guideline indication (class I or IIa) for all HF patients across different LVEF groups.

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