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Heart Failure in Diabetis

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ABSTRACT

Patients with diabetes mellitus have >2× the risk for developing heart failure (HF; HF with reduced ejection fraction and HF with preserved ejection fraction). Cardiovascular outcomes, hospitalization, and prognosis are worse for patients with diabetes mellitus relative to those without. Beyond the structural and functional changes that characterize diabetic cardiomyopathy, a complex underlying, and interrelated pathophysiology exists. Despite the success of many commonly used antihyperglycemic therapies to lower hyperglycaemia in type 2 diabetes mellitus the high prevalence of HF persists. This, therefore, raises the possibility that additional factors beyond glycemia might contribute to the increased HF risk in diabetes mellitus. This review summarizes the state of knowledge about the impact of existing antihyperglycemic therapies on HF and discusses potential mechanisms for beneficial or deleterious effects. Second, we review currently approved pharmacological therapies for HF and review evidence that addresses their efficacy in the context of diabetes mellitus. Dysregulation of many cellular mechanisms in multiple models of diabetic cardiomyopathy and in human hearts have been described. These include oxidative stress, inflammation, endoplasmic reticulum stress, aberrant insulin signalling, accumulation of advanced glycated end-products, altered autophagy, changes in myocardial substrate metabolism and mitochondrial bioenergetics, lipotoxicity, and altered signal transduction such as GRK (g-protein receptor kinase) signalling, renin angiotensin aldosterone signalling and β-2 adrenergic receptor signalling. These pathophysiological pathways might be amenable to pharmacological therapy to reduce the risk of HF in the context of type 2 diabetes mellitus. Successful targeting of these pathways could alter the prognosis and risk of HF beyond what is currently achieved using existing antihyperglycemic and HF therapeutics.

Keywords- ***Diabetes Mellitus, Complications, Heart Failure, Risk Factors, Managment***

INTRODUCTION

Having an A1C of more than 7% was tied a greater chance of developing later stages of heart failure. For example, people with very early stages of heart failure are 1.5 and 1.8 times more likely to develop later stages of heart failure. Diabetes is also tied to developing heart failure more quickly and at a younger age.

Heart Failure Risk Is Significantly Increased in Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is a global epidemic and is expected to affect over 592 million people worldwide by 2035, a dramatic increase from 382 million people with diabetes mellitus in 2013,[1] a prevalence that is likely underestimated.[2] In the United States alone, an estimated 30.2 million adults or 12.2% had diabetes mellitus in 2015, of which 7.2 million (23.3%) were not aware or did not report having diabetes mellitus.[3] Both type 1 diabetes mellitus and T2DM are heterogenous diseases in which clinical presentation and disease progression may vary considerably. T2DM accounts for 90% to 95% of all diabetes mellitus cases,[4] for this reason, this review will focus on pharmacological treatments for T2DM and their impact on heart failure (HF) development. Patients with diabetes mellitus have over twice the risk of developing HF than patients without diabetes mellitus.[5,6]

The Framingham Heart Study suggests that diabetes mellitus independently increases the risk of HF up to 2-fold in men and 5-fold in women compared with age-matched controls,[7,8] highlighting a sex discrepancy that is incompletely understood. The increased incidence of HF in diabetic patients persists even after adjusting for other risk factors such as age, hypertension, hypercholesterolemia, and coronary artery disease. Thus, the term diabetic cardiomyopathy was coined over 40 years ago and was initially used to describe ventricular dysfunction in the absence of coronary artery disease and hypertension in diabetic patients.[9]

However, its use has been broadened to describe the increased vulnerability of the myocardium to dysfunction that characterizes individuals with diabetes mellitus. While 10% to 15% of the general population have diabetes, a recent study suggested that 44% of patients hospitalized for HF have diabetes mellitus.[10] The coexistence of comorbidities pose unique clinical challenges.[10] While the association between mortality and HbA_{1c} in diabetes mellitus patients with HF appears to be U-shaped, with the lowest risk of death in patients with HbA_{1c} levels of ≈7.1%,[11] other studies suggest that diabetes mellitus is independently associated with greater risk of death and rehospitalization compared with

nondiabetics with HF.[12] Additionally, observational data suggests a higher HbA_{1c} level was associated with increased incidence of HF.[13] Therefore, an important question to address is whether improved glycemic control improves HF outcomes.

MATERIALS AND METHODS

HF Epidemiology

Prevalence and Incidence of HF Among Individuals With Diabetes

The epidemiologic association between HF and diabetes is well recognized. Results of several longitudinal observational studies of population-based cohorts with diabetes and prediabetes, including Framingham Heart Study (**8**), First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (**9**), Reykjavik Study (**10**), and the Scottish diabetes mellitus register (**3**), have shown a two- to fourfold increased risk of HF among men and women with diabetes or prediabetes compared with those without (**8**,**10**). Additionally, HF was the most common first presentation of cardiovascular disease in individuals with T2D when evaluated in contemporary cohorts including millions of people with linked primary care, hospital admission, disease registry, and death certificate records in England. T2D was an independent risk factor for incident HF and increased HF-associated morbidity and mortality during a median 5.5-year follow-up period (**2**,**3**)

Prevalence Rate-

Given heightened risk for diabetes in those with HF, it is not surprising that data indicate a high prevalence of dysglycemia in this population, with prevalence ranging from 20% in community-based cohorts to ∼34% in pharmacological intervention trials for systolic HF , and up to 47% in acute decompensated HF.

Race-related differences have also emerged in the prevalence of diabetes in individuals with HF. Several studies have found the prevalence of diabetes to be 47–56% for Black, Hispanic, and Native American individuals with HF. Similarly, among individuals with impaired myocardial diastolic relaxation, diabetes is more common in Black (40.5%) and Hispanic (40.9%) individuals compared with White counterparts (27.2%) .

Risk Factors

The risk factors for HF in both T2D and T1D include diabetes duration, poor glycemic control, uncontrolled hypertension, hyperlipidemia, higher BMI, microalbuminuria, renal dysfunction, ischemic heart disease, and peripheral artery disease (**2**,**12**,**13**). Current trends suggest control of modifiable risk factors is poor in those with diabetes , emphasizing the importance of careful review of each during clinical visits.

HF Risk and Glycemic Control

Many landmark clinical trials have addressed the relationship between tight glycemic control and cardiovascular end points. The ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) showed that intensive glucose control, which lowered HbA_{1c} to 6.5% in type 2 diabetics, showed no evidence of a reduction in macrovascular events with no increase in mortality.[14] In contrast, the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes), which targeted HbA_{1c} to 6% in the intensive therapy group, had an increased mortality of 22% suggesting a potentially unexpected increased risk of intensive glucose lowering in high-risk patients with T2DM.

The finding of higher mortality resulted in this arm of the trial being terminated.[15] These findings were further supported by intensive glycaemic control in a veteran cohort over a 7.5-year period. They too reported intensive glycaemic control in patients with poorly controlled T2DM (baseline HbA_{1c} of 9.4%) had no significant effect on rates of major cardiovascular events or death.[16] Similarly, the UKPDS (United Kingdom Prospective Diabetes Study) successfully reduced HbA_{1c} by 11% over a 10-year follow-up but did not substantially reduce diabetes mellitus related mortality or myocardial infarction (MI).[17] Together these studies suggested that despite the efficacy of diabetes mellitus therapies in achieving lower HbA_{1c}, these therapies were not necessarily advantageous from a cardiovascular standpoint and some studies even showed an increase in cardiovascular events.

These findings underscore the important conundrum that normalization of glycemia might not restore risk of cardiovascular disease (CVD) to the nondiabetic baseline. Although HF was not a primary end point of these studies, post hoc analyses also suggested that intensive glucose lowering did not reduce and in some cases, increased the risk for HF or HF hospitalization.[18] Table 1 summarizes the relationship between diabetes mellitus therapy and HF. In summary, pharmacological agents that may have beneficial effects on cardiovascular outcomes include metformin, SGLT2i (sodium-glucose cotransporter 2 inhibitor) and certain GLP1RA (glucagon-like peptide 1 receptor agonist). However, others such as sulfonylureas (SUs), thiazolidinediones (TZDs), insulin, some GLP1RAs and some DPP4i (dipeptidyl peptidase 4 inhibitor) might exacerbate or increase the risk for HF.

Table 1. Summary of Effects of Diabetes Mellitus Treatments on Risk of Heart Failure

DM Therapy	Effects of Diabetes Mellitus Treatments on Risk of HF
Biguanide (Metformin)	Associated with better short-term and long-term prognosis in patients with HF[19]
	Associated with reduced mortality in HF patients[19]
	Reduces cardiac hypertrophy by AMPK-mediated repression of mTOR and as a consequence protein synthesis[20]
	AMPK activation by metformin can stimulate cardiac glucose uptake
Sulfonylureas (SU)	Originally thought to increase mortality
	No definitive CV outcome trial to evaluate CV safety of SUs vs placebo or other diabetic agents
	Meta-analysis reports no increased CV risk with SU treatment vs metformin
	Retrospective cohort study reported an increased CV risk in patients on SU vs metformin or DPP4 inhibitor
	No definitive CV outcome trials examining SUs in HF have been conducted
Thiazolidinediones (TZDs)	Reports on effects of TZDs on CV safety are conflicting.
	Beneficial effects were anticipated given improvements in glycemic control, inflammatory biomarkers, BP, TG levels and HDL
	PROactive trial showed no reduction in CV outcomes in patients on pioglitazone
	A meta-analysis reported an increased risk of MI with rosiglitazone
	IRIS trial reported lower risk of stroke and MI in patients on pioglitazone vs placebo
	Occurrence of fluid retention and weight gain is a reproducible side-effect of TZD therapy, which precludes its use in NYHA III and IV HF
Glucagon-like peptide-I (GLP-I) receptor agonist	Meta-analysis reports no increase risk in HF or hospitalization for HF among type 2 diabetics
	A meta-analysis revealed a modest improvement in ejection fraction in HF patients
	Trial of GLP-1 agonist in advanced HF revealed a trend toward increased hospitalization in diabetes mellitus subgroup
Dipeptidyl peptidase 4 (DPP4) Inhibitors	SAVOR-TIMI-53 Trial reported a significant increase in hospitalization for HF in patients on saxagliptin vs placebo
	EXAMINE and TECOS trials do not reveal increased HF risk
	Experimental studies in humans and animals show improvements in cardiac function when GLP-1 was activated by DPP4 inhibitor
	DPP4 knock out mice showed induction of cardioprotective gene signature post-MI
Sodium-glucose cotransporters 1 and 2 (SGLT1 and 2) Inhibitors	SGLT2 improves CV risk factors (weight reduction, reduction in SBP and improved lipid profile)
	EMPA-REG OUTCOME trial reported a reduction in CV mortality and hospitalization from HF using empagliflozin[42]
	CANVAS trial reported similar results for canagliflozin
	Meta-analysis of CV events in type 2 diabetics on dapagliflozin reported no increased risk for CV events
Insulin	Some observational trials have suggested a relationship between insulin use and HF risk
	CVOT with long acting insulin analogs do not demonstrate increased CV event rate or HF

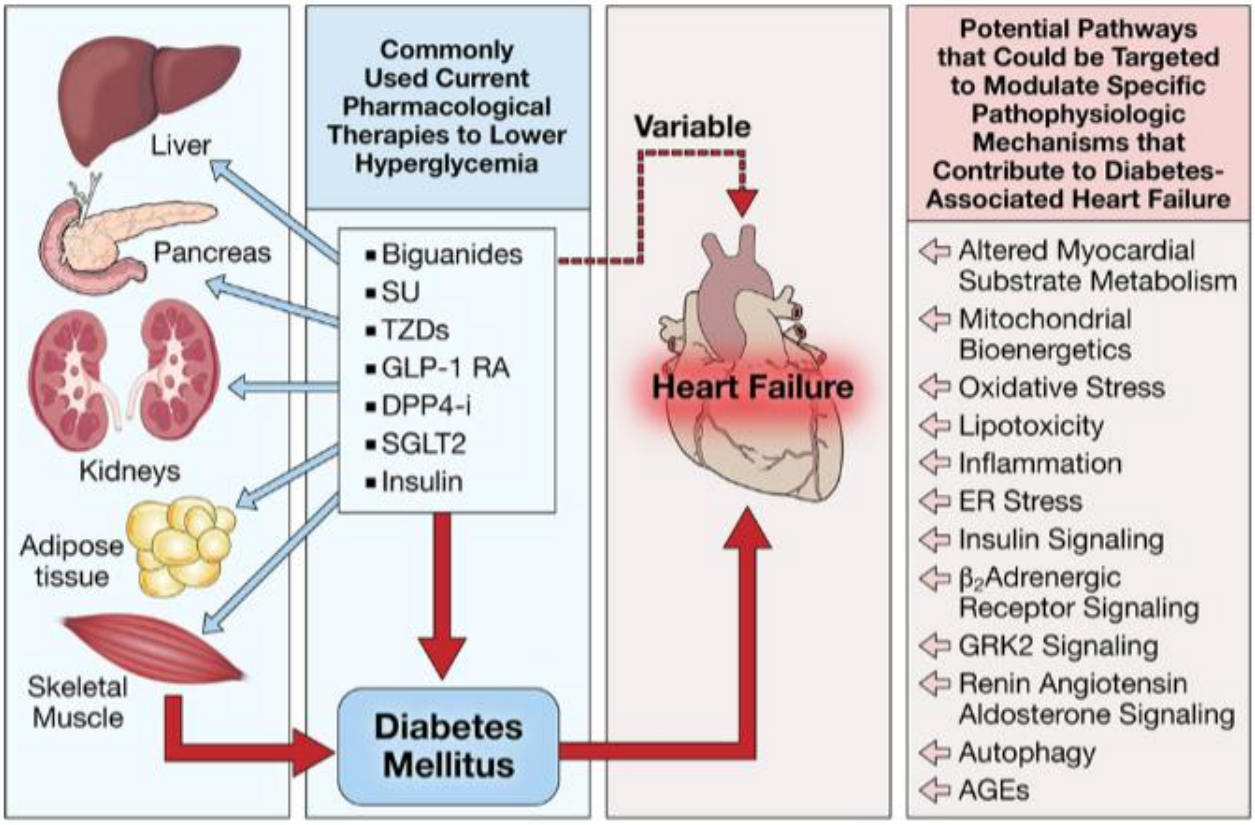

Table 2. Diabetes Mellitus Therapies and Their Mode of Action and Physiological Effects

DM Therapy	Mode of Action and Physiological Effect
Biguanide (Metformin)	Glucose lowering effect through the reduction in hepatic glucose production by suppressing gluconeogenesis[55]
	This is achieved by inhibition of complex I of the mitochondrial respiratory chain
	This reduces ATP production and results in accumulation of AMP
	Changes in AMP/ATP ratio activates AMPK
	AMPK activation promotes glucose uptake at skeletal muscle and inhibits glucose production by hepatocytes
	Metformin also reduces circulating TGs and VLDL and increases HDL
Sulfonylureas (SU)	Closes K_{ATP} channels on pancreatic β-cell plasma membrane by binding to SU receptors (SUR)
	Membrane depolarization, promotes calcium influx and release of insulin
	Extrahepatic actions: SUR2 exists in cardiac and skeletal muscle
Thiazolidinediones (TZDs)	Mediated through the activation of the ligand activated transcription factor, PPAR-γ primarily expressed in adipose tissue
	Increases skeletal muscle glucose uptake thereby reducing insulin resistance
	Reduces hepatic glucose uptake, hepatic glucose production and postprandial gluconeogenesis
	Promotes adipogenesis
Glucagon-like peptide-I (GLP-I) receptor agonist	GLP-I is an incretin hormone whose secretion is increased with an oral glucose load
	GLP-I receptor agonists activate GLP-I receptors which stimulates glucose-dependent insulin secretion in response to oral glucose load
	Stimulates proinsulin gene in the islets to replenish insulin and may promote β-cell proliferation and survival

DM Therapy	Mode of Action and Physiological Effect
	Suppresses glucagon secretion
	Delays gastric emptying, increasing satiety and promoting weight loss
Dipeptidyl peptidase 4 (DPP4) Inhibitors	DPP4 inhibits GLP-1
	DPP4 inhibition increases postprandial active incretin (GLP-I) concentrations
	Improves glucose-dependent insulin secretion
	Inhibits secretion of glucagon, suppressing hepatic glucose production and improves insulin sensitivity
Sodium-glucose cotransporters 1 and 2 (SGLT1 and 2) Inhibitors	SGLT2 causes renal glucose reabsorption across the luminal membrane of the epithelial cells of the proximal convoluted tubule (PCT)
	SGLT2 inhibitors block SGLT2 in the proximal nephron and therefore glucose reabsorption causing glucosuria
Insulin	Insulin administration activates insulin receptors
	This results in increased glucose disposal and reduced hepatic glucose production

HF Therapies and Their Effect on Glycaemic Control

While it is important to determine the impact of antidiabetic drugs on HF, it is also important to address the effects of HF therapies on HF outcome measures and glycaemic control in the setting of diabetes mellitus. We will briefly review the relationship between commonly used HF therapies and their potential relationship with glycaemic homeostasis in diabetes mellitus.

Pathophysiology

The pathophysiology of HF in individuals with diabetes is complex and reflects the interactions of multiple risk factors acting in concert with dysregulated subcellular pathways that extend beyond the consequences of diabetes-associated hyperglycemia, all leading to functional and structural changes in the diabetic heart.

- Individuals with diabetes may develop “diabetic cardiomyopathy,” defined as left ventricular systolic or diastolic dysfunction in the absence of other causes (such as CAD or hypertension), with excess risk in women.
- Both HFpEF and HFrEF may be present in diabetes.
- The pathophysiology of HF in individuals with diabetes reflects complex interactions between numerous pathways with deleterious effects on myocardial remodelling and muscle function.

HF: Diagnosis and Clinical Stages

HF represents a continuum of cardiac structural abnormality and dysfunction and associated cardiovascular risk. Useful means by which to classify the various stages of HF have been articulated by the ACC/AHA/HFSA (Heart Failure Society of America) HF guidelines and recently affirmed by the Universal Definition and Classification of Heart Failure task force .

Detection of people at high risk for HF (stage A) or those with stage B HF (without symptoms but with either structural/functional cardiac abnormalities or elevated biomarkers natriuretic peptides or troponin) would permit earlier implementation of effective strategies to prevent or delay the progression to advanced HF in individuals with diabetes, such as optimizing use of RAAS inhibitors and β-blockers or earlier initiation of other therapies with more recently proven ability to prevent progression of HF such as sodiumglucose cotransporter 2 (SGLT2) inhibitors (SGLT2i). However, the implementation of available strategies to detect asymptomatic HF has been suboptimal, highlighting opportunities for more widespread awareness of the subject and need for more assiduous application of beneficial therapies in such individuals.

Recommendations for Detection of Subclinical HF in Individuals With Diabetes

Among individuals with diabetes, measurement of a natriuretic peptide or high-sensitivity cardiac troponin is recommended on at least a yearly basis to identify the earliest HF stages and implement strategies to prevent transition to symptomatic HF.

This recommendation is based on the substantial data indicating the ability of these biomarkers to identify those in stage A or B at highest risk of progressing to symptomatic HF or death, together with evidence that the risk in such individuals may be lowered through targeted intervention or multidisciplinary care.

Clinical Examination.
For most individuals clinical signs may include weight gain and lower extremity edema. As part of the clinical examination , vital signs and volume status should be assessed, including current weight and recent changes in weight and assessment for physical findings consistent with congestion such as pulmonary rales . During cardiac examination, a laterally displaced apical impulse and a third heart sound may be helpful in evaluating chamber dilation and left ventricular filling pressures, respectively , and cardiac murmurs may be detected. In more advanced HF, the extremities may be cool due to increased systemic vascular resistance; this finding is most common among individuals in stage D.

Laboratory Evaluations and Imaging.
For individuals presenting with suspected or confirmed HF, guidelines recommend initial laboratory testing: complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, glucose, HbA_{1c}, fasting lipid profile, liver function tests, iron studies, and thyroid-stimulating hormone . In addition, a 12-lead electrocardiogram is recommended , which may identify a specific cause of HF (i.e., myocardial ischemia, uncontrolled arrhythmia) and may provide information to guide management strategies (e.g., rhythm abnormalities, QRS width for consideration of resynchronization therapy).

Biomarker Testing
Biomarker testing for BNP or NT-proBNP is recommended in individuals presenting with dyspnea to identify or exclude HF and gauge its severity . For stage C HF, similar to stage B, because of their high negative predictive value normal BNP and NT-proBNP levels exclude a diagnosis of decompensated HF . While not as high as the negative predictive value, the positive predictive value of an elevated BNP or NT-proBNP for the diagnosis of HF remains robust.

Increased levels of natriuretic peptide levels can be associated with several noncardiac causes, including advanced age, anemia, renal failure, obstructive sleep apnea, pulmonary hypertension, critical illness, and sepsis, as well as severe burns . The diagnostic accuracy of natriuretic peptides appears to be unaffected by the presence of diabetes . Further diagnostic evaluation for HIV, rheumatological diseases, amyloidosis, or pheochromocytoma may be indicated if there is high clinical suspicion .

Noninvasive Cardiac Imaging
Non-invasive cardiac imaging includes a chest X-ray and echocardiography.

MANAGEMENT OF HF IN DIABETES

Lifestyle and Nutrition
Lifestyle therapy is an important part of the management of HF risk. Several multilifestyle approaches have been proposed in this regard, such as the “Life’s Simple 7,” which provide an important roadmap for addressing modifiable risk factors for HF.

General Recommendations
For all individuals with HF and diabetes, minimizing alcohol intake and avoidance of smoking are recommended. The appropriate quantity of fluid and salt intake is a subject of debate. Strict limits should be imposed when there is clear fluid overload or demonstrated sensitivity to fluid intake that is not easily controlled with diuretics .

Role of Nutrition
Evidence is emerging on the role of nutrition plans in people with diabetes and HF. Dietary recommendations should be individually tailored according to caloric requirements, personal and cultural food preferences, prescribed medications, presence of overweight or obesity, and comorbid medical conditions.

Considerations should also include reducing intake of saturated fat, completely eliminating *trans* fat intake, decrease of energy density (<125 kcal/100 g of consumed food), and a preference for dietary patterns with a focus on the intake of vegetables, moderate amounts of fruit and whole grains, poultry, fish, low-fat dairy, legumes, nontropical vegetable oils, and nuts, such as with the Dietary Approaches to Stop Hypertension (DASH) or Mediterranean-style diets).

Exercise
There is a strong association between HF and physical inactivity and low fitness in general including in individuals with diabetes, underlining the importance of regular physical activity and exercise for prevention and treatment of HF .For instance, cardiac stiffness typically accelerates in midlife but can be reversed by aerobic exercise . In individuals with HFpEF, regular physical activity counteracts many of the metabolic and functional changes observed.

Therefore in people with diabetes and HF, exercise is recommended to improve functional capacity . Individually tailored plans that include risk stratification, clinical assessment, and cardiopulmonary exercise testing should be undertaken before initiation of exercise training for these individuals .

Weight Loss
Weight loss generally has significant cardiometabolic benefits and may be important in reduction of HF events. Look AHEAD (Action for Health in Diabetes) was conducted to evaluate whether an intensive lifestyle intervention could alter the risk of cardiovascular outcomes among individuals with T2D who were overweight or obese, and the resu lts reported showed that reductions in BMI were associated with lower risk of HF ; reductions in fat mass and waist circumference were each significantly associated with lower risk of HF with decline in waist circumference specifically associated with lower risk of HFpEF.

Targeting Social Determinants of Health
Recognition of social determinants of health (SDOH) factors is a necessary initial step needed to implement targeted measures toward improving HF outcomes in individuals with diabetes adversely affected by health disparities and developing comprehensive and culturally sensitive approach

SPECIAL CONSIDERATIONS

Cardiac Rehabilitation
Cardiac rehabilitation programs are useful adjuncts for the management of HFrEF . Comprehensive cardiac rehabilitation programs typically include a focus on exercise (see also *LIFESTYLE AND NUTRITION*), along with education on cardiovascular risk factors, psychological support, lifestyle modification, and medical care (including a focus on medications with secondary cardiovascular prevention benefits). The benefit of comprehensive cardiac rehabilitation programs in people with diabetes is significant: improving exercise capacity and a possible effect on MACE. Participation of individuals with diabetes in cardiac rehabilitation was associated with 44% reduction in all-cause mortality and 23% reduction in composite of mortality, myocardial infarction, or revascularization during a median follow-up of 8.1 years .

Current clinical practice guidelines have given a class I recommendation for use of cardiac rehabilitation for HFrEF. Troublingly, presence of diabetes as a comorbidity has been associated with lower likelihood for use of cardiac rehabilitation .

Cardiac Implantable Devices and Revascularization in HF
The principal indications for coronary artery revascularization and device therapy, including implantable cardioverter defibrillators (ICD) and cardiac resynchronization therapy (CRT), in individuals with diabetes are similar to those for patients without diabetes

DISCUSSION

- Diabetes medications have differential effects on HF risk, and each individual's cardiovascular risk factors should be carefully reviewed and considered in selecting a therapeutic regimen for diabetes.
- SGLT2i are an expected element of care in all individuals with diabetes and symptomatic HF and should be used in individuals with high cardiovascular risk, including those with stage B HF.
- If additional glycemic control is needed for an individual with T2D at high risk for or with established HF, use of GLP-1RA, metformin, or both should be favored over sulfonylureas.
- DPP-4 inhibitors or TZDs are not recommended for patients with diabetes with stage B, C, and D HF.
- Insulin treatment could be added if additional glycemic control is indicated.
- Periodic serum potassium monitoring and minimizing alcohol intake and avoidance of smoking are recommended.
- Regular tailored exercise is recommended as it has been shown to be beneficial in individuals with diabetes and HF.
- Weight loss improves cardiometabolic risk factors and may lower risk for HF.
- Hospitalization for decompensation or new-onset HF represents a pivotal moment in the disease journey of individuals with diabetes, as risk for adverse outcome rises substantially in this setting.
- During hospitalization, individuals with diabetes and HF should receive standard management per contemporary guidelines and consensus documents, which includes assessment for cause of acute HF and optimization of outpatient GDMT.
- Consider initiation or continuation of SGLT2i in the inpatient management for those with diabetes and acute HF.
- Given the proven CGM benefits in minimizing hypoglycaemia risk and optimizing glucose control in T1D and T2D across the age continuum, and across racially and socioeconomically diverse populations, the integration of CGM in the management of all individuals with diabetes at risk for or with HF should be considered.
- Metabolic surgery promotes improvements in risk factors relevant to HF and is directly associated with reduction in major cardiovascular events in those with HF and obesity and thus should be considered in these individuals to improve HF outcomes.

- The recommendations for advanced HF management, including automated ICD implantation and CRT, are similar to those for patients without diabetes.

CONCLUSION

Both T1D and T2D increase the risk of developing HF, and HF may be the first presentation of cardiovascular disease in many individuals with diabetes. A person with established diabetes (particularly in the presence of other risk factors) should be considered in stage A HF, and many people with diabetes have stage B HF.

Early diagnosis of HF could enable targeted treatment to prevent progression of disease and other adverse outcomes, but HF in individuals with diabetes is frequently underdiagnosed. Among individuals with diabetes, measurement of a natriuretic peptide or high-sensitivity cardiac troponin on at least a yearly basis is recommended to identify possible presence of stage B HF and to prognosticate risk for progression to symptomatic stages of the diagnosis. The management decisions that follow identification of an abnormal natriuretic peptide or high-sensitivity cardiac troponin should be individualized and might include further diagnostic studies, avoidance of treatments that increase HF risk, introduction of therapies with proven usefulness to prevent HF events, and involvement of a cardiovascular specialist. Conversely, pursuing further diagnostics or treatment regardless of negative biomarker results is not recommended because normal BNP and NT-proBNP levels have high negative predictive value and thus can exclude a diagnosis of HF.

Recommendations for GDMT of patients with HF and diabetes are in general similar to those for patients with HF without diabetes and should include ARNI (or ACEi/ARB if ARNI is not prescribed), evidence-based β-blockers, MRA, and SGLT2i. SGLT2i are an expected element of care in all individuals with diabetes and symptomatic HF, and their use should be expected for individuals with stage B HF. If additional glycaemic control is needed for an individual with T2D at high risk for or with established HF, use of metformin, GLP-1RA, or insulin should be favoured. Use of diabetes technologies, cardiac rehabilitation programs, and weight loss strategies should be considered to optimize care and adherence to optimal care. Women, individuals with T1D, and those with high-burdened SDOH should have access to and be offered the same management framework.

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