Circulation

AHA SCIENTIFIC STATEMENT

Type 2 Diabetes Mellitus and Heart Failure

A Scientific Statement From the American Heart Association and the Heart Failure Society of America

This statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update.

ABSTRACT: Type 2 diabetes mellitus is a risk factor for incident heart failure and increases the risk of morbidity and mortality in patients with established disease. Secular trends in the prevalence of diabetes mellitus and heart failure forecast a growing burden of disease and underscore the need for effective therapeutic strategies. Recent clinical trials have demonstrated the shared pathophysiology between diabetes mellitus and heart failure, the synergistic effect of managing both conditions, and the potential for diabetes mellitus therapies to modulate the risk of heart failure outcomes. This scientific statement on diabetes mellitus and heart failure summarizes the epidemiology, pathophysiology, and impact of diabetes mellitus and its control on outcomes in heart failure; reviews the approach to pharmacological therapy and lifestyle modification in patients with diabetes mellitus and heart failure; highlights the value of multidisciplinary interventions to improve clinical outcomes in this population; and outlines priorities for future research.

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More than 29 million adults in the United States have type 2 diabetes mellitus (DM),[1] whereas 6.5 million have heart failure (HF),[2] and both conditions are expected to continue to increase in prevalence over time. Although DM and HF are each individually associated with considerable morbidity and mortality, they often occur together, which further worsens adverse patient outcomes, quality of life, and costs of care. Identifying and implementing optimal treatment strategies for patients living with DM and HF is critical to improving outcomes in this high-risk population. Although there are separate, dedicated guidelines for the management of DM and HF as isolated conditions,[3–8] there is insufficient guidance on caring for patients with both DM and HF. Such guidance is necessitated by the shared pathophysiology of the 2 conditions, the potentially intersecting and discordant treatment approaches, and their synergistic effects on patient health. Furthermore, recent data from DM cardiovascular outcomes trials have underscored that HF is a critical outcome in patients with DM and suggest that glucose-lowering medications may influence the risk of HF development and progression. The purpose of this American Heart Association/Heart Failure Society of America joint scientific statement is to summarize current understanding of the epidemiology, pathophysiology, and outcomes of patients with type 2 DM and HF. In addition, it provides a review of contemporary data on the efficacy and safety of pharmacological and lifestyle management options in patients with DM at risk for HF and those with established disease. This document is not intended to replace or update the 2017

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Table 1. Incidence of HF in Individuals With and Without DM in Selected US Observational Studies

Study	Cohort	N	Follow-Up, y	Incidence of HF	Adjusted Risk of HF With vs Without DM	Population-Attributable Fraction
Framingham[21] (study sample included ages 45–74 y)	45–74 y	5209	Up to 20	Age-adjusted rates (person-years): DM (men): 7.6/1000 No DM (men): 3.5/1000 DM (women): 11.4/1000 No DM (women): 2.2/1000	RR (men): 1.82 RR (women): 3.75	Men: 7.7% Women: 18.0%
Cardiovascular Health Study[22]	>65 y	5888	Mean 5.5	Rates (person-years): DM (men): 44.6/1000 No DM (men): 22.9/100 DM (women): 32.5/1000 No DM (women): 12.1/1000	RR: 1.74 (95% CI, 1.38–2.19)	8.3%
Heart and Soul Study[23]	Stable CAD	839	Mean 4.1	Rates (person-years): DM: 36.6/1000 No DM: 17.9/1000	HR, 3.34 (95% CI, 1.65–6.76)	…
MESA[24]	4–84 y	6814	Median 4	…	HR, 1.99 (95% CI, 1.08–3.68)	DM-attributable risk: 19 per 1000
NHANES[25]	25–74 y	13643	Mean 19	Cumulative incidence at age 85 y: DM (men): 65.5% No DM (men): 36.9% DM (women): 61.8% No DM (women): 28.9%	RR, 1.85 (95% CI, 1.51–2.28) Similar in men and women	…
Retrospective cohort of Kaiser Permanente Northwest Database[17]		8231 +DM, 8845 no DM	Up to 6	Rates (person-years): DM: 30.9/1000 No DM: 12.4/1000 Rate ratio, 2.5 (95% CI, 2.3–2.7)	…	…

CAD indicates coronary artery disease; DM, diabetes mellitus; ellipses (…), not reported; HF, heart failure; HR, hazard ratio; MESA, Multi-Ethnic Study of Atherosclerosis; NHANES, National Health and Nutrition Examination Survey; and RR, relative risk.

American College of Cardiology/American Heart Association/Heart Failure Society of America heart failure guideline update.[7]

EPIDEMIOLOGY OF DM AND HF

Epidemic of DM and HF

The prevalence of type 2 DM has increased by 30% globally in the past decade, with the number affected increasing from 333 million in 2005 to 435 million in 2015.[9] As of 2015, 30.3 million Americans (9.4% of the US population) had DM.[1] HF affects at least 26 million people worldwide and is increasing in prevalence.[10] In the United States, an estimated 6.5 million adults have HF.[2]

DM and HF often occur concomitantly, and each disease independently increases the risk for the other. In HF cohorts, including both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), the prevalence of DM ranges from 10% to 47%.[11–15] The prevalence of DM is higher in patients hospitalized with HF, with some reports of >40%.[16] In patients with DM, the prevalence of HF is between 9% and 22%, which is 4 times higher than the general population,[17] and the prevalence is even higher in patients with DM who are ≥60 years old.[18–20]

DM as a Risk Factor for HF

Observational studies have consistently demonstrated a 2- to 4-fold increased risk of HF in individuals with DM compared with those without DM (Table 1). In the Framingham Heart Study, DM was associated with a nearly 2-fold increase in the risk of incident HF in men and a 4-fold increase in women, even after adjustment for other cardiovascular risk factors.[21] In patients with known coronary artery disease (CAD) in the Heart and Soul Study, DM was also associated with a higher adjusted risk of incident HF (hazard ratio [HR], 3.34 [95% CI, 1.65–6.76]).[23] The risk of HF associated with DM might be even higher in younger adults[17] and women.[21] DM is also an important predictor of the development of symptomatic HF in patients with asymptomatic left ventricular (LV) systolic dysfunction.[12] Furthermore, poor glycemic control is associated with greater risk for the development of HF; for each 1% increase in hemoglobin A_{1c} (HbA_{1c}), the risk of incident HF increases by 8% to 36%.[23,26–28] The risk of incident HF among patients with DM increases with older age,

CAD, peripheral arterial disease, nephropathy, retinopathy, longer duration of DM, obesity, hypertension, and higher NT-proBNP (N-terminal pro-B-type natriuretic peptide).[17,18,29,30]

The risk of HF is increased even with milder abnormalities in glucose regulation. In a prospective cohort study of 18 084 people without DM at high risk for cardiovascular disease, a 1-mmol/L higher fasting plasma glucose was associated with a 1.23-fold increased risk of HF hospitalization (95% CI, 1.03–1.47).[31] The ARIC study (Atherosclerosis Risk in Communities) similarly demonstrated a progressively increasing risk of incident HF hospitalization with a rising HbA_{1c} among participants without DM or HF.[32] Smaller studies further linked insulin resistance to an increased risk of incident HF[33] and the development of LV systolic and diastolic dysfunction.[34,35]

Subclinical Cardiac Abnormalities in Patients With DM

Patients with DM without symptomatic HF nevertheless often have subclinical abnormalities of cardiac structure and function corresponding to American College of Cardiology/American Heart Association stage B HF.[8] These changes include LV systolic dysfunction; DM-associated increases in LV mass, relative wall thickness, and left atrial size; diastolic dysfunction; and an increase in extracellular volume fraction.[36–43] The presence of each of these abnormalities is associated with increased risk of symptomatic HF and death.[40,41]

HF as a Risk Factor for DM

Metabolic impairment is intrinsic to HF pathophysiology, and insulin resistance is present in up to 60% of patients with HF.[44] Among nondiabetic patients with HF enrolled in the CHARM Program (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity)[45] and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure),[46] the incidence of DM was 28 and 21 per 1000 person-years, respectively, which is substantially higher than adults of similar age in the general population (9.4–10.9 per 1000 person-years for adults 45 and older).[47] The predictors of incident DM among patients with HF include elevated body mass index and waist circumference, history of smoking, elevated glucose or HbA_{1c}, higher systolic blood pressure, longer duration of HF, diuretic therapy, and higher New York Heart Association functional class.[45,46,48,49]

PATHOPHYSIOLOGY OF DM AND HF

DM can contribute to the development of structural heart disease and HF via systemic, myocardial, and cellular mechanisms. A recent state-of-the art review provides a detailed account of the underlying mechanisms of DM-associated HF.[50]

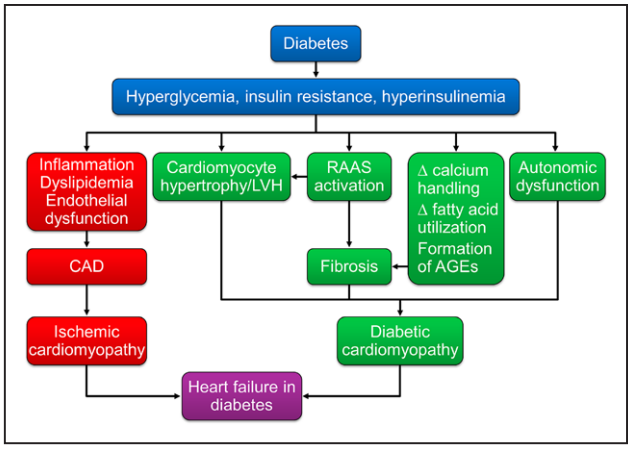

Figure 1. Pathophysiology of heart failure in diabetes mellitus. The hyperglycemia, insulin resistance, and hyperinsulinemia that often accompany diabetes mellitus trigger a cascade of deleterious effects that contribute to the development of heart failure in diabetes mellitus. AGEs indicates advanced glycation end products; CAD, coronary artery disease; LVH, left ventricular hypertrophy; and RAAS, renin-angiotensin-aldosterone system.

DM commonly causes structural heart disease and HF via myocardial ischemia/infarction.[51] Hyperglycemia and hyperinsulinemia accelerate atherosclerosis via vascular smooth muscle cell proliferation and inflammation (Figure 1). DM is also associated with more atherogenic dyslipidemia, in which low-density lipoprotein cholesterol particles are more atherogenic, and with endothelial dysfunction, which promotes leukocyte and platelet adhesion, thrombosis, inflammation, and coronary plaque ulceration.

DM can also cause myocardial disease in the absence of major epicardial CAD. The term *diabetic cardiomyopathy* was first introduced in 1972 by Rubler et al,[52] who found postmortem evidence of cardiomegaly in the absence of major CAD in 4 individuals with DM. Diabetic cardiomyopathy is defined as the presence of diastolic or systolic dysfunction in a patient with DM without other obvious causes for cardiomyopathy, such as CAD, hypertension, or valvular heart disease.

Imaging studies have shown that LV hypertrophy, thought to be caused by insulin resistance and hyperinsulinemia, is an important characteristic of the diabetic heart.[53] LV hypertrophy causes diastolic dysfunction, which is an early functional manifestation of diabetic cardiomyopathy and is present in 40% to 75% of patients with DM.[54] Hyperglycemia results in the formation of advanced glycation end products; advanced glycation end products cause cross-links in collagen molecules, leading to increased fibrosis with increased myocardial stiffness and impaired cardiac relaxation.[55] Maladaptive calcium homeostasis and endoplasmic reticular stress may also play a role in cardiomyocyte fibrosis and diastolic dysfunction.[56] Finally, hyperglycemia contributes to activation of the local renin–angiotensin–aldosterone system (RAAS), which leads to overproduction of angiotensin II

and aldosterone, which induces cardiac hypertrophy and fibrosis and exacerbates diastolic dysfunction.[57]

The diabetic heart is energy starved because of impaired glucose utilization and accordingly relies more heavily on free fatty acid utilization.[58] Excessively high fatty acid oxidation rates contribute to the abnormalities in energy metabolism and cardiac dysfunction that are observed in diabetic cardiomyopathy. Elevated levels of free fatty acids cause lipid accumulation in cardiomyocytes and lipotoxicity, which manifests as contractile dysfunction and eventual cardiomyocyte apoptosis. Cardiac magnetic resonance imaging studies have demonstrated that insulin resistance and DM are associated with a significant increase in cardiac lipid content.[59] In addition, an increase in mitochondrial reactive oxygen species production could explain metabolic substrate dysregulation, inflammation, increased apoptosis, and impaired calcium handling.[50] Recent human studies further linked mitochondrial dysfunction with cardiac abnormalities such as cardiac hypertrophy and fibrosis.[60,61] Analysis of myocardial tissue obtained from patients with DM at the time of elective heart surgery revealed a higher apoptosis rate.[62] Finally, DM and obesity may overlap in up to one-third of patients with HFpEF, and recent data suggest that this may be a distinct pathophysiological subgroup with increased plasma volume, greater LV and right ventricular remodeling, and worse exercise-induced hemodynamics.[63]

IMPACT OF DM ON HF OUTCOMES

Patients with HF and DM have worse clinical outcomes than patients with HF without DM. In population-based studies, concomitant DM increases the risk of death in both hospitalized and ambulatory patients with HF.[11,64–66] Multivariable HF risk models (eg, the MAGGIC [Meta-analysis Global Group in Chronic Heart Failure] risk score[67]) frequently highlight DM as an independent risk factor for death.[68] Outcomes other than mortality in patients with HF are also adversely affected by DM. Risk of hospitalization is up to 50% higher in patients with DM than in those without DM.[69–71] Hospital readmission is modestly increased in patients with DM.[72] Finally, patients with DM and HF have worse health-related quality of life than patients with HF alone.[73,74]

In community-based HF cohorts, presence of DM carries adverse risk of death and hospitalization for patients with HFrEF and HFpEF.[75] In the CHARM trial, DM was associated with a greater relative risk of cardiovascular death or HF hospitalization in patients with HFpEF (HR, 2.0 [95% CI, 1.70–2.36]) than in those with HFrEF (HR, 1.60 [95% CI, 1.44–1.77]; interaction P=0.0009), but for all-cause mortality, the risk conferred by DM was similar in both HFpEF and HFrEF.[76] In the I-PRESERVE trial (Irbesartan in Heart Failure With Preserved Ejection Fraction), over a median follow-up of 4.1 years, cardiovascular death or HF hospitalization occurred in 34% of patients with DM and HFpEF versus 22% of HFpEF patients without DM (adjusted HR, 1.75), and all-cause mortality was 28% and 19%, respectively (adjusted HR, 1.59).[77] A recent network analysis showed that biomarker profiles specific for HFrEF are related to cellular proliferation and metabolism, whereas those specific for HFpEF are related to inflammation and extracellular matrix reorganization.[78] How these pathophysiological differences might translate into different outcomes in patients with DM and HFpEF versus HFrEF remains to be determined.

MANAGEMENT OF DM IN HF

In this section, we will first review glycemic goals in patient with DM and HF. We will then provide a thorough discussion of the available glucose-lowering medications for patients with DM and their potential impact on cardiovascular and HF outcomes.

Glycemic Goals in Patients With DM and HF

Intensive treatment to achieve low HbA_{1c} targets in type 2 DM reduces the long-term risk of microvascular events (retinopathy, nephropathy, and peripheral neuropathy).[79–85] Although intensive glycemic control does not appear to reduce the risk of all-cause mortality, cardiovascular mortality, or stroke, it may reduce the risk of nonfatal myocardial infarction (MI).[86] Although hyperglycemia with or without DM is associated with increased risk of developing HF,[23,26–28] available data suggest that intensive glycemic control in patients with established DM does not reduce the risk.[87] The UKPDS (UK Prospective Diabetes Study),[84] ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation),[83] ACCORD (Action to Control Cardiovascular Risk in Diabetes),[88] and VADT (Veterans Affairs Diabetes Trial)[81] studies reported on HF as a secondary end point and found no difference in event rates between the intensive (mean HbA_{1c} 6.4%–7.0%) and standard (mean HbA_{1c} 7.3%–8.4%) treatment arms. Long-term follow-up of VADT reported no difference in the risk of new or worsening HF.[89] A meta-analysis of 8 randomized controlled trials (RCTs) that included 37 229 patients found no significant difference in the risk of HF between intensive glycemic control and standard treatment arms (odds ratio, 1.20 [95% CI, 0.96–1.48]).[87]

More recent RCTs have focused on the cardiovascular safety of glucose-lowering drugs (as mandated by the US Food and Drug Administration [FDA]) rather than the potential benefits of lower HbA_{1c} targets or more intensive therapies. These trials focused on the conventional 3-point major adverse cardiovascular event end point (cardiovascular death, MI, or stroke) but sometimes included

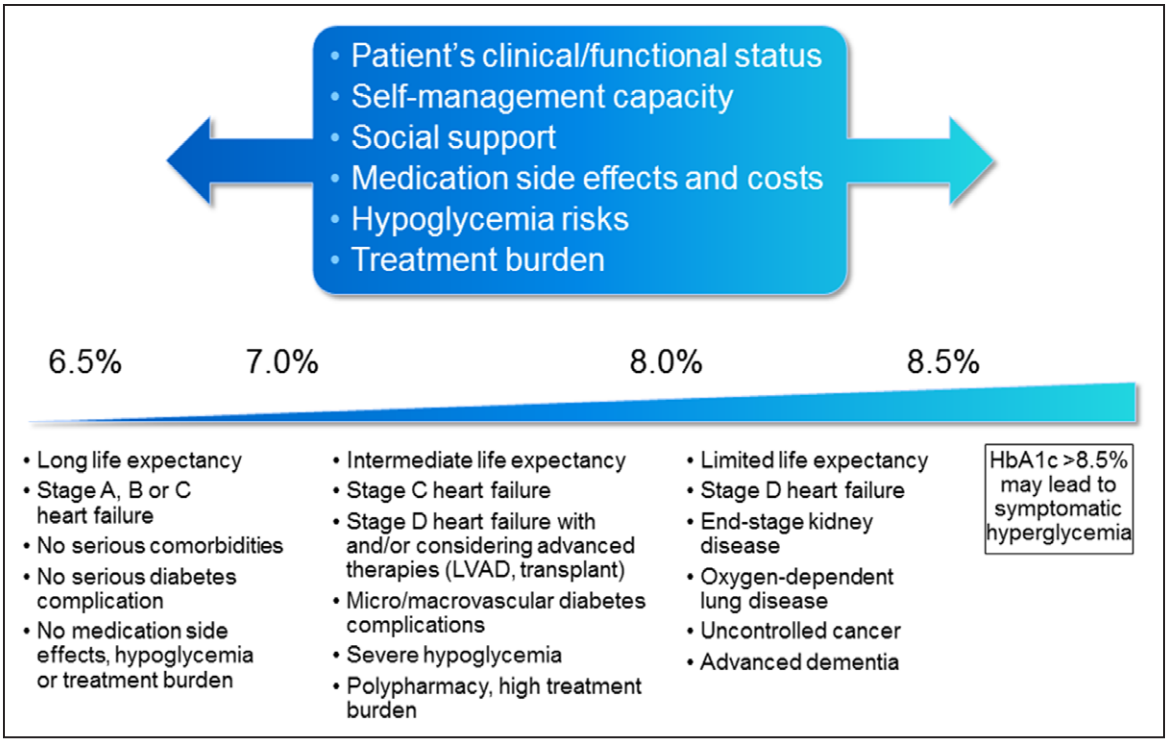

Figure 2. Hemoglobin A_{1c} (HbA_{1c}) goals in patients with diabetes mellitus and heart failure.
The HbA_{1c} goal should be individualized in patients with heart failure and diabetes mellitus based on the patient's clinical/functional status (life expectancy, comorbidities, presence of complications of diabetes mellitus), history of hypoglycemia, self-management capacity and support system, and overall treatment burden. LVAD indicates left ventricular assist device.

HF as a secondary end point (see Choice of Glucose-Lowering Pharmacotherapy in Patients With DM at High Risk for HF or With Established HF). Although participants in the investigational drug arms of these trials achieved net HbA_{1c} reductions between 0.3% and 0.6% compared with the comparator arms, any observed cardiovascular or HF benefits did not correlate with the degree of HbA_{1c} reduction and were thus largely independent of glycemic control.[90–98]

Observational studies suggest that moderate glycemic control may be optimal for patients with DM and HF. Although studies consistently demonstrated a progressive increase in the risk of incident HF or HF hospitalization with rising HbA_{1c},[27,99–103] this was most apparent when HbA_{1c} levels exceeded 8%,[100] 9%,[101,102] or even 10%.[104] Indeed, some studies identified higher HF event rates when HbA_{1c} levels fell below 6%.[100,104] The association between HbA_{1c} and mortality among patients with HF is consistently U shaped, with the lowest mortality in patients with HbA_{1c} 7% to 8%.[105–108]

Current DM management guidelines vary in the precise glycemic targets or ranges recommended, but most agree on HbA_{1c} thresholds ≤7.0% for the majority of adults with DM and no significant comorbidities or DM complications who are not experiencing severe hypoglycemia.[3–6] Older patients, particularly those with established microvascular or macrovascular complications or extensive comorbid conditions, are advised to target higher HbA_{1c} levels, up to 8% to 8.5%, depending on the guideline. Patients with short life expectancy, advanced microvascular or macrovascular complications, or any end-stage comorbidity are advised to treat to minimize symptomatic hyperglycemia and hypoglycemia, corresponding to HbA_{1c} 8% to 9%.[3–6]

Clinical Considerations

Optimal glycemic targets for patients with DM and HF should be individualized to reflect comorbidity burden, including the severity of HF, and to balance the benefits likely to be achieved by lowering HbA_{1c} with the potential risks. Potential harms of intensive treatment include hypoglycemia, polypharmacy, treatment burden, and high costs of care. The benefits of glucose-lowering therapy should also be considered within a broader context of the patient's life expectancy, because there is nearly a 10-year lag period to demonstrable benefit of more intensive glycemic control.[82,89] Moreover, treatment decisions need to consider potential benefits and harms of individual glucose-lowering medications (discussed in Choice of Glucose-Lowering Pharmacotherapy in Patients With DM at High Risk for HF or With Established HF).

Given the lack of HF-specific data to guide HbA_{1c} goals in patients with DM and HF, we suggest a target range of HbA_{1c} 7% to 8% for most patients with HF (Figure 2), consistent with DM clinical practice guidelines for

Table 2. Considerations for Use of Glucose-Lowering Medications

Class/Medication	Oral/SC	Cost	Hypoglycemia	Impact on Weight	Adjustment With CKD	FDA Black Box Warnings and Other Considerations
Biguanides Metformin	Oral	Low	No	Neutral, potential weight loss	Contraindicated with eGFR <30 Do not affect progression of kidney disease	FDA Black Box Warning: Lactic acidosis rare but can result in death, hypothermia, hypotension, and resistant bradyarrhythmias. Risk factors include renal impairment, concomitant use of certain drugs (eg, carbonic anhydrase inhibitors), age ≥65 y, having a radiologic study with contrast, surgery and other procedures, hypoxic states (eg, acute HF), excessive alcohol intake, and hepatic impairment. Discontinue immediately if lactic acidosis is suspected; prompt hemodialysis is recommended. Common side effects: nausea, diarrhea, potential for vitamin B_{12} deficiency with prolonged use Cardiovascular side effects: chest discomfort, palpitations
Sulfonylureas (2nd generation) Glipizide Glimepiride Glyburide	Oral	Low	Yes	Weight gain	Glyburide not recommended; glipizide and glimepiride can be used with caution Do not affect progression of kidney disease	Common side effects: dizziness/nervousness Cardiovascular side effects: may increase cardiovascular mortality,* syncope
Thiazolidinediones Rosiglitazone Pioglitazone	Oral	Low	No	Weight gain	Generally not recommended in CKD because of potential for fluid retention Do not affect progression of kidney disease	FDA Black Box Warning: Thiazolidinediones, including rosiglitazone, may cause or exacerbate HF; closely monitor for signs and symptoms of HF, particularly after initiation or dose increases. If HF develops, treat accordingly and consider dose reduction or discontinuation. Not recommended for use in any patient with symptomatic HF. Common side effects: fluid retention, bladder cancer (pioglitazone), increased LDL cholesterol (rosiglitazone), bone fractures
Insulin Human insulins: regular, NPH Analog insulins: Rapid-acting: aspart, lispro, glulisine, inhaled Long-acting: glargine, detemir, degludec Premixed insulins	SC	Human: low Analog: high	Yes	Weight gain	Can use at any eGFR but may require lower doses and frequent monitoring with worsening renal function Do not affect progression of kidney disease	Common side effects: weight gain Cardiovascular side effects: fluid retention
GLP-1 receptor agonists Liraglutide Lixisenatide Semaglutide Exenatide Albiglutide Dulaglutide	SC	High	No	Weight loss	Exenatide: not recommended if eGFR <30 Lixisenatide: caution with eGFR <30 Others can be used with dose adjustment Use caution with renal impairment; acute renal failure and worsening of chronic renal failure have been reported Liraglutide: may slow progression of kidney disease	FDA Black Box Warning: GLP-1 receptor agonists can increase the risk of thyroid C-cell tumors. They are contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2. Common side effects: nausea, diarrhea, cholelithiasis Cardiovascular side effects: increased heart rate

(*Continued*)

Table 2. Continued

Class/Medication	Oral/SC	Cost	Hypoglycemia	Impact on Weight	Adjustment With CKD	FDA Black Box Warnings and Other Considerations
DPP-4 inhibitors Saxagliptin Sitagliptin Alogliptin Linagliptin	Oral	High	No	Neutral	Can be used in renal impairment, but dose adjustment required	Common side effects: joint pain, acute pancreatitis have been reported Cardiovascular side effects: Saxagliptin has been associated with increased risk of HF hospitalization. Use DPP-4 inhibitors with caution in patients at risk for HF (eg, history of HF or renal impairment) and monitor for signs and symptoms of HF during therapy; consider discontinuation if HF develops. Peripheral edema is common.
SGLT-2 inhibitors Empagliflozin Canagliflozin Dapagliflozin	Oral	High	No	Weight loss	Contraindicated with eGFR <30† Canagliflozin not recommended if eGFR <45† Dapagliflozin not recommended if eGFR <60† Canagliflozin and empagliflozin may slow progression of kidney disease	FDA Black Box Warning: Canagliflozin has been associated with lower-limb amputations, most frequently of the toe and midfoot, in patients with type 2 DM who have established CVD or are at risk for CVD. Common side effects: bone fractures (canagliflozin), genital mycotic infections, ketoacidosis Cardiovascular side effects: hypotension,‡ elevated LDL cholesterol, volume depletion

CKD indicates chronic kidney disease; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate (in mL·min^{-1}·1.73 m^{-2}); FDA, US Food and Drug Administration; GLP-1, glucagon-like peptide-1; HF, heart failure; LDL, low-density lipoprotein cholesterol; NPH, neutral protamine Hagedorn; SC, subcutaneous; and SGLT-2, sodium glucose cotransporter type 2.

*Data to support this association are limited, and several studies, including a large prospective trial (UKPDS [UK Prospective Diabetes Study]), have not supported an association.

†Recommendation to not use with low eGFR is because of attenuated glycemic efficacy.

‡Caused by intravascular volume depletion.

patients with DM and serious comorbidities. For patients with advanced, stage D HF not pursuing mechanical circulatory support or transplantation, less stringent goals may be appropriate.

Choice of Glucose-Lowering Pharmacotherapy in Patients With DM at High Risk for HF or With Established HF

Available data to guide the clinical use of glucose-lowering medications are reviewed in this section by medication class. Potential considerations for use of glucose-lowering medications, including route of administration, cost, hypoglycemia risk, use in chronic kidney disease (CKD), contraindications, and adverse effects, are summarized in Table 2. The associations of glucose-lowering medications with cardiovascular outcomes in the cardiovascular outcomes trials are shown in Table 3 and Figure 3. In Table 4, clinical vignettes are used to demonstrate the application of these data to guide glucose-lowering medication choice in patients with DM.

Metformin

Metformin is currently recommended as the preferred initial pharmacotherapy in patients with type 2 DM in the absence of contraindications.[111] Metformin is effective, safe, and generally well tolerated. Although metformin was previously contraindicated in HF because of concerns regarding the rare risk of lactic acidosis, multiple observational studies suggest a survival benefit.[112–116] In a meta-analysis of 9 cohort studies of nearly 34 000 patients, metformin was associated with reduced mortality (pooled adjusted risk estimate, 0.80 [95% CI, 0.74–0.87]) and a small reduction in all-cause hospitalization (pooled adjusted risk estimate, 0.93 [95% CI, 0.89–0.98]) in patients with HF compared with control subjects.[117] In a large, propensity-matched observational study, initiation of metformin was associated with lower risk of HF hospitalization than sulfonylurea drugs.[118] Whether this reflects potential benefits of metformin or an adverse effect of sulfonylurea drugs is unknown. Small, randomized clinical trials (not powered to examine cardiovascular outcomes), including a subset of the UKPDS, also demonstrated metformin-associated reductions in macrovascular events, including MI and all-cause mortality.[85,119] In light of these findings, the FDA removed HF as a contraindication to metformin use in 2006.

Clinical Considerations

It is reasonable to use metformin in patients with DM at risk of or with established HF. Metformin should be discontinued in patients presenting with acute conditions associated with lactic acidosis, such as cardiogenic or distributive shock (Table 2).

Table 3. Impact of Glucose-Lowering Medications on Cardiovascular End Points in Cardiovascular Outcomes Trials

Medication Trial (Year)	Population	N	% HF	Median Follow-Up, y	Primary Outcome	Impact on Primary Cardiovascular End Point	Impact on HF Hospitalization
GLP-1 agonists							
Lixisenatide - ELIXA (2015)[93]	Recent ACS	6068	22	2.1	Cardiovascular death, MI, UA, stroke	No difference in risk (HR, 1.02 [95% CI, 0.89–1.17])	No difference in risk (HR, 0.96 [95% CI, 0.75–1.23])
Liraglutide - LEADER (2016)[91]	CVD or high risk	9340	14	3.8	Cardiovascular death, MI, stroke	Decreased risk (HR, 0.87 [95% CI, 0.78–0.97])	No difference in risk (HR, 0.87 [95% CI, 0.73–1.05])
Semaglutide - SUSTAIN-6 (2017)[92]	CVD or high risk	3297	24	2.1	Cardiovascular death, MI stroke	Decreased risk (HR, 0.74 [95% CI, 0.58–0.95])	No difference in risk (HR, 1.11 [95% CI, 0.77–1.61])
Exenatide - EXSCEL (2017)[109]	+/– CVD	14752	16	3.2	Cardiovascular death, MI, stroke	No significant difference* (HR, 0.91 [95% CI, 0.83–1.00])	No difference in risk (HR, 0.94 [95% CI, 0.78–1.13])
DPP-4 inhibitors							
Saxagliptin - SAVOR TIMI-53 (2014)[30,97]	CVD or high risk	16492	13	2.1	Cardiovascular death, MI, stroke	No difference in risk (HR, 1.00 [95% CI, 0.89–1.12])	Increased risk of HF (HR, 1.27 [95% CI, 1.07–1.51])
Alogliptin - EXAMINE (2013)[98]	Recent ACS	5380	28	1.5	Cardiovascular death, MI, stroke	No difference in risk (HR, 0.96; *P*<0.001 for noninferiority)	No difference in risk (HR, 1.19 [95% CI, 0.90–1.58])
Sitagliptin - TECOS (2016)[95,110]	CVD	14724	18	3.0	Cardiovascular death, MI, UA, stroke	No difference in risk (HR, 0.98 [95% CI, 0.88–1.09])	No difference in risk (HR, 1.00 [95% CI, 0.83–1.20])
SGLT-2 inhibitors							
Empagliflozin - EMPA-REG OUTCOME (2015)[90]	CVD	7020	10	3.1	Cardiovascular death, MI, stroke	Decreased risk (HR, 0.86 [95% CI, 0.74–0.99])	Decreased risk (HR, 0.65 [95% CI, 0.50–0.85])
Canagliflozin - CANVAS Program (2017)[94]	High cardiovascular risk	10142	14	3.6	Cardiovascular death, MI, stroke	Decreased risk (HR, 0.86 [95% CI, 0.75–0.97])	Decreased risk (HR, 0.67 [95% CI, 0.52–0.87])

ACS indicates acute coronary syndrome; CANVAS, Canagliflozin Cardiovascular Assessment Study; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG OUTCOME, BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EXAMINE, Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; GLP-1, glucagon-like peptide-1; HF, heart failure; HR, hazard ratio; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI, myocardial infarction; SAVOR TIMI-53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53; SGLT-2, sodium glucose cotransporter type 2; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin; and UA, unstable angina.

*In EXSCEL, the difference in the primary composite end point did not reach statistical significance (*P*=0.06). However, there was a significant reduction in all-cause mortality with exenatide (HR, 0.86 [95% CI, 0.77–0.97]).

Sulfonylurea Drugs

Limited data exist regarding the use of sulfonylurea therapy and the development of HF in individuals with DM. In the UKPDS, intensive glycemic control with sulfonylurea drugs or insulin in patients with newly diagnosed DM was not associated with increased rates of HF compared with conventional diet-based therapy.[84] In the BARI-2D trial (Bypass Angioplasty Revascularization Investigation 2 Diabetes) of patients with DM and CAD, treatment with sulfonylurea drugs, insulin, or both was associated with a similar risk of HF as a strategy of metformin, thiazolidinedione drugs (TZDs), or both.[120] In the ADVANCE trial, no difference in HF hospitalization was observed in patients randomized to standard glucose control (with no sulfonylurea drugs) or intensive glucose control with the use of gliclazide (plus other medications).[83] Contrary to these limited prospective trials, several observational studies have suggested that sulfonylurea therapy may be associated with increased risk of HF events compared with metformin[118,121,122] or newer agents,[123,124] although not all studies have yielded consistent findings.[125]

Despite the common use of sulfonylurea drugs in patients with HF, there are no RCTs examining their effect on clinical outcomes. In an observational study of Medicare beneficiaries with DM discharged after an HF hospitalization, there was no association between sulfonylurea use and subsequent mortality.[126] In observational studies of patients with DM and HF, sulfonylurea therapy was associated with greater risk of death than metformin.[113,114,127]

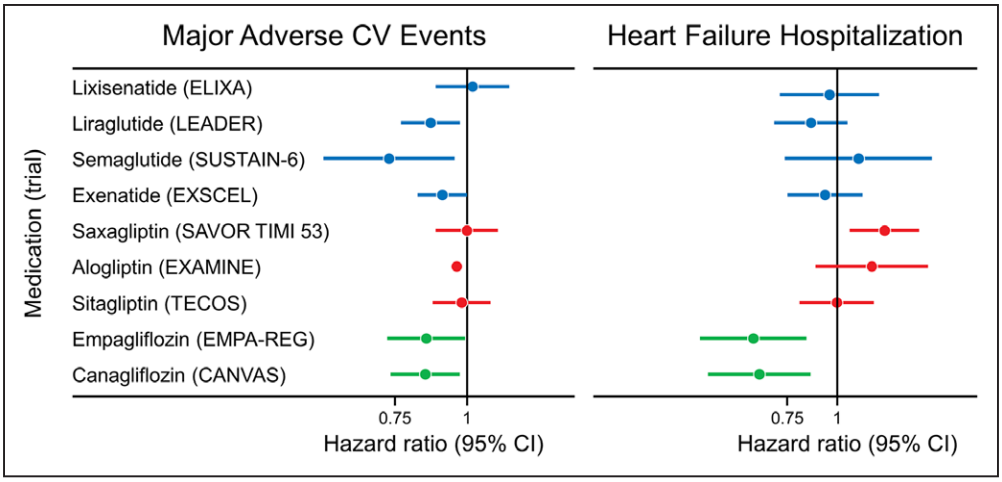

Figure 3. Associations of glycemic medications with risks of cardiovascular events and heart failure hospitalization.
The risks of major adverse cardiovascular events (**left**) and heart failure hospitalization (**right**) in the cardiovascular outcomes trials are shown. Trials of GLP-1 (glucagon-like peptide 1) receptor agonists are shown in blue, DPP-4 (dipeptidyl peptidase-4) inhibitors in red, and SGLT-2 (sodium glucose cotransporter type 2) inhibitors in green. The EXAMINE trial (Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care) was powered for noninferiority of cardiovascular events, with only a hazard ratio and 99% upper-limit CI reported. CANVAS indicates Canagliflozin Cardiovascular Assessment Study; CV, cardiovascular; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SAVOR TIMI-53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; and TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

Clinical Considerations

On the basis of the available data, use of other agents, such as metformin and SGLT-2 (sodium glucose cotransporter type 2) inhibitors (see SGLT2 Inhibitors), is preferable to use of sulfonylurea drugs in patients at high risk for HF and those with established HF**.** The ongoing CAROLINA trial (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes; URL: ClinicalTrials.gov. Unique identifier: NCT01243424) will offer the best evidence to date on the cardiovascular safety of sulfonylurea drugs, including effects on hospitalization for HF.

Insulin

Many patients with DM require insulin as monotherapy or in combination with other glycemic agents to achieve adequate glycemic control. The only RCT to specifically assess the cardiovascular safety of insulin was the ORIGIN trial (Outcome Reduction With Initial Glargine Intervention),[128] which randomized 12 537 individuals with pre-DM or DM to insulin glargine or standard care and found no difference in any cardiovascular outcomes, including hospitalization for HF.[128,129] Other trials of DM treatment strategies that have included insulin, such as UKPDS[84] and BARI-2D,[120] have not demonstrated increased rates of HF with insulin.

In contrast, observational studies suggested an increase in HF with insulin therapy.[17,130,131] Most[71,77,131–133] but not all[126] observational studies and subgroup analyses of clinical trials have demonstrated that insulin use is associated with greater risk of death in patients with DM and HF. Despite attempts to statistically adjust for differences between insulin users and nonusers, residual confounding is possible.

Clinical Considerations

Insulin is sometimes required to achieve adequate glycemic control in individuals with DM and HF. Insulin use is associated with weight gain and risk of hypoglycemia and should be used with caution and close monitoring. Other agents, such as metformin and SGLT-2 inhibitors, are preferred if adequate glycemic control can be achieved without insulin (Table 4).

Thiazolidinedione Drugs

RCTs have demonstrated that TZDs are associated with increased rates of HF hospitalization in patients without HF at baseline. In the PROactive trial (Prospective Pioglitazone Clinical Trial in Macrovascular Events), which included 5238 individuals with macrovascular disease, pioglitazone was associated with a reduced risk of cardiovascular death, MI, or stroke but an increased risk of HF events compared with placebo.[134] Similarly, in the RECORD trial (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) of 4447 patients with DM without HF,[135] the risk of HF hospitalization or death approximately doubled with rosiglitazone compared with sulfonylurea plus metformin.[135,136] Meta-analyses of randomized trials confirmed an increased risk of HF events with rosiglitazone or pioglitazone in individuals with DM.[137–139]

The association of TZDs with increased HF risk has also been demonstrated in patients with DM and HFrEF. Both rosiglitazone and pioglitazone are associated with fluid retention and HF events.[140,141] Despite this, no re-

Table 4. Patient Case Examples

Clinical Presentation	Choice of Glucose-Lowering Medication	
	Best Options	Avoid/Contraindicated
Case #1: 68-year-old woman at high risk for HF with DM, hypertension, hyperlipidemia, and coronary artery disease. Creatinine 1.1 mg/dL, eGFR 55 mL·min^{-1}·1.73 m^{-2}	Metformin SGLT-2 inhibitor: may decrease risks of cardiovascular events and HF hospitalization GLP-1 receptor agonist: may decrease risk of cardiovascular events	TZDs may increase the risk of HF DPP-4 inhibitors, sulfonylureas, insulin should be considered only if unable to achieve adequate glycemic control with alternative options
Case #2: 78-year-old man with DM, recently diagnosed stage C HFrEF caused by nonischemic cardiomyopathy (EF 30%). Creatinine 1.0 mg/dL, eGFR 77 mL·min^{-1}·1.73 m^{-2}	Metformin SGLT-2 inhibitor: may decrease risk of HF hospitalization	TZDs are contraindicated in HF Avoid DPP-4 inhibitors, because some may increase the risk of HF hospitalization (no increased HF signal with sitagliptin) Avoid GLP-1 receptor agonists if recent HF decompensation Sulfonylureas and insulin should be considered only if unable to achieve adequate glycemic control with alternative options
Case #3: 59-year-old man with DM and recently diagnosed stage C HFpEF (EF 60%). Creatinine 1.1 mg/dL, eGFR 71 mL·min^{-1}·1.73 m^{-2}	Metformin SGLT-2 inhibitor: may decrease risk of HF hospitalization	TZDs are contraindicated in HF Avoid DPP-4 inhibitors, because some may increase the risk of HF hospitalization (no increased HF signal with sitagliptin)
Case #4: 72-year-old woman with DM, stage C HFrEF caused by ischemic cardiomyopathy (EF 35%). Creatinine 2.0 mg/dL, eGFR 25 mL·min^{-1}·1.73 m^{-2}	Insulin	TZDs are contraindicated in HF Metformin should not be used with eGFR <30 mL·min^{-1}·1.73 m^{-2} Trials of SGLT-2 inhibitors at eGFR as low as 20 mL·min^{-1}·1.73 m^{-2} ongoing, but for now, should not use if eGFR <30 mL·min^{-1}·1.73 m^{-2} Other options (sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists if no recent HF decompensation) could be considered, but use with caution; may require dose adjustment

DM indicates diabetes mellitus; DPP-4, dipeptidyl peptidase-4; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SGLT-2, sodium glucose cotransporter type 2; and TZDs, thiazolidinedione drugs.

duction in ejection fraction (EF) was observed with TZD use,[140,142] which suggests that the predominant mechanism for increased HF events may be volume expansion caused by increased renal sodium reabsorption.[143] Observational data have also demonstrated increased risk of HF hospitalization with TZDs.[126]

Clinical Considerations

TZDs are not recommended in patients with established HF[144,145] and may increase the risk of HF events in individuals with DM without HF.

GLP-1 Receptor Agonists

GLP-1 (glucagon-like peptide-1) receptor agonists stimulate glucose-dependent insulin release with a low risk of hypoglycemia. Important secondary effects include a decrease in appetite and food intake, which leads to weight loss of 2 to 4 kg, and improved lipid levels, with decreased triglyceride levels and increased high-density lipoprotein levels. Albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide are FDA approved for the treatment of type 2 DM (Table 2). GLP-1 receptor agonists are administered subcutaneously and can be given alone or in addition to other glucose-lowering agents, including insulin.

In large-scale postmarketing cardiovascular outcomes trials required by the FDA to demonstrate the cardiovascular safety of glucose-lowering medications, GLP-1 receptor agonists have shown mostly beneficial effects on cardiovascular outcomes but no effect on HF hospitalization (Table 3; Figure 3). In the ELIXA RCT (Evaluation of Lixisenatide in Acute Coronary Syndrome),[93] lixisenatide, a short-acting and less potent GLP-1 agonist (up to 20 µg/d), did not alter the rate of major cardiovascular events compared with placebo in patients with recent acute coronary syndrome. However, in the LEADER study (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), liraglutide, a more potent and longer-acting GLP-1 agonist (up to 1.8 mg/d),[91] decreased the risk of cardiovascular death, MI, or stroke by 13%, as well as cardiovascular death and all-cause death, in patients at high risk for or with established cardiovascular disease. Although SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) was not powered to demonstrate cardiovascular superiority, semaglutide (0.5 or 1.0 mg/wk) decreased the rate of cardiovascular death, MI, or stroke by 26% compared with placebo.[92] In the EXSCEL trial (Exenatide Study of Cardiovascular Event Lowering), the risk of major cardiovascular events was numerically lower with exenatide (2 mg) versus placebo, although this difference did not reach not statistical significance.[96] Across all 4 trials, there was no difference in the risk of HF hospitalization in patients randomized to GLP-1 agonists compared with placebo. Notably, the baseline prevalence of HF in these studies ranged from 14.0% in LEADER to

23.6% in SUSTAIN-6. Because limited data characterizing the type of HF were provided, differential effects of medication by EF are unknown.

Despite no impact on HF hospitalization risk observed in the cardiovascular outcomes trials, results of animal and human studies suggested that GLP-1 receptor agonists may be beneficial in patients with established HF. In dogs with dilated cardiomyopathy, an infusion of recombinant GLP-1 improved LV contractility and cardiac output and decreased LV filling pressure and systemic vascular resistance.[146] In a mouse model of diabetic cardiomyopathy, administration of a selective GLP-1 agonist reduced LV hypertrophy, attenuated oxidative stress, and improved survival.[147] Nikolaidis et al[148] administered a 72-hour infusion of GLP-1 to 10 patients with acute MI and LV dysfunction and demonstrated improvement in regional and global LV function. In an open-label study, Sokos et al[149] infused GLP-1 for 5 weeks in 12 patients with New York Heart Association functional class III to IV HF. GLP-1 agonists increased EF, exercise capacity, and quality of life. More recently, Nathanson et al[150] studied the hemodynamic effects of exenatide in patients with DM and HFrEF. Compared with placebo, exenatide increased cardiac index and decreased pulmonary capillary wedge pressure; however, there were also concerns about increased heart rate because of its direct effect on the sinus node.

Against this background, Margulies et al[151] sought to determine whether a GLP-1 receptor agonist could improve clinical stability after hospitalization for acute HF. The FIGHT study (Functional Impact of GLP-1 for Heart Failure Treatment) randomized 300 patients with chronic HFrEF and recent HF hospitalization to liraglutide (1.8 mg/d) or placebo for 6 months. Compared with placebo, liraglutide had no effect on posthospitalization clinical stability and tended to increase the risk of HF readmission (41% versus 34%; HR, 1.30 [95% CI, 0.89–1.88]). Similar disappointing results with liraglutide were reported in an RCT from Denmark.[152] In 241 patients with stable HFrEF with or without DM, liraglutide (1.8 mg/d) had no effect on LV function at 24 weeks and was associated with an increase in heart rate and more serious cardiac events. Lastly, a 12-week study of albiglutide, a novel long-acting GLP-1 agonist, in stable patients with HFrEF demonstrated no significant effect on LVEF, submaximal exercise capacity, or quality of life.[153] As expected, both liraglutide and albiglutide resulted in a 1 to 2 kg weight loss.

Other cardiovascular and off-target effects of GLP-1 agonists may explain the variable results in patients with cardiovascular risk and those with HF.[154] GLP-1 agonists increase heart rate by 3 to 10 beats/min while lowering systolic blood pressure by 2 to 3 mm Hg.[155] The latter effect could be caused in part by improved endothelium-dependent vasodilation.[156] Preclinical and clinical data also suggest that GLP-1 agonists can improve renal function by enhancing natriuresis and reducing albuminuria and can decrease systemic inflammation and platelet aggregation. In addition to cost and the need for parenteral administration, adverse effects of GLP-1 agonists that have slowed their uptake in clinical practice include delayed gastric emptying leading to nausea, vomiting, and possible increase in the risk of cholelithiasis (Table 2).

Clinical Considerations

GLP-1 receptor agonists may reduce the risk of major adverse cardiovascular events and mortality in the general population of patients with DM. GLP-1 receptor agonists have had no impact on the risk of HF hospitalization in large RCTs, which suggests they are safe to use but not beneficial in preventing HF in patients at risk for HF. In patients with established HFrEF and recent decompensation, GLP-1 receptor agonists should be used with caution, given no evidence of benefit and a trend toward worse outcomes in 2 small RCTs. There are no data to guide their use in HFpEF.

Dipeptidyl Peptidase-4 Inhibitors

DPP-4 (dipeptidyl peptidase-4) is an enzyme involved in the rapid degradation of GLP-1, and thus, the effects of the incretin system could be enhanced by DPP-4 inhibition.[157] Alogliptin, linagliptin, saxagliptin, and sitagliptin are FDA approved for the treatment of type 2 DM (Table 2). These oral medications are included in practice guidelines as a second-line option after metformin.[158]

Several DPP-4 inhibitors have been evaluated in large-scale cardiovascular outcomes trials (Table 3; Figure 3). In SAVOR TIMI-53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53), the risk of cardiovascular events was similar with saxagliptin compared with placebo in patients with DM at high risk for cardiovascular events; however, there was a surprising 27% relative increase in the risk of HF hospitalization.[30] In the EXAMINE trial (Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care), alogliptin had no effect on the risk of cardiovascular events compared with placebo in patients with DM and recent acute coronary syndrome.[98] In contrast to SAVOR TIMI-53, no significant difference in the risk of HF hospitalization was observed. Finally, the TECOS trial (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) demonstrated no impact of the DPP-4 inhibitor sitagliptin on risk of cardiovascular events or HF hospitalization.[110] Two meta-analyses evaluating the risk of HF hospitalization with DPP-4 inhibition showed no statistically significant increase in risk compared with placebo (relative risk, 1.118 [95% CI, 0.997–1.254]; P=0.06[159] and HR, 1.13 [95% CI, 1.00–1.28][160]). However, in a recent network meta-analysis of 236 trials,

the risk of HF was higher with DPP-4 inhibitors than with either GLP-1 receptor agonists (HR, 1.22 [95% CI, 1.05–1.42]) or SGLT-2 inhibitors (HR, 1.81 [95% CI 1.50–2.18]).[160]

Importantly, only a small minority of patients enrolled in the SAVOR TIMI-53, EXAMINE, and TECOS trials had established HF. The VIVIDD trial (Vildagliptin in Ventricular Dysfunction Diabetes) of vildagliptin, another DPP-4 inhibitor, was a mechanistic study that specifically enrolled patients with DM and reduced EF. The primary end point, a change in EF from baseline to 52 weeks, showed no difference between vildagliptin and placebo; however, LV diastolic and systolic volumes were both significantly higher in patients treated with vildagliptin.[161] Somewhat reassuringly, a real-world observational study of nearly 1.5 million patients across several countries compared incretin-based therapies, both GLP-1 receptor agonists and DPP-4 inhibitors, to other glucose-lowering drugs, using claims data to evaluate HF outcomes.[162] There was no increase in HF hospitalization with either GLP-1 receptor agonists or DPP-4 inhibitors compared with other glucose-lowering therapies.

Additional data are still needed to determine whether there is, in fact, a higher risk of HF with DPP-4 inhibitors in individuals with DM. Some additional information could come from the CARMELINA trial (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus; URL: ClinicalTrials.gov. Unique identifier: NCT01897532), which compares linagliptin versus placebo in ≈7000 patients. In addition, the currently ongoing MEASURE-HF trial (Mechanistic Evaluation of Glucose-lowering Strategies in Patients With Heart Failure; URL: ClinicalTrials.gov. Unique identifier: NCT02917031), which is evaluating the effects of saxagliptin, sitagliptin, or placebo in patients with DM and HFrEF, will provide additional mechanistic data via detailed evaluation of LV size and function using cardiac magnetic resonance.

Clinical Considerations

There is no evidence that DPP-4 inhibitors provide cardiovascular benefit. In patients with DM at high cardiovascular risk, some DPP-4 inhibitors could increase the risk of hospitalization for HF. The effects in patients with established HF have not been well studied, with some potentially concerning signals in mechanistic trials. On the basis of these data, the risk-benefit balance for most DPP-4 inhibitors does not justify their use in patients with established HF or those at high risk for HF.

SGLT-2 Inhibitors

SGLT-2 inhibitors lower glucose via an insulin-independent mode of action through increased urinary excretion of glucose.[163] In addition to glucose excretion, SGLT-2 inhibitors increase fractional excretion of sodium and have modest diuretic and natriuretic effects. Canagliflozin, dapagliflozin, and empagliflozin are FDA approved for the treatment of type 2 DM (Table 2).

The EMPA-REG OUTCOME trial (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) randomized patients with DM and cardiovascular disease to 10 or 25 mg of empagliflozin versus placebo (Table 3; Figure 3).[90] Patients treated with empagliflozin experienced a 14% relative decrease in the risk of major cardiovascular events compared with placebo; this was primarily driven by a 38% reduction in cardiovascular death.[90] Although the trial enrolled primarily patients with DM and atherosclerotic cardiovascular disease (≈10% of patients had HF at baseline), there was also a 35% reduction in HF hospitalizations, an effect that was observed within weeks of randomization. This lower risk of acute HF was consistent between those with and without a history of HF.[164]

The CANVAS Program was a combination of the original canagliflozin cardiovascular safety trial (CANVAS [Canagliflozin Cardiovascular Assessment Study]) and a separate CANVAS-R trial (CANVAS-Renal) designed to examine cardiovascular safety. Patients with established cardiovascular disease (65%) or at high risk for cardiovascular events (35%) who were treated with canagliflozin experienced a 14% reduction in the risk of major cardiovascular events and a 33% relative reduction in the risk of HF hospitalization compared with placebo.[94] Additional analyses suggested the morbidity and mortality benefits might be greater in patients with a prior history of HF.[165] A large, international observational study (CVD-REAL [Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors]) combined registry data across 6 countries and evaluated >300 000 patients with DM, 87% of whom did not have cardiovascular disease at baseline.[166] After propensity matching, initiation of SGLT-2 inhibitors versus other glucose-lowering agents was associated with a 39% relative decrease in the risk of HF hospitalization, which suggests that HF benefits observed in clinical trials might extend to a broader population of patients with DM seen in clinical practice.[166] In the subsequent multinational CVD-REAL2 study, which used a similar approach but included patients from 6 other countries, SGLT-2 inhibitors were associated with a 49% lower risk of death and 36% lower risk of HF hospitalization.[167]

The potential mechanisms by which SGLT-2 inhibitors might reduce HF-associated risk remain unclear and are the subject of ongoing investigation.[168] In fact, mechanisms beyond glucose lowering or diuresis might explain the reduction in HF events.[163] Provocative animal studies of SGLT-2 inhibitors show reductions in oxidative stress, improvement in endothelial function and neurohormonal modulation, and anti-inflammatory effects.[163,169] Most recently, it has been postulated that reduction in plasma volume without neurohormonal

activation,[170,171] or possibly a change in metabolic fuel sources away from glucose oxidation to free fatty acid and ketone bodies, could play a role in improving myocardial efficiency.[172] Supporting a pleotropic effect of SGLT-2 inhibitors is a recent randomized controlled study in older patients with DM, in which canagliflozin attenuated a rise in serum NT-proBNP and high-sensitivity troponin I at 26, 52, and 104 weeks.[173]

Potential benefits of SGLT-2 inhibitors in patients with established HF are being investigated in several large outcomes trials. The EMPEROR-PRESERVED (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; URL: ClinicalTrials.gov. Unique identifier: NCT03057951) and EMPEROR-REDUCED (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction; URL: ClinicalTrials.gov. Unique identifier: NCT03057977) trials will evaluate the effects of empagliflozin versus placebo on clinical outcomes in HFpEF and HFrEF, respectively, whereas DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure; URL: ClinicalTrials.gov. Unique identifier: NCT03036124), will evaluate the effects of dapagliflozin versus placebo on outcomes in 4500 patients with HFrEF, the complementary DELIVER trial (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; URL: ClinicalTrials.gov. Unique identifier: NCT03619213) will evaluate dapagliflozin versus placebo in HFpEF, and the SOLOIST-WHF trial (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure; URL: ClinicalTrials.gov. Unique identifier: NCT03521934) will evaluate the effects of sotagliflozin (a combined SGLT-1 and SGLT-2 inhibitor) in patients with worsening heart failure and EF <50%. The first 3 trials include patients with and without DM, thus specifically evaluating the potential role of SGLT-2 inhibition as a treatment for HF in patients without DM. In addition, the DEFINE-HF (Dapagliflozin Effect on Symptoms and Biomarkers in Patients With Heart Failure; URL: ClinicalTrials.gov. Unique identifier: NCT02653482), PRESERVED-HF (Dapagliflozin in Preserved Ejection Fraction Heart Failure; Unique identifier: NCT03030235), and EMBRACE-HF (Empagliflozin Impact on Hemodynamics in Patients With Heart Failure; Unique identifier: NCT03030222) trials are evaluating the potential mechanisms of SGLT-2 inhibitors in patients with established HFrEF and HFpEF.

Clinical Considerations

SGLT-2 inhibitors are the first class of glucose-lowering agents demonstrated to reduce the risk of HF hospitalization in patients with DM. Combined with significant reductions in cardiovascular and all-cause mortality seen with empagliflozin, it is reasonable to consider SGLT-2 inhibitor use as part of a prevention strategy in patients with DM at high risk for HF. Because secondary analyses of the cardiovascular outcomes trials have suggested that SGLT-2 inhibitors reduce the risk of HF hospitalization in patients with and without HF at baseline, SGLT-2 inhibitors are also a good glucose-lowering medication choice in patients with established HF and DM. Although this class appears promising for treatment of established HF in patients without DM, recommending their use in this patient group would be premature until appropriately powered trials are completed. Cardiovascular benefits of SGLT-2 inhibitors should be balanced with their potential risks, including genital candidiasis and other, rare potential complications, such as euglycemic diabetic ketoacidosis, lower-limb amputation, and fractures (the latter 2 complications only observed with canagliflozin to date; Table 2).

MANAGEMENT OF HF IN DM

In this section, we will first summarize existing data comparing the effectiveness of HF therapies in patients with and without DM from RCTs. Next, we will discuss the safe use of HF medications in patients with CKD. Finally, we will review the impact of HF medications on glycemic control.

Summary of DM Subgroup Data From Pivotal HF Studies

RAAS and Angiotensin Receptor Neprilysin Inhibitors

A meta-analysis[174] of 6 angiotensin-converting enzyme (ACE) inhibitor trials (Table 5) demonstrated similar reductions in morbidity and mortality in patients with HF with or without DM. The pooled analysis of 2398 patients found a relative risk for death of 0.84 (95% CI, 0.70–1.00) in patients with DM versus 0.85 (95% CI, 0.78–0.92) in those without DM. The absolute reduction in mortality with ACE inhibitors in individuals with DM is substantial because of their baseline higher mortality risk. Similar results were seen in pivotal HF trials of angiotensin receptor blockers (ARBs), including CHARM, where the effect of candesartan in reducing cardiovascular morbidity and mortality was not modified by DM.[76] Moreover, a recent subgroup analysis of PARADIGM-HF (Prospective Comparison of ARNI With an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) demonstrated consistent treatment benefits with the angiotensin receptor neprilysin inhibitor (ARNI) sacubitril-valsartan in patients with and without DM.[184] Finally, mineralocorticoid receptor antagonists (MRAs) have consistent benefits in HFrEF patients with and without DM.[192,194]

Table 5. DM Subgroup Data From Pivotal HF Trials

Trial and Year	Drug/Device Studied	Patient Population	N	% With DM	Treatment Effects by DM Status
ACE inhibitor					
CONSENSUS[175] 1987	Enalapril	NYHA IV	253	22	From meta-analysis[174]: mortality RR of 0.64 (95% CI, 0.46–0.88) in non-DM vs 1.06 (95% CI, 0.65–1.74) in DM
SAVE[176] 1992	Captopril	Recent MI EF ≤40% No overt HF	2231	22	No interaction by DM status (*P*=0.45) Benefit of captopril was similar among non-DM (HR, 0.80 [95% CI, 0.64–0.94]) and DM (HR, 0.83 [95% CI, 0.63–0.87])[132]
SOLVD-Treatment[177] 1991	Enalapril	Chronic HF EF ≤35%	2569	26	From meta-analysis[174]: mortality RR of 0.84 (95% CI, 0.74–0.95) in non-DM vs 1.01 (95% CI, 0.85–1.21) in DM
TRACE[178] 1995	Trandolapril	NYHA IIIB-IV EF ≤25%	1749	14	Multivariable analysis[179]: interaction analysis (*P*=0.3). Mortality RR of 0.82 (95% CI, 0.69–0.97) in non-DM vs 0.64 (95% CI, 0.45–0.91) in DM
ARB					
Val-HeFT[180] 2001	Valsartan	NYHA class II–IV EF <40%	5010	25	Primary text: "Valsartan improved the composite outcome in those with and without diabetes" For overall trial, combined end-point mortality and morbidity, 3.3% ARR (28.8% vs 32.1%; RRR, 13%; *P*=0.009)
HEAAL[181] 2009	Losartan 150 mg vs 50 mg daily (target doses)	NYHA classes II–IV EF ≤40% Intolerant of ACE inhibitors	3846	31	No interaction by DM status (*P*=0.35) Death or HF admission: 0.87 (95% CI, 0.77–0.98) in non-DM vs HR 0.96 (95% CI, 0.82–1.12) in DM for 150 mg vs 50 mg
VALIANT[182] 2003	Valsartan vs valsartan plus captopril vs captopril	MI complicated by LVSD, HF, or both within past 10 d	14 703	23	A prespecified subgroup analysis found that patients with DM experienced similar treatment effects as patients without DM for death and cardiovascular death, reinfarction, or hospitalization for HF. Overall trial found no difference in mortality for valsartan vs captopril (HR, 1.00 [97.5% CI, 0.90–1.11]; *P*=0.98).
CHARM-Program 2008	Candesartan	Multiple trials: CHARM-Alternative, Added, and Preserved	7599	28	Summary paper from the CHARM Program[76]: the effect of candesartan was not modified by DM status (*P*=0.09 test for interaction).
ARNI					
PARADIGM-HF[183] 2014	Sacubitril-valsartan vs enalapril	NYHA II–IV EF ≤40%	8442	35	Primary paper: ARR of 4.7% in cardiovascular death or HF hospitalization with sacubitril/valsartan vs enalapril. Primary end-point interaction for DM subgroup not significant (*P*=0.40). The interaction *P* value for cardiovascular mortality was 0.05. Secondary paper: the benefit of sacubitril-valsartan was consistent across the range of HbA_{1c}.[184]
β-Blocker					
CIBIS-II[185] 1999	Bisoprolol	NYHA III–IV EF ≤35%	2647	12	Primary paper: Interaction *P*=0.48 for mortality benefit by DM status Secondary paper: RR of mortality was 0.66 (95% CI, 0.54–0.81) in non-DM vs 0.81 (95% CI, 0.51–1.28) in DM[186]
COPERNICUS[187] 2001	Carvedilol	HF with EF ≤25%	2289	26	Data from meta-analysis[174]: Mortality RR of 0.67 (95% CI, 0.52–0.85) in non-DM vs 0.68 (95% CI, 0.47–1.00) in DM. RRR of 1.02 (95% CI, 0.65–1.61)
MERIT-HF[188] 1999	Metoprolol succinate	NYHA IIIB-IV EF ≤25%	3991	25	Primary paper with DM subgroup predefined; similar mortality in DM and non-DM Data from meta-analysis[174]: mortality RR of 0.62 (95% CI, 0.48–0.79) in non-DM vs 0.81 (95% CI, 0.57–1.15) in DM. RRR of 1.32 (95% CI, 0.86–2.02) Secondary paper: similar reductions for mortality and hospitalization in DM and non-DM[189]
MRA					
RALES[190] 1999	Spironolactone	NYHA III–IV EF ≤35%	1663	22	Not reported in primary paper; not one of the 6 prespecified subgroups of interest
EMPHASIS-HF[191] 2011	Eplerenone	NYHA II EF ≤35%	2737	32	No interaction by DM status Secondary paper: HR, 0.72 (95% CI, 0.58–0.88; *P*=0.002) in non-DM vs 0.54 (95% CI, 0.42–0.70; *P*<0.0001) in DM[192]

(*Continued*)

Table 5. Continued

Trial and Year	Drug/Device Studied	Patient Population	N	% With DM	Treatment Effects by DM Status
EPHESUS[193] 2003	Eplerenone	Acute MI complicated by LVSD (EF ≤40%) and HF	6632	32	No interaction of DM status with mortality (*P*=0.35) Secondary paper: RRR for cardiovascular death or cardiovascular hospitalization of 17% in DM (*P*=0.031); greater ARR hospitalization in DM cohort (5.1%) than non-DM (3%)[194]
Ivabradine					
SHIFT[195] 2010	Ivabradine	HF with LVEF ≤35% in normal sinus rhythm with HR ≥70 bpm	6558	30	Secondary paper: ivabradine significantly reduced cardiovascular death or HF hospitalization in patients with and without DM (interaction *P*=0.57); HR, 0.84 (95% CI, 0.75–0.95) in non-DM vs 0.80 (95% CI, 0.68–0.94) in DM[196] For HF hospitalization, HR 0.77 (95% CI, 0.67–0.89) in non-DM vs 0.71 (95% CI, 0.59–0.86) in DM. Interaction *P*=0.53
ICD/CRT					
MADIT-II[197] 2002	ICD	Prior MI EF ≤30%	1232	35	Primary paper indicated no differential effect of defibrillator therapy on survival according to DM status Secondary paper: reduction in death with ICD was similar in non-DM (HR, 0.71 [95% CI, 0.49–1.05]) and DM (HR, 0.61 [95% CI, 0.38–0.98])[198]
SCD-HeFT[199] 2005	ICD vs amiodarone vs placebo	NYHA II–III EF ≤35%	2521	30	DM was not a prespecified subgroup of interest Reduction in death with ICD in non-DM was 0.67 (97.5% CI, 0.50–0.90) vs 0.95 (97.5% CI, 0.68–1.33) in DM
COMPANION[200] 2004	CRT-P, CRT-D, or medical therapy	NYHA III–IV QRS ≥120 ms	1520	41	Secondary paper: CRT (pooled) had a consistent benefit in DM patients across the trial end points.[201] With CRT, patients with DM had reduced all-cause mortality or all-cause hospitalization (HR, 0.77 [95% CI, 0.62–0.97]), all-cause mortality or HF hospitalization (HR, 0.52 [95% CI, 0.40–0.69]), and all-cause mortality (HR, 0.67 [95% CI, 0.45–0.99]) compared with medical therapy.
CARE-HF[202] 2005	CRT	NYHA III–IV EF ≤35% QRS ≥120 ms LVEDD ≥30 mm	813	29	Secondary paper: DM did not influence the beneficial effect of CRT on any end point.[203] CRT reduced all-cause mortality and HF hospitalization with similar echocardiographic benefits in those with and without DM.
MADIT-CRT[204] 2009	CRT-D vs ICD alone	NYHA I-II EF ≤30% QRS ≥130 ms	1820	30	Secondary paper: CRT-D was associated with a significant reduction in risk of death or HF hospitalization[205] in both DM (HR, 0.56; *P*=0.001) and non-DM (HR, 0.67; *P*=0.003) patients (interaction *P*=0.44).
RAFT[206] 2010	CRT-D vs ICD alone	NYHA II-III EF ≤30% Intrinsic QRS ≥120 ms or paced ≥200 ms	1798	34	A prespecified DM interaction analysis was not significant (*P*=0.22).

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; ARR, adjusted relative risk; CARE-HF, Cardiac Resynchronization-Heart Failure; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CIBIS-II, Cardiac Insufficiency Bisoprolol Study II; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; CRT, cardiac resynchronization therapy; CRT-D, CRT with defibrillator; CRT-P, CRT with pacemaker; DM, diabetes mellitus; EF, ejection fraction; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HbA_{1c}, hemoglobin A_{1c}; HEAAL, Heart Failure Endpoint Evaluation of AII-Antagonist Losartan; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MADIT-II, Multicenter Automatic Defibrillator Implantation Trial II; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PARADIGM-HF, Prospective Comparison of ARNI With an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; RALES, Randomized Aldactone Evaluation Study; RR, relative risk; RRR, relative risk reduction; SAVE, Survival and Ventricular Enlargement; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; SHIFT, Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial; SOLVD, Studies of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Evaluation; Val-HeFT, Valsartan Heart Failure Trial; and VALIANT, Valsartan in Acute Myocardial Infarction Trial.

β-Blockers

Most meta-analyses of β-blocker trials by DM status have demonstrated a consistent benefit in individuals with DM and HFrEF,[174,207–209] although one suggested a comparatively greater benefit in individuals without DM.[210] The latter meta-analysis of 6 pivotal β-blocker studies, including 3230 patients with DM (25% of the cohort), showed that β-blockers significantly reduced

mortality in individuals with (relative risk, 0.84 [95% CI, 0.73–0.91]) and without (relative risk, 0.72 [95% CI, 0.65–0.79]) DM,[210] although the magnitude of the reduction was greater in patients without DM (*P*=0.023). Overall, the 3 FDA-indicated β-blockers for use in HFrEF (carvedilol,[48,207] metoprolol succinate,[189,209] and bisoprolol[186]) have been shown to substantially reduce morbidity and mortality in individuals with DM.

Ivabradine

In the SHIFT trial (Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial), ivabradine significantly reduced the primary end point of cardiovascular death or HF hospitalization in patients with and without DM (interaction *P*=0.57).[196] There was also a significant reduction in HF hospitalization in both groups.

Implantable Cardioverter-Defibrillator/Cardiac Resynchronization Therapy

In general, pivotal trials of both implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) found consistent benefits in patients with and without DM. For instance, MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) demonstrated reduced mortality with ICD compared with conventional therapy in individuals with (HR, 0.61 [95% CI, 0.38–0.98]) and without (HR, 0.71 [95% CI, 0.49–1.05]) DM, without evidence of interaction.[198] However, in SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial),[199] the magnitude of ICD benefit appeared to be less in individuals with DM (HR, 0.95 [95% CI, 0.68–1.33]) than in those without (HR, 0.67 [95% CI, 0.50–0.90]), although DM was not a prespecified subgroup analysis. This is consistent with other data demonstrating that the relative benefit of ICDs may be attenuated with an increasing comorbidity burden.[211] The overall benefit of CRT was also similar in patients with and without DM in COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure),[201] CARE-HF (Cardiac Resynchronization-Heart Failure),[203] MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy),[205] and RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial).[206] Moreover, procedure-related complications and length of stay were similar in patients with and without DM.[201] Patients with DM and HbA_{1c} <7.0% have better outcomes after CRT than do those with suboptimal glycemic control.[212]

Clinical Considerations

Given the strength of the data regarding benefits of RAAS inhibitors, ARNIs, β-blockers, ivabradine, and ICDs/CRT in HFrEF regardless of DM status, these therapies should routinely be implemented in patients with DM and HFrEF who meet guideline indications.[7,8]

Impact of HF Medications on Glycemic Control

RAAS Inhibitors and ARNIs

ACE inhibitors and ARBs may reduce the risk of new-onset DM in patients with HFrEF. Post hoc analyses of the SOLVD (Studies of Left Ventricular Dysfunction)[213] and CHARM[214] trials demonstrated a reduction in the incidence of DM among patients treated with enalapril and candesartan, respectively; however, there are limited data on their impact on glycemic control in patients with HF and preexisting DM. In the PARADIGM-HF trial, patients randomized to enalapril (rather than sacubitril-valsartan) experienced an average reduction in HbA_{1c} of 0.16% in the first year on treatment.[215] However, there was no placebo arm for comparison, and patients receiving sacubitril-valsartan experienced even greater improvements in HbA_{1c} (mean reduction of 0.26%).

Use of sacubitril-valsartan in patients with HFrEF enrolled in the PARADIGM-HF trial was associated with a 29% reduction in new insulin use compared with enalapril.[215] The observed improved glycemic control with sacubitril-valsartan compared with enalapril has physiological plausibility and could be attributable to the incremental effect of neprilysin inhibition. Neprilysin is known to stimulate lipolysis, increase lipid oxidation, and enhance muscle oxidative capacity. Inhibition of neprilysin by sacubitril could contribute to improved glycemic parameters.[216] In addition, because GLP-1 is degraded not only by DPP-4 but also by neprilysin, potentiation of GLP-1 receptor signaling could contribute to the glycemic-lowering actions of sacubitril-valsartan.[217]

MRAs have been demonstrated to negatively impact some glycemic measures when used in patients without HF. A 2016 systematic review of 18 placebo-controlled trials found that spironolactone increased HbA_{1c} by an average of 0.16% (95% CI, 0.02–0.30) but had no clear effect on fasting glucose or insulin levels.[218] In the EMPHASIS-HF trial, which randomized patients with HFrEF to eplerenone or placebo, eplerenone had no effect on the development of DM.[46] In a small comparative effectiveness study in HFrEF, HbA_{1c} significantly increased in patients treated with spironolactone but not in those treated with eplerenone, a more selective MRA.[219] These limited data suggest that eplerenone might have a more favorable impact on glycemic control than spironolactone.

β-Blockers

Data in patients with and without HF suggest that β-blockers with α-blocking properties might have more favorable effects on glucose metabolism than those without.[48,220–223] In patients with DM and hypertension, but not HF, carvedilol was associated with improved in-

sulin sensitivity and better glycemic control than metoprolol tartrate.[220] In patients with HFrEF, carvedilol has been shown to decrease fasting insulin levels, reduce HbA_{1c}, and reduce the incidence of DM.[48,221,223] Similar improvements in glycemic parameters were not seen in patients with HFrEF treated with metoprolol tartrate or bisoprolol.[48,223]

Ivabradine

There are no data on the impact of ivabradine on glycemic control in patients with HF. In patients with angina and DM, ivabradine was associated with a modest (mean 0.1%) decrease in HbA_{1c}.[224]

Clinical Considerations

Overall, ACE inhibitors, ARBs, and ARNIs have favorable effects on the development of DM and glycemic control in patients with HFrEF and should be used according to guideline recommendations. Spironolactone may modestly worsen glycemic control in patients with DM and HFrEF. Carvedilol might have more favorable effects on glycemic control than metoprolol succinate and bisoprolol and could be preferentially used in patients with HFrEF and DM with poor glycemic control.

Use of Glucose-Lowering and HF Medications in Patients With CKD

Use of Glucose-Lowering Medications With CKD

Despite the high prevalence of CKD among individuals with both DM and HF,[225] there are limited data to guide the selection of optimal pharmacotherapy of DM in this group. Guidance for use of glycemic medications in patients with CKD is shown in Table 2. Metformin can be used safely and effectively in patients with an estimated glomerular filtration rate (eGFR) as low as 30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, albeit at reduced doses.[226] The short-acting sulfonylurea agents (eg, glipizide, glimepiride) are considered safe in patients with eGFR <30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ but should be used cautiously at reduced doses because of their risk of hypoglycemia. Long-acting sulfonylurea agents (eg, glyburide) should not be used. Insulin can be used at any eGFR, but lower doses might be required with worsening renal function. Most GLP-1 agonists can be used with eGFR >15 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ with no dose reduction, although there is limited evidence for liraglutide and dulaglutide at lower eGFR levels. DPP-4 inhibitors require dose reduction with lower eGFR levels. In EMPA-REG[227] and CANVAS,[94] SGLT-2 inhibitors slowed progression of CKD and lowered rates of clinically significant renal events compared with placebo. Although current recommendations are that SGLT-2 inhibitors should not be used with eGFR <30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, ongoing trials (CREDENCE [just stopped prematurely for efficacy], DAPA-CKD [Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease; URL: ClinicalTrials.gov. Unique identifier: NCT03036150], EMPA-KIDNEY [Study of Heart and Kidney Protection With Empagliflozin; URL: ClinicalTrials.gov. Unique identifier: NCT03594110]) will provide more conclusive data on the effects of SGLT-2 inhibitors in patients with eGFR as low as 20 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$.

Clinical Considerations

As in those without CKD, metformin is reasonable first-line therapy in patients with HF and CKD, as long as eGFR exceeds 30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$. Insulin is safe to use in patients with CKD and HF, although lower doses are required with impaired renal function. Other hypoglycemic agents can be considered, although dose adjustment might be needed in those with CKD, and the risk of adverse effects can be enhanced as renal function declines. Use of SGLT-2 inhibitors in patients with CKD seems promising given their HF benefit and potential for renal protection, but results of ongoing RCTs are needed to ensure they are safe to use at lower eGFR levels.

Use of HF Medications With CKD

Use of RAAS inhibitors to treat HF in patients with DM is frequently complicated by the presence of CKD,[228] which can enhance the risk of adverse effects, including worsening renal function and hyperkalemia.[229] Although the benefits of ACE inhibitors/ARBs, ARNIs, and MRAs generally appear to be similar in patients with and without CKD,[183,190,230,231] most studies systematically excluded patients with moderate or severe CKD (stage 3B or worse), for whom the balance of benefit and risk is particularly uncertain. Although data from randomized trials of patients with DM, CKD, and microalbuminuria or macroalbuminuria suggest that use of RAAS inhibitors alone or in combination can slow progression of renal dysfunction,[232,233] these data do not inform the effects in patients with HF, who were typically excluded from those studies.

The risk of hyperkalemia during treatment of HFrEF with ACE inhibitors/ARBs is dose dependent, amplified by both DM and CKD, and further increased by the addition of an MRA.[234–236] The incidence of hyperkalemia (potassium level >5.5 mmol/L) among patients with DM and HFrEF assigned to enalapril in the ATMOSPHERE trial (Aliskiren Trial to Minimize Outcomes in Patients With Heart Failure) was 11.8%, with rates of severe hyperkalemia (potassium level >6.0 mmol/L) approaching 4% over a median follow-up of 27 months.[237] However, these rates in a clinical trial likely underestimate those in real-world clinical practice, where patient selection can be less restricted and laboratory surveillance less inten-

sive.[238–240] Dual RAAS inhibition with an ACE inhibitor and ARB or an ACE inhibitor and a plasma renin inhibitor in patients with DM is associated with even higher rates of hyperkalemia.[234,241] The triple combination of an ACE inhibitor, ARB, and MRA is therefore discouraged.[8] Data from PARADIGM-HF suggest that rates of hyperkalemia in patients with DM and HFrEF might be slightly lower with sacubitril-valsartan than with enalapril, particularly during concomitant treatment with an MRA.[184,242]

Clinical Considerations

In patients with HFrEF, DM, and moderate CKD, it is reasonable to initiate an RAAS inhibitor at a low dose and titrate gradually to guideline-recommended doses with careful monitoring of renal function and serum potassium levels. Consideration should then be given to initiating an MRA in patients with eGFR >30 mL·min^{-1}·1.73 m^{-2} and potassium ≤5.0 mmol/L after optimization of an ACE inhibitor/ARB/ARNI and β-blocker, while reducing or discontinuing potassium supplements. Patients should be educated to avoid over-the-counter potassium supplements and potassium-based salt substitutes, limit intake of high-potassium food and beverages, and avoid medications that may increase risk for hyperkalemia (such as nonsteroidal anti-inflammatory drugs).

Use of Glucose-Lowering and HF Medications With eGFR <30 mL·min^{-1}·1.73 m^{-2}

Management of DM and HF can be particularly challenging in patients with severely reduced renal function. In patients with eGFR <30 mL·min^{-1}·1.73 m^{-2}, insulin is safe to use but might require lower doses and frequent monitoring. Other selected agents, including glimepiride, glipizide, DPP-4 inhibitors, and selected GLP-1 receptor agonists (Table 2) can be considered but should be used with caution and might require dose adjustment. Because major HF trials of ACE inhibitors and ARBs excluded patients with severe renal dysfunction, little is known about their safety in this population. The European Society of Cardiology guidelines recommend their use only if eGFR is >30 mL·min^{-1}·1.73 m^{-2},[243] although the American College of Cardiology Foundation/American Heart Association Guideline for the Management of Heart Failure suggests they should be used with caution in patients with creatinine >3 mg/dL.[8] If used in patients with advanced CKD, close monitoring of renal function and potassium is required. Data on safety and effectiveness of ARNIs in advanced CKD are limited because patients with eGFR <30 mL·min^{-1}·1.73 m^{-2} were excluded from the PARADIGM-HF trial.[183] Recent data from the UK HARP-III trial (United Kingdom Heart and Renal Protection-III) suggest that sacubitril-valsartan and irbesartan have similar rates of adverse events in patients with eGFR as low as 20 mL·min^{-1}·1.73 m^{-2}.[244] Hyperkalemia was common in patients treated with sacubitril-valsartan (32%) and irbesartan (24%), which underscores the importance of close monitoring of potassium if ACE inhibitors, ARBs, or ARNIs are used in patients with CKD. MRAs should not be initiated in patients with eGFR <30 mL·min^{-1}·1.73 m^{-2}.

COLLABORATIVE MANAGEMENT OF DM AND HF

Complexity of Medical Regimen

Despite evidence-based therapies to improve glycemic control and, recently, cardiovascular outcomes, less is known about the translation and implementation of this clinical knowledge into practice. Patients with DM and HF can have extremely complex medical regimens. For example, glycemic control, an essential component of DM self-care, includes medication adherence, glucose monitoring, dietary modification, physical activity, weight and stress management, and individualized decision making.[245,246] This is in addition to requisite HF self-care that includes all of the above plus restricted dietary sodium and fluid intake and symptom management.[247] In a small, qualitative meta-analysis, patients with DM and HF reported lack of knowledge, skill, and efficacy in integrating multiple self-care behaviors, which led them to prioritize some over others (eg, glucose monitoring, but not daily weights).[248,249] In a large, national survey of predominantly older adults, severe HF was associated with lower DM prioritization and self-care scores.[250] These challenges to self-care across multiple conditions may be attributed to lack of integration of information received from multiple providers. Furthermore, as HF becomes more symptomatic, DM self-care is deemed a lesser priority and perhaps more difficult. Interventions are needed to integrate self-care behaviors across both DM and HF, including guidance from healthcare providers in setting priorities when capacity is limited.

Team-Based Care

The National Institutes of Health has called for definitive strategies that bridge the gap between clinical knowledge, optimized practice, and improved outcomes[251,252] The chronic care model collaborative addresses how to translate clinical research findings into real-world practice using a proactive, process-driven, team-based approach.[253] An essential premise of the chronic care model is team-based care that typically includes physicians and advanced practice providers, nurses, pharmacists, dietitians, social workers, and community health workers (Figure 4).[254] Central to team-based care is the recognition that approaches to chronic disease management require the development of individualized plans of care that consider patient preferences and effective coordination of care across all members of the

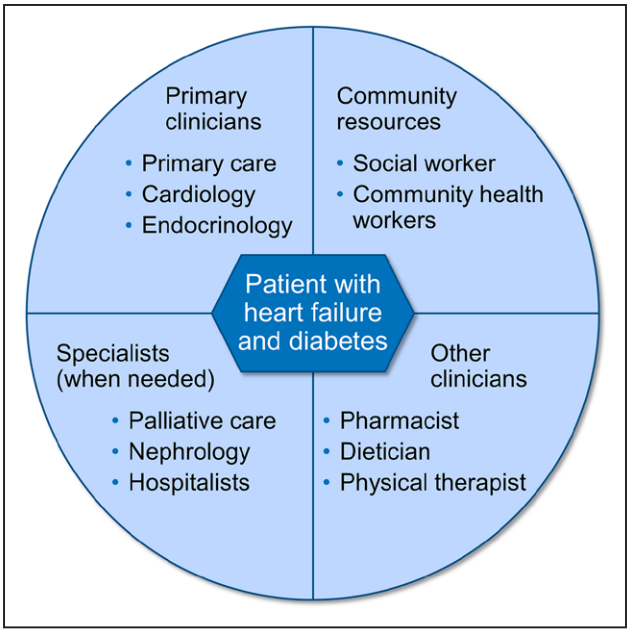

Figure 4. Interdisciplinary team-based care in patients with heart failure and diabetes mellitus.
Team-based care should include primary clinicians, specialists, and community workers collaborating together to meet the needs of the patient. The ideal clinicians and community resources constituting the team may vary from patient to patient.

healthcare team.[255,256] According to the National Academy of Sciences, to improve outcomes for patients with chronic health conditions such as DM and HF, teams must consider the interpersonal, organizational, community, and societal factors that influence patient behavioral decision making.[257] Although there is evidence that these factors influence clinical outcomes in people with HF and in those with DM,[258,259] few studies have focused on individuals with both DM and HF. In one promising pilot study, an integrated HF-DM self-care intervention was effective in improving essential components of self-care, including HF knowledge and DM self-efficacy, with sustained effects on selected self-care behaviors.[260] Additional multicenter studies that test the sustainability of results and examine clinical outcomes in this high-risk population are needed.

Lifestyle Management

Lifestyle management should be integral to the care of patients with DM and HF. DM is linked to obesity, inactivity, and poor dietary choices, which in turn are linked to cardiovascular diseases, including HF. Exercise can improve functional capacity for patients with DM and HF. In the HF-ACTION trial (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training), 2331 individuals with HFrEF were randomized to exercise training or optimal medical care.[261] Patients with DM (32% of those enrolled) had more impaired functional status at baseline and were less adherent to exercise training. Despite this, patients with DM randomized to exercise had significant improvements in peak oxygen consumption ($\dot{V}o_2$) and 6-minute walk distance (both $P<0.001$) compared with usual care, without safety concerns. Cardiac rehabilitation programs represent an excellent avenue to encourage exercise participation in patients with DM and HF. Referral is critical and represents a primary barrier to cardiac rehabilitation enrollment.[262]

Although unintentional weight loss is associated with poor prognosis in HF,[263,264] limited data suggest that intentional weight loss can improve exercise capacity in obese patients with HF, including those with DM.[265–267] Weight loss through calorie restriction, when combined with exercise, holds particular promise in patients with HFpEF. Using a 2×2 factorial design, a recent study randomized 100 obese patients (body mass index 38–40 kg/m^2) with HFpEF and a high prevalence of DM to diet, exercise, both, or neither. Patients treated with either exercise or diet had improvements in peak $\dot{V}o_2$, and the combination was additive.[267] However, neither diet nor exercise had a significant effect on quality of life.

Clinical Considerations

Exercise is safe and beneficial in patients with HF and DM. Patients referred to cardiac rehabilitation should be counseled on the importance of adherence to training. In patients with HFpEF and obesity, many of whom also have DM, a combined diet and exercise program can improve functional capacity.

DM: IMPLICATIONS FOR ADVANCED HF THERAPIES

Approximately 18% of patients undergoing heart transplantation have DM.[268] Analyses from the United Network of Organ Sharing database have demonstrated similar long-term survival in patients with uncomplicated DM compared with those without DM.[268] However, DM associated with end-organ damage (other than nonproliferative retinopathy) is a relative contraindication to transplantation.[269] Still, patients with diabetic nephropathy who are otherwise good candidates should be considered for combined heart and kidney transplantation, because survival is similar to heart transplantation alone.[270] Before transplantation, patients should work with their clinicians to achieve a target HbA_{1c} of <7.5%.[269] After transplantation, immunosuppressive agents, including corticosteroids and calcineurin inhibitors, can promote development of DM or worsen glycemic control among those with DM.[271] Management of DM after heart transplantation is beyond the scope of this statement, but a helpful guideline was published previously.[272] Collaboration with an endocrinologist with experience in management of posttransplantation DM can be helpful.

Approximately 30% to 40% of patients undergoing placement of an LV assist device (LVAD) have DM.[273,274] Most[273,275–278] but not all[274] studies have demonstrated worse post-LVAD outcomes in patients with DM, including higher risk of death,[273,277] persistently poor quality of life,[275,278] and thromboembolic events.[273,276] Similar to heart transplantation, DM with end-organ damage is a relative contraindication to durable mechanical circulatory support.[279] Consultation with an endocrinologist is recommended for patients with poorly controlled DM before LVAD implantation,[279] although limited available data have found no association of pre-LVAD glycemic control (HbA_{1c} level) with post-LVAD outcomes in patients without DM.[273,274] Glycemic control often improves after LVAD placement, and patients may require fewer glucose-lowering medications.[273,280–283] In a single-center study, HbA_{1c} decreased from a mean of 7.4% before LVAD to 6.0% at 3 months and 6.3% at 1 year after LVAD implantation.[273] Whether this benefit is attributable to reversal of the HF state, increased physical activity, improved self-care, or other factors remains to be determined.

Clinical Considerations

Endocrinology consultation is strongly advised for patients with end-stage HF, DM, and poor glycemic control undergoing evaluation for advanced HF therapies.

FUTURE DIRECTIONS AND UNANSWERED QUESTIONS

There are many unanswered questions regarding the epidemiology, pathobiology, optimal pharmacotherapy, and co-disease management strategies for patients with DM and HF (Table 6). The epidemiology of both DM and HF may be changing because of modification of risk factors and introduction of novel therapies. Well-powered clinical trials and prospective population-based studies are needed to elucidate these changes. As with many complex diseases, genetic susceptibilities likely exist but will require large databases and powerful bioinformatics to uncover. The intensity of glycemic control may need to be tailored to the stage and severity of HF, with close monitoring for safety and efficacy of DM therapies. Likewise, more data are needed on the impact of old and new HF therapies on the incidence and progression of DM. Further research is needed to elucidate safe use of glycemic-lowering medications in patients with HF and renal dysfunction. Because both DM and HF are chronic diseases, integrated care that actively engages patients, family, and providers is key to optimizing both quality and quantity of life. Whether novel ambulatory or remote monitoring strategies can aid in this collateral benefit remains to be determined.

Table 6. Unanswered Questions Regarding the Intersection of DM and HF

Is the epidemiology of DM and HF changing?
Development of HF in patients receiving new DM therapies (eg, SGLT-2 inhibitors)
Development of and risk factors for DM in patients on new HF therapies (eg, ARNI)
Is there a genetic susceptibility to DM in HF or HF in DM?
Is diabetic cardiomyopathy reversible? Which patients will have myocardial recovery vs remission?
What is the optimal method to identify patients with type 2 DM at highest risk for developing HF?
What are the optimal HbA_{1c} targets for patients with stages B, C, and D HF?
Safety and efficacy of glucose-lowering medications:
Are sulfonylureas safe in patients with DM and increased cardiovascular risk (CAROLINA)?
What is the safety and efficacy of DPP-4 inhibitors in HFrEF (MEASURE-HF)?
Do SGLT-2 inhibitors reduce morbidity and mortality in HFrEF and HFpEF (EMPEROR, DAPA-HF, SOLOIST-WHF)?
What are the mechanistic benefits of SGLT-2 inhibition beyond diuresis?
What is the optimal glycemic-lowering medication regimen for patients with HF and advanced (stage 4–5) CKD (DAPA-CKD, EMPA-KIDNEY)?
Off-target effects of HF therapies:
What are the mechanisms by which ARNI improves glycemic control?
Should carvedilol be preferred over metoprolol succinate in patients with HF and DM?
Should eplerenone be preferred over spironolactone in patients with HF and DM?
Optimizing resources for care of patients with DM and HF:
What strategies should be implemented to help patients/families integrate self-care behaviors across DM and HF?
What are the optimal resources required in an ambulatory clinic?
What are the optimal interventions to be used after an acute HF hospitalization?
How can barriers to enrollment in cardiac rehabilitation be lowered?
What is the role of the HF specialist in choice and monitoring of DM therapies?
The future of remote monitoring beyond signs, symptoms, and blood glucose:
Are there biological sensors to manage both HF and DM?
What is the value added with remote monitoring for the patient, family, and provider?
What is the best way to integrate smartphones and social media in health promotion?

ARNI indicates angiotensin receptor neprilysin inhibitor; CAROLINA, Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes; CKD, chronic kidney disease; DAPA-CKD, Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; EMPA-KIDNEY, Study of Heart and Kidney Protection With Empagliflozin; EMPEROR, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure; HbA_{1c}, hemoglobin A_{1c}; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MEASURE-HF, Mechanistic Evaluation of Glucose-Lowering Strategies in Patients With Heart Failure; SGLT-2, sodium glucose cotransporter type 2; and SOLOIST-WHF, Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure.

ARTICLE INFORMATION

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The American Heart Association and the Heart Failure Society of America make every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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