Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association

Rodica Pop-Busui,[1] James L. Januzzi,[2] Dennis Bruemmer,[3] Sonia Butalia,[4] Jennifer B. Green,[5] William B. Horton,[6] Colette Knight,[7] Moshe Levi,[8] Neda Rasouli,[9] and Caroline R. Richardson[10]

Diabetes Care 2022;45:1670–1690 | https://doi.org/10.2337/dci22-0014

CONSENSUS REPORT

Heart failure (HF) has been recognized as a common complication of diabetes, with a prevalence of up to 22% in individuals with diabetes and increasing incidence rates. Data also suggest that HF may develop in individuals with diabetes even in the absence of hypertension, coronary heart disease, or valvular heart disease and, as such, represents a major cardiovascular complication in this vulnerable population; HF may also be the first presentation of cardiovascular disease in many individuals with diabetes. Given that during the past decade, the prevalence of diabetes (particularly type 2 diabetes) has risen by 30% globally (with prevalence expected to increase further), the burden of HF on the health care system will continue to rise. The scope of this American Diabetes Association consensus report with designated representation from the American College of Cardiology is to provide clear guidance to practitioners on the best approaches for screening and diagnosing HF in individuals with diabetes or prediabetes, with the goal to ensure access to optimal, evidence-based management for all and to mitigate the risks of serious complications, leveraging prior policy statements by the American College of Cardiology and American Heart Association.

BRIEF OVERVIEW OF SCOPE AND NEED

Traditionally, the prevention and management of chronic complications in individuals with type 1 (T1D) and type 2 (T2D) diabetes have been focused on nephropathy, retinopathy, neuropathy, and atherosclerotic cardiovascular disease (ASCVD) (including ischemic heart disease, stroke, and peripheral vascular disease) (1). However, heart failure (HF) has been recognized as a common complication of diabetes, with a prevalence of up to 22% in individuals with diabetes and increasing incidence rates (2–4). This recognition stems in part from trials focused on cardiovascular safety of newer drugs to treat diabetes. Data also suggest HF may develop in individuals with diabetes even in the absence of hypertension, coronary heart disease, or valvular heart disease and, as such, represents a major cardiovascular complication in this vulnerable population (5). Given that during the past decade, the prevalence of diabetes (particularly T2D) has risen by 30% globally (6) (with prevalence expected to increase further), the burden of HF on the health care system will continue to rise.

The scope of this American Diabetes Association (ADA) consensus report with designated representation from the American College of Cardiology (ACC) is to

[1]Division of Metabolism, Endocrinology and Diabetes, Department of Internal Medicine, University of Michigan, Ann Arbor, MI
[2]Cardiology Division, Massachusetts General Hospital, and Cardiometabolic Trials, Baim Institute for Clinical Research, Boston, MA
[3]Center for Cardiometabolic Health, Section of Preventive Cardiology and Rehabilitation, Robert and Suzanne Tomsich Department of Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, OH
[4]Departments of Medicine and Community Health Sciences, Cumming School of Medicine, University of Calgary, Alberta, Canada
[5]Division of Endocrinology and Duke Clinical Research Institute, Department of Medicine, Duke University Medical Center, Durham, NC
[6]Division of Endocrinology and Metabolism, Department of Medicine, University of Virginia, Charlottesville, VA
[7]Inserra Family Diabetes Institute, Hackensack University Medical Center, Hackensack Meridian School of Medicine, Hackensack, NJ
[8]Department of Biochemistry and Molecular & Cellular Biology, Georgetown University, Washington, DC
[9]Division of Endocrinology, Metabolism and Diabetes, Department of Medicine, University of Colorado School of Medicine, Aurora, CO
[10]Department of Family Medicine, University of Michigan Medical School, Ann Arbor, MI

Corresponding author: Rodica Pop-Busui, rpbusui@med.umich.edu

R.P.-B. served as chair and J.L.J. served as vice chair of the writing committee.

This consensus report has been reviewed and endorsed by the American College of Cardiology.

provide clear guidance and to recommend best approaches to general internists, primary care providers, and endocrinologists for HF screening, diagnosis, and management in individuals with T1D, T2D, or prediabetes to mitigate the risks of serious complications, leveraging prior policy statements by the ACC (7) and American Heart Association (AHA) (2). This consensus report was developed by the writing group convened by ADA with representation from ACC through a series of conference calls, emails, and independent work from March 2021 through March 2022.

HF EPIDEMIOLOGY

Prevalence and Incidence of HF Among Individuals With Diabetes

The epidemiologic association between HF and diabetes is well recognized (Supplementary Table 1) (2,3). Results of several longitudinal observational studies of population-based cohorts with diabetes and prediabetes, including Framingham Heart Study (8), First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (9), Reykjavik Study (10), and the Scottish diabetes mellitus register (3), have shown a two- to fourfold increased risk of HF among men and women with diabetes or prediabetes compared with those without (8,10). Additionally, HF was the most common first presentation of cardiovascular disease in individuals with T2D when evaluated in contemporary cohorts including millions of people with linked primary care, hospital admission, disease registry, and death certificate records in England. T2D was an independent risk factor for incident HF and increased HF-associated morbidity and mortality during a median 5.5-year follow-up period (2,3). These data are further supported by recent evidence from the UK Prospective Diabetes Study (UKPDS), with incidence rates of up to 11.9 per 1,000 patient-years over 10 years of follow-up (11).

The incidence and prevalence of HF are also increased among patients with T1D, as highlighted by findings from the Scottish diabetes mellitus register (3), while the Swedish National Diabetes Registry (12) also reported a two to five times higher crude incidence rate of HF hospitalization and mortality for men and women with T1D compared with those without diabetes (3,13) and higher prevalence of diastolic dysfunction (14). In a recent systematic review including 12 million global participants, investigators found that HF may be even more prevalent among men and women with T1D than among those with T2D (4).

The deleterious relationship between diabetes and HF persists after adjustment for age and relevant comorbidities (15). While a longer duration of diabetes is clearly linked to higher risk for incident HF, the association between diabetes and HF is observed even in individuals with recent-onset diabetes or younger age (14,16). Glycemic control and insulin resistance are strongly associated with risk for incident HF, suggesting a continuous relationship between any blood glucose abnormality and HF risk and HF prognosis (10,11,17) (Supplementary Table 1).

Prevalence and Incidence of Diabetes Among People With HF

The relationship between diabetes and HF has a unique bidirectional association. For example, insulin resistance is prevalent in >60% of individuals with HF (18) and new-onset diabetes is common among those with HF, as shown in several large cohorts (19,20,21) (Supplementary Table 2).

Given heightened risk for diabetes in those with HF, it is not surprising that data indicate a high prevalence of dysglycemia in this population, with prevalence ranging from 20% in community-based cohorts (22) to ~34% in pharmacological intervention trials for systolic HF (23–27), and up to 47% in acute decompensated HF (28–30).

Race-related differences have also emerged in the prevalence of diabetes in individuals with HF. Several studies have found the prevalence of diabetes to be 47–56% for Black, Hispanic, and Native American individuals with HF (31–33). Similarly, among individuals with impaired myocardial diastolic relaxation, diabetes is more common in Black (40.5%) and Hispanic (40.9%) individuals compared with White counterparts (27.2%) (33). Moreover, in the Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry, 41.3% of individuals from 11 Asian regions suffering from HF were also affected by diabetes (34). Clearer data are needed regarding race-related impacts on health and risk for the intersection of diabetes and HF.

Few studies have directly compared the prevalence and incidence rates of diabetes in people with HF and reduced ejection fraction (HFrEF) versus those with preserved ejection fraction (HFpEF). However, in a study of hospitalized individuals with HF, prevalence of diabetes was ~40% among both HFrEF and HFpEF patients (35). More specific data regarding distribution of diabetes burden among those with HFrEF and HFpEF are needed.

Key Points

- Both T1D and T2D increase the risk of developing HF across the entire range of glucose levels, but HF may be more prevalent in people with T1D compared with T2D.
- There is increased incidence rate of HF among people with diabetes even after adjustment for age and comorbidities.
- HF may be the first presenting cardiovascular complication in individuals with diabetes.

Received 25 March 2022 and accepted 29 March 2022

This article contains supplementary material online at https://doi.org/10.2337/figshare.19538869.

A consensus report of a particular topic contains a comprehensive examination and is authored by an expert panel (i.e., consensus panel) and represents the panel's collective analysis, evaluation, and opinion. The need for a consensus report arises when clinicians, scientists, regulators, and/or policy makers desire guidance and/or clarity on a medical or scientific issue related to diabetes for which the evidence is contradictory, emerging, or incomplete. Consensus reports may also highlight gaps in evidence and propose areas of future research to address these gaps. A consensus report is not an American Diabetes Association (ADA) position but represents expert opinion only and is produced under the auspices of the ADA by invited experts. A consensus report may be developed after an ADA Clinical Conference or Research Symposium.

Risk Factors

The risk factors for HF in both T2D and T1D include diabetes duration, poor glycemic control, uncontrolled hypertension, hyperlipidemia, higher BMI, microalbuminuria, renal dysfunction, ischemic heart disease, and peripheral artery disease (2,12,13). Current trends suggest control of modifiable risk factors is poor in those with diabetes (36), emphasizing the importance of careful review of each during clinical visits. An overview of their impact on HF is presented in Supplementary Material.

PATHOPHYSIOLOGY

The pathophysiology of HF in individuals with diabetes is complex and reflects the interactions of multiple risk factors acting in concert with dysregulated subcellular pathways that extend beyond the consequences of diabetes-associated hyperglycemia, all leading to functional and structural changes in the diabetic heart, as illustrated in Supplementary Fig. 1.

"Diabetic cardiomyopathy," defined as ventricular dysfunction in the absence of coronary artery disease (CAD) and hypertension (37), is an increasingly recognized entity. Several potential mechanisms contributing to the development of HF in diabetes include renin-angiotensin-aldosterone system (RAAS) activation, mitochondrial dysfunction, oxidative stress, inflammation, changes in intracellular calcium homeostasis, increased formation of advanced glycation end products, and myocardial energy substrate alterations including increased free fatty acid utilization, decreased glucose utilization, and increased oxygen consumption, resulting in decreased cardiac efficiency (2,15,37–40) (Supplementary Fig. 1). Despite the increased rates of fatty acid utilization, triglycerides and other lipid metabolites (e.g., ceramides, diacylglycerol, etc.) accumulate in the myocardium of individuals with diabetes (15,41). These derangements in myocardial lipid and glucose metabolism are increasingly recognized as an early event in the deterioration of diabetes-related cardiac function (41). Ultimately, these result in maladaptive fibrosis, microvascular rarefaction, lipotoxicity, and decreased nitric oxide availability, leading to further cardiovascular dysfunction. While the predominant mechanisms for HFrEF are considered to be direct myocardial injury due to associated CAD or hypertension, a unifying theory of the pathophysiology of HFpEF suggests a central role for endothelial and microvascular dysfunction (42). We point the reader to review articles (15,43) and scientific statements (2) that describe these mechanisms in detail.

While individuals with T1D exhibit select structural features characteristic of an early HFpEF phenotype reflective of increased left ventricle stiffness (38), there are also notable HF similarities between T1D and T2D. Shared mechanisms include cardiovascular autonomic neuropathy (38,44), specifically associated with impaired left ventricle diastolic relaxation in both people with T2D (45) and people with T1D (40), and coronary microvascular dysfunction (46–48) with the associated functional and/or structural abnormalities of the coronary microvasculature (47,49) resulting in myocardial perfusion impairment (39,40).

Sex differences in endothelial and microvascular function may also play pivotal pathogenic roles in the etiology of HF in women with diabetes (50). Accumulating evidence shows that women with diabetes exhibit greater endothelial (51), coronary microvascular (52), and diastolic (48) abnormalities compared with men with diabetes. Underlying mechanisms for the increased risk of HF in women with diabetes are not entirely clear, but sex hormones, a different spectrum of cardiovascular risk factors, and/or differences in prescription patterns between men and women may play a role (53). Further research is needed to clarify the exact mechanisms contributing to this excess HF risk in women with diabetes (particularly T1D) and identify appropriate sex-specific prevention and treatment strategies.

Key Points

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

HF: DIAGNOSIS AND CLINICAL STAGES

HF represents a continuum of cardiac structural abnormality and dysfunction and associated cardiovascular risk. Useful means by which to classify the various stages of HF have been articulated by the ACC/AHA/HFSA (Heart Failure Society of America) HF guidelines (54) and recently affirmed by the Universal Definition and Classification of Heart Failure task force (55).

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

Although echocardiography might identify signs of maladaptive left ventricular remodeling, its routine use has not been considered cost-effective and thus has not been systematically recommended for asymptomatic individuals, including those with diabetes. On the other hand, the addition of relatively inexpensive biomarker testing as part of the standard of care may help to refine HF risk prediction in individuals with diabetes (Table 1).

Stage A: Individuals at Risk for HF

The presence of established diabetes indicates that an individual is at risk for HF, and these patients should be considered in the stage A category and at heightened risk for progression to later stages of HF. In this stage, the achieved control of glycemia and other risk factors may modify (or instead amplify) risk for clinical HF. These risk factors are discussed above in *HF EPIDEMIOLOGY* and in

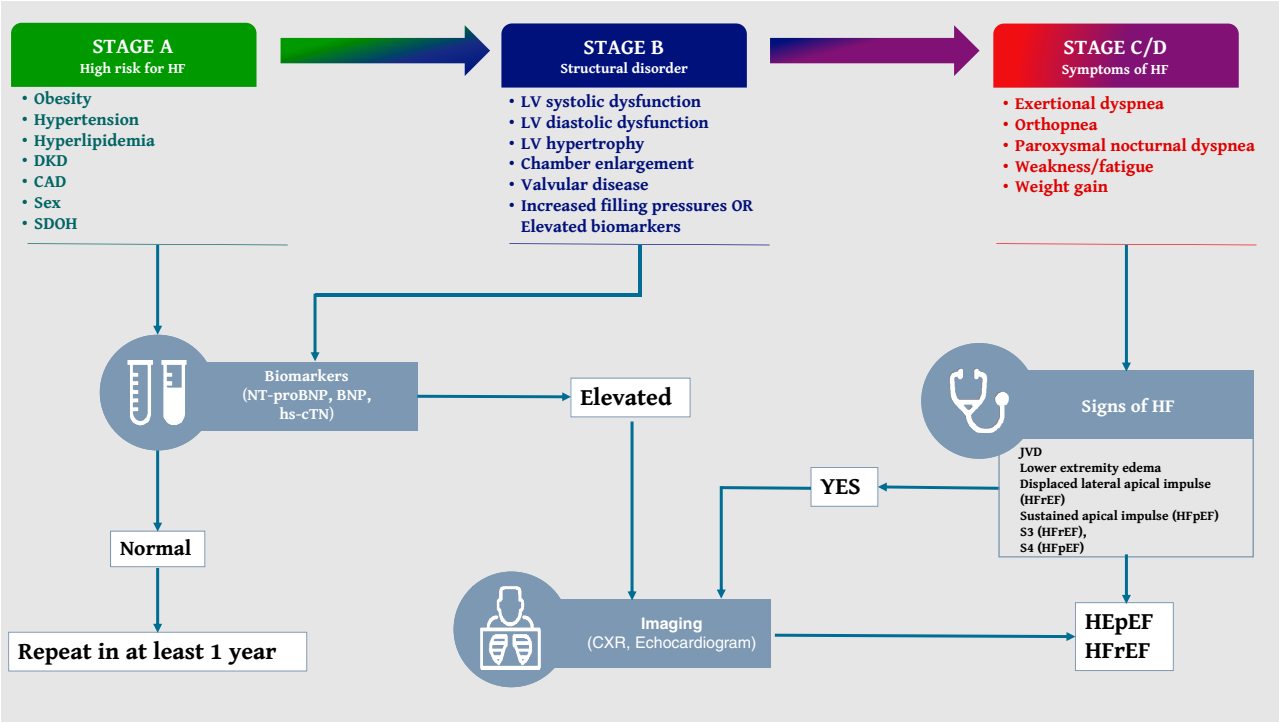

Figure 1—Stepwise approach for screening and diagnosis across HF stages. CXR, chest X-ray; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs-cTN, high-sensitivity cardiac troponin; JVD, jugular vein distension; LV, left ventricle.

Supplementary Material and should be considered when evaluating an individual with diabetes.

Key Points

- Anyone with a diagnosis of diabetes and the risk factors shown in Fig. 1 is in the stage A category of HF.

Stage B: Pre-HF/Early Detection

ACC/AHA (2,55) stage B HF is linked to increased risks of cardiovascular and all-cause mortality, as well as progression to more advanced stages of overt HF (2,54) (Fig. 1), and may be referred to as "pre-HF." Many individuals with diabetes can be classified in stage B (54).

In recognition of the importance of biomarkers to support the detection of cardiac dysfunction at an early stage, the definition of stage B in the recent Universal Definition and Classification of Heart Failure was revised to include asymptomatic individuals with at least one of the following: *1*) evidence of structural heart disease, *2*) abnormal cardiac function, or *3*) elevated natriuretic peptide levels or elevated cardiac troponin levels (55). This approach is compatible with the 2017 ACC/AHA HF Focused Update, which issued a class IIa recommendation for use of natriuretic peptide measurement to identify HF at an early stage (2).

Subclinical Structural Heart Disease

Subclinical changes that may be present in stage B include ventricular systolic or diastolic dysfunction, LV hypertrophy, chamber enlargement, valvular disease, and/or evidence of increased filling pressures.

Biomarkers for Detection of Stage B HF

Specific to individuals with diabetes, measurement of natriuretic peptides (B-type natriuretic peptide [BNP]; N-terminal pro-BNP [NT-proBNP]) or high-sensitivity cardiac troponin is particularly helpful to identify stage B HF and predict progression to symptoms or death from HF (55,56) (Table 1). Furthermore, while one natriuretic peptide or troponin measurement may provide important prognostic insights, serial measurements to detect rising values of either increase sensitivity for identifying those at highest risk for incident HF (57). As an example, in individuals with T2D in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial, two NT-proBNP measurements spaced 6 months apart were able to identify those at highest risk (both elevated), rising risk (baseline low, follow-up higher), or lower risk (6-month measurement lower) (57).

Though most of the data regarding biomarker testing to predict HF onset have been gathered with a focus on those with T2D, available data suggest similar associations in those with T1D as well (58).

Recommendations for Detection of Subclinical HF in Individuals With Diabetes

Among individuals with diabetes, measurement of a natriuretic peptide or high-sensitivity cardiac troponin is recommended on at least a yearly basis to identify the earliest HF stages and implement strategies to prevent transition to symptomatic HF. This recommendation is based on the substantial data indicating the ability of these biomarkers to identify those in stage A or B at highest risk of progressing to symptomatic HF or death, together with evidence that the risk in such individuals may be lowered through targeted intervention or multidisciplinary care.

Results from two randomized controlled trials of individuals at risk for HF (one enrolling exclusively participants

Table 1—Biomarkers and optimal cutoffs for incident HF in diabetes

Cohort	Population studied	Biomarker(s) studied	Median follow-up	Outcome	Biomarker thresholds and results
Thousand & 1 Study (58)	1,093 individuals with T1D, ≥18 years old, with no known heart disease at baseline	NT-proBNP	6.3 years	Incident MACE* HF	**NT-proBNP >300 pg/mL:** 41 per 1,000 person-years **NT-proBNP <150 pg/mL:** 10 per 1,000 person-years
Pooled cohort from Atherosclerosis Risk in Communities (ARIC), Dallas Heart Study (DHS), and Multi-Ethnic Study of Atherosclerosis (MESA) (56)	6,799 individuals with dysglycemia (diabetes 33.2%, prediabetes 66.8%), and no CVD at baseline	NT-proBNP, hs-CRP, and hs-cTN	17 years	Incident HF: prediabetes vs. diabetes	hs-cTN ≥6 ng/L NT-proBNP ≥125 pg/mL hs-CRP ≥3mg/L **Biomarker score= 1** HR1.40 (1.09–1.80) vs. 1.82 (1.31–2.53) **Biomarker score = 2** HR 1.83 (1.37–2.45) vs. 2.42 (1.71–3.43) **Biomarker score ≥3** HR 3.68 (2.53–5.34) vs. 4.72 (3.16–7.04)
EXAMINE (57)	5,224 individuals with T2D and a recent acute coronary syndrome event	NT-proBNP	597 days	Incident HHF	**NT-proBNP 154.1–420.4:** HR 3.27 (1.20, 8.92) **NT-proBNP 420.4 to <1,084.0:** HR 7.24 (2.84–18.49) **NT-proBNP ≥1,084.0:** HR 29.3 (12.0–71.5)
St Vincent's Screening to Prevent Heart Failure (STOP-HF) (59)	1,374 participants at HF risk, ∼20% with diabetes	BNP	4.2 years	LV dysfunction or newly diagnosed HF for intensive intervention vs. usual care	**At least one BNP >50 pg/mL** OR for intervention 0.55 (0.37–0.82); P =0.003
NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease (PONTIAC) (60)	300 individuals with T2D with no history of CVD	NT-proBNP	2 years	HHF or death	**NT-proBNP >125 pg/mL** 65% risk reduction with intervention in primary endpoint 40% risk reduction in HHF
Canagliflozin Cardiovascular Assessment Study (CANVAS) (131,211)	4,330 individuals with T2D and either CVD or multiple risk factors	NT-proBNP	6 years	Incident HHF; HHF or death	**NT-proBNP ≥125 pg/mL** Incident HHF: HR 5.40 (2.67–10.9) HHF or death: HR: 3.52 (2.38–5.20)

All HR and OR values are shown with 95% CI. HHF, hospitalization for HF; HR, hazard ratio; hs-cTN, high-sensitivity cardiac troponin; LV, left ventricular; OR, odds ratio. *MACE: hospital admissions for acute coronary syndrome, HF, stroke, and cardiac revascularization and death.

with T2D) show that more intensive interventions in those with higher levels of natriuretic peptide reduce risk for LV dysfunction, newly diagnosed HF, or HF hospitalization (59,60) (Table 1). A randomized trial of intensified medical therapy (ACE inhibitor [ACEi], angiotensin II receptor blocker [ARB], or β-blocker) versus usual care among 2,400 individuals with T2D and NT-proBNP >125 pg/mL is currently underway (61).

Table 1 summarizes data from these and several other large cohorts regarding threshold values for each biomarker and associations with HF risk. When BNP, NT-proBNP, and high-sensitivity cardiac troponin are used as continuous variables, higher values are associated with higher relative risk of HF onset; however, for clinical utility, dichotomous cutoffs must be applied.

Based on aggregate population and clinical trial data, the biomarker thresholds for clinical use include a BNP ≥50 pg/mL and NT-proBNP ≥125 pg/mL and for high-sensitivity cardiac troponin a value >99th percentile for a healthy patient population (the usual upper reference limit for high-sensitivity assays).

Using biomarkers to identify and in turn reduce risk for HF should always be done within the context of a thoughtful clinical evaluation, supported by all information available, and with

an understanding regarding the known confounders that may reduce reliability of testing for natriuretic peptides or troponin. Among patients with advancing age, more advanced chronic kidney disease (CKD) or atrial fibrillation may lead to higher concentrations of prognostic biomarkers, while obesity may lower natriuretic peptide concentrations even in the presence of significant HF risk.

Although biomarker testing itself is not medically harmful, there is the potential for cascade testing following recognition of an abnormal result to increase costs and complexity of existing diabetes care recommendations. However, because normal BNP and NT-proBNP levels have high negative predictive value, and thus can be used to exclude a diagnosis of HF (62–64), such a finding would preclude pursuing further diagnostics or treatment. Furthermore, a substantial gap in diagnosis and treatment of HF exists and the preponderance of accumulating evidence suggests that detection of a signal of HF risk would increase intervention with treatments to reduce the potential for development of symptomatic HF. It is therefore impossible to understate the importance of early recognition of HF at a time when intervention might be expected to be even more impactful (65).

The decisions that follow identification of an abnormal natriuretic peptide or high-sensitivity cardiac troponin result should be individualized to the patient but might include further diagnostic studies, avoidance of treatments that might increase HF risk, and introduction of therapies with proven usefulness to prevent HF in this vulnerable population. Such steps might be made with collaboration between diabetologists/endocrinologists, internists and primary care providers, and cardiovascular specialists as appropriate. While no precedent data exist to suggest specific populations of those with diabetes more likely to benefit from testing of natriuretic peptides or high-sensitivity cardiac troponins, certain higher-risk populations such as those with long-standing diabetes, CKD, or microalbuminuria are particularly likely to be a group with a higher yield from testing (66).

Key Points

- Many people with diabetes have stage B HF, defined as asymptomatic with at least one of the following: *1*) evidence of structural heart disease, *2*) abnormal cardiac function, or *3*) elevated natriuretic peptide levels or elevated cardiac troponin levels.
- Early diagnosis of HF could enable targeted treatment to prevent adverse outcomes.
- Measurement of a natriuretic peptide or high-sensitivity cardiac troponin on at least a yearly basis is recommended to identify the presence of stage B HF and to determine risk for progression to symptomatic HF.
- Useful cutoff values for BNP (50 pg/mL), NT-proBNP (125 pg/mL), or high sensitivity cardiac troponin (>99th percentile upper reference limit) to determine HF risk are based on population-based data and/or clinical trials.
- The identification of an abnormal natriuretic peptide or high-sensitivity cardiac troponin should be part of individualized management decision plans (Fig. 2).

Stages C and D: Symptomatic HF in Individuals With Diabetes

Current HF guidelines (54,67) provide general recommendations for the evaluation and management of HF. In the following sections, we will only provide a succinct overview for the evaluation and management of symptomatic HF, which are largely the same for individuals with diabetes.

Diagnosis of HF Stage C and D

Individuals considered to be at stages C and D have had prior or have current symptoms of HF (54). The initial diagnosis of HF is based on the assessment of symptoms at the time of presentation, key clinical findings of the physical examination, and the results of initial testing supporting HF diagnosis and excluding an alternative cause of the individual's presentation (Fig. 1).

Symptoms of HF. Clinicians should obtain a comprehensive history to recognize symptoms and signs of HF that are key for making a clinical diagnosis of HF. Common symptoms and signs can be found in Fig. 1 and typically reflect fluid retention and congestion, or those of low cardiac output. Generally, individuals with HFpEF present with symptoms (54,55) similar to those of individuals with HFrEF, most commonly exertional dyspnea, fatigue, and edema (54,55).

Clinical Examination. For most individuals clinical signs may include weight gain and lower extremity edema. As part of the clinical examination (Fig. 1), vital signs and volume status should be assessed, including current weight and recent changes in weight and assessment for physical findings consistent with congestion such as pulmonary rales (68). During cardiac examination, a laterally displaced apical impulse and a third heart sound may be helpful in evaluating chamber dilation and left ventricular filling pressures, respectively (54), and cardiac murmurs may be detected. In more advanced HF, the extremities may be cool due to increased systemic vascular resistance; this finding is most common among individuals in stage D.

Laboratory Evaluations and Imaging. For individuals presenting with suspected or confirmed HF, guidelines recommend initial laboratory testing: complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, glucose, HbA_{1c}, fasting lipid profile, liver function tests, iron studies, and thyroid-stimulating hormone (54). In addition, a 12-lead electrocardiogram is recommended (54), which may identify a specific cause of HF (i.e., myocardial ischemia, uncontrolled arrhythmia) and may provide information to guide management strategies (e.g., rhythm abnormalities, QRS width for consideration of resynchronization therapy).

Biomarker Testing. Biomarker testing for BNP or NT-proBNP is recommended in individuals presenting with dyspnea to identify or exclude HF and gauge its severity (67). For stage C HF, similar to stage B, because of their high negative predictive value normal BNP and NT-proBNP levels exclude a diagnosis of decompensated HF (62–64,69). While not as high as the negative predictive value, the positive predictive value of an elevated BNP or NT-proBNP for the diagnosis of HF (70) remains robust. Increased levels of natriuretic peptide levels can be associated with several noncardiac causes, including advanced age, anemia, renal failure, obstructive sleep apnea, pulmonary hypertension, critical illness, and sepsis, as well as severe burns (67). The

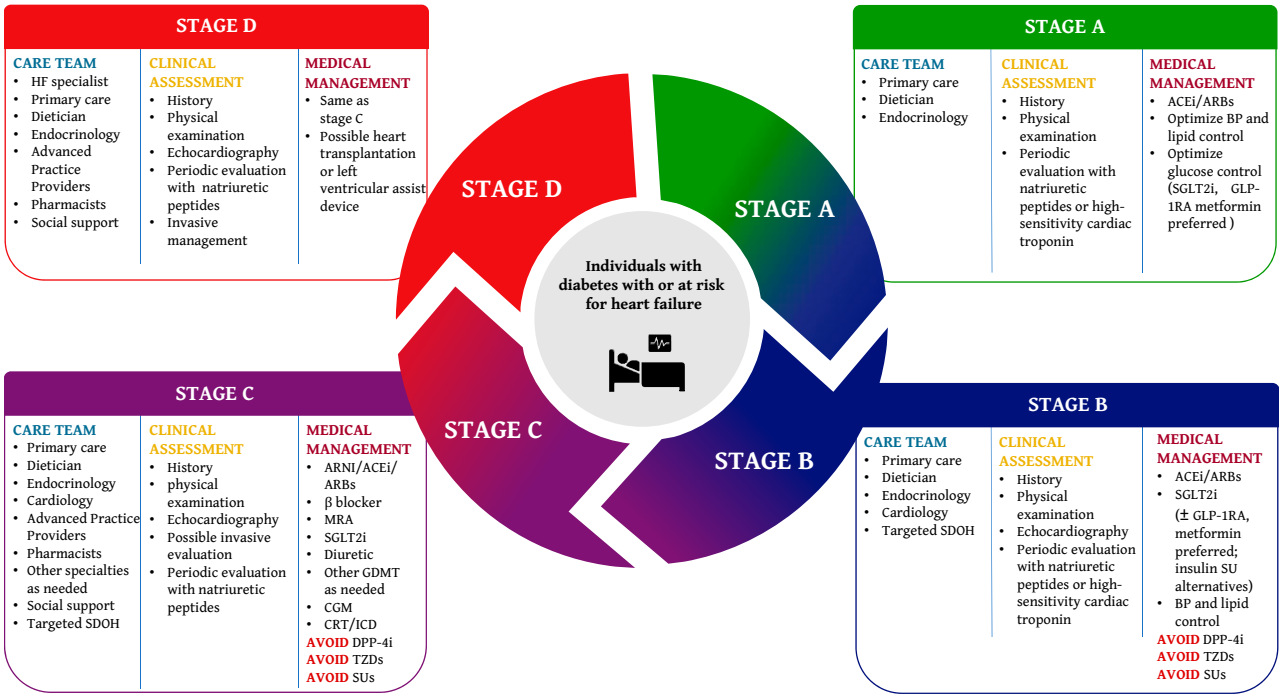

Figure 2—Multidisciplinary personalized care for in individuals with HF and diabetes. DPP-4i, DPP-4 inhibitors; SUs, sulfonylureas.

diagnostic accuracy of natriuretic peptides appears to be unaffected by the presence of diabetes (71). Further diagnostic evaluation for HIV, rheumatological diseases, amyloidosis, or pheochromocytoma may be indicated if there is high clinical suspicion (54).

Noninvasive Cardiac Imaging. Noninvasive cardiac imaging includes a chest X-ray and echocardiography. A chest X-ray may be used to assess heart size and pulmonary congestion and evaluate for alternative causes of dyspnea (54). Cardiomegaly and pulmonary redistribution are among the most commonly observed findings in individuals with HF (69,72). However, the sensitivity of chest X-ray for making a diagnosis is poor (73); one of five individuals with acute HF has no signs of congestion on a chest X-ray (74).

Transthoracic two-dimensional echocardiography with Doppler assessment is a key diagnostic test in establishing the initial diagnosis and cause of clinical HF, providing information on cardiac structural and functional changes and etiology, and will differentiate between HFpEF and HFrEF (54). Classically, preserved ejection fraction (EF) is defined as an EF ≥50%, although recent data suggest this might be extended up to ≥55%; this together with echocardiographic findings of impaired myocardial relaxation constitute important diagnostic criteria for HFpEF and are part of algorithms validated for the diagnosis (73,75). Those with a left ventricular EF (LVEF) between 41% and 49% are referred to as having HF with "mildly reduced" EF and those with LVEF ≤40% as having HFrEF (55). Due to challenges of securing a diagnosis of HFpEF, validated risk scores and biomarker cutoffs as shown in Table 1 may be useful to support clinical judgment (73,75).

Given the associations between diabetes and risk for ASCVD, when an individual with diabetes is diagnosed with HF, subsequent evaluation for obstructive CAD is strongly advisable in the absence of contraindication. While stress testing has played a role in the past for such an indication, with increasing availability of noninvasive coronary computed tomographic imaging, anatomic definition might represent a more desirable means by which to avoid risk for a false-negative nuclear test.

Invasive coronary angiography should be reserved for individuals with a high pretest probability of obstructive CAD who may need consideration for revascularization or for those with indeterminate stress testing and/or coronary computed tomographic examinations. Clinicians should be mindful that the contrast used for both coronary computed tomography and invasive coronary angiography may result in acute kidney injury, particularly in those individuals with abnormal kidney function and individuals with diabetes who are at risk for contrast nephropathy.

Key Points

- Clinicians should be aware of the multiple symptoms, signs, and physical findings in patients with HF.
- Recommended laboratory evaluations for patients with HF include natriuretic peptide, complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function, and thyroid-stimulating hormone. A chest X-ray and 12-lead electrocardiogram are also recommended.
- Imaging studies such as transthoracic echocardiography will add meaningful information to the evaluation of a patient with suspected or proven HF.
- When HF is diagnosed in individuals with diabetes, clinicians should evaluate for evidence of obstructive CAD as the cause.

MANAGEMENT OF HF IN DIABETES

Lifestyle and Nutrition

Lifestyle therapy is an important part of the management of HF risk. Several

multilifestyle approaches have been proposed in this regard, such as the "Life's Simple 7," which provide an important roadmap for addressing modifiable risk factors for HF (76) (Supplementary Table 3).

General Recommendations

For all individuals with HF and diabetes, minimizing alcohol intake and avoidance of smoking (2,77) are recommended. The appropriate quantity of fluid and salt intake is a subject of debate. Strict limits should be imposed when there is clear fluid overload or demonstrated sensitivity to fluid intake that is not easily controlled with diuretics (67,77).

Serum potassium disturbances are frequent in individuals with HF due to associated comorbidities and use of diuretic therapy, potassium supplements, and RAAS blockers, including the combination of ARB and neprilysin inhibitors (78). Serum potassium concentrations independently predict mortality in HF: a U-shaped association, with higher risk at both ends of the distribution (79). People with diabetes are at increased risk of developing hyperkalemia in the setting of RAAS blockade; thus, clinicians should be aware of this potential complication (2,80) and implement periodic potassium monitoring as currently recommended (8,81) (Supplementary Table 3). In addition, individuals should receive targeted dietary counseling to maintain normal potassium levels by avoiding over-the-counter potassium supplements and potassium-based salt substitutes, limiting intake of high-potassium food and beverages, and avoiding other medications that may increase risk for hyperkalemia (such as nonsteroidal anti-inflammatory drugs) (2).

Role of Nutrition

Evidence is emerging on the role of nutrition plans in people with diabetes and HF. Dietary recommendations should be individually tailored according to caloric requirements, personal and cultural food preferences, prescribed medications, presence of overweight or obesity, and comorbid medical conditions. Considerations should also include reducing intake of saturated fat, completely eliminating *trans* fat intake, decrease of energy density (<125 kcal/100 g of consumed food), and a preference for dietary patterns with a focus on the intake of vegetables, moderate amounts of fruit and whole grains, poultry, fish, low-fat dairy, legumes, nontropical vegetable oils, and nuts, such as with the Dietary Approaches to Stop Hypertension (DASH) or Mediterranean-style diets (82) (Supplementary Table 3).

Exercise

There is a strong association between HF and physical inactivity and low fitness in general including in individuals with diabetes, underlining the importance of regular physical activity and exercise for prevention and treatment of HF (83). For instance, cardiac stiffness typically accelerates in midlife but can be reversed by aerobic exercise (83). In individuals with HFpEF, regular physical activity counteracts many of the metabolic and functional changes observed.

In HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training), 2,331 people (32% with diabetes) with HFrEF were randomized to aerobic exercise training or to usual care for a median follow-up of 2.5 years. All individuals had lower baseline functional capacity, but, importantly, those in the exercise group had significant improvements in peak oxygen consumption and 6-min walk distance compared with those in usual care (84).

Therefore in people with diabetes and HF, exercise is recommended to improve functional capacity (84). Individually tailored plans that include risk stratification, clinical assessment, and cardiopulmonary exercise testing should be undertaken before initiation of exercise training for these individuals (Supplementary Table 3) (83).

Weight Loss

Weight loss generally has significant cardiometabolic benefits and may be important in reduction of HF events. Look AHEAD (Action for Health in Diabetes) was conducted to evaluate whether an intensive lifestyle intervention could alter the risk of cardiovascular outcomes among individuals with T2D who were overweight or obese, and the results reported showed that reductions in BMI were associated with lower risk of HF (85); reductions in fat mass and waist circumference were each significantly associated with lower risk of HF (86) with decline in waist circumference specifically associated with lower risk of HFpEF.

Key Points

- Periodic serum potassium monitoring and minimizing alcohol intake and avoidance of smoking are recommended.
- Regular tailored exercise is recommended as it has been shown to be beneficial in individuals with diabetes and HF.
- Weight loss improves cardiometabolic risk factors and may lower risk for HF.

Targeting Social Determinants of Health

Recognition of social determinants of health (SDOH) factors is a necessary initial step needed to implement targeted measures toward improving HF outcomes in individuals with diabetes adversely affected by health disparities and developing comprehensive and culturally sensitive approaches to care. Thus, providers should actively screen and identify specific SDOH for all individuals with diabetes and HF such as job and food insecurity, health literacy, appropriate and secure housing, and access to health care and medication (87–91), with implementation of a comprehensive multidisciplinary team approach to mitigate the challenges that these individuals face in their quest for longitudinal care.

Key Points

- Providers should identify SDOH factors that might adversely affect an individual's access to care (job and food insecurity, health literacy, access to housing, and safe environment) in order to mitigate their impact.

Pharmacologic Treatment

Interventions recommended for individuals with stages A and B HF include risk factor modification and treatment to stabilize structural heart disease (54,92). Effective management of known risk factors, including hypertension, diabetes, obesity, dyslipidemia, and atherosclerotic disease, can reduce the risk of progression to overt HF (54), although achieving (36) the currently recommended targets for glucose, blood pressure (BP), and lipids remains suboptimal. Use of ACEi or

β-blocker therapy may be particularly effective in slowing the progression of HF in asymptomatic individuals with significantly reduced LVEF (92). With effective treatment, individuals in stage B HF may remain stable for many years (92).

Management of Hypertension in Individuals With Diabetes in Stage A or B HF

Although optimal control of BP remains a primary goal for all individuals at risk for HF, there are some particularities in the intersection of hypertension with diabetes. For instance, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), treatment with doxazosin was associated with increased rate of HF, compared with chlorthalidone, in individuals with diabetes despite a similar reduction in BP (93). Findings of the Swedish Trial in Old Patients with Hypertension-2 (STOP-2) showed that ACEi were superior to calcium channel blockers in preventing HF in the subgroup of elderly individuals with diabetes (94).

ACEi or ARB are preferred agents in the management of individuals with either T1D or T2D and hypertension, especially in the presence of albuminuria, to reduce the risk of progressive kidney disease, and their dose should be optimized (95). Treatment with a thiazide-type diuretic or an ACEi has been shown to be more effective than treatment with a calcium channel blocker in improving HF outcomes (96). Thiazide diuretic use occasionally results in worsening glycemic control and/or raising serum triglycerides in individuals with diabetes.

Despite treatment with what is considered to be optimal doses of ACEi or ARB, there remains overactivation of the mineralocorticoid receptor in hypertension. Mineralocorticoid receptor antagonists (MRA) such as spironolactone or eplerenone are thus important adjuncts for management of hypertension. Recent studies determined that finerenone, a nonsteroidal selective MRA with more potent anti-inflammatory and antifibrotic effects than steroidal MRA, has superior benefits in diabetic kidney disease (DKD). In the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial, in 5,734 individuals with CKD and T2D, it was determined that treatment with finerenone resulted in lower risks of DKD progression and cardiovascular events, myocardial infarction, and hospitalization for HF (97,98), while Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) showed that finerenone significantly reduced cardiovascular death and nonfatal cardiovascular disease endpoints including hospitalization for HF in 7,400 individuals with T2D and DKD (99,100). Thus, finerenone is now approved by the U.S. Food and Drug Administration for reducing progression of DKD and reducing risk for cardiovascular complications including HF.

These agents are associated with risk for hyperkalemia and require careful serum potassium monitoring when used (as detailed in Supplementary Table 3).

Key Points

- ACEi and ARB are preferred agents in the management of stage A or B patients with either T1D or T2D and hypertension, especially in the presence of albuminuria and/or CAD.
- Treatment with a thiazide-type diuretic or an ACEi has been shown to be more effective than treatment with a calcium channel blocker in preventing progression to symptomatic HF, and their use is recommended for treatment of individuals with diabetes and hypertension.
- Among patients with diabetes and DKD without symptomatic HF, the use of finerenone, a nonsteroidal MRA, may reduce progression of DKD and lower risk for incident HF.
- Careful monitoring of serum potassium levels is needed with the use of MRA and other RAAS blockers.

Pharmacologic Therapy for Stages C and D HF: Guideline-Directed Medical Therapy

Recent clinical practice guidelines and expert consensus statements are available for detailed guidance regarding rationale for use, initiation and titration, and monitoring of the standard guideline-directed medical therapy (GDMT) for HFrEF treatment (67,101); clinicians are directed to these useful documents for specific advice regarding selection of agents, doses, and titration strategies. Here, we will only review the expected components of care, referring mainly to diabetes-specific topics related to use of GDMT in the presence of HFrEF or HFpEF.

For those individuals with diabetes with symptomatic HFrEF, barring contraindication, the expected components of GDMT include the following: *1*) angiotensin receptor/neprilysin inhibitor (ARNI) or ACEi/ARB, *2*) evidenced-based β-blocker, *3*) MRA, and *4*) SGLT2i. While the GDMT options for HFpEF are less well-defined, SGLT2i are now also recommended in HFpEF, as discussed below (1).

RAAS Inhibitors for Treatment of HFrEF. Inhibitors of the RAAS represent foundational therapy for the management of HFrEF, increasing LVEF even in those previously taking ACEi or ARB (102), reducing risk for hospitalization or death, and improving health status. Agents in this class include the ARNI sacubitril/valsartan, ACEi, ARB, and MRA.

ACEi have been a mainstay of treatment for such patients (with ARB reserved for those with intolerance to ACEi). With the development of the prototype ARNI sacubitril/valsartan, ACEi and ARB are no longer considered the gold standard renin-angiotensin inhibitors for care of HFrEF. Sacubitril/valsartan contains a neprilysin inhibitor plus an ARB, and there is evidence of benefits in HFrEF being superior to those with ACEi. In the landmark Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial (103), treatment with sacubitril/valsartan was associated with a 20% reduction in cardiovascular death or HF hospitalization compared with enalapril, a benefit that was observed also in participants with diabetes (104). These results and others led to embedding of sacubitril/valsartan as class I in clinical practice guidelines (67) and as the preferred frontline treatment for HFrEF (101). ARNI therapy is associated with higher rates of hypotension compared with ACEi or ARB, and individuals should be monitored for hyperkalemia or worsening kidney function and the drug should not be used in individuals with a history of angioedema.

The steroidal MRA spironolactone and eplerenone have been shown in large-scale prospective double-blind trials to reduce cardiovascular mortality and hospitalizations for HF in individuals with HFrEF. These drugs are critically important components of the GDMT for HFrEF; however, among individuals with

diabetes the risk of hyperkalemia and acute renal insufficiency may limit ability to prescribe these beneficial agents (105,106). Monitoring of potassium levels and use of potassium binding agents may facilitate use of MRA.

β-Blockers for Treatment of HFrEF. Use of β-blockers in individuals with HFrEF is associated with improvement of LVEF, reduced risk for major HF complications such as arrhythmia, pump failure, or death, and improved health status. β-Blockers for which there is evidence to support use in HFrEF include metoprolol succinate, carvedilol, and bisoprolol. Use of an evidence-based β-blocker is associated with benefit among individuals with HFrEF and T2D (107).

SGLT2i as a Treatment for HFrEF. Recent trials of SGLT2i that included individuals with HFrEF such as Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) (45% with T2D) (108), as well as Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) (50% with T2D) reported significant reductions in risk of cardiovascular death or hospitalization for HF and improvements in health status and quality of life (109,110) associated with treatment with dapagliflozin and empagliflozin, respectively, independent of baseline diabetes status and across the continuum of HbA_{1c} (111). Notably, treatment with empagliflozin in EMPEROR-Reduced led to less discontinuation of MRA (112), and in DAPA-HF new-onset diabetes was less common among patients randomized to receive dapagliflozin (113)

Other Agents in the Care of HFrEF. Less commonly used GDMT for HFrEF includes the pure heart rate–reducing agent ivabradine, the combination of hydralazine and isosorbide dinitrate, and loop diuretics.

Ivabradine is recommended for use in those with HFrEF, in sinus rhythm with resting heart rate ≥70 bpm, and receiving maximally tolerated β-blocker to reduce the risk of HF hospitalization (114). The combination of hydralazine and isosorbide dinitrate is a useful alternative to ARNI, ACEi, or ARB in specific situations, particularly in Black individuals with HFrEF (115) and individuals who develop hyperkalemia and/or worsening kidney function in response to first-line renin-angiotensin blockade or who remain symptomatic despite first-line GDMT. No specific randomized data regarding alteration of the efficacy of hydralazine/isosorbide dinitrate by diabetes status exist.

Vericiguat is a soluble guanylate cyclase stimulator recently studied and indicated for treatment of individuals with chronic HF and EF <45% and recent HF hospitalization (116) but should be added only after other GDMT has been optimized.

Loop diuretics are frequently necessary for the care of individuals with HF and fluid retention. Unlike other GDMT, higher loop diuretic dose is associated with elevated risks for adverse outcomes and side effects. The minimally effective dose should be used to avoid risk of worsening kidney function, electrolyte abnormalities, or hypotension owing to intravascular depletion. Careful clinical evaluation for signs of congestion is recommended when decisions are made regarding change of loop diuretic dose to avoid risk for over- or underhydration. Excellent application of GDMT may help to reduce or remove loop diuretics; this is particularly so with greater use of ARNI and SGLT2i (81,117). Among those with resistance to loop diuretics, thiazide diuretics are sometimes added to "boost" the diuretic effect. Close monitoring of electrolytes and kidney function is recommended should this approach be used.

Key Points

- Recommendations for GDMT of individuals with HFrEF and diabetes are similar to those for HFrEF patients without diabetes and include ARNI, ACEi, or ARB, evidence-based β-blockers, MRA, and SGLT2i.
- Sacubitril/valsartan is the first-line therapy in individuals with diabetes and HFrEF and is preferred to ACEi or ARB.

Pharmacologic Treatment of HFpEF. Individuals with HF and LVEF >40% have more limited drug options, since most GDMT explored in this population has reduced risk less consistently than in those with LVEF ≤40%. Thus, treatment of such individuals has typically focused on management of hypertension with ACEi or ARB, loop diuretics to manage congestion, and treatment of precipitating factors (valvular heart disease, atrial arrhythmia). Most recent trials of HFpEF therapies have included individuals with HF with mildly reduced EF together with those with "classical" HFpEF; accordingly, the LVEF range in these studies was typically >40%.

On the basis of recent studies, use of spironolactone and sacubitril/valsartan is now supported for the care of individuals with HF and an LVEF up to ∼57%. In the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial, while the primary results of the trial were neutral, stronger estimated benefits of spironolactone were present for those with LVEF <50% (102), particularly in individuals with diabetes (118). In the Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial, treatment with sacubitril/valsartan was associated with a 13%, nonsignificant, reduction in the composite of total HF hospitalizations and death from cardiovascular causes in individuals with HF and LVEF of ≥45%; among subgroups, benefit appeared greater among women and in those with an LVEF ≤57%, although no specific data are available for those with diabetes (119). The U.S. Food and Drug Administration recently issued an indication for sacubitril/valsartan for care of HF and abnormal LVEF, covering most of the LVEF range discussed.

The SGLT2i represent more recent strategies for the management of HFpEF. In the Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial (120) and the Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial (121), reduced event rates were reported with sotagliflozin (a dual SGLT2 and SGLT1 inhibitor) in individuals with diabetes and recent worsening HF or DKD, among those with preserved EF. Lastly, among 5,988 participants with HFpEF (∼50% with T2D) in the EMPEROR-Preserved trial (122), empagliflozin significantly reduced risk of the composite of cardiovascular death or hospitalization for HF in adults with or without diabetes. This

effect was mainly related to a lower risk of hospitalization for HF in the empagliflozin group (123). These findings establish SGLT2i as a clinically proven, effective therapy for HFpEF.

Key Points

- Among individuals with HFpEF it is reasonable to consider treatment with spironolactone or sacubitril/valsartan.
- In individuals with HFpEF, treatment with an SGLT2i is clinically proven therapy to reduce HF hospitalizations.

Management of Hyperlipidemia in Individuals With Diabetes at High Risk for or Established HF

Current clinical practice guidelines recommend treating all individuals over age 40 years with diabetes with statins, while statins are recommended in younger individuals (20–39 years) with additional ASCVD risk factors beyond diabetes. The benefit of statins in older individuals with diabetes (>75 years) remains more ambiguous (124,125); however, benefit is assumed. Whether LDL-lowering interventions prevent HF per se in individuals with diabetes is not certain; however, in a retrospective study of 600 participants with T2D, use of baseline moderate-intensity statins, in comparison with low-intensity or no statin, was associated with lower HF incidence over the course of the median 6-year follow-up independent of LDL levels or CAD events (126).

Key Points

- Clinical practice guidelines recommend treating individuals with diabetes with statins based on age and background risk factors.

Management of Hyperglycemia in Individuals With Diabetes at High Risk for or Established HF

Traditionally, intensive management of hyperglycemia had been at the center of medical management for all individuals with diabetes because targeting near-normal glycemia reduces the risk of microvascular complications (nephropathy, retinopathy, and neuropathy) (1,127). In addition, as amply discussed above in BRIEF OVERVIEW OF SCOPE AND NEED, the presence of hyperglycemia per se has been shown to increase the risk for HF, even in the absence of known diabetes (Supplementary Table 1); this risk was most apparent when HbA_{1c} levels exceeded 8% (92,128). However, there are no data to support intensive glycemic control as a strategy to reduce HF risk or outcomes in T2D.

Evidence from several large prospective trials in individuals with T2D that included HF as a secondary outcome showed no difference in HF rates between the intensive (mean HbA_{1c} 6.4–7.0%) and standard (mean HbA_{1c} 7.3–8.4%) treatment arms (2,127,129). Moreover, evidence from observational studies suggests that the association between HbA_{1c} and mortality among individuals with HF is consistently U shaped, with the lowest mortality in individuals with HbA_{1c} 7–8% (92).

Consequently, current diabetes management guidelines vary in the precise glycemic targets recommended. Optimal glycemic targets for individuals with diabetes and HF should be individualized to reflect comorbidity burden (including severity of HF), potential benefits associated with lowering HbA_{1c} (92,124), the patient's life expectancy, and potential harms of intensive treatment such as risk of hypoglycemia, polypharmacy, treatment burden, and high costs of care (92).

There are specific considerations associated with several of the glucose-lowering medications in individuals with diabetes and various stages of HF (Supplementary Table 4).

SGLT2i. Several clinical trials have shown the beneficial effects of SGLT2i on cardiac outcomes in individuals with T2D, with a consistent notable reduction in incident HF demonstrated in patients across a broad range of ASCVD risk, as amply covered in previous publications (130–133). These trials included T2D participants with or at high risk for ASCVD but did not specifically recruit patients with HF, and as such there was variability in the baseline prevalence of the diagnosis. After a range of ~2.4–3.1 years of follow-up there was a significant reduction in the risk of major adverse cardiovascular events (MACE) with empagliflozin (that included 48% risk reduction in cardiovascular death) and with canagliflozin (130,131,134,135) and significant reduction in the risk of HF hospitalization with all (130–132,134–136). In individuals with T2D with high cardiovascular risk enrolled in these trials, SGLT2i also were associated with benefits in several composite renal outcomes (131,132,137). In contrast to empagliflozin, canagliflozin, and dapagliflozin, ertugliflozin, in Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV), performed in individuals with T2D and ASCVD, was only found to be noninferior to placebo with respect to risk reduction for MACE or HF (138).

In the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) and Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) trials, investigators have further examined the role of SGLT2i in the high-risk population of individuals with CKD on maximum RAAS inhibition. Treatment with SGLT2i in these trials was associated with significant reductions in the risks of CKD progression or cardiovascular death, and reduction in hospitalization for HF, compared with placebo (139–141).

The precise mechanisms through which SGLT2i provide cardiorenal benefits are not conclusively understood. They may include increased natriuresis (142), with associated decrease in plasma volume and cardiac preload (142), all leading to improved vascular resistance and lower systolic BP, improvement of endothelial function, and decreased aortic stiffness (143), weight loss due to calorie loss from increased glycosuria (142), and reductions in oxidative stress, advanced glycemic end products, and inflammation including adipose tissue release of proinflammatory and profibrotic cytokines (144,145). SGLT2i also promote more efficient ketone-based myocardial metabolism and through inhibition of the sodium-hydrogen cotransport may promote myocardial resistance to hypoxia and stress (145). These findings provide the rationale for two recent studies that have shown beneficial effects of sotagliflozin, a dual SGLT2 and SGLT1 inhibitor, in individuals with diabetes and recent worsening HF (120) and in individuals with diabetes and CKD (121).

In summary, findings from the constellation of clinical trials focused on SGLT2i are applicable to phenotypes across the spectrum of HF stages; this information should be incorporated into personalized clinical care (Fig. 2 and Supplementary Table 4). SGLT2i are recommended for all individuals with HF.

Glucagon-Like Peptide 1 Receptor Agonists. Cardiovascular effects of the glucagon-like peptide 1 receptor agonists (GLP-1RA) that may mediate HF risk include reduced RAAS activity, reduced oxidative stress, decreased BP, improved endothelial function, weight loss, and reduced triglyceride and LDL cholesterol levels. There are also some potential negative effects of the class including increased sympathetic nervous system activity and direct sinoatrial node simulation, with a resulting increase in heart rate (146).

Several cardiovascular outcomes trials have evaluated the cardiovascular safety of GLP-1RA. In patients with T2D and established ASCVD enrolled in the Harmony Outcomes trial, treatment with the GLP-1RA albiglutide was shown to reduce the risk of incident HF hospitalizations compared with placebo; however, this medication is no longer available (147). In outcomes trials of patients with T2D and high cardiovascular risk, treatment with liraglutide (148), exenatide (149), semaglutide (150,151), lixisenatide (152), and dulaglutide (153) did not significantly alter rates of HF hospitalization compared with placebo. Only small trials of GLP-1RA treatment in patients with established HF have been completed, with results not suggestive of an outcomes benefit (151,152). In addition, in a recent analysis from Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) (148), no significant difference was found in risk of HF hospitalization with liraglutide versus placebo in individuals with or without HF at baseline (154). These data suggest that GLP-1RA may be used in patients with HF but not with the goal of improving HF outcomes.

Thus, despite the lack of conclusive evidence of direct HF risk reduction with GLP-1RA to date, their indirect beneficial effects on weight and BP reduction, and reduced hypoglycemia risk, and impact on atherothrombotic disease are important considerations in selecting the best therapeutic strategies for individuals with T2D with or without prevalent HF.

Metformin. Metformin remains the most widely used of oral medications for T2D (1,155). Metformin improves insulin sensitivity, is typically weight neutral or may induce weight loss, effectively prevents diabetes development, and is affordable given its low costs (156).

Although historically metformin was contraindicated in individuals with HF, a meta-analysis of nine cohort studies of nearly 34,000 individuals suggested that metformin was associated with a 20% reduced mortality risk and a smaller but significant reduction in all-cause hospitalization in individuals with HF compared with control subjects (2,157). In another large, propensity-matched observational study, initiation of metformin was associated with lower risk of HF hospitalization than sulfonylurea drugs (4,158). However, no randomized controlled trials of metformin relative to HF risk have been performed, making these results hypothesis generating at best. Metformin should be discontinued in individuals presenting with acute conditions associated with lactic acidosis, such as cardiogenic or distributive shock.

While metformin is still considered first-line therapy for many individuals and is preferred to sulfonylureas as discussed below, current treatment recommendations are to favor SGLT2i and GLP-1RA in those with HF or atherothrombotic disease (7,159).

Sulfonylureas. Sulfonylureas, including glyburide, glipizide, and glimepiride, continue to be widely used oral medications for T2D (160,161) but, given their mechanism of action, promote weight gain and fluid retention (161), with a perennial uncertainty about cardiovascular safety.

The evidence regarding use of sulfonylureas and development of HF in individuals with T2D is quite limited. However, in contrast to the safety and possible benefits of metformin, several observational studies have suggested that sulfonylurea therapy may be associated with increased risk of HF events compared with metformin or with other agents (2). Evidence from a large retrospective cohort, with data combined from the National Veterans Health Administration, Medicare, Medicaid, and the National Death Index, that included 24,685 metformin users and 24,805 sulfonylurea users with reduced kidney function (median age 70 years, estimated glomerular filtration rate 55.8 mL/min/1.73 m^2) showed significantly fewer HF hospitalizations per 1,000 person-years for metformin compared with sulfonylurea users (155). In addition, in a most recent comparative effectiveness study with analysis of data from 128,293 participants with T2D in the U.S. Department of Veterans Affairs, of whom 23,870 received an SGLT2i and 104,423 received a sulfonylurea, it was reported that SGLT2i treatment was associated with a reduced risk of all-cause mortality compared with sulfonylureas (162). These studies provide real-world data that might help further guide the choice of antihyperglycemic therapy.

Insulin. In the treatment of T2D, insulin is often initiated when there is a need to intensify glycemic management, particularly in specific settings such as more advanced stages of CKD when other agents cannot be used. Recently, several studies have investigated the relationship between insulin use and development of adverse cardiac outcomes including HF. In Outcome Reduction With Initial Glargine Intervention (ORIGIN Trial), individuals with T2D were randomized to insulin glargine versus standard of care, with no increase found in the occurrence of hospitalization for HF associated with insulin glargine use (163). In the Degludec Cardiovascular Outcomes Trial (DEVOTE) there was no difference in HF events in patients with T2D with high risk for CVD randomized to insulin glargine or insulin degludec (164).

Although insulin remains available to optimize diabetes management in general, it should be used judiciously in individuals with HF given its effects in inducing fluid retention, weight gain, and hypoglycemia, each of which can negatively affect HF outcomes and management.

Dipeptidyl Peptidase 4 Inhibitors. Dipeptidyl peptidase 4 (DPP-4) inhibitors have been evaluated in several cardiovascular outcomes trials, and their impact on HF (165,166) has been mixed. In Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53), those who were randomized to saxagliptin were more likely to be hospitalized for HF within the first year of treatment relative to those on placebo (167). In EXAMINE, individuals with T2D and cardiovascular disease who were randomized to alogliptin did not have an increased risk of

hospitalization with HF in the original study. However, a post hoc analysis revealed that there was a relative increase in risk for hospitalization due to HF in the alogliptin group (165,168). In contrast, neither sitagliptin nor linagliptin increased hospitalizations for HF (169–171).

Thus, given beneficial effects of other hypoglycemic agents on HF outcomes as discussed above, in treatment of T2D in individuals with stage B, C, and D HF, DPP-4 inhibitors are not recommended.

Thiazolidinediones. Several reports and evidence from meta-analyses and randomized trials showed that use of thiazolidinediones (TZDs) increased risk of HF, HF hospitalization, or death, as they promote weight gain, lower extremity edema, and increased cardiovascular risk, especially when used in combination with insulin therapy (172–176).

Given these findings, TZDs are not recommended for use in individuals with stage B, C, and D HF.

Recommendations for Treatment of Hyperglycemia. This consensus recommends prioritizing the use of SGLT2i in individuals with stage B HF and that SGLT2i be an expected element of care in all individuals with diabetes and symptomatic HF (stages C and D) including those with HFpEF. If additional glycemic control is indicated in individuals at risk for or with established HF, use of GLP-1RA, metformin, or insulin should be considered. The consensus recommends against using DPP-4 inhibitors and TZDs for individuals with diabetes and symptomatic HF or individuals with stage B HF and that practitioners judiciously consider the use of sulfonylureas in those situations when therapies with proven benefit are not available.

Key Points

- Diabetes medications have differential effects on HF risk, and each individual's cardiovascular risk factors should be carefully reviewed and considered in selecting a therapeutic regimen for diabetes.
- SGLT2i are an expected element of care in all individuals with diabetes and symptomatic HF and should be used in individuals with high cardiovascular risk, including those with stage B HF.
- If additional glycemic control is needed for an individual with T2D at high risk for or with established HF, use of GLP-1RA, metformin, or both should be favored over sulfonylureas.
- DPP-4 inhibitors or TZDs are not recommended for patients with diabetes with stage B, C, and D HF.
- Insulin treatment could be added if additional glycemic control is indicated. (See Fig. 2 for these Key Points.)

Special Considerations

Cardiac Rehabilitation

Cardiac rehabilitation programs are useful adjuncts for the management of HFrEF (177). Comprehensive cardiac rehabilitation programs typically include a focus on exercise (see also *LIFESTYLE AND NUTRITION*), along with education on cardiovascular risk factors, psychological support, lifestyle modification, and medical care (including a focus on medications with secondary cardiovascular prevention benefits) (Supplementary Fig. 2). The benefit of comprehensive cardiac rehabilitation programs in people with diabetes is significant: improving exercise capacity (178) and a possible effect on MACE. Participation of individuals with diabetes in cardiac rehabilitation was associated with 44% reduction in all-cause mortality and 23% reduction in composite of mortality, myocardial infarction, or revascularization during a median follow-up of 8.1 years (179).

Current clinical practice guidelines (54,180) have given a class I recommendation for use of cardiac rehabilitation for HFrEF. Troublingly, presence of diabetes as a comorbidity has been associated with lower likelihood for use of cardiac rehabilitation (179).

Efforts to increase routine referral of eligible individuals with diabetes and HFrEF to comprehensive cardiovascular rehabilitation are justified. Home-based cardiac rehabilitation may be an alternative for selected clinically stable individuals at low to moderate risk and may therefore increase the treatment reach to individuals who might otherwise not attend traditional programs (181).

Key Points

- Cardiac rehabilitation programs are underutilized for those with diabetes and HFrEF.
- Participation in cardiac rehabilitation is associated with improvement in exercise capacity and health status and possibly reduces mortality.
- Efforts to increase routine referral of eligible individuals to cardiac rehabilitation are encouraged.

Considerations on Metabolic Surgery for Diabetes and HF

Metabolic surgery is emerging as a powerful treatment for severe obesity and T2D, given its effects in metabolic regulation and promoting improvement in cardiometabolic risk factors relevant to HF including various degrees of weight reduction, modulations of incretins and other noninsulinotropic peptides, and reductions in lipotoxicity, inflammation, and insulin resistance, thus preventing T2D, improving overall glycemic control, and leading to significant rates of T2D remission, as well as reducing total and cause-specific mortality (182,183).

Beyond improvements in risk factors relevant to HF, the significant loss of body weight associated with metabolic surgery is also directly associated with reduction in major cardiovascular events in those with HF (184), notably including those with HFpEF (185). Furthermore, mechanistically, metabolic surgery has also been linked to reversing cardiac remodeling with improved systolic and diastolic function (186,187).

Key Points

- Metabolic surgery promotes improvements in risk factors relevant to HF and is directly associated with reduction in major cardiovascular events in those with HF and obesity and thus should be considered in these individuals to improve HF outcomes.

Cardiac Implantable Devices and Revascularization in HF

The principal indications for coronary artery revascularization and device therapy, including implantable cardioverter defibrillators (ICD) and cardiac resynchronization therapy (CRT), in individuals with diabetes are similar to those for patients without diabetes (2). These have been reviewed in detail in current guideline recommendations and are only summarized in this statement (188,189).

The benefit of CRT and ICD therapy in individuals with HF to reduce mortality and hospitalization is observed in individuals with and without diabetes (190–192).

Coronary revascularization is frequently used among patients with HF. Outcomes following coronary revascularization are less robust among individuals with diabetes (193). The main indications for coronary revascularization in individuals with diabetes on optimal GDMT are for management of limiting angina and/or to reduce mortality (194,195). Indications specifically for coronary artery bypass grafting for mortality benefit following coronary revascularization include left main CAD and multivessel CAD with reduced left ventricular function (193,196).

Key Points

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

Use of Diabetes Technologies and Mobile Health

Novel technologies such as the real-time continuous glucose monitoring (CGM) devices that enable real-time actions are emerging as powerful tools. Strong evidence shows that the persistent use of CGM is the most effective strategy for reduction of the incidence of hypoglycemia and severe hypoglycemia in both T1D and T2D, in addition to improvement of glycemic control (197,198), both adding substantial benefit for HF outcomes in diabetes. Moreover, these benefits are maintained in older adult populations with diabetes (197) and, importantly, are also observed across racially and socioeconomically diverse populations with T2D (198)—all of whom are at higher risk for worse HF outcomes. Additionally, CGM allows for nuanced assessment of the impact of food, activity, and medications on blood glucose, facilitating personalized care when used consistently, and thus very relevant for those at risk for or with HF.

Similarly, integrated mobile health (mHealth) programs are emerging as low-cost, widely accessible strategies, using mobile communication such as text messages to deliver consistent interventions, and have been shown to be effective in changing health-related behaviors and promoting self-management of chronic diseases that in turn could improve clinical outcomes in those with diabetes and HF (199,200).

Key Points

- Given the proven CGM benefits in minimizing hypoglycemia risk and optimizing glucose control in T1D and T2D across the age continuum, and across racially and socioeconomically diverse populations, the integration of CGM in the management of all individuals with diabetes at risk for or with HF should be considered.

Considerations Regarding Hospital Management of Patients With Diabetes and Acute HF

Hospitalization is a pivotal moment in the disease journey of individuals with HF (201). Each hospitalization for HF is associated with 90-day readmission rates and 1-year mortality approaching 30% (202). Therefore, the individual hospitalized with HF should be treated with priority: in addition to providing an opportunity to identify and treat causes of HF decompensation, the inpatient setting is also an ideal environment to add or optimize therapies used for outpatient care discussed above (such as initiation or transition to ARNI, optimization of β-blocker therapy, addition of MRA, or initiation of an SGLT2i) (203). A comprehensive approach to treating the hospitalized individual with HF was recently published (203).

Specific to persons with diabetes, the recently published results of the SOLOIST-WHF trial demonstrated that initiation of sotagliflozin (a dual SGLT2/SGLT1 inhibitor) in individuals with T2D and acute HF stabilized prior to discharge or shortly thereafter is safe and effective in reducing serious CV outcomes including cardiovascular death and HF readmission (120). Importantly, the evidence for benefit of sotagliflozin emerged as early as 28 days after initiation, and these benefits were consistent in both those with HFrEF and those with HFpEF (120). These findings emphasize both salutary effects of these agents and safety in stabilized HF individuals as discussed above.

It is well-known that diabetes and uncontrolled hyperglycemia are common in the hospital setting and are associated with increases in hospital complications, length of stay, and mortality (204). For the past 15 years, insulin therapy has been considered the cornerstone of the management of individuals with hyperglycemia in the hospital (205). However, an important complication of insulin therapy in hospitalized people is inpatient hypoglycemia, which is consistently associated with poorer inpatient outcomes and higher mortality risk (204,205), possibly leading to acquired long QT syndrome, which could in turn precipitate fatal cardiac arrhythmia (204). While intravenous insulin therapy remains the treatment of choice in the critical care setting (205), in nonintensive care settings, insulin may not necessarily be the only choice and other therapies should be considered.

Key Points

- Hospitalization for decompensation or new-onset HF represents a pivotal moment in the disease journey of individuals with diabetes, as risk for adverse outcome rises substantially in this setting.
- During hospitalization, individuals with diabetes and HF should receive standard management per contemporary guidelines and consensus documents, which includes assessment for cause of acute HF and optimization of outpatient GDMT.
- Consider initiation or continuation of SGLT2i in the inpatient management for those with diabetes and acute HF.

CLINICAL IMPACT AND TRAJECTORIES IN DIABETES

Understanding disease trajectory is an important tool to help educate individuals about their medical condition and prevent disease progression, including HF-related hospitalizations and death. Findings of a recent prospective echocardiography study showed that individuals with T2D had a more pronounced LVEF decline after 9 years (suggesting that factors related to diabetes, including diabetic cardiomyopathy, may underlie the functional decline observed) (206). Unfortunately, data contrasting the clinical impact or trajectories of HF among individuals specifically with T1D, T2D, or prediabetes are very limited.

Key Points

- Diabetes worsens the clinical trajectory of individuals with HF.
- People with diabetes and HF should be educated about the likely trajectory of their heart disease, and management strategies that can improve their outcomes, to limit disease progression,

including HF-related hospitalizations and death.

MULTIDISCIPLINARY CARE FOR PERSONALIZED TREATMENT: CHALLENGES AND OPPORTUNITIES

Individuals with diabetes at risk for HF or with diagnosed HF often require complex, personalized care that involves collaborative care and interactions between primary care clinicians, advanced practice providers, specialists, and other health care team members. Broader social and community engagement with individuals and their families, caregivers, and communities to deliver the highest quality of care across multiple settings is also needed (207). While electronic medical records should theoretically support health care team coordination, as currently implemented they often cause confusion and result in lack of follow-up, partly due to unclear roles and responsibilities (208,209). Newer approaches to mitigate confusion and improve efficiency of care might include messaging tools embedded within electronic medical records or virtual/E-consults (210). Regardless, a collaborative approach for identification and thorough treatment of persons with HF and diabetes is critical.

A proposed paradigm for multidisciplinary personalized care for individuals with diabetes across the HF continuum is shown in Fig. 2.

Considerations for When to Refer to Cardiovascular Specialists

The evaluation and management of the person with diabetes at risk for HF or with established HF may be challenging. Those with risk factors for HF (stage A) or pre-HF (stage B) may require complex decision-making regarding management of risk factors, diagnostic evaluation, and/or treatment. Care of individuals with symptomatic HF (stages C and D) is often complex, requiring frequent visits to initiate, titrate, and assess effects of GDMT. Thus, appropriate, and timely, referral to a cardiovascular specialist (including an advanced HF clinician) is an important part of optimal care for many persons at the various stages of HF.

For individuals at stage A, referral to cardiovascular specialists might be made for consultation regarding management of risk factors such as hypertension or hyperlipidemia as well as further global assessment of cardiovascular risk. For most people in stage A, longitudinal involvement of cardiovascular specialists might be best envisioned on an as-needed basis following initial consultation and recommendation.

For individuals identified to be in stage B, cardiovascular consultation will be helpful for global risk assessment, determination of possible causes of pre-HF, and initiation of therapies with proven benefit in this population including SGLT2i. This population is where targeted risk factor modification is likely to have the largest long-term benefit for the largest number of individuals. For many people in stage B, longitudinal follow-up with a cardiovascular specialist may be helpful (but is not necessarily mandatory).

For individuals with symptomatic HF (stages C and D), referral should be made to a cardiovascular specialist for all the same aspects of care delivered to those in stages A or B and for more intensive diagnostic evaluation (if appropriate), recognition and management of specific or unusual cardiomyopathies, consideration of GDMT eligibility, GDMT initiation and titration, consideration for enrollment to clinical trials, and (if appropriate) evaluation for advanced therapies (heart transplantation or mechanical circulatory support). Ongoing titration of GDMT to goal should be coordinated between cardiovascular specialists, primary care clinicians, advanced practice providers, and endocrinologists/diabetologists; however, given the complexity of their cases and risk, long-term follow-up of individuals with diabetes and stage C or D HF should involve the cardiovascular specialist working in a team manner.

KNOWLEDGE GAPS

The writing committee identified several key areas with significant gaps in knowledge that highlight important areas for future research, which are outlined in Table 2.

SUMMARY AND CONCLUSIONS

The main objective of this consensus report, convened as a result of a unanimous request from the at-large diabetes care provider community, is to provide clear guidance to practitioners on the best approaches for screening and diagnosing HF in individuals with diabetes or prediabetes, with the goal of ensuring access to optimal, evidence-based management for all.

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

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

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

Table 2—Knowledge gaps and future directions for research regarding the intersection of diabetes and HF

Epidemiology
- What is the diabetes burden in those with HFrEF and HFpEF?
- What is the link between advanced HF and diabetes risk?
- What is the distribution of T1D vs. T2D among people with HF?
- What are the impacts of HF on clinical trajectories in people with prediabetes, T1D, and T2D?
- What is the impact of new therapies on rates of developing HF?

Mechanisms
- What are the mechanisms contributing to the excess HF risk in certain groups with diabetes, such as people with T1D and women?
- Are there race-specific mechanisms for HF risk?

Care and management
- What are the best HF prevention strategies for people with T1D and T2D?
- What is the optimal approach to recognize and diagnose diabetic cardiomyopathy in clinical care?
- What are the optimal approaches to manage diabetic cardiomyopathy?
- Are there potential benefits of statins in reducing HF risk in T1D?
- Is high-intensity statin therapy as effective in reducing HF risk as in reducing MACE?
- Do SGLT2i confer a benefit in people with HFpEF similar to that seen in people with HFrEF?
- What are the HF clinical trajectories across the spectrum of dysglycemia?
- Are there additional benefits for HF in using SGLT2i-metformin or SGLT2i–GLP1-RA combinations?
- How to best achieve optimal titration of evidence-based GDMT in daily clinical care?
- What is the role of SGLT2i in HF outcomes in individuals with T1D?
- Should SGLT2i be started during hospitalization with acute HF?
- What are the optimal CGM-mHealth programs for those with diabetes and HF?

Equity, diversity, and inclusion
- Are sex-specific prevention and treatment approaches needed?
- What are the best tools and strategies to address the impacts of SDOH in people with diabetes and HF?
- How to best implement exercise programs across the entire spectrum of racially and socioeconomically diverse populations?

high-burdened SDOH should have access to and be offered the same management framework.

In summary, the writing group sought to emphasize the importance of early recognition of HF using the provided algorithms and tools at a time when choice of interventions is expected to be even more impactful, with requisite thoughtful clinical evaluation and involvement of multidisciplinary care, so that all individuals with HF and diabetes may benefit from optimal personalized care.

Funding and Duality of Interest. R.P.-B. served as an associate editor for *Diabetes*; received grant support from AstraZeneca; conducts research for and receives personal compensation from Boehringer Ingelheim–Lilly Alliance; and is a paid consultant for Novo Nordisk, Averitas Pharma, Nevro, Regenacy Pharmaceuticals, and Roche Diagnostics. J.L.J. is a trustee of the ACC; has received grant support from Innolife, Applied Therapeutics, Roche Diagnostics, and Abbott Diagnostics; has received consulting income from Abbott, Jana Care, Janssen, Novartis, Pfizer, Prevencio, Merck, and Roche Diagnostics; and participates in clinical endpoint committees/data safety monitoring boards for Abbott, AbbVie, Bayer, CVRx, Siemens, and Takeda. D.B. receives research funding through Cleveland Clinic as a principal investigator in a research trial for Novartis Pharmaceuticals and AstraZeneca. J.B.G. is a paid consultant for AstraZeneca, Bayer, Boehringer Ingelheim/Lilly, Hawthorne Effect/Omada, Pfizer, Novo Nordisk, and Sanofi/Lexicon and receives research funding from Boehringer Ingelheim/Lilly, Merck, Roche, and Sanofi/Lexicon. W.H. receives grant support from the American Heart Association. N.R. received grant support from Novo Nordisk; conducts research for Novo Nordisk and Eli Lilly; and served on the advisory boards for Novo Nordisk, Eli Lilly, and Sanofi. C.R.R. received grants from Dexcom, Apple, and Twine Consulting; conducted research for Abbott; serves as an editor for *Annals of Family Medicine* and *JMIR Diabetes*; is a board member of Washtenaw County Community Mental Health; and is the director of the Michigan Collaborative for Type 2 Diabetes, which is funded by Blue Cross Blue Shield. No other potential conflicts of interest relevant to this article were reported.

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