Current and Emerging Issues in the Management of Heart Failure in Primary Care

Robert Chilton, DO, FACC; Stephen Brunton, MD, FAAFP

LEARNING OBJECTIVES

- Describe the epidemiology of heart failure in people with diabetes mellitus.
- Implement evidence-based nonpharmacologic and pharmacologic therapies for heart failure with preserved ejection fraction and heart failure with reduced ejection fraction as recommended in current guidelines.
- Characterize the role of glucose-lowering medications, focusing on the sodium glucose cotransporter-2 inhibitors, for the treatment of people with type 2 diabetes mellitus.

EPIDEMIOLOGY

Heart failure (HF) is a debilitating, often fatal disease that results in major health and socioeconomic consequences. The 5-year mortality rate for HF is similar to many types of cancer, eg, prostate, bladder, and colorectal cancers in men, and breast, colorectal, and ovarian cancers in women.[1] Far exceeding hospitalizations for heart attack, coronary artery disease, or atrial fibrillation, HF was the primary diagnosis for 978,135 hospitalizations in the United States in 2014.[2] Estimates are that the prevalence of HF will increase 46% from 2012, reaching >8 million adults in 2030.[3] A major factor contributing to this rising prevalence of HF is the increasing prevalence of obesity,[4] which serves as an independent risk factor for HF, as well as many other common risk factors for HF, such as coronary heart disease, diabetes mellitus, and hypertension.[5-8] In fact, people with type 2 diabetes mellitus (T2DM) have more than twice the risk of HF than people without T2DM.[3,9-12] Despite this strong association, the mechanism(s) for the increased risk of HF in people with T2DM is unclear, as some evidence indicates that lowering the blood glucose concentration does not necessarily result in improved cardiovascular (CV) outcomes.[13-16]

HF is the most common CV complication in people with T2DM[3] and is a common initial presentation of CV disease in T2DM.[11] While the median age at HF diagnosis in the general US adult population is 59 years, it is 56 years in people with diabetes and 55 years in people with obesity.[17] The onset of changes in the myocardium in people with T2DM generally precedes HF symptoms by several years, as shown by the SHORTWAVE trial.[18] The trial involved 386 people with T2DM (median duration ~5 years), of whom 68% had echocardiographic evidence of systolic and/or diastolic left ventricular dysfunction despite being clinically asymptomatic.

TYPES OF HEART FAILURE

Chronic HF has 2 distinct phenotypes. One is HF with reduced ejection fraction (HF*r*EF), or systolic HF, and the other is HF with preserved ejection fraction (HF*p*EF), primarily diastolic HF (**FIGURE 1**).[8] HF*r*EF is defined as a left ventricular ejection fraction ≤40%, while HF*p*EF is defined as an ejection fraction ≥50%. Approximately half of people with HF have HF*r*EF and the other half HF*p*EF.[19,20] A small subset of people have a midrange ejection fraction between 40% and 50%, with many similarities to HF*p*EF, and may also benefit from treatment.

Robert Chilton, DO, FACC, FAHA, MACOI, FSCAI, Professor of Medicine, Associate Program Director Interventional Cardiology, Director Catheterization Lab UT/Clinical Proteomics, Division of Cardiology, University of Texas Health Science Center, San Antonio, TX.

Stephen Brunton, MD, FAAFP, Adjunct Associate Professor, Touro University California, College of Osteopathic Medicine, Vallejo, CA; Executive Vice President for Education, Primary Care Education Consortium, Murrieta, CA.

DISCLOSURES

Dr. Chilton discloses that he is a consultant for MSD, Pfizer, Boston Scientific, Boehringer Ingelheim, Lilly, AstraZeneca, and Novo Nordisk.

Dr. Brunton discloses that he serves on the advisory boards of Abbott Diabetes, Sanofi, Xeris, Novo Nordisk, Janssen, Bayer, and AstraZeneca and on the speakers' bureau for Lilly, Novo Nordisk, AstraZeneca, Bayer, and Janssen.

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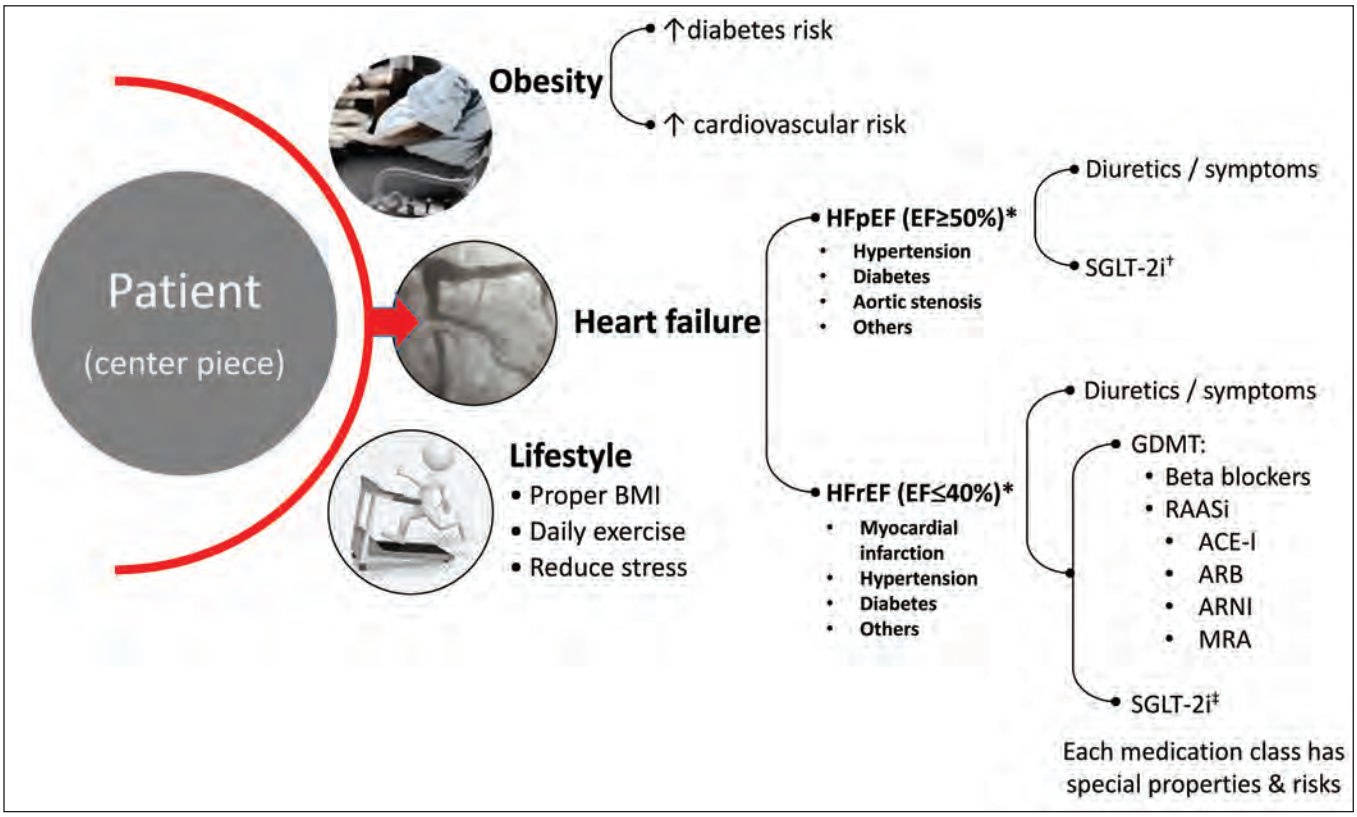
FIGURE 1. **Phenotypes of heart failure and key treatment options**



Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin/neprilysin inhibitor; BMI, body mass index; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF*p*EF, heart failure with preserved ejection fraction; HF*r*EF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor; SGLT-2i, sodium glucose cotransporter-2 inhibitor.

* Patients with EF >40% to <50% are identified as either HF*p*EF borderline or HF*p*EF improved.

† Preliminary evidence suggests possible benefit with canagliflozin, dapagliflozin in HF*p*EF.

‡ Evidence indicates benefit with canagliflozin, dapagliflozin, empagliflozin in HF*r*EF, with greatest benefit with dapagliflozin.

HF*r*EF is most often caused by ischemic heart disease (myocardial infarction [MI]) and is characterized by the loss, function, and stretch of cardiomyocytes resulting in marked left ventricular enlargement and large increases in circulating natriuretic peptides, eg, brain natriuretic peptide (BNP).[21] Consequently, drugs that interfere with neurohormonal systems (eg, angiotensin-converting enzyme inhibitors [ACE-Is], angiotensin receptor blockers [ARBs], beta-blockers, mineralocorticoid receptor antagonists [MRAs], and neprilysin inhibitors) have been used to treat people with HF*r*EF. More recently a new class of agents, sodium glucose cotransporter-2 inhibitors (SGLT-2is), has shown clinical benefit in reducing hospitalization for HF in patients with or without diabetes. In addition, both SGLT-2is and glucagon-like-receptor agonists (GLP-1RAs) currently used for the treatment of diabetes were found to reduce CV events with important kidney protection.[22,23] Patients with HF in general have systemic and adipose tissue inflammation that results in microvascular dysfunction and myocardial fibrosis. Patients with HF*p*EF frequently have a small stroke volume with thick ventricular walls, in contrast to patients with HF*r*EF, who have a large stroke volume and thin ventricular walls. Treatment of HF with a diuretic is recommended acutely for symptomatic relief of shortness of breath due to pulmonary edema, while beta-blockers and neurohormonal antagonists have ongoing effects of improved ventricular remodeling and reduction of cardiac events. SGLT-2is have been found to have acute benefits of reduction in CV events and improved kidney function. Studies with GLP-1RAs have not found significant benefit in reducing hospitalizations for HF.[21]

The New York Heart Association (NYHA) classifies HF in 4 stages based on exercise capacity and symptomatic status.[24] The stages of HF are as follows:

1. Class I: No symptoms and no limitation in ordinary physical activity, eg, no shortness of breath when walking, climbing stairs, etc.

2. Class II: Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
3. Class III: Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20–100 m). Comfortable only at rest.
4. Class IV: Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Although the NYHA classification is based on subjective assessment, it is an independent predictor of mortality.

DIAGNOSIS

The history and physical examination remain the cornerstones of the clinical evaluation of HF, in addition to new biomarkers (eg, BNP) in patients with unclear shortness of breath.[8] A key objective of the diagnostic evaluation is to stratify the patient's CV risk so as to guide therapeutic decision making. The difficulty in patients with diabetes is the inherent risk of ischemic heart disease. Patients also often have metabolic syndrome features with hypertension.

Patients with HF*p*EF classically present with shortness of breath and a hypertension history. Certainly, they also can present with other features such as electrocardiogram (ECG) findings indicating left ventricular hypertrophy, small stroke volume, and atrial enlargement. The echocardiogram frequently is reported to have findings compatible with diastolic dysfunction with normal ejection fraction. The BNP level can be elevated; however, in obese individuals it can be normal. Clinical evaluation with wet lungs, pretibial pitting edema, and distended neck veins can be helpful signs of HF.

Patients with HF*r*EF usually present with a history of ischemic heart disease, eg, MI or coronary artery bypass graft surgery. They also will have shortness of breath with edema and elevated BNP level. Moreover, many have a history of diabetes and hypertension, which increases their CV risks.

Laboratory evaluation includes complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, glucose, nonfasting lipids, liver function tests, and thyroid-stimulating hormone.[8] The N-terminal pro BNP (NT-proBNP) level is useful to establish prognosis and disease severity, particularly in people with obesity, because findings from the clinical evaluation may be equivocal. Also included in the initial evaluation are a 12-lead electrocardiogram, chest x-ray, and 2-dimensional echocardiograph with Doppler to assess heart size and function, pulmonary congestion, and to rule out other disorders. Noninvasive evaluation is warranted due to the high suspicion for obstructive coronary artery disease. Help from a cardiologist in directing the next best option is often important. Noninvasive imaging also can be considered to detect myocardial ischemia and viability in people presenting with new-onset HF who have known coronary heart disease and no angina.

CARDIOVASCULAR OUTCOME TRIALS

In 2008, the US Food and Drug Administration (FDA) began requiring manufacturers of new medications for T2DM to conduct clinical trials to compare the CV safety of the new medication vs placebo as part of standard care.[25] This includes the dipeptidyl peptidase-4 inhibitor, GLP-1RA, and SGLT-2i classes of medications. Since then, more than 20 CV outcome trials (CVOTs) have been completed, with nearly all demonstrating that the CV safety of each of these medications is noninferior to placebo as part of standard care. Noninferiority was assessed based on the composite outcome of CV death, nonfatal MI, and nonfatal stroke.

The methods and patient populations in the CVOTs varied; thus, comparing the results is not possible. All CVOTs investigated the use of the glucose-lowering medication in people who had had a CV event, ie, secondary prevention. Most CVOTs also included people who were at high CV risk, but who had not had a CV event, ie, primary prevention.

Beyond CV safety, several of these medications have shown a significant reduction in CV risk vs placebo. These medications are the GLP-1RAs dulaglutide, liraglutide, and semaglutide, and the SGLT-2is canagliflozin, dapagliflozin, and empagliflozin. Ertugliflozin showed noninferiority, but not superiority, compared with placebo for the composite of major CV events.[26] With respect to HF, the GLP-1RAs did not significantly reduce HF hospitalization.[27] In contrast, the SGLT-2is canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin were associated with a reduction in HF hospitalization, although the trials were not designed to look at this outcome in all cases and in different populations.[26-35]

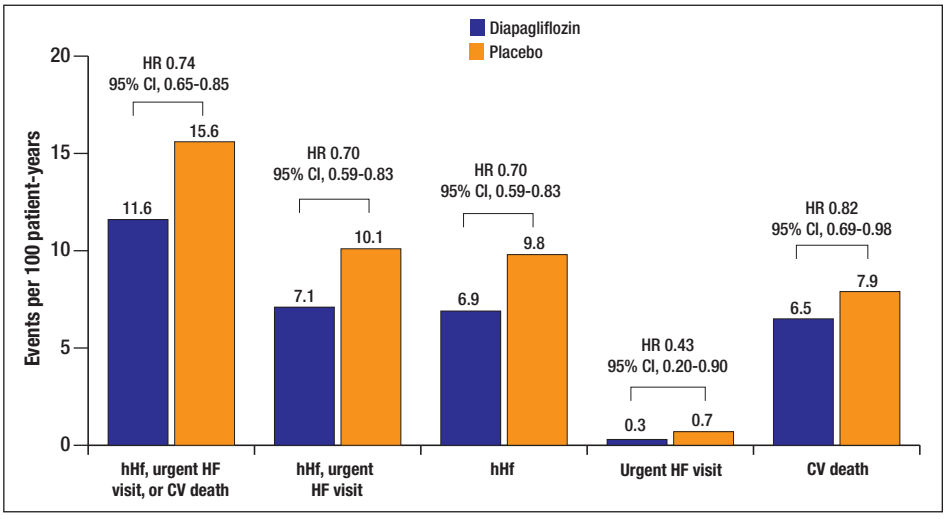
In patients with T2DM, the HF hospitalization benefit with canagliflozin was observed in those with a history of HF, but not in patients with no history of HF.[36] For dapagliflozin and empagliflozin, the HF hospitalization benefit was observed in patients with and without a history of HF.[37,38]

In these CVOTs involving an SGLT-2i in patients with T2DM, the proportion of people with established atherosclerotic CV disease (ASCVD) was 66% for canagliflozin, 41% for dapagliflozin, and 100% for empagliflozin. The proportion of people with a history of HF was 14.4% for canagliflozin, 10.0% for dapagliflozin, 10.1% for empagliflozin, and 23.7% for ertugliflozin, thus making it clear that only a small minority of people with T2DM in the SGLT-2i CVOTs had HF at baseline.

Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure (DAPA-HF) trial

The phase 3 DAPA-HF trial is the only CVOT that has prospectively evaluated the efficacy and safety of a glucose-lowering medication only in subjects meeting standard criteria for HF*r*EF, including elevated NT-proBNP.[39] All subjects received standard therapy for HF*r*EF. Forty-two percent of subjects in both the dapagliflozin and placebo groups had T2DM at baseline, all of whom received standard therapy for T2DM.

FIGURE 2. **Cardiovascular outcomes observed in the DAPA-HF trial**[40]



Abbreviations: CI, confidence interval; CV, cardiovascular; DAPA-HF, Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure; HF, heart failure; hHF, hospitalization for heart failure; HR, hazard ratio.

Subjects (N=4744) were randomized 1:1 to treatment with dapagliflozin or placebo. The primary outcome was a composite of CV death or hospitalization/urgent visit for HF resulting in the initiation of intravenous therapy. After a median of 18.2 months, the primary outcome occurred in 16.3% and 21.2% of dapagliflozin and placebo subjects, respectively (hazard ratio [HR] 0.74; 95% confidence interval [CI], 0.65-0.85; *P*<.001) (**FIGURE 2**).[40] Fewer subjects treated with dapagliflozin were hospitalized for HF (9.7% vs 13.4%, respectively; HR 0.70; 95% CI, 0.59-0.83) or had an urgent HF visit (0.4% vs 1.0%, respectively; HR 0.43; 95% CI, 0.20-0.90). Additionally, CV death occurred in 9.6% in the dapagliflozin group and 11.5% in the placebo group (HR 0.82; 95% CI, 0.69-0.98).

The effect of dapagliflozin on the primary outcome was generally consistent across prespecified subgroups, including subjects with or without diabetes at baseline. This latter finding not only suggests that the benefits of dapagliflozin in subjects with preexisting HF involve nonglycemic mechanisms, it has led some to recommend inclusion of dapagliflozin as standard therapy for patients with HF*r*EF regardless of diabetes history.[21,41] The trial also showed that subjects in NYHA functional class III or IV experienced less benefit than subjects in class II. The occurrence of a serious adverse event related to volume depletion or renal adverse event was similar in the dapagliflozin and placebo groups.

Significantly more subjects in the dapagliflozin group than in the placebo group experienced significant improvement in symptoms based on the Kansas City Cardiomyopathy Questionnaire.[40,42] Similarly, significantly fewer subjects in the dapagliflozin group experienced significant symptom deterioration.

Additional analyses of DAPA-HF have shown improved outcomes with dapagliflozin vs placebo across various subgroups. Age group (<55, 55–64, 65–74, and ≥75 years) had no significant effect on the rate of the primary outcome, adverse events, or study drug discontinuation.[43] Another analysis found that the benefit of dapagliflozin over placebo on the primary outcome was consistent regardless of background guideline-recommended pharmacotherapy or device therapy for HF*r*EF,[44] thus suggesting that the effects of dapagliflozin are incremental and complementary to conventional therapies for HF*r*EF.[45] Further analysis showed a similar reduction in the risk of the primary composite endpoint with dapagliflozin in subjects treated with a neprilysin inhibitor, ie, sacubitril/valsartan, or not treated with a neprilysin inhibitor.[40] Finally, significantly fewer patients without T2DM at baseline developed T2DM on trial. Subjects in whom T2DM developed generally had a higher mean baseline A1C, body mass index, and lower estimated glomerular filtration rate.[46]

Ongoing CVOTs

Additional clinical trials involving SGLT-2i therapy in people with HF are underway. In people with HF*r*EF, these include the DETERMINE-Reduced (NCT03877237) with dapagliflozin and EMPEROR-Reduced (NCT03057977) with empagliflozin. In people with HF*p*EF, these include the DETERMINE-Preserved (NCT03877224) and DELIVER (NCT03619213) trials with dapagliflozin and EMPEROR-Preserved (NCT03057951) with empagliflozin.

Implications for patient care

The results of the CVOTs have reshaped recommendations regarding the treatment of people with HF and T2DM. For secondary prevention, the American Diabetes Association *Standards of Medical Care in Diabetes–2020* recommends an SGLT-2i in people with T2DM and HF who do not achieve adequate glycemic control with the combination of lifestyle management plus metformin.[22] Among the SGLT-2i agents, dapagliflozin is preferred based on the results of the DAPA-HF trial. The American Association of Clinical Endocrinologists/American College of Endocrinology provides similar recommendations.[23]

For the treatment of patients with T2DM for primary prevention, the American College of Cardiology/American Heart Association recommends considering an SGLT-2i or a GLP-1RA in people with T2DM and additional ASCVD risk factors who do not achieve glycemic control with the combination of lifestyle management plus metformin.[47]

Finally, the product labeling approved by the FDA reflects key results from CVOTs.[48-51] Of the 4 SGLT-2i agents, the labeling for canagliflozin reflects a benefit in reducing the risk of hospitalization for HF in patients with T2DM and chronic kidney disease, while the benefit with dapagliflozin is in patients with T2DM and established CV disease or multiple CV risk factors. Dapagliflozin is also indicated to reduce the risk of CV death and hospitalization for HF in adults with HF*r*EF (NYHA class II-IV).

BOTTOM LINE

Several points are key regarding the management of people with T2DM. First, HF, as well as ASCVD, is common in people with T2DM. For people with T2DM, treatment is shifting beyond a glucocentric focus to include CV risk reduction. Therefore, it is critical that glycemia, CV disease, and other risk factors be managed as recommended in evolving guidelines and consistent with FDA-approved labeling. Because guidelines and product labeling are rapidly changing to reflect data from clinical trials, it is important to check this information frequently. Finally, while the benefits of lifestyle management are established, the pharmacotherapeutic management with SGLT-2is in patients with HF with or without T2DM is a rapidly evolving field. Therefore, it is important to educate and support people with T2DM – in fact, all people – to adopt and maintain a healthy lifestyle with normal body weight, good nutrition, and daily physical activity. ●

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