Contemporary Management of Heart Failure in Patients With Diabetes

James A. Shaw[1,2] and Mark E. Cooper[2,3,4]

Both heart failure and diabetes are increasing in prevalence in Western communities. The interrelationship between these two conditions is well known, with conventional heart failure therapies including several newer drug classes providing benefit to subjects with diabetes. Furthermore, several of the more recently introduced medications for type 2 diabetes have resulted in significant cardiovascular morbidity and mortality benefits with a marked improvement in heart failure symptoms and hospital presentations as well as deaths. This review outlines current therapies used to treat patients with or at risk for heart failure and their particular role in subjects with diabetes. Newer therapies, including certain glucose-lowering medications and their benefits in treating heart failure patients with and without diabetes, are also discussed. Finally, heart failure is also observed in long-duration, aging patients with type 1 diabetes, but this clinical issue has not been as extensively explored as in patients with type 2 diabetes and warrants further clinical investigation.

DIABETES AND HEART FAILURE INCIDENCE AND PREVALENCE

Heart failure remains a significant health issue. It is one of the most common causes of hospital admissions and carries a poor prognosis. While there have been numerous new efficacious therapies to treat heart failure with reduced ejection fraction (HFrEF), defined as an ejection fraction (EF) <40%, over the last 30 years that have resulted in improved outcomes, the mortality for patients with HFrEF remains high (1). Heart failure with preserved ejection fraction (HFpEF), defined as an EF >50%, is also an increasingly recognized clinical problem that is very challenging to treat with no proven therapies; like HFrEF, it has a poor prognosis (2). HFpEF is increasing in prevalence especially as a result of the aging of the population and has historically been neglected in subjects with diabetes (2). There is also a group of patients with an EF between 40% and 50%, known as heart failure with mid-range EF (HFmrEF) (3), but this group has not been specifically studied in the context of diabetes.

Diabetes, which is increasing in prevalence due largely to the obesity epidemic (4), is known to be associated with at least a doubling in the risk of cardiovascular (CV) disease, but historically this was considered to be primarily because of an increased risk of atherosclerotic disease in subjects with diabetes. However, it has recently become evident that heart failure is the most common and morbid complication of diabetes, in particular in those with type 2 diabetes (5). More than 29 million adults in the U.S. have type 2 diabetes, whereas 6.5 million have heart failure, with both conditions expected to continue to increase in prevalence over the next few decades (6). Furthermore, heart failure is increasingly appreciated as a clinical issue in subjects with type 1 diabetes, possibly as a result of increasing numbers of older subjects with

[1]Department of Cardiology, The Alfred Hospital, Melbourne, Australia
[2]Baker Heart and Diabetes Institute, Melbourne, Australia
[3]Department of Diabetes, Central Clinical School, Monash University, Melbourne, Australia
[4]Deparment of Endocrinology and Diabetes, Central Clinical School, The Alfred Hospital, Melbourne, Australia

Corresponding author: Mark E. Cooper, mark.cooper@monash.edu

long-duration type 1 diabetes because of an improved life span. This may be occurring, in part, as a result of a better outlook due to improvements in the clinical course of diabetic microvascular complications such as diabetic kidney disease.

A wealth of epidemiological evidence demonstrates that diabetes is independently associated with the risk of developing heart failure, with the risk increasing by more than twofold in men and by more than fivefold in women (7). Heart failure is highly prevalent in up to 40% of patients with diabetes, with both acute heart failure presentations as well as chronic heart failure (8,9). Patients with heart failure and diabetes have increased mortality, approximately twice that seen in the population without diabetes (10). Furthermore, while the risk of heart failure increases with age, the relative risk goes in the reverse direction. Subjects with diabetes aged 45–54 years have nine times higher relative risk of developing heart failure, while in those individuals aged 75–84 years it is only 1.8 times higher than in subjects without diabetes (11). The contributory role that diabetes plays in the development of heart failure is clearly demonstrated in the report by Rosano et al. (12) where the authors showed that patients with diabetes without heart failure have an increased risk of developing heart failure compared with an age-matched population without diabetes (29% vs. 18%, respectively).

Both population studies and clinical trials have demonstrated that diabetes significantly increases the risk of recurrent hospitalizations for heart failure and prolongs the duration of the hospital stay in these patients with heart failure. For example, in the Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity (CHARM) program, the presence of diabetes was associated with a twofold increase in either death or the composite outcome of CV death or hospitalization for heart failure in insulin users and a 50% increase in risk in noninsulin-treated subjects with diabetes (10).

HOW DOES DIABETES INCREASE RISK OF HEART FAILURE?

The exact mechanisms responsible for the increased incidence in heart failure

seen in subjects with diabetes are complex and not fully understood (5). Obesity, which predisposes patients to insulin resistance and hyperglycemia, also leads to the development of heart failure as seen in those with diabetes (9). There are multiple mechanisms contributing to diabetes-associated cardiac dysfunction, including impaired microvascular endothelial function (13), abnormal cardiac metabolism (specifically, abnormal cardiac handling of glucose and free fatty acids), increased myocardial fibrosis (12), increased oxidative stress, and local activation of neurohormonal systems including the renin-angiotensin and sympathetic nervous systems, as well as other less well-characterized pathways such as endothelin (14). With respect to a change in cardiac metabolism, it has been postulated that the switch from glucose to free fatty acid metabolism in the diabetic heart has a negative effect on cardiac contractility inducing left ventricular systolic and diastolic dysfunction even in the absence of coronary artery or structural heart disease (15). However, as recently reviewed, this postulate is highly controversial with other groups suggesting the opposite, hypothesizing that sodium–glucose cotransporter 2 (SGLT2) inhibitors do not enhance fuel supply but rather induce a "hibernation state" that essentially leads to energy preservation and resistance to stressors such as glucose (16).

Although there have been numerous preclinical studies to suggest a specific diabetic cardiomyopathy, the relevance of these findings to human diabetes-associated cardiac dysfunction remains controversial. Nevertheless, these preclinical studies have allowed investigators to identify potential pathways (17), many of which remain difficult to target. Furthermore, some potentially beneficial preclinical approaches have not yet been extended to human trials. Since, historically, most research in the diabetic context has focused on atherosclerosis rather than a direct effect of diabetes on cardiac function, this field has been relatively neglected when compared with the fields of diabetic micro- and macrovascular complications. With increasing sophistication in preclinical and clinical techniques, including genomics, metabolomics, proteomics, and newer approaches to assess mitochondrial function, it is anticipated that over the next decade

our understanding of the pathophysiology of diabetes-associated heart failure, both with reduced and preserved EF, will expand greatly.

SPECIFIC HEART FAILURE MEDICATIONS AND THEIR ROLE IN PATIENTS WITH DIABETES

The pharmacologic therapies for HFrEF have resulted in a significant improvement in outcomes in symptomatic patients. The main focus for therapies has historically centered around the renin-angiotensin and the sympathetic nervous systems. Large, well-designed randomized controlled clinical trials have shown that ACE inhibitors (18), angiotensin II receptor blockers (ARBs) (19), β-blockers (20,21), mineralocorticoid receptor antagonists (MRAs) (22,23), direct sinus node inhibitors such as ivabradine (24), and, more recently, sacubitril/valsartan, a neprilysin inhibitor/ARB (ARNI) (25) have all resulted in a significant reduction in CV events in patients with HFrEF (Table 1). While none of these medications have been studied exclusively in patients with diabetes, the incidence of diabetes among study participants varied from 20% to almost 50% with the proportion of subjects with diabetes gradually increasing over the last two decades in the major clinical trials of heart failure (Fig. 1). In the most recent randomized trials—the Vericiguat Global Study in Subjects with Heart Failure With Reduced Ejection Fraction (VICTORIA) and the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-Reduced)—the proportion of subjects with diabetes was almost 50% (26,27). This contrasts with the Studies of Left Ventricular Dysfunction (SOLVD) completed almost 30 years ago that compared enalapril to placebo, in which the incidence of diabetes was 26.7% in the placebo group and 24.9% in the enalapril group (18).

In the Randomized Aldactone Evaluation Study (RALES), the MRA spironolactone was compared with placebo in patients with an EF <35% and New York Heart Association (NYHA) class III/IV symptoms (22). As this study was commenced before the widespread use of β-blockers in patients with heart failure, only 10% of the participants were on β-blockers (22). Nevertheless, the addition of MRAs reduced both death and heart failure. In the Eplerenone in Mild

Table 1—Medications and devices beneficial in HFrEF

Drug/device class	Total no. of patients (% with diabetes), follow-up	Reduction in death and HHF (95% CI)	Effect of diabetes Rx	Reference
ACE inhibitors	2,569 (25.8%), follow-up 41.4 months	HR 0.74 (0.66–0.82)	Interaction not significant	(18)
ARB	7,599 (28.4%), follow-up 38 months	HR 0.88	No effect on CV death or first HHF admission in the DM subpopulation ($P = 0.09$) for the interaction	(33)
β-Blocker	3,991 (25%), follow-up 12 months	HR 0.81 (0.73–0.90)	Reduced HHF 37% in subjects with DM 35% in those without DM	(21)
Sacubitril/valsartan	8,442 (35%), follow-up 27 months	HR 0.80 (0.73–0.87)	HR death and HHF 0.87 in subjects with DM	(25)
Aldosterone antagonists	2,737 (31.4%), follow-up 21 months	HR 0.63 (0.54–0.74)	Benefits regardless of DM	(23)
Ivabradine	6,528 (30.5%), follow-up 23 months	HR 0.82 (0.75–0·90)	For the primary end point: HR 0.81 (0.69–0.95) with DM and 0.83 (0.74–0.93) without DM ($P = 0.861$ for interaction)	(24)
Ventricular assist device	1,120 (43%), meta-analysis		No increase in all-cause mortality in DM patients	(38)
Implantable defibrillator	2,521 (30%), follow-up 45 months	HR 0.77 (0.62–0.96)		(34)
Guanylate cyclase stimulators	5,050 (47%), follow-up 10.8 months	HR 0.90 (0.82–0.98)		(26)
SGLT2 inhibitors				
Dapagliflozin	4,744 (42%), follow-up 18.2 months	HR 0.74 (0.65–0.85)	HR 0.75 (95% CI 0.63–0.90) with DM, 0.73 (0.60–0.88) without DM	(51)
Empagliflozin	3730 (49.8%), follow-up 16 months	HR 0.75 (0.65–0.86)	HR 0.72 (95% CI 0.60–0.87) with DM, 0.78 (0.64–0.97) without DM	(27)

DM, diabetes; HHF, hospitalization for heart failure; Rx, prescription.

Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), which used another MRA, eplerenone, in patients with an EF <35% and NYHA class II symptoms (23), a 37% relative risk reduction was seen for CV death or hospitalization for heart failure in the eplerenone-treated group. In that study approximately 30% of the patients in each arm had diabetes (23). The EMPHA-SIS-HF trial was a more contemporary study than RALES with a higher use of β-blockers. This MRA treatment had not been widely used in the population with diabetes because of the higher risk of hyperkalemia in subjects with diabetes receiving these agents. The advent of a newer third generation MRA, finerenone, has led to a potential new therapeutic option that has been reported to have a lower risk of hyperkalemia. In the phase 2 program, the minerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF) trial (28) reported a comparable efficacy among all dose groups of finerenone and eplerenone in the primary end point of that study, a >30% reduction in N-terminal pro–B-type natriuretic peptide (NT-proBNP). An exploratory composite end point comprising death from any cause, CV hospitalizations, and emergency presentation for worsening heart failure showed a significant reduction in the 10- to 20-mg finerenone group compared with eplerenone (28). Subsequent phase 3 studies in subjects with diabetic kidney disease, FIDELIO-DKD (FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease) and FIGARO-DKD (Finerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease), are in progress. Indeed, the top-line result for FIDELIO-DKD has indicated that the trial has reached its primary end point, which was renal, as well as achieving a secondary CV end point. Specific effects on heart failure have not been disclosed, but a new study focusing on heart failure is now planned—the FINEARTS-HF study (FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure)—which will include patients with diabetes.

There were some initial concerns regarding the use of β-blockers in patients with diabetes with heart failure. However, on assessment of the cohort in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) using the β-blocker extended-release metoprolol, in which 25% of the cohort had diabetes, it was evident, first, that the risk for heart failure hospitalization (21) was higher in the group with diabetes and, second, that treatment with the β-blocker resulted in a 37% reduction in hospitalization for heart failure, similar to that observed in the group without diabetes (29). Pooling of the mortality data from various β-blocker trials, specifically the Cardiac Insufficiency Bisoprolol Study II (CIBIS II), MERIT-HF, and the Carvedilol Prospective Randomized Cumulative Survival trial (COPERNICUS), showed similar survival benefits in patients with and without diabetes (30). In that meta-analysis the relative risk for all-cause mortality as a result of β-blocker therapy in patients with diabetes was 0.76 (95% CI 0.60–0.96), and in those without
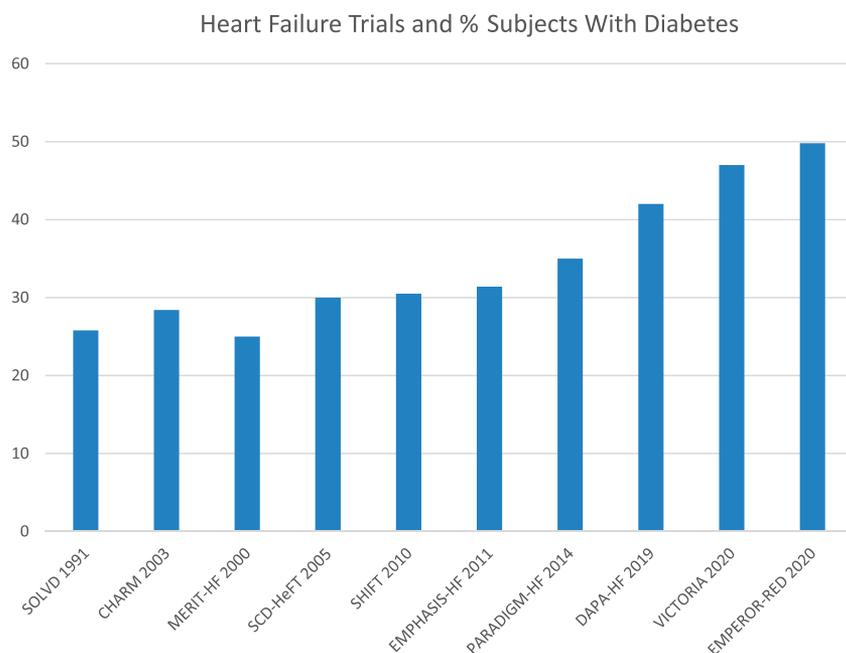
Heart Failure Trials and % Subjects With Diabetes

Figure 1—Large heart failure trials with current evidence-based therapies and the percentage of subjects with diabetes in each trial: SOLVD (18), CHARM (33), MERIT-HF (21), SCD-HeFT (34), SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial) (24), EMPHASIS-HF (23), PARADIGM-HF (25), DAPA-HF (51), VICTORIA (26), and EMPEROR-Reduced (EMPEROR-RED) (27).

diabetes it was 0.64 (0.56–0.73), with no heterogeneity observed between subjects with and without diabetes (30).

The benefits of lowering patients' heart rates in the setting of HFrEF was further confirmed with the use of the sinus node blocker ivabradine (24). When used in combination with β-blockers in patients with an EF <35% and a heart rate >70 bpm, the addition of ivabradine resulted in an 18% risk reduction in risk of death and hospitalization for heart failure. This benefit was seen in subjects with and without diabetes (24).

A major advance in neurohormonal modulation was the advent of the drug LCZ696, an ARNI, which is a combination of the neprilysin inhibitor sacubitril and the ARB valsartan. The Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) study showed that sacubitril/valsartan was superior to enalapril in reducing the combination of death and hospitalization for heart failure in over 8,000 patients with an EF <40% and NYHA Class II–IV heart failure symptoms (25). Thirty-five percent of the patients in both groups had diabetes. In the subgroup with

diabetes, there was a trend toward a reduction in mortality in the sacubutril/valsartan group, with a statistically significant reduction in heart failure hospitalization of 21% compared with the enalapril group (31). Of interest is the modest reduction in HbA$_{1c}$ seen with this drug, albeit this effect is unlikely to explain the benefits of this agent on CV end points (32).

One of the most recent new treatments for HFrEF is vericiguat, an oral soluble guanylate cyclase stimulator (26). In the VICTORIA study, vericiguat was studied in patients with symptomatic HFrEF and an EF <45%. In that study 48% of the subjects had diabetes. Compared with placebo, those in the vericiguat arm had a 10% risk reduction in the primary end point (death and heart failure hospitalization) at a median follow-up of 10.8 months, although a specific analysis in the cohort with diabetes has not been reported (26).

Therapies for HFpEF have been far less successful than those for HFrEF, and despite the large number of studies performed in patients with this condition, including a significant proportion with diabetes, no current therapies have been proven to reduce CV end points (2).

MECHANICAL INTERVENTIONS FOR HEART FAILURE

Biventricular Pacemakers and Defibrillator Devices

Indeed, not only do subjects with diabetes have an increased risk of heart failure presentations but they also have an increased risk of sudden death. This was shown in the CHARM study (33) in patients with both HFpEF and HFrEF, in which there were 40 vs. 25.9 events/ 1,000 patient-years of follow-up in the subjects with and without diabetes, respectively (10). Thus, it is not surprising that trials looking at the roles of biventricular pacemakers/defibrillators and defibrillators alone in patients with symptomatic heart failure have shown that subjects with diabetes benefit from these devices. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), which included 30% of participants with diabetes, randomized patients with an EF <35% to an implantable cardiac defibrillator (ICD), amiodarone, or placebo. Overall, those in the defibrillator group had a significant mortality reduction with a similar benefit seen in the subjects with diabetes (34). The Danish Study to Assess the Efficacy of ICDs in Patients With Nonischemic Systolic Heart Failure on Mortality (DANISH), which looked at ICD versus medical therapy in patients with nonischemic cardiomyopathy, included approximately 19% of patients with diabetes (35). Again, no difference in treatment benefit was seen for those with and without diabetes. In trials looking at the role of biventricular pacing, which restores normal coordinated pumping action of the ventricles in patients with symptomatic heart failure and a broad left bundle branch block on electrocardiogram, once again similar improvements in heart failure symptoms and left ventricular volumes and EF were seen in subjects with and without diabetes (36). There was no evidence of an increased risk of complications in subjects with diabetes, including no increased infection risk.

Left Ventricular Assist Device and Cardiac Transplantation

The use of left ventricular assist devices (LVADs) both as a bridge to cardiac transplantation and as destination therapy for end-stage heart failure is well established. Destination therapy with an LVAD is chosen when the patients are in

end-stage heart failure with NYHA class III–IV symptoms despite optimal medical therapy and are not a cardiac transplant candidate. The aim of the LVAD is to improve heart function and thus reduce the patients' heart failure symptoms and improve their prognosis. The safety of both cardiac transplantation and LVAD insertion in subjects with diabetes is controversial. A retrospective single-center study of 341 patients who underwent LVAD implantation between 2007 and 2016 either as a bridge to transplant or as destination therapy showed that diabetes was associated with an increase in all-cause mortality, with a hazard ratio (HR) of 1.73, as well as an increased risk of nonfatal LVAD complications, which included a composite of stroke, pump thrombosis, and device infection, when compared with subjects without diabetes (37). However, a recent meta-analysis of four studies of patients undergoing insertion of continuous-flow LVAD, which included a total of 1,120 patients (478 with diabetes), did not show any increased risk of either death or postoperative complications in the subjects with diabetes (38).

Cardiac transplantation is performed in subjects with diabetes unless they have multiple diabetic complications. Data from a registry published in 2012 (39) showed that diabetes was an independent predictor of increased mortality in patients post–heart transplantation. However, with newer immunosuppressive medications that allow prednisolone to be weaned more quickly and more patients able to remain steroid free, transplantation remains a viable option in appropriately selected patients with diabetes with end-stage heart failure.

A schema for the management of a subject with diabetes presenting with heart failure symptoms is shown in Fig. 2.

GLUCOSE-LOWERING AGENTS AND HEART FAILURE RISKS/BENEFITS

In the last 10–15 years, there have been concerns that some of the glucose-lowering medications were increasing patients' risk of developing symptomatic heart failure and consequently leading to increased hospital presentations. This was particularly seen with thiazolidinediones (TZDs) and was also observed in a trial of the dipeptidyl peptidase 4 (DPP-4) inhibitor saxagliptin (40). In the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) (41) and the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trials (42), patients randomized to TZDs, rosiglitazone, and pioglitazone, respectively, had more heart failure events than those on placebo. In the SAVOR-TIMI 53 trial (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53) (saxagliptin vs. placebo), saxagliptin increased the risk for heart failure hospitalizations by 27% (40). Although patients at greatest risk were those with a history of heart failure, an estimated glomerular filtration rate $\leq$60 mL/min/1.73 m^2, or elevated baseline levels of NT-proBNP, no increase in death was seen with saxagliptin treatment. As a result of these trials, pioglitazone, rosiglitazone, and saxagliptin are contraindicated in patients with or at risk for heart failure.

It should be appreciated that not all DPP-4 inhibitors are associated with higher rates of heart failure. In the Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care (EXAMINE) trial of alogliptin versus placebo in patients who had had an acute coronary syndrome, no increased risk of heart failure hospitalizations was seen in the patients randomized to alogliptin (43). In the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS), again there was no increase in heart failure (HR 0.98) (44). Finally, in the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) study, the DPP-4 inhibitor linagliptin was evaluated in a high-risk group of subjects with type 2 diabetes with a significant proportion having established CV and/or renal disease (45). In that trial there was no increased risk of hospitalization for heart failure with linagliptin treatment (HR 0.90) (45). Nevertheless, despite differences in results among the four DPP-4 inhibitor trials, the U.S. Food and Drug Administration (FDA) continues to recommend avoidance of this class in the setting of heart failure.

As a result of the concerns with respect to increased CV events with certain glucose-lowering therapies, CV events became an FDA-mandated end point with trials involving novel glucose-lowering therapies. Interestingly, the SGLT2 inhibitors have been shown in recent studies to be beneficial in terms of reducing heart failure hospitalization and also, albeit not universally, cardiac mortality (46). The initial studies with these agents were performed in subjects with diabetes with coexistent CV disease. The mechanisms of action by which these drugs afford CV benefit are not fully elucidated, with weight loss, reduction in blood pressure, and glucose-lowering effects unable to fully explain their benefits (47). There is also a view that has not been definitively proven that a change in fuel utilization by the heart toward ketone bodies could be a biochemical mechanism to explain improved cardiac function in response to SGLT2 inhibition, although as outlined previously this postulate remains highly speculative with ongoing controversy (15). It is likely with respect to heart failure that these agents' natriuretic actions are critical. These drugs also have favorable effects on markers of arterial stiffness and vascular resistance, visceral adiposity, albuminuria, and plasma urate.

Initially, in the seminal BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), empagliflozin was compared with placebo in 7,020 subjects with diabetes who had established CV disease. The primary outcome was a composite of death from CV causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke (48). The median duration of follow-up was 2.6 years. There was a lower rate of the primary composite outcome (3-point major adverse cardiovascular event [3P-MACE]) of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke in those receiving empagliflozin compared with placebo (48). The difference between empagliflozin and placebo was driven by a significant reduction in death from CV causes, with no significant between-group difference in the risk of myocardial infarction or stroke. A significant reduction in heart failure hospitalization (HR 0.67) was also seen in the empagliflozin group. This benefit became evident early, seen within the first month of treatment, and was observed across a range of prespecified subgroups, including patients with (10% of the total population) and without investigator-reported heart failure at baseline. No
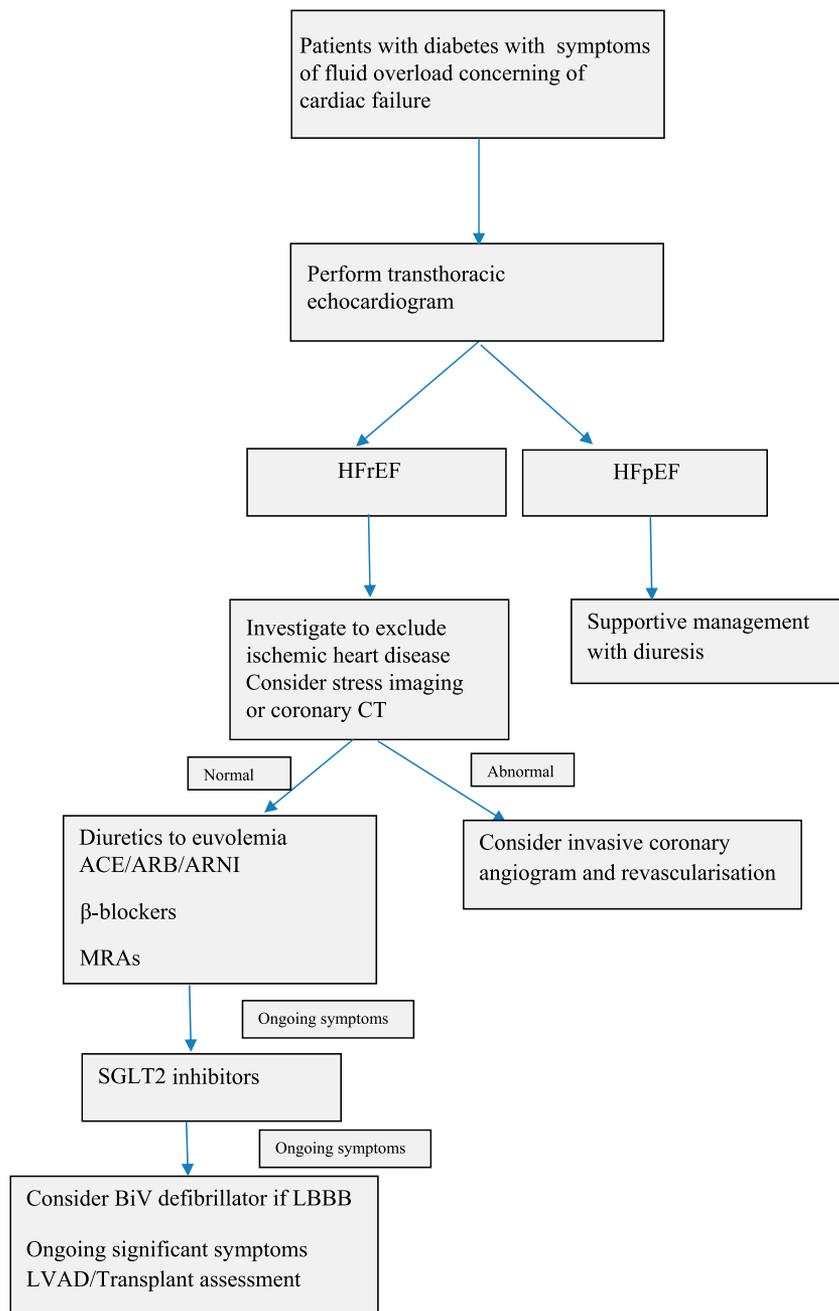
Figure 2—Schema outlining the management of a subject with diabetes presenting with heart failure symptoms. BiV, biventricular; CT, computed tomography; LBBB, left bundle branch block.

echocardiographic or natriuretic peptide measurements were available from the EMPA-REG OUTCOME trial to assist in delineating the beneficial effect on heart failure hospitalization (48). In the Canagliflozin Cardiovascular Assessment Study (CANVAS) in patients with type 2 diabetes (*n* = 10,143) either with established CV disease or at high risk of CV disease, those who were randomized to canagliflozin had a significantly lower risk of heart failure hospitalization (49). The Dapagliflozin Effect on Cardiovascular Events–

Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial randomized subjects with type 2 diabetes either with confirmed atherosclerotic CV disease or with multiple risk factors for atherosclerotic CV disease to dapagliflozin or placebo. Those in the treatment arm had a lower rate of CV death and heart failure hospitalization (4.9% vs. 5.8%) (46). The most recently reported trial, eValuation of ERTugliflozin efficacy and Safety CardioVascular outcomes trial (VERTIS-CV), evaluated the SGLT2 inhibitor ertugliflozin.

This SGLT2 inhibitor did not reduce 3P-MACE but, as seen with other SGLT2 inhibitors, was associated with a similar reduction in hospitalization for heart failure (HR 0.70) (50).

Building on the spectacular findings on heart failure with various SGLT2 inhibitors, a new series of trials was instituted, including studying these agents in the absence of diabetes. The first of these trials to report was the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study, which examined the SGLT2 inhibitor dapagliflozin in patients with and without diabetes with an EF <40%. Forty-two percent of the participants had type 2 diabetes (51). The primary outcome was a composite of worsening heart failure or death from CV causes. An episode of worsening heart failure was either an unplanned hospitalization or an urgent visit resulting in intravenous therapy for heart failure. The study included patients aged at least 18 years, with an EF of 40% or less, and NYHA class II, III, or IV symptoms. Patients were required to have a plasma NT-proBNP level of at least 600 pg/mL (or ≥400 pg/mL if they had been hospitalized for heart failure within the previous 12 months). Patients with atrial fibrillation or atrial flutter on baseline electrocardiography were required to have an NT-proBNP level of at least 900 pg/mL, regardless of their history of hospitalization for heart failure. The patients had widespread use of β-blocker (>90%) and MRA (70%) treatment, and >90% were on either an ACE inhibitor, an ARB, or sacubitril/valsartan. The primary end point was significantly reduced in the dapagliflozin arm (16.3% vs. 21.2%; HR 0.74) (51). A significant reduction was seen for both CV death and hospitalization for heart failure, and benefits were similar in both subjects with diabetes and those without. Indeed, these exciting findings are now being incorporated into contemporary guidelines. For example, the recent Canadian heart failure guidelines strongly recommend dapagliflozin in subjects with type 2 diabetes with HFrEF in order to improve symptoms and quality of life as well as reduce hospitalization for heart failure and CV death (52).

In the recently published EMPEROR-Reduced study, 3,730 patients with NYHA class II–IV symptoms and EF <40% with and without diabetes were randomized

to either placebo or the SGLT2 inhibitor empagliflozin 10 mg/day. At a median of 16 months of follow-up there was a 25% reduction in the primary end point (CV death or hospitalization for heart failure) in the empagliflozin group (HR 0.75) (27). The benefit was seen regardless of the presence or absence of diabetes. This was a similar population to that studied in the DAPA-HF trial except that there were more subjects on ARNIs or treated with mechanical interventions. Furthermore, whereas in the DAPA-HF trial a decrease in mortality was observed, this benefit was not observed in the EMPEROR-Reduced trial. Nevertheless, it is now clear that SGLT2 inhibitors provide significant clinical benefits with respect to HFrEF in both subjects with and without diabetes and should be used in these patients in conjunction with other evidence-based therapies (see Fig. 2).

Extrapolating from findings from another SGLT2 inhibitor study, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) (53), which evaluated subjects with diabetes with chronic kidney disease and where a reduction in heart failure was observed in many subjects even in the absence of a reduction in blood glucose, as well as the benefits seen in the cohorts without diabetes from the DAPA-HF and EMPEROR-Reduced trials (27,51), it is clear that the benefits of this class on HFrEF do not rely on these agents' glucose-lowering actions. Furthermore, in results from the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) trial (54), which is primarily a renal end-point trial including both subjects with diabetes and those without with baseline glomerular filtration rate and albuminuria levels that overlap those seen in the CREDENCE trial, the secondary end point of CV death or hospitalization for heart failure was reduced by ~30%. Therefore, the recent Canadian heart failure guidelines have added that canagliflozin is recommended in subjects with type 2 diabetes aged >30 years with macroalbuminuria as an approach to not only reduce progression of renal disease but also heart failure (52).

The 2019 American Heart Association/ Heart Failure Society of America statement recommends the use of SGLT2 inhibitors as a preventative strategy in patients with type 2 diabetes at high risk of HFrEF and as glucose-lowering therapy in patients with established HFrEF (55). Similar recommendations recently updated by the American Diabetes Association emphasize the utility of SGLT2 inhibitors as a preventative and therapeutic approach in subjects with diabetes with or at risk for HFrEF (56). It is important to ensure that one weighs risks and benefits of this group of medications. Such risks include genital candidiasis and rarer side effects such as euglycemic diabetic ketoacidosis (55). There are also large studies such as EMPEROR-Preserved and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) currently in progress studying the role of empagliflozin and dapagliflozin, respectively, in HFpEF, a condition with no proven therapy.

Another recently introduced class of drugs for type 2 diabetes are the glucagon-like peptide 1 receptor agonists. Although benefits on CV and renal events with these agents have been reported, no benefit on heart failure has been observed (57). There have been suggestions of increased heart failure with some of these peptide agonists, but this has not been confirmed in the larger trials. In contrast to SGLT2 inhibitors, these agents are associated with a modest increase in heart rate, but, importantly, no adverse CV effects have been linked to the chronotropic action of these drugs.

TYPE 1 DIABETES AND HEART FAILURE

As a result of improved management of subjects with type 1 diabetes, namely, more aggressive glycemic control partly as a consequence of the impressive results of the Diabetes Control and Complications Trial (DCCT), as well as improved management of micro- and macrovascular complications, their life span has increased. Unfortunately, subjects with type 1 diabetes have an increased risk of presenting with heart failure compared with those without (58). Furthermore, the same study found that 30-day heart failure case fatality rates were higher in subjects with type 1 diabetes compared with subjects with no diabetes or with type 2 diabetes (58). A study from Sweden showed that compared with the control group, patients diagnosed with diabetes before the age of 10 years had a 30 times greater risk of serious heart problems. The risk remained about six times higher for people whose type 1 diabetes was diagnosed between ages 26 and 30 years (59). The 30-year follow up of the DCCT trial, known as Epidemiology of Diabetes Interventions and Complications (EDIC), has shown that those in the aggressive glucose-lowering arm had a reduced incidence of ~30% in any CV disease, and the incidence of stroke, myocardial infarction, or CV death was also decreased by 30% (60). Heart failure was a rare complication in DCCT/EDIC, but numerically there was a marked reduction in heart failure in the previously intensively treated group (60). In the majority of the large heart failure medication and device trials, the number of subjects with type 1 diabetes was very low and often not specified, and thus choice of their treatment is extrapolated from the results in subjects with type 2 diabetes. Therefore, similar therapies are used to prevent and treat heart failure in type 1 diabetes without a strong evidence base to justify such use.

CONCLUSIONS

The interrelationship between two major current epidemics, cardiac failure and diabetes, is a very important one. The concept of a diabetic cardiomyopathy is now well established. Historically, therapies for heart failure have focused on the renin-angiotensin-aldosterone and sympathetic nervous systems with ACE inhibitors/ARBs/MRAs and β-blockers being the major focus of therapy. These medications have resulted in reductions in mortality and hospitalization for heart failure for patients with HFrEF, including those with diabetes. However, more recently, newer therapies—namely, the SGLT2 Inhibitors whose main role initially was to lower glucose—have been shown to provide symptomatic and prognostic benefit in subjects both with and without diabetes and thus should be considered as additional therapy to all patients with HFrEF, not just those with diabetes.

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