Diabetes Mellitus and Heart Failure

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Epidemiologic and clinical data from the last 2 decades have shown that the prevalence of heart failure in diabetes is very high, and the prognosis for patients with heart failure is worse in those with diabetes than in those without diabetes. Experimental data suggest that various mechanisms contribute to the impairment in systolic and diastolic function in patients with diabetes, and there is an increased recognition that these patients develop heart failure independent of the presence of coronary artery disease or its associated risk factors. In addition, current clinical data demonstrated that treatment with the sodium glucose cotransporter 2 inhibitor empagliflozin reduced hospitalization for heart failure in patients with type 2 diabetes mellitus and high cardiovascular risk. This review article summarizes recent data on the prevalence, prognosis, pathophysiology, and therapeutic strategies to treat patients with diabetes and heart failure. **(Am J Cardiol 2017;120[suppl]:S37−S47)**

Epidemiologic and clinical data from the last 2 decades have led to the recognition that, in addition to myocardial infarction and other atherosclerosis-related cardiovascular events, heart failure is a major contributor to cardiovascular morbidity and mortality in patients with diabetes. In certain patients with diabetes, the observation that myocardial dysfunction is present in the absence of coronary artery disease, valvular disease, and the sequelae of associated cardiovascular risk factors[1] has led to the use of the poorly understood term "diabetic cardiomyopathy." This term was first used in 1972 by Rubler et al,[2] describing myocardial dysfunction in patients with diabetes in the absence of coronary artery disease, hypertrophy, or valvular heart disease. There is ongoing discussion whether diabetic cardiomyopathy exists as a specific entity or not, as considered by Ernande and Derumeaux in their review from 2012, "Diabetic cardiomyopathy: myth or reality?"[3]

This ongoing discussion reflects the fact that little is known about the pathophysiology and the underlying molecular mechanisms of heart failure in patients with diabetes. Only recently have clinical and epidemiologic data demonstrated the incidence, prevalence, and prognosis of heart failure in patients with diabetes. To date, heart failure has been described as *heart failure with preserved ejection fraction* (HFpEF) or *heart failure with reduced ejection fraction* (HFrEF), according to left ventricular function. To dichotomize heart failure into these 2 entities has certain limitations and probably does not cover an intermediate stage that the most recent guidelines of the European Society of Cardiology (ESC) termed *heart failure with a mid-range ejection fraction* (HFmrEF; ejection fraction 40%-49%).[4] This extended definition is a first step to better phenotyping and an improved taxonomy of heart failure. Nevertheless, clinical and epidemiologic data, as well as experimental data, have only focused on HFrEF and HFpEF. Therefore, we have used these 2 entities as the basis for the overview provided in this article.

Incidence and Prevalence of Heart Failure in Diabetes

Various epidemiologic data have shown that prediabetes is associated with a high risk of heart failure and suggest an

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age-adjusted hazard ratio (HR) between 1.2 and 1.7 in different populations of patients with impaired fasting glucose,[5,6] although not confirmed in all studies.[7] A large community-based cohort study of 6814 subjects without coronary vascular disease at baseline was followed for 4 years, and the incidence of heart failure, depending on the presence of metabolic syndrome, was analyzed.[8] This study showed that features of metabolic syndrome are associated with an increased risk of heart failure, with two-thirds of patients developing HFrEF. The risk of developing heart failure in subjects with "prediabetes" is lower than in subjects with manifest diabetes.[6]

A retrospective cohort study analyzed data from the Kaiser Permanente Northwest database of 8231 patients with diabetes, none of whom had HF at baseline, and 8845 matched subjects without diabetes; the follow-up period was up to 6 years.[9] Incident heart failure was 30.9 per 1000 person-years in subjects with diabetes and 12.4 per 1000 person-years in subjects without diabetes.[9] Similar results were found in the Heart and Soul study, which showed a doubling of the risk of incident heart failure in patients with diabetes compared with subjects without diabetes in a population of 839 patients with stable coronary artery disease and no signs of heart failure at baseline.[10] However, neither study differentiated between HFrEF and HFpEF.

Prevalence of prediabetes and diabetes is high among patients with heart failure and proves as a relevant predictor of prognosis. Data from Matsue et al[11] suggest that more than one-third of patients who are hospitalized for heart failure without a diagnosis of diabetes exhibit impaired fasting glucose or impaired glucose tolerance. As they discuss, more recent data from various registries show that the prevalence of diabetes in patients with heart failure ranges from approximately 25% to 40%, depending on the population studied.[11] Again, none of these studies differentiated between HFrEF and HFpEF.

Prognosis of Patients with Diabetes and Established Heart Failure

The most meaningful clinical endpoints for prognosis in patients with heart failure are mortality and hospitalization for heart failure. The risk for these endpoints is markedly increased in subjects with diabetes compared with those without diabetes. The Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) study assessed the influence of diabetes on the risk of death in 5491 patients hospitalized with congestive heart failure when followed up for 5 to 8 years.[12] In this study population 16% of patients had diabetes at baseline, and approximately 50% had an ejection fraction <35%, suggesting that both HFrEF and HFpEF were present in this subpopulation.[12] Crude mortality analyses suggested a 1-year mortality of 31%, much higher than in subjects without diabetes, and 50% of all heart failure patients with diabetes died after 3 years. Additional data on the prognosis of patients with diabetes and established heart failure came from large heart failure trials, such as the Survival And Ventricular Enlargement (SAVE) trial,[13,14] the Valsartan in Acute Myocardial Infarction Trial (VALIANT),[15] and the Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) trial.[16] All of these trials showed an increased risk of death in men and women with diabetes. For example, in CHARM, which analyzed the effect of candesartan versus placebo in a population with HFrEF and HFpEF, it was shown that both men and women with diabetes exhibited a higher risk of cardiovascular death or hospitalization for heart failure compared with subjects without diabetes, with a cumulative incidence rate of approximately 40% over 3 years.[16] Further differentiated analyses in patients with or without diabetes and HFpEF or HFrEF showed that the highest mortality or hospitalization for heart failure risk occurred in patients with diabetes and low ejection fraction (ie, HFrEF), followed by patients with diabetes and HFpEF.[16] The cumulative incidence rate of cardiovascular death and heart failure hospitalization in subjects with diabetes plus HFpEF was similar to that in subjects without diabetes but with HFrEF. A similar trend was true for all-cause mortality. In patients with diabetes, cardiovascular mortality was 58.6 per 1000 patient-years in those with HFpEF and 119.1 per 1000 patient-years in those with a low ejection fraction (ie, HFrEF). Similarly, in patients with diabetes, the risk for first hospital admission for heart failure was 116.6 per 1000 patient-years for those with HFpEF, whereas the rate was 155.4 per 1000 patient-years for those with HFrEF.[16] Compared with subjects without diabetes, the risk of hospitalization for heart failure was almost doubled in patients with diabetes independent of HFpEF or HFrEF.[16] Consequently, among patients with HF, those with diabetes have a higher risk of mortality and hospitalization for HF than those without diabetes.

Structural and Functional Characteristics of Cardiac Dysfunction in Diabetes

Structural Changes: Imaging studies have revealed left ventricular concentric remodeling as a relevant characteristic of diabetic myocardium, which may be associated with impaired myocardial energetics and reduced systolic strain.[17,18] Hypertrophy of the diabetic heart is the consequence of myocardial triglyceride deposition[17] and/or increased extracellular volume as an indicator for collagen deposition and fibrosis,[19,20] with the increased extracellular volume being predictive for mortality and heart failure in this population.[20] In addition, hyperinsulinemia due to insulin resistance is also thought to directly promote myocardial hypertrophy.[21] Others have found direct association among myocardial tissue perfusion, oxygen supply, energetic substrate availability, and myocardial function in patients with diabetes, suggesting microcirculatory damage as a contributing cause for diabetic cardiomyopathy.[22]

Deposition of advanced glycation end products constitutes a driving factor for microvascular damage in diabetes and has been associated with cardiomyocyte stiffness and myocardial collagen deposition.[19,23] Advanced glycation end products are created by nonenzymatic reactions of glucose and other glycating compounds with lipid and protein moieties, causing structural and functional modifications. Glycated molecules are identified by a pattern recognition receptor of the immune globulin family termed *receptor for advanced glycation end product*, which initiates inflammatory signaling and propagates apoptosis, fibrotic remodeling, and immune cell infiltration.[24] The consequential increase in myocardial stiffness translates to diastolic dysfunction, reduced myocardial strain, and atrial enlargement, which has been associated with an increased prevalence of atrial fibrillation in patients with diabetes.[19,25–27]

Myocardial Energy Supply in Diabetes: Alterations of myocardial energy metabolism are central for cardiac dysfunction in diabetes.[28] Obesity is the primary risk factor for insulin resistance and type 2 diabetes mellitus and resembles a state of energetic oversupply.[29] Increased circulating concentrations of glucose and free fatty acids lead to inappropriate lipid deposition in extra-adipose tissues, including the heart.[29] Cardiomyocytes are insufficiently equipped to store larger amounts of lipids with accumulated acylglycerols and ceramides, causing cellular damage by lipotoxicity. Insufficiently processed lipid fragments lead to activation of inflammatory signaling pathways, including protein kinase C and nuclear factor κ, which interfere with insulin signaling.[30] The occurrence of insulin resistance limits cardiac glucose supply and creates a shift toward fatty acid oxidation, which is a hallmark of the diabetic heart.[31] This is associated with functional impairment of oxidative phosphorylation as a consequence of excessive caloric supply in the absence of sufficient energetic demand.[28,32,33]

In the balanced state, the nutrient (ie, fuel) supply is sufficient to sustain energy demand (ie, adenosine triphosphate [ATP]), and waste, or inefficiency in the form of heat, is minor (Figure 1).[33] Nutrient excess in the form of excessive supply in the absence of a parallel increase in demand characterizes a state in which the energy required to satisfy ATP demand is lower than the available energy. This creates inefficiency, waste in the form of heat, via mitochondrial proton leak. This process can slow down nutrient accumulation and prevent the development of reductive stress (accumulation of nicotinamide adenine dinucleotide) and reactive oxygen species (ROS) production.

The excessive availability of glucose and fatty acids similarly feeds the tricarboxylic acid cycle to provide energetic products as electron donors for the respiratory chain. The thereby-created proton gradient over the inner mitochondrial membrane drives ATP synthesis as the main cellular energy carrier. Insufficient energetic demand in an energetically saturated environment shortens the requirement for ATP and

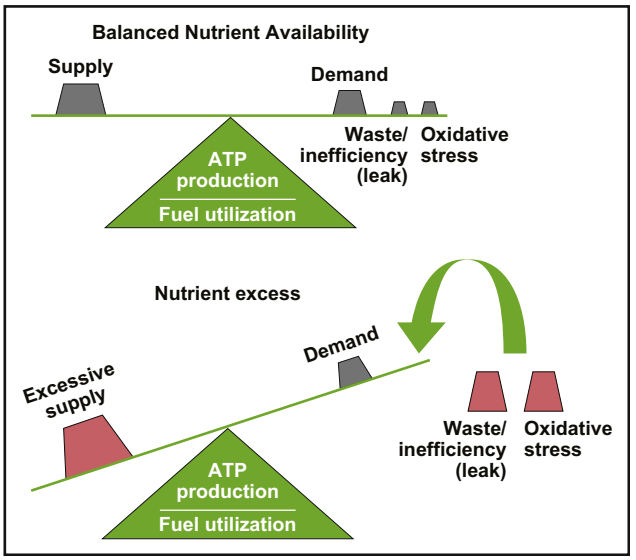

Figure 1. Regulation of cellular bioenergetics efficiency under conditions of balanced nutrient availability and under conditions of nutrient excess. See text for details.[33] ATP = adenosine triphosphate. Adapted from Liesa M, Shirihai OS. Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure. *Cell Metab.* 2013;17(4):491-506. Copyright 2013, with permission from Elsevier.

causes a backlog of electrons along the respiratory chain.[33,34] As a consequence, electrons leak to react with molecular oxygen and form ROS.[33] These are neutralized by cellular detoxification machinery; however, it is overwhelmed by excessive substrate delivery, causing oxidative stress (Figure 1).[33,35] Increased mitochondrial ROS production is a central pathology of diabetes complications, and strategies aimed at avoiding cardiac ROS production may be able to reverse metabolically induced cardiac dysfunction.[36,37]

Importantly, the occurrence of heart failure has a major impact on cardiac metabolism and causes a shift in cardiac substrate utilization from fatty acids to glucose oxidation, and therefore is the opposite from what is happening in the diabetic situation.[38] Metabolic profiling of cardiac tissue from patients with advanced heart failure revealed decreased cellular abundance of fatty acids, with suppression of the fatty acid oxidation machinery.[39] The failing heart consequently relies more on the oxidation of glucose. Occurrence of insulin resistance in this situation has the potential to limit energetic supply and further impair cardiac function. Systemic insulin resistance is further promoted by heart failure, which has been attributed to increased sympathetic tone and stress-dependent perturbation within metabolic pathways.[40] Heart failure has therefore been considered "an engine out of fuel,"[38] whereas insulin resistance proves to be an independent predictor of poor prognosis in patients with heart failure.[41] Interestingly, cardiac ketone body metabolism was recently identified as an alternative energy supply for the failing heart.[42] Circulating concentrations of ketone bodies are increased in heart failure and enter the cell in an insulin-independent manner. Induction of ketone body–processing enzymes, including β-hydroxybutyrate dehydrogenase 1, is

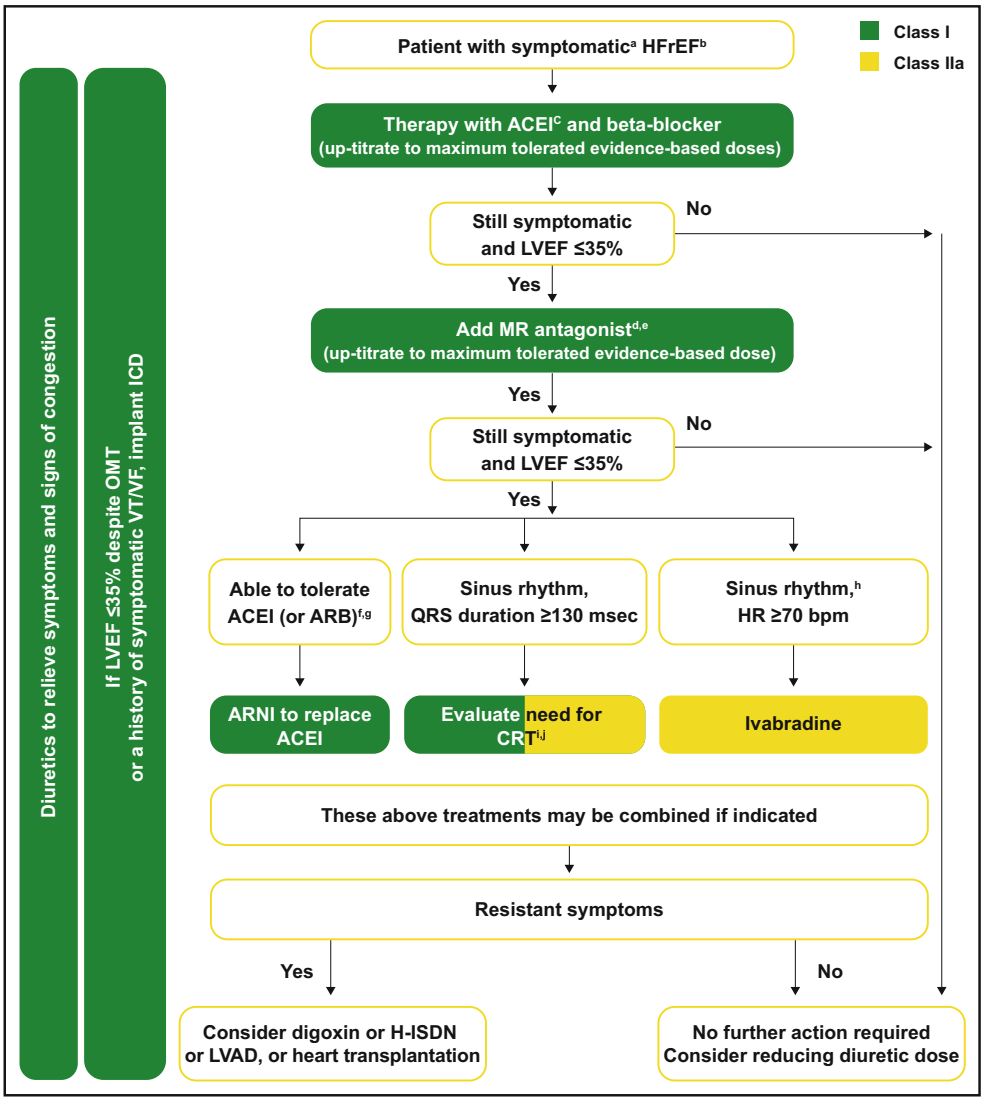

Figure 2. Therapeutic algorithm for a patient with symptomatic heart failure with reduced ejection fraction.[4] From Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2016;18:891-975. Copyright © 2016 European Society of Cardiology. Reproduced with permission of John Wiley & Sons Ltd. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BNP = B-type natriuretic peptide; CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; H-ISDN = hydralazine and isosorbide dinitrate; HR = heart rate; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MR = mineralocorticoid receptor; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; OMT = optimal medical therapy; VF = ventricular fibrillation; VT = ventricular tachycardia. [a]Symptomatic = NYHA class II-IV. [b]HFrEF = LVEF <40%. [c]If ACE inhibitor not tolerated/contraindicated, use ARB. [d]If MR antagonist not tolerated/contraindicated, use ARB. [e]With a hospital admission for HF within the last 6 months or with elevated natriuretic peptides (BNP >250 pg/mL or NT-proBNP >500 pg/mL in men and 750 pg/mL in women). [f]With an elevated plasma natriuretic peptide level (BNP ≥150 pg/mL or plasma NT-proBNP ≥600 pg/mL, or if HF hospitalization within recent 12 months plasma BNP ≥100 pg/mL or plasma NT-proBNP ≥400 pg/mL). [g]In doses equivalent to enalapril 10 mg twice daily. [h]With a hospital admission for HF within the previous year. [i]CRT is recommended if QRS ≥130 milliseconds and LBBB (in sinus rhythm). [j]CRT should/may be considered if QRS ≥130 milliseconds with non-LBBB (in sinus rhythm) or for patients with atrial fibrillation provided a strategy to ensure biventricular capture is in place (individualized decision).

found in the hypertrophied and failing heart, and shifts energy production to ketone body oxidation in the absence of sufficient fatty acid oxidation capacities.[42,43] Future studies are warranted to determine whether this fuel shift is adaptive or maladaptive and whether it can be used for therapeutic approaches.

Heart Failure Therapy in Patients with Diabetes

Current guidelines from the European[4] as well as the American[44] cardiology societies do not recommend specific therapeutic approaches in patients with diabetes compared with subjects without diabetes. Various studies, including some cluster analyses, suggest that the prognosis of patients

with symptomatic HFrEF is mainly determined by comorbidities and other factors, but not by left ventricular ejection fraction (LVEF) itself.[45] Therefore, we can expect that therapeutic regimens in patients with heart failure will be more individualized in the future, especially in high-risk patients with diabetes.

Treatment of Patients with Diabetes and HFrEF: In patients with symptomatic New York Heart Association (NYHA) class II-IV heart failure and reduced ejection fraction (LVEF <40%), treatment with angiotensin-converting enzyme (ACE) inhibitors (alternative: angiotensin receptor blockers [ARBs]) and β-blockers is recommended, with titration to the maximum tolerated evidence-based dose (Figure 2).[4] If patients are still symptomatic and exhibit an LVEF ≤35%, the addition of mineralocorticoid receptor antagonists is recommended. If still symptomatic, various therapeutic options exist for patients with NYHA II-IV heart failure. In patients who are able to tolerate ACE inhibitors or ARBs, angiotensin receptor neprilysin inhibitors should be used to replace ACE inhibitors or ARBs. In patients with sinus rhythm and a QRS duration ≥130 milliseconds, implantation of a cardiac resynchronization therapy device is recommended. Finally, patients with sinus rhythm and a heart rate ≥70 bpm should receive ivabradine; patients with symptoms and signs of congestion should receive diuretics. Moreover, patients with an LVEF ≤35% despite optimum medical therapy or a history of symptomatic ventricular tachycardia or ventricular fibrillation should receive an implantable cardioverter defibrillator. Similar recommendations were stated in a recent 2016 update of the American College of Cardiology/American Heart Association/Heart Failure Society of America heart failure guideline.[46] Trials in patients with HFrEF are underway (eg, EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction [EMPEROR-Reduced]; NCT03057977). These results, as well as those from future trials in patients with HFpEF, may inform future guidelines.

Treatment of Patients with Diabetes and HFpEF: Presently, treatment for HFpEF has not been shown to reduce mortality or morbidity; therefore, the guidelines recommend treatment of any comorbidities (eg, hypertension, chronic kidney disease, chronic obstructive pulmonary disease).[4] In addition, symptomatic therapy usually includes diuretics, especially in patients with congestion. The effect of various agents, including empagliflozin,[47] on cardiovascular morbidity and mortality in patients with HFpEF will be determined by future trials in heart failure (eg, EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction [EMPEROR-Preserved; NCT03057951]; and Dapagliflozin in Type 2 Diabetes or Pre-diabetes, and PRESERVED Ejection Fraction Heart Failure [PRESERVED-HF; NCT03030235]); however, thus far, symptom control is the major therapeutic goal.

Treatment of Diabetes in Patients with Heart Failure

Given the association of cardiac dysfunction with glucose metabolism, cardiac energy reserve, and steatosis, metabolic interventions aiming to improve glucose metabolism might have beneficial impact on cardiac function. Still, the optimal treatment strategy in patients with diabetes and HF remains controversial, and only some glucose-lowering medications have specifically been studied in patients with heart failure, which will be reviewed in the following section.

Lifestyle: The efficacy of lifestyle intervention in comparison with standard of care was investigated in the Action for Health in Diabetes (Look-AHEAD) trial with 5145 overweight or obese adults with type 2 diabetes mellitus.[48] Despite significant weight loss in the intensive lifestyle intervention group (−8.6%) versus the control group (−0.7%) after 1 year, and initial improvement in physical fitness and glycated hemoglobin (HbA1c), intensive lifestyle intervention failed to improve cardiovascular outcomes during a mean follow-up of 9.6 years (HR 0.95; 95% confidence interval [CI], 0.83-1.09; $P = .51$).[48] Heart failure events were numerically but not significantly reduced by intensive lifestyle intervention (HR 0.80; 95% CI, 0.61-1.04; $P = .10$). Interestingly, a recent post hoc analysis reported a significant reduction of cardiovascular events in patients who lost at least 10% of their body weight during the first year (21% of all individuals from both intervention arms; adjusted HR 0.79; 95% CI, 0.64-0.98; $P = .034$) in comparison with patients with stable body weight or weight gain. In addition, achievement of increased physical fitness (improvement by >2 metabolic equivalents reached by 13% of all individuals from both intervention arms) was associated with a significant reduction of the secondary composite endpoint that included heart failure (adjusted HR 0.77; 95% CI, 0.61-0.96; $P = .023$) but not of the original primary outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (adjusted HR 0.78; 95% CI, 0.60-1.03; $P = .079$).[49] These results highlight the difficulty in performing lifestyle intervention trials, which largely depend on the motivation of individual study participants. Others have found that weight loss interventions reduce cardiac hypertrophy, decrease left atrial volume, and improve diastolic function in cohorts of obese individuals (approximately 30% of those experiencing weight loss had diabetes) with paroxysmal atrial fibrillation.[50,51] Metabolically induced left ventricular dysfunction can consequently be reversed by lifestyle intervention.[50,51] Importantly, both studies reported a potent reduction in atrial fibrillation as a primary endpoint, which gave weight loss management in

obese patients a level IIa recommendation in the 2016 ESC guidelines on atrial fibrillation.[52]

Glycemic Control: A variety of studies, including the UK Prospective Diabetes Study (UKPDS), the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, the Action in Diabetes and Vascular Disease−Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study, and the Veterans Affairs Diabetes Trial (VADT), have aimed to reduce the cardiovascular risk of patients with diabetes by intensification of glycemic control. This led to a modest reduction in myocardial infarction but not cardiovascular mortality or heart failure hospitalization, and predisposed to more frequent hypoglycemia.[53] Current guidelines suggest individualized, patient-centered HbA1c targets, which remain looser in patients with long-standing diabetes and established cardiovascular disease, but tighter in younger patients without manifest complications.[54] More attention has since been given to drug-specific actions of diabetes medications on cardiovascular outcomes and heart failure, which will be discussed in the following sections.

Metformin: Metformin is the first-line oral glucose-lowering drug for patients with diabetes. However, metformin therapy has long been avoided in patients with heart failure, attributable to its rare potential to cause lactic acidosis in unstable hemodynamic circumstances or renal impairment. Observational studies, however, suggest reduced mortality in metformin-treated patients with heart failure.[55,56] This led the US Food and Drug Administration (FDA) to remove congestive heart failure as a contraindication to metformin use in 2006, although acute or unstable heart failure remained a precaution.[57] Metformin is now considered safe and the treatment of choice in patients with heart failure in the 2016 ESC guidelines.[4] In 2016 new FDA recommendations now allow metformin use also in patients with mild to moderate kidney dysfunction, defined as an estimated glomerular filtration rate of 30-60 mL/min/1.73 m^2, but not in those with severe kidney dysfunction (estimated glomerular filtration rate <30 mL/min/1.73 m^2).[58] A recent meta-analysis of 17 observational studies compared medical regimens that included metformin with those that did not in patients with diabetes and moderate impairment of kidney function, congestive heart failure, or chronic liver disease.[59] Metformin use was associated with reduced all-cause mortality in all 3 patient groups and with fewer heart failure readmissions in patients with chronic kidney disease or congestive heart failure. Still, no reduction in heart failure events has been reported in a meta-analysis of randomized metformin intervention trials.[60] Additional studies prospectively investigating the efficacy of metformin in patients with heart failure are consequently needed, as also pointed out by the American College of Cardiology Foundation/American Heart Association Guideline for the Management of Heart Failure 2013.[61]

Sulfonylureas/Insulin: Limited data exist about the use of sulfonylureas or insulin and heart failure incidence. No difference in heart failure events was recorded in the UKPDS trial comparing sulfonylureas or insulin treatment with dietary intervention in 3867 newly diagnosed patients with diabetes.[62] A recent propensity score−matched analysis of 10,089 patient pairs with diabetes treated with dipeptidyl peptidase-4 (DPP-4) inhibitors or sulfonylureas as add on to metformin reported DPP-4 inhibitors to be associated with a lower risk for all-cause mortality (HR 0.63; 95% CI, 0.55-0.72) and major adverse cardiac events (HR 0.68; 95% CI, 0.55-0.83) compared with sulfonylureas; however, no difference in heart failure hospitalization was reported.[63] Nevertheless, others found sulfonylurea treatment to be associated with increased heart failure risk when compared with metformin in a retrospective cohort study.[64] The impact of a glucose-lowering strategy with either an insulin-providing (sulfonylurea or insulin) or an insulin-sensitizing (metformin or thiazolidinedione) strategy was investigated in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, which enrolled 2368 patients with diabetes and coronary artery disease; among these, 141 had a history of heart failure.[65] No difference for the primary endpoint of death, myocardial infarction, or stroke was found between both therapeutic strategies during a mean follow-up of 5.3 years. In addition, no difference in heart failure events was found in patients with or without heart failure at baseline.[65] Still, a recent post hoc analysis reported older patients (>75 years; n = 182; 8% of the cohort) to have impaired cardiovascular outcome with the insulin-providing strategy (HR 1.65; 95% CI, 0.99-2.72; $P = .050$ by multivariate analysis), although no separate analysis for heart failure was reported.[66]

Other retrospective studies have suggested that insulin treatment worsens the prognosis of patients with diabetes and heart failure.[67] Still, no increase in heart failure hospitalization or cardiovascular events was observed in the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial.[68] That study randomized 12,537 patients with impaired fasting glucose, impaired glucose tolerance, or T2DM to receive insulin glargine to target a fasting blood glucose level ≤95 mg/dL (5.3 mmol/L), which required approximately 30 units of insulin per day (0.31 to 0.40 units/kg).[68] Whether higher daily doses of insulin could be considered safe was recently investigated in a cohort study of 6072 patients with new insulin therapy added to pre-existing metformin therapy. A requirement of more than 100 units of insulin per day was associated with increased cardiovascular mortality (HR 2.65; 95% CI, 1.65-4.25) when compared with a requirement of 25 units insulin per day or less. Still, no association of higher insulin doses was found with heart failure events.[69] Further, adjustment to time-dependent variables, including HbA1c, body weight, and hypoglycemic/cardiovascular events, weakened the association of high insulin dose with cardiovascular mortality.

Thiazolidinediones: Thiazolidinediones (glitazones) have fluid retention potential, which leads to increased heart failure events. Thiazolidinediones are not recommended in patients with symptomatic heart failure, and initiation of therapy is contraindicated in patients with established NYHA III/IV heart failure.[70]

DPP-4 Inhibitors: The DPP-4 inhibitors were the first class of diabetes agents for which trials were designed according to new requirements by the FDA and European Medicines Agency for cardiovascular safety.[71] Cardiovascular safety sufficient to gain market approval is defined according to trial data showing that the upper bound of the 95% CI for the risk ratio of major adverse cardiovascular events compared with placebo is <1.3. Trial designs have typically aimed for glycemic equipoise in the drug and placebo groups; consequently, results are often independent of the HbA1c-lowering efficacy of the tested drug. This also results in more intensive adjustment of background diabetes medications in subjects assigned to placebo.

The DPP-4 inhibitors increase the bioavailability of the incretin hormones glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (among other substrates), leading to glucose-dependent insulin secretion with no relevant effect on body weight. Three independent cardiovascular safety trials have been reported for the DPP-4 inhibitors saxagliptin (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus−Thrombolysis in Myocardial Infarction [SAVOR-TIMI 53][72]), alogliptin (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care [EXAMINE][73]), and sitagliptin (Trial Evaluating Cardiovascular Outcomes with Sitagliptin [TECOS][74]). These trials demonstrated cardiovascular safety in high-risk populations of patients with diabetes, although none of the substances proved superior to placebo on top of standard care. The secondary endpoint of heart failure hospitalization events was unexpectedly increased with saxagliptin in SAVOR-TIMI 53 (HR 1.27; 95% CI, 1.07-1.51; $P = .007$).[72,75] A similar, albeit not significant, trend was found with alogliptin in the smaller EXAMINE trial (106 events [3.9%] vs 89 events [3.3%]; HR 1.19; 95% CI, 0.90-1.58; $P = .22$),[73] whereas no difference in heart failure hospitalization was found with sitagliptin in TECOS (HR 1.00; 95% CI, 0.83-1.20; $P = .98$).[74] This suggests the absence of a class effect, which will be further evaluated in upcoming DPP-4 inhibitor trials. Retrospective propensity score−matched analysis of patients with heart failure and diabetes receiving DPP-4 inhibitors or other glucose-lowering drugs found DPP-4 inhibitor treatment to be associated with reduced cardiac and all-cause mortality.[76] Further, a large retrospective analysis including 78,553 new saxagliptin or 298,124 new sitagliptin users reported lower risk for heart failure hospitalization with DPP-4 inhibitor treatment in comparison with pioglitazone, sulfonylureas, or insulin treatment.[77] In addition, neither DPP-4 inhibitors nor GLP-1 receptor agonists (GLP-1 RAs) were associated with increased heart failure hospitalization in a retrospective cohort analysis of 1,499,650 patients with diabetes, including 79,800 with a history of heart failure.[78]

GLP-1 RAs: The GLP-1 RAs can be divided by their half-life as short- and long-acting substances.[79] Short-acting agonists more efficiently reduce postprandial glucose and have little effect on body weight, whereas long-acting substances primarily target fasting glucose levels and more efficiently cause weight loss.[79]

Fundamental differences have been found with respect to cardiovascular outcomes among these different agents. The short-acting lixisenatide (half-life 2-4 hours; administered once daily) proved safe, but not superior to placebo, in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial in patients with diabetes and acute coronary syndrome.[80] In contrast, the long-acting liraglutide (half-life 13 hours[81]; administered once daily) and the very long-acting semaglutide (half-life approximately 160 hours; administered once weekly[82]) both significantly reduced cardiovascular events in high-risk patients with diabetes in the larger Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial (LEADER; n = 9340 patients) and the smaller Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6; n = 3297 patients).[83,84] This was driven by a reduction in cardiovascular mortality in the LEADER trial (HR 0.78; 95% CI, 0.66-0.93; $P = .007$), which importantly translated to a reduction in total mortality (HR 0.85; 95% CI, 0.74-0.97; $P = .02$).[83] In addition, nonsignificant reductions in nonfatal myocardial infarction, nonfatal stroke, and heart failure hospitalization were found. In contrast, semaglutide caused a significant reduction in nonfatal stroke (HR 0.61; 95% CI, 0.38-0.99; $P = .04$) and a nonsignificant reduction in nonfatal myocardial infarction (HR 0.74; 95% CI, 0.51-1.08; $P = .12$) with no difference in cardiovascular mortality or heart failure.[84]

These results demonstrate relevant differences among the different types of GLP-1 RAs. The reduction in cardiovascular mortality in the absence of heart failure improvement in LEADER suggests vasoprotective efficacy as a primary cardioprotective mechanism, which is supported by the SUSTAIN-6 results.

Driven by favorable effects of GLP-1 and GLP-1 RAs in preclinical studies,[85] a variety of smaller randomized trials have explored the efficacy of GLP-1 RAs for heart failure treatment in patients with or without diabetes. In the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) trial, liraglutide did not improve cardiac function in 300 patients with advanced heart failure (LVEF ≤40%: 29% NYHA II and 68% NYHA III/IV; 60% with diabetes) during a period of 180 days.[86] Unexpectedly, liraglutide

numerically increased the combined endpoint of death and heart failure (HR 1.30; 95% CI, 0.92-1.83; log-rank $P = .14$), which became borderline significant in the subgroup of patients with diabetes (HR 1.54; 95% CI, 0.97-2.46; log-rank $P = .07$). No liraglutide-dependent increase of heart rate was observed in this trial,[86] which has consistently been found in other studies using GLP-1 RAs.[83,84] Further, liraglutide did not change LVEF in the Effect of Liraglutide on Left Ventricular Function in Chronic Heart Failure Patients With and Without Type 2 Diabetes Mellitus (LIVE) trial, in which 241 patients with reduced LVEF (≤45%; among these 31% with diabetes) were randomly treated for 24 weeks.[87] Heart rate increased in response to liraglutide by a mean of 7 beats per minute, whereas serious cardiac events occurred more often with liraglutide (n = 12; 10%) than with placebo (n = 3; 3%).[87] Similarly, the GLP-1 RA albiglutide failed to improve LVEF of NYHA II/III heart failure patients without diabetes (LVEF <40%), while also leaving 6-minute walk distance, myocardial glucose uptake, or myocardial oxygen consumption unaffected.[88] These data question the translatability of beneficial preclinical effects of GLP-1 in the context of manifest heart failure to the clinic.

SGLT2 Inhibitors: The SGLT2 inhibitors are a new class of antidiabetes drugs that block the SGLT2 receptor in the proximal tubule of the kidney, thus leading to increased urinary glucose excretion along with sodium. The first published cardiovascular outcomes trial to assess the effect of an SGLT2 inhibitor was Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME), evaluating whether empagliflozin compared with placebo on top of standard-of-care treatment influences the incidence of cardiovascular events.[89] The study in a high-risk population of 7020 patients with type 2 diabetes mellitus and prior cardiovascular disease showed a significant 14% relative risk reduction in the primary endpoint of cardiovascular death, myocardial infarction, and stroke; a significant 38% relative risk reduction in cardiovascular death; as well as a significant 32% relative risk reduction in overall mortality, which translated into a number-needed-to-treat of 39 over 3 years to prevent 1 death.[89] In addition, in a secondary analysis, empagliflozin led to a significant 35% relative risk reduction in hospitalization for heart failure (HR 0.65; 95% CI, 0.50-0.85; $P < .002$), with separation of the curves evident almost immediately during trial observation, suggesting a very early effect of the SGLT2 inhibitor on heart failure risk.[89,90]

The early effects of empagliflozin on cardiovascular mortality and hospitalization for heart failure suggest early hemodynamic effects of the drug. Furthermore, SGLT2 inhibition has been found to increase the concentration of circulating ketone bodies, which might provide an alternative energy source for the diabetic heart in the presence of insulin resistance.[91] In addition, other potential mechanisms, such as weight loss, reduced blood pressure, sodium depletion, reduced oxidative stress, and arterial stiffness, as well as a reduction in sympathetic nerve activation, are currently being discussed.[92]

To date, prospective cardiovascular outcomes trial data for the SGLT2 inhibitor class are only available for empagliflozin. Because many of the potential mechanistic effects have also been described for other SGLT2 inhibitors, it will be interesting to see the results of the ongoing cardiovascular outcomes trials with dapagliflozin, canagliflozin, and ertugliflozin to determine whether the beneficial cardiovascular outcomes effects reported from the EMPA-REG OUTCOME trial are a class effect or unique to empagliflozin.

Conclusion

Considering current trial results, patients with diabetes and heart failure may benefit most from glucose-lowering therapies with SGLT2 inhibition. This might relate to the elimination of glucose via the kidney, with net reduction of energetic substrate availability following SGLT2 inhibition, among other possible mechanisms. Reduced energetic substrate availability is also obtained with lifestyle intervention,[48,49] which beneficially affects myocardial function in obese patients with and without diabetes. Furthermore, limited evidence suggests beneficial effects with metformin, which reduces energetic substrate availability by decreasing endogenous glucose production, on heart failure in patients with diabetes.[56,93] In contrast, no improvement in heart failure, or potential detrimental effects, have been reported for glucose-lowering strategies that directly or indirectly increase the availability of insulin. These considerations should be addressed in future study designs to optimize heart failure therapy in patients with diabetes.

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