ARTICLE TITLE

Title of your article.

Heart Failure: Epidemiology, Pathophysiology and Management of Heart Failure in Diabetes Mellitus

AUTHOR NAMES AND DEGREES

Full name and degrees of each author exactly as they should appear in print. REMINDER: Everyone listed as an author is expected to have contributed to the article to a significant extent in line with ICMJE guidelines. Please see the Clinics Authorship Guidelines for more information.

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KEYWORDS

4-8 keywords to enhance online search results.

Cardiac function; cardiovascular events; glucagon-like peptide-1 agonists; glucose lowering therapy; glycemia; heart failure; sodium glucose co-transporter 2 inhibitors; type 2 diabetes mellitus.

KEY POINTS

3 to 5 bullet points of approximately 25 words each that summarize the main ideas of your article. Key points appear at the very beginning of your article in print and online.

- Heart failure is a common comorbidity in diabetes and patients with both conditions have a particularly poor prognosis
- Most clinical outcome trials investigating the effects of glucose-lowering agents have excluded patients with heart failure
- Glitazones and, possibly, some DPP-4 inhibitors, cause an increased risk of developing heart failure and deterioration in existing heart failure
- One class of drugs, the sodium glucose co-transporter 2 inhibitors, reduce the risk of developing heart failure

SYNOPSIS

Brief summary of your article (100 words or fewer; no references or figures/tables). The synopsis appears only in the table of contents, and is often used by indexing services such as PubMed.

We briefly discuss the epidemiology of heart failure and diabetes and summarize the key findings from the recent cardiovascular outcome trials in patients with type 2 diabetes, with a focus on heart failure as an endpoint.

HEART FAILURE SYNDROME

Heart failure is a clinical syndrome characterized by symptoms and signs caused by structural or functional abnormalities of the heart. Typical symptoms are breathlessness, ankle swelling and fatigue. Typical signs are increased jugular venous pressure, third heart sound, peripheral edema and pulmonary crackles, however the condition can be present in the absence of these findings. It is important to address the underlying cause of heart failure, as the specific pathology determines choice of treatment. Common causes of heart failure are ischemic heart disease, dilated cardiomyopathies, valvular lesions, atrial fibrillation and hypertension. The toxic impact of chemotherapy and high levels of alcohol consumption can also lead to systolic left ventricular failure.[1,2] Diabetes accelerates atherosclerosis and often leads to hypertension, but it is still debated whether diabetes causes a specific cardiomyopathy. Some data suggest that type 2 diabetes and hyperinsulinemia promote a “diabetic cardiomyopathy”.[3]

The management of cardiovascular disease has undergone much change in recent years in general; notably recent advances in the management of acute coronary syndromes have significantly reduced both short-term and long-term mortality.[4] This has led to increased survival, and thus, it could be argued, an increasing number of individuals with myocardial damage at risk of developing heart failure. The medical and device treatment of patients with established heart failure has also improved considerably, reducing both morbidity and mortality.[5-8] Both changes are thought to have led to an increase in prevalence of heart failure. Thus, heart failure has become one of the most common cardiovascular diseases in the Western world. Epidemiological data show a prevalence of heart failure of 2%; and among individuals above 75 years, nearly 10% suffer from heart failure.[9] Notably, the prevalence is even higher in patients with diabetes.[10,11] Conversely, the prevalence of diabetes is very high in patients with heart failure with estimates of up to 40% in patients hospitalized with worsening symptoms.[12,13]

EPIDEMIOLOGY OF HEART FAILURE AND DIABETES

Compared with other cardiovascular events, observational data reveal a frequent occurrence of heart failure in patients with diabetes.[14,15] The *incidence* of hospital admission for heart failure in 65,619 patients with type 2 diabetes treated with insulin exceeded both myocardial infarction and stroke.[16] Heart failure also appears to be the most common complication in several clinical outcome trials, especially in patients with diabetes and nephropathy.[17,18] This is emphasized by the Irbesartan Diabetic Nephropathy Trial in which hospitalization for heart failure was the most frequent cardiovascular event, despite exclusion of patients with heart failure at baseline.[17] The *prevalence* of heart failure in individuals with diabetes is also high, with one estimate of approximately 12%.[10] Furthermore, heart failure in diabetes is associated with very poor outcomes and huge healthcare expenses.[11,19] Once heart failure develops in individuals with diabetes mellitus, the outlook is grim with as much as a 10-fold higher mortality, compared to people with diabetes without heart failure, and a 5-year survival rate of only 12.5%.[11] Although more recent data have shown a better prognosis with a 3-year mortality of 40%,[20] these findings highlight the clinical importance of the combination of heart failure and diabetes. Fortunately, the response to therapy for heart failure is similar in patients with and without diabetes,[21,22] and is standardized in evidence-based international guidelines.[1,2]

MANAGEMENT OF DIABETES MELLITUS IN HEART FAILURE

While observational data suggest an association between lower glucose and less risk of macrovascular disease, randomized controlled trial data are generally not supportive.[23] The one exception is the extended follow-up of the UK Prospective Diabetes Study (UKPDS), which studied patients with newly diagnosed diabetes, and showed a 16% reduction in the risk of heart failure per 1% absolute decrease in HbA_{1c}.[24] Other large-scale randomized controlled trials investigating the effect of more versus less intensive glycemic control, including The Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Veterans Affairs Diabetes Trial (VADT), did not report a reduced risk of heart failure[25-27], and neither did extended follow-up of VADT

show a reduction in new or worsening heart failure.[28] Indeed, some glucose-reducing agents are associated with either increased risk of developing heart failure or caused further deterioration of existing heart failure.[29] This is a major concern, especially in light of the absence of hospital admissions for heart failure as a prespecified component of primary composite cardiovascular outcomes in most large-scale trials investigating glucose-lowering agents. Furthermore, the optimal level of glycemic control in heart failure is uncertain, with some evidence suggesting that tight glycemic control may be associated with poorer outcomes in heart failure, possibly because of a cardiovascular risk related to hypoglycemia.[30] Thus, how best to achieve glycemic control in patients with diabetes and heart failure remains an important and yet unanswered clinical question. Below, we will summarize the main findings from key clinical outcome trials, and discuss the potential mechanisms of benefit and harm of different glucose-lowering agents in heart failure.

PHYSICAL TRAINING AND WEIGHT LOSS

By reducing weight and blood pressure and perhaps by improving insulin sensitivity and other cardiovascular risk factors, regular exercise might be expected to reduce the risk of developing heart failure in patients with type 2 diabetes mellitus. However, in the one large prospective randomized trial testing this hypothesis, the Action for Health in Diabetes (Look-AHEAD) trial, carried out in 5,145 overweight or obese adults with type 2 diabetes mellitus, an intensive lifestyle intervention promoting weight loss through decreased caloric intake and increased physical activity (intervention group) failed to improve cardiovascular outcomes compared to standard treatment. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina during a maximum follow-up of 13.5 years and this was not reduced by the lifestyle intervention (hazard ratio [HR] = 0.95; 95% CI: 0.83 - 1.09). However, there was a trend towards a reduction in episodes of heart failure (99 versus 119 episodes, respectively) but this was not significant (HR = 0.80; 95% CI 0.61 - 1.04).[31]

In patients with established heart failure and diabetes, regular exercise is thought to be beneficial by helping improve insulin sensitivity. By reducing blood pressure, cardiac hypertrophy, and left atrial volume, exercise

and weight loss might be especially beneficial in patients with heart failure and preserved ejection fraction (HFpEF).[32] Two clinical trials provide data on the effects of exercise in patients with both diabetes and heart failure. One study in patients with heart failure and reduced ejection fraction (HFrEF) suggested that exercise improved ejection fraction but was too small to provide robust evidence (N=42).[33] In the only large trial examining the effect of regular exercise on outcomes in heart failure, the Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION), heart failure patients with and without diabetes (N=2331) were randomized to aerobic exercise on top of usual care, or usual care alone, and exercise was shown to reduce the secondary composite endpoint of cardiovascular mortality or hospitalization due to heart failure after adjustment for prognostic baseline variables (HR = 0.85; 95% CI: 0.74 - 0.99).[34] Importantly, there was no interaction between baseline diabetes status and the benefits of exercise training.[35] The patients in HF-ACTION had HFrEF, and it is unknown whether patients with diabetes and HFpEF might benefit from exercise. The only low quality evidence comes from one small-randomized study of caloric restriction and exercise training in 100 severely obese HFpEF patients with (N=35) and without (N=65) diabetes which suggested that these interventions led to both weight loss and improved functional capacity.[36]

ALPHA-GLUCOSIDASE INHIBITORS

Alpha-glucosidase inhibition lowers body weight and triglycerides. The efficacy and safety of two drugs in this class has recently been tested in randomized, placebo-controlled, clinical trials. In the first, the Alpha-glucosidase-inhibitor Blocks Cardiac Events in Patients with Myocardial Infarction and Impaired Glucose Tolerance (ABC) trial, patients with impaired glucose tolerance and coronary heart disease and a LVEF > 40% were randomized to placebo or voglibose. The original intent was to enroll approximately 3000 patients but the trial was stopped early because an interim analysis of outcomes in the first 870 participants suggested a low probability of a positive outcome i.e. the trial was terminated for futility. Only 12 patients were hospitalized for heart failure during a follow-up period of 24 months.[37] The much larger Acarbose Cardiovascular Evaluation (ACE) trial randomized 6522 patients with coronary heart disease and impaired

glucose tolerance to either acarbose or placebo. After a median follow-up of 5 years there was no difference in the primary five-point composite outcome of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospital admission for unstable angina, or hospital admission for heart failure (HR = 0.98; 95% CI: 0.86–1.11). There were 65 hospitalizations for heart failure in the acarbose group and 73 in the placebo group (HR = 0.89; 95% CI 0.63–1.24).[38]

There are few data from studies conducted in patients with heart failure. A small non-randomized and underpowered study investigated the effect of 24 weeks of treatment with open-label voglibose on cardiovascular function in 30 patients with dilated cardiomyopathy and impaired glucose tolerance. Voglibose treatment was associated with reduced left ventricular dimensions, NYHA functional classification, and plasma BNP levels, compared with control subjects.[39] Clearly, the safety of alpha-glucosidase inhibitor treatment in patients with diabetes and chronic heart failure has not been adequately evaluated and should be in light of its frequent use in Asian countries.

BIGUANIDES (METFORMIN)

There is a widely held view that metformin is cardioprotective, and proposed mechanisms of action include direct myocardial effects, and indirect effects related to weight loss and improved insulin sensitivity. The evidence for cardio-protection is, however, weak in general and non-existent for heart failure in particular. The United Kingdom Prospective Diabetes Study (UKPDS) randomized 753 overweight (>120% ideal bodyweight) patients with newly diagnosed type 2 diabetes and raised fasting plasma glucose (FPG; 6.1–15.0 mmol/L) despite 3 months of dietary intervention to conventional treatment, primarily with diet alone (n=411), or an intensive blood-glucose control approach with metformin, aiming for a FPG below 6 mmol/L (n=342). Median follow-up was 10.7 years. There were few episodes of heart failure and these did not differ between treatment groups.[40] Long-term follow-up of UKPDS has been published recently but heart failure was not reported.[41]

There is even less evidence about the potential actions of metformin in patients with established heart failure (as opposed to preventing incident heart failure). At present, the largest randomized study to evaluate the effect of metformin in heart failure patients randomized only 60 insulin resistant subjects to treatment for four months. Metformin did not improve the primary endpoint cardiopulmonary exercise.[42]

Consequently, we have to rely on observational studies to examine associations between metformin use and clinical outcomes in patients with heart failure, with the recognized and significant limitations of such studies. Metformin use seems to be associated with better outcomes than treatment with other glucose lowering treatments in several observational studies. First, a Canadian cohort study examined outcomes in 1,833 patients with diabetes and incident heart failure. The study demonstrated that use of metformin either as monotherapy or combined with a sulfonylurea was associated with a lower 1-year mortality compared to sulfonylurea treatment alone (HR = 0.83; 95% CI: 0.70 - 0.99).[43] The use of metformin in diabetic patients with heart failure has been associated with better outcomes, including hospitalization for heart failure in several other cohort studies.[44-50] Although metformin use may be associated with both lower mortality and morbidity in heart failure, compared with other treatments, it is important to stress the limitations of observational studies, principally due to confounding. For example, it is possible that the prescription of metformin is just a marker of less severe disease, but despite the lack of data from randomized trials, these observational analyses have led to the view that metformin is safe in heart failure in patients with eGFR above 30 ml/min. However, it is also important to point out that metformin can potentially cause lactic acidosis, and should not be used in patients with severe disease such as those who have become acutely decompensated or those with renal failure. Caution should also be exercised when administrating iodine contrast agent, during perioperative periods, and in situations with possible hypoxic states like respiratory failure, myocardial infarction, shock or sepsis.

Ideally, a large randomized clinical trial is required to investigate the effects of metformin treatment on mortality and morbidity in heart failure patients, but one attempt to conduct such a trial failed because it

appears that physicians did not accept that there was equipoise and preferred to prescribe metformin, rather than randomize patients.[51]

SULFONYLUREAS

Sulfonylureas increase insulin release thereby reducing blood glucose. However, the increases in insulin levels may cause hypoglycemia and weight gain. These actions could potentially exacerbate heart failure. The University Group Diabetes Program (UGDP) was the first large randomized trial in patients with type 2 diabetes mellitus conducted between 1961 and 1975. One treatment group received a fixed dose of the sulfonylurea tolbutamide (1.5 g daily in divided dose, regardless of plasma glucose response) and there were two insulin groups and a placebo group (a phenformin group was added later). An interim analysis of this trial in 1969 revealed a statistically significant excess of cardiovascular deaths in the tolbutamide arm, leading to premature discontinuation of this arm of the trial.[52] The number of heart failure events were not reported, only the number of patients receiving heart failure medication at any time after randomization (tolbutamide = 22 vs. placebo = 13, p=0.13), but the type of drug and doses were not reported.[53]

In the united Kingdom Prospective Diabetes Study (UKPDS), 3867 newly diagnosed patients with type 2 diabetes, who had a fasting plasma glucose (FPG) concentrations of 6.1–15.0 mmol/l despite 3 months treatment with diet, were randomly assigned to intensive treatment with a sulphonylurea (chlorpropamide, glibenclamide, or glipizide; N=1234) or with insulin (N=911), or conventional treatment with diet (N=896). The aim in the intensive group was FPG less than 6 mmol/l. There were 48 new cases of heart failure in the sulfonylurea group compared with 62 in the conventional therapy group.[54]

As with metformin, the evaluation of the safety of sulfonylureas as a treatment for diabetes in patients with established heart failure has relied mainly on observational data. A retrospective cohort study of 16,417 patients with type 2 diabetes and heart failure found no evidence that mortality was higher in individuals treated with a sulfonylurea compared with other glucose lowering drugs (HR = 0.99; 95% CI: 0.91 - 1.08).[44] However, follow-up in this study was limited to one year and treatment with sulfonylurea was compared to

other glucose-lowering agents that in themselves may worsen heart failure, including insulin and thiazolidinedione. In another study, Eurich et al. identified 1,833 patients with incident heart failure who were treated with an oral glucose-lowering agent. The mean follow-up time was 2.5 years. Mortality, as well as the rate of hospitalization for heart failure, was higher in patients taking sulfonylurea monotherapy compared with metformin (metformin versus sulfonylurea HR = 0.83; 95% CI: 0.70 - 0.99).[43] A Danish registry study with more than 10,000 patients reported a similar finding.[48] Thus, the existing literature indicates that the safety of sulfonylureas in heart failure is uncertain, principally due to the reliance on observational studies and lack of randomized controlled trials.

INSULIN

Insulin may have positive inotropic effects on myocardial tissue and improve other hemodynamic measures, but may also cause sodium retention, weight gain and possibly edema which are likely to be undesirable in heart failure. Sodium retention is dose dependent and present even in physiologic concentrations of insulin.[55] Fluid retention due to insulin is usually mild, but it could potentially increase the severity of heart failure, and several case reports of new-onset heart failure in patients who started insulin treatment have been published. However, in the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial 12,537 patients with impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes and cardiovascular risk factors were randomized to insulin or standard care alone. Insulin had a neutral effect on the composite outcome including death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, cardiovascular revascularization procedures, or hospitalization for heart failure (HR = 1.04; 95% CI: 0.97–1.11).[56] There were 310 patients hospitalized with heart failure in the insulin group and 343 in the placebo group (HR 0.90, 0.77–1.05; p=0.16). These findings are somewhat reassuring, but patients in the ORIGIN trial did not all have diabetes or had diabetes for a very short time, and the risk of heart failure rises with increasing age and duration of diabetes.

Only one small and short-term randomized clinical trial has evaluated the effect of insulin in patients with diabetes and established heart failure. This trial randomized 40 patients with type 2 diabetes, reduced left ventricular systolic function and HbA1c > 7.5% to optimized diabetes treatment including insulin use, or no optimization for four months. The primary outcome was defined as changes in left ventricular contractile reserve capacity from baseline to follow-up. The study showed no impairment of cardiac function and no patients were hospitalized for heart failure during the study period.[57] On the other hand, in a variety of retrospective analyses of trials and in observational studies, treatment with insulin has been consistently associated with worse outcomes than no treatment with insulin. As with all observational studies it is impossible to know whether these findings reflect "cause and effect" (i.e. that insulin is harmful) or confounding, especially as insulin treated patients are usually older with longer-standing diabetes, more advanced cardiovascular and renal disease and other adverse prognostic characteristics.[58-60] The bottom line is that the existing data available to the clinical community are insufficient to exculpate insulin from causing worse outcomes in patients with heart failure. If it proves necessary to start insulin in a patient with heart failure, it is important to monitor the patient for signs of fluid retention.

THIAZOLIDINEDIONES (GLITAZONES)

Thiazolidinediones (glitazones) enhance insulin sensitivity by increasing the efficiency of glucose transporters. On the other hand, these agents also cause weight gain, edema and fractures. The mechanisms underlying edema are unknown, but may include activation of collecting duct sodium channels, and proximal tubular sodium channel, as well as peripheral arteriolar vasodilation.[61-63] The clinical manifestations are an essential part of the heart failure syndrome, and robust data suggest an increased risk of incident heart failure in patients with pre-diabetes as well as type 2 diabetes treated with thiazolidinedione.[64] This was exemplified by the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial in which 4,447 patients with type 2 diabetes and dysglycemia on metformin or sulfonylurea monotherapy were randomized to either add-on rosiglitazone or a combination of metformin and sulfonylurea.[65] Patients were

followed over an average period of 5.5 years, and rosiglitazone treatment was associated with a doubled risk of fatal or non-fatal heart failure events (61 versus 29; HR = 2.10; 95% CI: 1.35-3.27).[66] There are three large trials with pioglitazone in patients with diabetes and/or impaired glucose tolerance and these have shown a less striking increase in risk of heart failure (and a reduction in athero-thrombotic events).[67-69]

There are few data from studies in patients with established heart failure. Only two small and short-term randomized clinical trials have investigated the effect of thiazolidinediones in heart failure patients with type 2 diabetes. The primary outcome was change in LVEF. There was no negative effect on left ventricular function in either study; however, thiazolidinedione treatment were associated with an increase in B-type natriuretic peptide (BNP), a marker of increased left ventricular wall stress and predictor of adverse cardiovascular outcomes.[70,71] Dargie et al. investigated the effect of rosiglitazone, compared to placebo, given for 52 weeks in 224 patients with type 2 diabetes and HFrEF. Rosiglitazone treatment was associated with a tendency towards increased risk of all-cause mortality and hospitalization due to heart failure (HR = 1.28; 95% CI: 0.51-3.21).[70] Giles et al. investigated the effect of pioglitazone in a similar way. In total, 300 patients with diabetes and HFrEF were randomized to 12 months' treatment with pioglitazone or glyburide; treatment with pioglitazone was associated with worsening heart failure symptoms as well as a larger number of hospitalizations for heart failure.[71] The US Food and Drug Administration has given thiazolidinediones a "black box" warning in relation to use in acute or symptomatic chronic heart failure patients.[72]

INCRETIN THERAPIES

The incretins are a family of gut hormones produced by enteroendocrine cells. The two main molecules of interest are glucagon-like peptide-1 (GLP-1) and the gastric inhibitory hormone (GIP). GLP-1 hormone is secreted in response to food intake; it decreases glucagon excretion and increases insulin levels.[73] The protease dipeptidyl peptidase-4 (DPP-4) rapidly decomposes native GLP-1. Pharmacological inhibitors of DPP-4 and GLP-1 receptor agonists with longer bioavailability have been developed.[74]

DPP-4 INHIBITORS

DPP-4 has several postulated substrates in addition to GLP-1, including BNP, erythropoietin, glucagon, vasoactive intestinal peptide, and vasostatin.[75] Thus, DPP-4 inhibition could affect pathways involving cardiac signaling, collagen turnover, and the sodium hydrogen exchanger in the renal proximal tubule.[76]

Clinical outcomes have been reported in three randomized controlled trials using of DPP-4 inhibitors. The Saxagliptin Assessment of vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial was the first large-scale outcome trial to investigate the cardiovascular safety of a DPP-4 inhibitor in 16,492 patients with type 2 diabetes and either a high risk of cardiovascular disease or known cardiovascular disease. The trial did not show a reduction in the primary composite outcome of cardiovascular death, myocardial infarction or ischemic stroke. Surprisingly, there was an increase in the risk of hospitalization for heart failure with saxagliptin, compared with placebo (289 versus 228 patients hospitalized, respectively; HR = 1.27; 95% CI: 1.07 - 1.51).[77] Subsequent analysis showed that the risk of heart failure was highest in patients with elevated BNP, a history of heart failure and chronic kidney disease.[78] Whether this completely unexpected finding reflected the play of chance, or, if real, was a DPP-4 inhibitor class effect (or even an issue for other incretin-based therapies including GLP-1 receptor agonists) or a drug-specific hazard was unknown at that point, but emphasized the importance of heart failure as an outcome in trials testing new therapies for diabetes. Therefore, the outcomes of subsequent trials with DPP4-inhibitors were eagerly awaited after SAVOR-TIMI 53. In the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial 5,380 patients with type 2 diabetes and recent acute coronary syndrome were randomized to receive alogliptin or placebo. There was a non-significant trend to an increase in heart failure hospitalization with alogliptin compared to placebo (106 versus 89 case, respectively; HR = 1.07; 95% CI: 0.79 – 1.46).[79] However, in the Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin (TECOS), no such risk was seen with sitagliptin. TECOS randomized 14,671 patients with type 2 diabetes and a history of major coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease to DPP-4 inhibitor therapy or placebo.[80] There were a similar number of patients

hospitalized with heart failure in the sitagliptin group (228 cases) and placebo group (229 cases); HR = 1.00; 95% CI: 0.83 - 1.20. There were 2643 patients with heart failure at baseline in TECOS and the treatment effect in this subgroup was similar to that in the trial overall; however the phenotype of patients with heart failure at baseline (and occurring following randomization) was not defined. While TECOS may have been reassuring, none of these studies included a substantial number of patients with a diagnosis of heart failure at baseline, leaving uncertainty about the safety of DPP4-inhibitors in patients with established heart failure. The US Food and Drug administration has issued a safety communication concerning saxagliptin and alogliptin stating that health care professionals should consider discontinuing both drugs in patients who develop heart failure (http://www.fda.gov/Drugs/DrugSafety/ucm486096.htm).

As with the other blood glucose-lowering drugs discussed so far, there are few data on the use of DPP-4 inhibitors specifically in patients with established heart failure. The effects of alogliptin, saxagliptin and sitagliptin on heart failure hospitalization in the subgroups of patients with prevalent heart failure at baseline in EXAMINE, SAVOR-TIMI 53 and TECOS are shown Table 1, but, as pointed out, the heart failure phenotype in these patients was not characterized. The Vildagliptin in Ventricular Dysfunction Diabetes Trial (VIVIDD) investigated the effect of vildagliptin on cardiac function in 254 patients with type 2 diabetes and HFrEF. The study met the primary endpoint of statistical non-inferiority in terms of change in LVEF, and no difference in time to any first cardiovascular event between the two groups was observed (35 events in the vildagliptin group vs. 31 in the placebo group). However, there were 11 deaths from any cause in the vildagliptin arm and four deaths in the placebo arm.[81] Although the study was not powered to evaluate hard endpoints, it highlights the uncertainty of DPP4-inhibitor use in patients with chronic heart failure.

GLP-1 RECEPTOR AGONISTS

The effect of GLP-1 receptor agonists on glucose lowering and weight loss exceeds the effects of DPP4-inhibitors. Substances can be divided in to two groups according to their structural basis (exendin or GLP-1 related) and their half-life:

I. *Short acting (terminal half-life <24 hours)/exendin-4 based: exenatide*

II. *Long acting (>24 hours)/exendin-4 based: extended duration exenatide*

III. *Short-acting (<24 hours)/GLP-1 based: lixisenatide, liraglutide*

IV. *Long-acting (>24 hours)/GLP-1 based: dulaglutide, albiglutide and semaglutide*

The effect of the short-acting GLP-1 analogue lixisenatide on cardiovascular outcomes was tested in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial. Patients with type 2 diabetes and an acute coronary syndrome (N=6,068) within 15 to 180 days were randomized to receive lixisenatide or placebo in addition to standard of care. Lixisenatide had a neutral effect on the primary and secondary outcomes, including hospitalization for heart failure (122 versus 127 patients hospitalized; HR = 0.96; 95% CI: 0.75 - 1.23).[82] The effect of the longer-acting GLP-1 analogue liraglutide was tested in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial. LEADER included patients (N=9340) with type 2 diabetes and established cardiovascular disease or cardiovascular risk factors, and 14% of patients in LEADER had a history of NYHA functional class II or III heart failure at enrolment (probably a mixture of HFrEF and HFpEF).[83] Liraglutide reduced the risk of the primary composite endpoint (HR = 0.87; 95% CI: 0.78 - 0.97) as well as cardiovascular and all-cause mortality; there was also a nominally statistically significant reduction in myocardial infarction. The risk of heart failure hospitalization, however, did not differ between groups (218 versus 248 patients hospitalized; HR = 0.87; 95% CI: 0.73 - 1.05).[84] In the subgroup of 1305 patients with heart failure at baseline the treatment effect of liraglutide was consistent with that observed in the trial overall; however the phenotype of patients with heart failure at baseline (and occurring following randomization) was not defined.

Consistent with these findings, a very long-acting GLP-1 agonist, semaglutide, was shown in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6; N=3297) to reduce the same combined primary cardiovascular endpoint (HR = 0.74; 95% CI: 0.58 -

0.95) although without a statistically significant effect on mortality or myocardial infarction (but with a reduction in stroke). Semaglutide did not reduce the risk of heart failure hospitalization (HR = 1.11; 95% CI: 0.77 - 1.61).[85]

Most recently, the Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL) tested an alternative long-acting GLP-1 receptor agonist, with a different structural basis than liraglutide and semaglutide, but similar to that of lixisenatide (exenatide and lixisenatide are exendin-4 based). In EXSCEL, 14.572 patients were randomized equally to exenatide once weekly or placebo. There was a trend to a reduction in the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke with exenatide (HR 0.91, 0.83 - 1.00; p=0.061 for superiority) and a nominally statistically significant reduction in all-cause death. There were 219 patients hospitalized with heart failure in the exenatide group and 231 in the placebo group (HR 0.94, 0.78-1.13).[86] In keeping with all other large cardiovascular outcome trials in patients with diabetes, none of these trials reported data on left ventricular ejection fraction (LVEF).

Once again, there are few data about the effects of GLP-1 receptor agonists in patients with established heart failure. The effects of lixisenatide and liraglutide on heart failure hospitalization in the subgroups of patients with prevalent heart failure at baseline in ELIXA and LEADER are shown in Table 1, but, as pointed out, the heart failure phenotype in these patients was not characterized. The Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) study and the Effect of Liraglutide on Left Ventricular Function in Stable Chronic Heart Failure Patients (LIVE) study investigated the effects of liraglutide in more than 500 patients with HFrEF. Neither of these studies showed an effect on LVEF, but they raised concerns about the safety of liraglutide in patients with HFrEF.[87,88] In LIVE, liraglutide increased heart rate by 7 beats per minute compared with placebo and there were more serious cardiac events (composite of death or hospitalization for any cardiovascular event). A total of 12 patients in the treatment group and 3 patients in the placebo group experienced a serious cardiac event (HR = 3.9; 95% CI: 1.1 - 13.8). The FIGHT study reported a trend towards more serious cardiac events in liraglutide-treated patients. This was notable for the combined endpoint of death and rehospitalization due to heart failure (liraglutide = 43 and placebo = 30, HR = 1.54; 95% CI: 0.97 - 2.46).[87]

Although not powered to evaluate clinical outcomes, the results of these two studies demonstrate why outcome trials with diabetes drugs are needed specifically in patients with heart failure – it cannot be assumed that treatments will have the same safety profile in patients with heart failure as in those without. Furthermore, the effect of treatments may be very different in patients with HFrEF compared to HFpEF.

SODIUM GLUCOSE TRANSPORT 2 RECEPTOR INHIBITORS

Sodium glucose co-transport 2 receptor (SGLT2) is a low-affinity, high-capacity sodium glucose co-transporter thought to be exclusively located in the renal proximal tubule. SGLT2 is responsible for 90% of glucose reabsorption, and inhibition induces a decrease in blood glucose due to glycosuria. Secondary effects of SGLT2 inhibition include a modest diuretic effect, weight loss, lowering of blood pressure and reduced levels of uric acid and triglycerides.[89] The first cardiovascular outcome trial with a SGLT2 inhibitor to report, the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME), included 7,020 patients with type 2 diabetes and known cardiovascular disease. EMPA-REG OUTCOME showed a significant reduction in the primary composite outcome of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke with empagliflozin (HR 0.86, 95.02% confidence interval 0.74 -0.99; p = 0.04 for superiority). This treatment benefit was mainly due to a relative-risk reduction of 38% in death from cardiovascular causes (HR = 0.62; 95% CI: 0.49 - 0.77). There was also a 35% relative risk reduction in hospitalization for heart failure (HR = 0.65; 95% CI: 0.50 - 0.85) with empagliflozin compared to placebo.[90] It is noteworthy that this effect was independent of baseline treatment with anti-congestive medication and consistent in the subgroup of patients with heart failure at baseline (N= 706, again, without the phenotype defined). The findings from EMPA-REG have been supported by the CANagliflozin cardioVascular Assessment Study program (CANVAS) which consisted of two trials enrolling 10,142 participants with type 2 diabetes and either established cardiovascular disease or with cardiovascular risk factors, randomized to receive canagliflozin or placebo. Overall, the findings of CANVAS were broadly similar to EMPAREG-OUTCOME with a 14% relative risk reduction in the same primary outcome in the canagliflozin group (HR 0.86, 0.75 to

0.97; p = 0.02 for superiority). Although there was not a statistically significant reduction in cardiovascular mortality, there was a 33% relative risk reduction in hospitalization for heart failure (HR = 0.67; 95% CI: 0.52 - 0.87), similar to that seen in EMPAREG-OUTCOME. The benefit of canagliflozin seemed to be consistent in the subgroup of 1461 patients with heart failure at baseline (not phenotyped) and possibly greater in participants treated with a diuretic at baseline.[91] The mechanism or mechanisms by which SGLT-2 inhibitors reduce heart failure hospitalization are unknown; however, natriuresis and blood pressure reduction may be important, leading to a reduction in pre-load and afterload. Other suggestions include an improvement in myocardial metabolism as a result of the mild ketonemia caused by SGLT-2 inhibition (damaged myocardium may use ketones as a more metabolically efficient substrate) and a possible inhibition of sodium/hydrogen exchange in cardiomyocytes (potentially reducing intracellular calcium accumulation and risk of arrhythmias).

There are no substantial completed trials in patients with established heart failure, so, to date we must rely on the subgroup analyses from EMPA-REG OUTCOME and CANVAS described above. The effects of empagliflozin on heart failure hospitalization in the subgroup of patients with prevalent heart failure at baseline in EMPAREG-OUTCOME is shown Table 1, but, as pointed out, the heart failure phenotype in these patients was not characterized. Fortunately, three large randomized outcome trials in patients with heart failure are underway. Two of these, with empagliflozin and dapagliflozin, are in patients with HFrEF (NCT03036124 and NCT03057977) and one, with empagliflozin, in HFpEF (NCT03057951).

OTHER GLUCOSE LOWERING DRUGS

Nateglinide

The meglitinides ("glinides") bind to an ATP-dependent K1 channel on the membrane of pancreatic beta cells in a similar manner to sulfonylureas and lead to a short-term increase secretion of insulin. The safety of nateglinide - in addition to lifestyle modification - was evaluated in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial.[92] In total, 9306 participants with impaired glucose tolerance and either cardiovascular disease or cardiovascular risk factors received nateglinide (up to 60 mg

three times daily) or placebo, in a 2-by-2 factorial design with valsartan or placebo. Patients were followed for a median of 5.0 years and one co-primary outcomes was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Nateglinide did not reduce the incidence of the composite endpoint, and although hospitalizations for heart failure were numerically fewer, this reduction was not statistically significant (nateglinide 5 85 vs. placebo 5 100, HR, 0.85; 95% CI, 0.64–1.14).[93]

Bromocriptine

Bromocriptine-QR (a quick-release formulation of bromocriptine mesylate), a dopamine D2 receptor agonist, is a US Food and Drug Administration–approved treatment for type 2 diabetes mellitus. Taken in the morning, bromocriptine-QR is thought to cause an increase in central dopaminergic tone at the time of day it normally peaks in healthy individuals (this circadian peak linked to preservation and/or induction of normal insulin sensitivity and glucose metabolism). A total of 3,095 patients with type 2 diabetes were randomized 2:1 to bromocriptine-QR or placebo in conjunction with the patient's usual diabetes therapy in a 52-week evaluation of cardiovascular and overall safety.[94,95] As part of this assessment there was a pre-specified analysis of a composite cardiovascular endpoint of myocardial infarction, stroke, coronary revascularization, and hospitalization for angina or congestive heart failure, evaluated using modified intent-to-treat analysis.94,95 Fewer people experienced this end point in the bromocriptine-QR group compared with the placebo group: 37 (1.8%) vs. 32 (3.2%), respectively, HR 0.60 (95% CI 0.35–0.96). Subsequently, a composite including death from cardiovascular causes was reported: 39 (1.9%) 33 (3.2%), respectively, HR 0.61 (0.38 to 0.97).[94,95] There were 9 patients (0.4%) hospitalized for heart failure in the bromocriptine-QR group and 6 (0.6%) in the placebo group.

SUMMARY AND INTERPRETATION

It is only in the past few years that, after decades of use, we are beginning to obtain evidence on the cardiovascular effects of glucose lowering drugs, although these recent data only apply to the newer agents and not to established therapies such as metformin and sulphonylureas. Notably, one class of treatment, the thiazolidinediones (glitazones) clearly increase the risk of developing heart failure and worsening of heart failure in patients with the syndrome. There is a similar concern about at least some DPP-4 inhibitors. While GLP-1 receptor agonists do not seem to increase the risk of developing heart failure, their safety and efficacy in patients with established heart failure is uncertain. Uniquely among all glucose lowering therapies, the SGLT-2 inhibitors reduce the incidence of heart failure in patients with type 2 diabetes and their safety and efficacy in patients with established heart failure are being extensively assessed in three new large mortality/morbidity outcome trials, setting a new benchmark for evaluation of the effects of new diabetes drugs on cardiovascular outcomes.

What can we conclude on the basis of the currently available evidence? Table 1 summarizes what we know about outcomes with glucose lowering agents in relation to heart failure. Clearly, at present, it is not possible to make firm evidence-based recommendations about *any* treatment for diabetes in patients with HFrEF or HFpEF. Our tentative conclusions from the available data are that the SGLT-2 inhibitors seem to be the class of treatment least likely to be harmful and TZDs should be avoided.

TABLES

	PROactive	RECORD	EXAMINE	SAVOR-TIMI 53	TECOS	ELIXA	LEADER	SUSTAIN-6	EXSCEL	EMPA-REG OUTCOME	CANVAS	ACE
Time of completion	2005	2009	2013	2013	2015	2015	2016	2016	2017	2015	2017	2017
Drug studied	Pioglitazone	Rosiglitazone	Alogliptin	Saxagliptin	Sitagliptin	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Empagliflozin	Canagliflozin	Acarbose
Class	TZD	TZD	DPP-4 I	DPP-4 I	DPP-4 I	GLP-1 RA	GLP-1 RA	GLP-1 RA	GLP-1 RA	SGLT2-i	SGLT2-i	α-glucosidase inhibitor
Participants (N)	5,238	4,447	5,380	16,492	14,671	6,068	9,340	3,297	14,752	7,020	10,142	6,522
Trial duration (median)	2.9 years†	5.5 years†	1.5 years	2.1 years	3.0 years	2.1 years	3.8 years	2.1 years	3.2 years	3.1 years	3.6 years†	5.0 years
Prevalent HF % (N)	N/A	N/A	28 (1501)	13 (2105)	18 (2643)	22.4 (1358)	18 (1667)*	23.6 (777)	16.2 (2389)	10 (706)	14.4 (1461)	3.7 (243)
Treatment effects on HF hospitalization in overall group and in those with prevalent HF												
HR overall (95% CI)	1.41 (1.10-1.80)	2.10 (1.35-3.27)	1.19 (0.9-1.58)	1.27 (1.07-1.51)	1.00 (0.83-1.19)	0.96 (0.75-1.23)	0.87 (0.73-1.05)	1.11 (0.77-1.61)	0.94 (0.78-1.13)	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.89 (0.63-1.24)
HR prevalent HF (95% CI)	N/A	N/A	1.00 (0.71-1.42)	1.21 (0.99-1.58)	1.03 (0.77-1.36)	0.93 (0.66-1.30)	0.95 (0.71-1.28)	NR	NR	0.75 (0.48-1.19)	NR	NR

TZD; thiazolidinedione, DPP-4 I; dipeptidyl peptidase-4 inhibitor, GLP-1 RA; glucagon-like peptide-1 analogue, SGLT2-i; sodium glucose co-transporter - 2 inhibitor, HF; heart failure.
**14% (1305) NYHA class II and III; 18% (1667) NYHA class I-III*
† Mean

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