

Heart Failure in Patients with Diabetes Mellitus

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Abstract

Diabetes and heart failure are closely related: patients with diabetes have an increased risk of developing heart failure and those with heart failure are at higher risk of developing diabetes. Furthermore, antidiabetic medications increase the risk of mortality and hospitalisation for heart failure in patients with and without pre-existing heart failure. When the two diseases are considered individually, heart failure has a much poorer prognosis than diabetes mellitus; therefore heart failure has to be a priority for treatment in patients presenting with the two conditions, and the diabetic patient with heart failure should be managed by the heart failure team. No specific randomised clinical trials have been conducted to test the effect of cardiovascular drugs in diabetic patients with heart failure, but a wealth of evidence suggests that all interventions effective at improving prognosis in patients with heart failure are equally beneficial in patients with and without diabetes. The negative effect of glucose-lowering agents in patients with heart failure or at increased risk of heart failure has become evident after the withdrawal of rosiglitazone, a thiazolidinedione, from the EU market due to evidence of increased risk of cardiovascular events and hospitalisations for heart failure. An important issue that remains unresolved is the optimal target level of glycated haemoglobin, as recent studies have demonstrated significant reductions in total mortality, morbidity and risk of heart failure despite achieving HbA1c levels similar to those observed in the UKPDS study conducted some decades ago. Meta-analyses showed that intensive glucose lowering is not associated with any significant reduction in cardiovascular risk but conversely results in a significant increase in heart failure risk. Different medications have different risk: benefit ratios in diabetic patients with heart failure; therefore, the heart failure team must judge the required intensity of glycaemic control, the type and dose of glucose lowering agents and any change in glucose-lowering therapy, according to the clinical conditions present.

Keywords

Heart failure, diabetes, mortality, glucose lowering agents, glycated haemoglobin

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Diabetes mellitus is highly prevalent amongst patients with heart failure, especially those with heart failure and preserved ejection fraction (HFpEF), and patients with the two conditions have a higher risk of mortality compared with patients without diabetes or heart failure.^{1–3} Diabetic patients have an increased risk of developing heart failure because of the abnormal cardiac handling of glucose and free fatty acids (FFAs), and because of the effect of the metabolic derangements of diabetes on the cardiovascular system. Furthermore, the metabolic risk of diabetes in heart failure is heightened by the effect of most anti-diabetic medications, as the use of certain anti-diabetic agents increase the risk of mortality and hospitalisation for heart failure both in patients with and without heart failure.⁴ This effect may be related to a direct effect of the glucose-lowering molecules on the cardiovascular system and/or to a negative effect of excessive glucose lowering, since lenient glycaemic control with newer therapeutic agents has shown to reduce significantly mortality, morbidity and risk of developing heart failure in diabetic patients with proven cardiovascular disease.⁵

A wealth of epidemiological evidence demonstrates that diabetes mellitus 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.^{1–3,6} Heart failure is highly prevalent (25 % in chronic heart failure and up to 40 % in acute heart failure) in patients with diabetes mellitus. Its prevalence is four-times higher than that of the general population, suggesting a pathogenetic role of diabetes in heart failure. This pathogenetic role is also suggested by the fact that patients with diabetes and without heart failure have an increased risk of developing heart failure compared with a matched population (29 versus 18 %, respectively).

In patients with diabetes mellitus, advanced age, duration of the disease, insulin use, presence of coronary artery disease and elevated serum creatinine are all independent risk factors for the development of heart failure.⁷

When the two diseases are considered individually, heart failure has a much poorer prognosis than diabetes mellitus, therefore heart failure has to be a priority for treatment in patients presenting with the two conditions, and the diabetic patient with heart failure should be managed by the heart failure team. This review will focus on the relationship between heart failure and type 2 diabetes mellitus.

Mechanisms of Cardiac Dysfunction in Diabetes Mellitus

The altered systemic and cardiac glucose metabolism of patients with the range of disease that go from impaired glucose control to diabetes mellitus contribute to the structural and functional abnormalities of the heart that culminate in cardiac dysfunction. In diabetic patients, heart failure develops not only because of the underlying coronary artery disease, but also because of the multiple pathophysiological and metabolic abnormalities induced by altered glucose metabolism.⁸ The impaired cardiac glucose metabolism and the switch of glucose to FFA oxidation that occurs in the diabetic heart has a significant negative effect on cardiac contractility and functioning thereby inducing left ventricular systolic and diastolic dysfunction even in the absence of coronary artery disease (CAD) or structured heart disease.^{9,10} The alteration of cardiac function in diabetics occurs through several different mechanisms, such as decreased glucose transport and carbohydrate oxidation, increase in FFA utilisation, decrease in sarcolemmal calcium transport, and alterations in myofibrillar regulatory contractile proteins. Cardiac glucose metabolism is compromised at several points in patients with diabetes mellitus: glucose uptake, glycolysis and intramitochondrial pyruvate oxidation. The reduction in the glucose uptake is due to the slow rate of glucose transport across the sarcolemmal membrane into the myocardium, secondary to a reduction in the myocardial concentration of glucose transporter type 1 (GLUT 1) and glucose transporter type 4 (GLUT 4). Patients with diabetes mellitus have higher plasma levels and myocardial uptake of FFA. High levels of circulating FFAs and their increased oxidation are primarily responsible for the inhibition of both glycolysis and glucose oxidation in the heart. Although the shift of cardiac energy substrate utilisation from glucose to FFA oxidation, occurring in the diabetic heart, is essential to ensure continuous adenosine triphosphate (ATP) generation to maintain heart function, this chronically maladaptation leads to decreased energetic reserves and cardiac efficiency. Indeed, diabetic hearts are characterised by a diminished production of high-energy phosphate, since the beta-oxidation of FFA is less efficient than the glycolysis in generating energy (in relation to oxygen consumption) and may increase the risk of cardiac dysfunction during increased metabolic demands or ischaemia.^{9,10}

Hyperglycaemia and insulin resistance also contribute to the development of heart failure through several different mechanisms acting independently and synergistically; such as impaired microvascular endothelial function, abnormal cardiac metabolism (shift myocardial utilisation of glucose toward less efficient fatty acid oxidation), increased myocardial fibrosis, increased oxidative stress and local activation of the renin-angiotensin system and sympathetic nervous system.^{9,10}

Diabetes in Patients with Heart Failure

Both population studies and clinical trials have demonstrated that diabetes mellitus significantly increases the risk of recurrent hospitalisations for heart failure and the duration of hospital stay in patients with heart failure, and it is associated with a significantly higher mortality compared with those without diabetes.¹¹

In the Candesartan in Heart failure – Assessment of Reduction in Mortality and Morbidity (CHARM) programme the presence of diabetes mellitus was associated with a twofold increase of either death or the composite outcome of cardiovascular death or hospitalisation for heart failure in insulin users, and a 50 % increase risk in non-insulin-treated diabetics.³

Diabetic patients with both reduced and preserved left ventricular ejection fraction show increased mortality and morbidity rates compared with patients without diabetes. This increased risk is also observed in those diabetic patients of either ischaemic or non-ischaemic origin. Of interest, the prognostic importance of diabetes mellitus becomes weaker in hospitalised patients for acute heart failure; suggesting that in these patients the prognosis depends more on the severity of cardiac decompensation rather than on metabolic abnormalities.

The Treatment of Heart Failure in Diabetics

No randomised clinical trials have been conducted to test the effect of cardiovascular interventions (drugs and/or devices) in diabetic patients with heart failure. However, abundant evidence suggests that all interventions effective at improving prognosis in patients with heart failure are equally beneficial in patients with and without diabetes.¹²

Beta-blockers and angiotensin-converting enzyme inhibitors are beneficial in patients with diabetes mellitus and their use is associated with reduced mortality and hospitalisations. Angiotensin II receptor blockers have shown similar efficacy in heart failure patients with and without diabetes.

Although non-selective beta-blockers may have a negative effect on glycaemic control and increase the risk of future diabetes, and these effects may be less frequent with the more selective agents like bisoprolol, carvedilol and nebivolol, there is no reason to suggest a preferential use of a beta-blocker over another on the basis of the possible negative effect on glucose control. Despite a clear benefit of beta-blockers in heart failure patients with diabetes, these patients are still less likely to be discharged from hospital on a beta-blocker than non-diabetic patients with heart failure.¹²

Mineralocorticoid receptor antagonists are equally effective in patients with heart failure with and without diabetes mellitus. However, because of the frequent coexistence of diabetic nephropathy, a close surveillance of electrolyte and renal function is recommended in order to exclude hyperkalaemia. The two most recent drugs introduced in heart failure treatment, LCZ696 and ivabradine, are similarly effective in heart failure patients with and without diabetes, and should be implemented as suggested by the guidelines of the European Society of Cardiology/Heart Failure Association.¹²

Anti-diabetic Treatment in Patients with Diabetes and Heart Failure

Glucose-lowering agents are known to increase the risk of cardiovascular events especially when a tight glycaemic control is pursued. Although initially linked to ischaemic heart disease, the negative effect of glucose-lowering agents in patients with heart failure or at increased risk of heart failure has become evident after rosiglitazone, a thiazolidinedione, was withdrawn from the EU market because of the evidence of increased risk of cardiovascular events.¹³ Despite the focus being mainly put on the risk of coronary events, it was evident even from the rosiglitazone saga that the most significant risk with the use of this drug(s) was related to heart failure.

Glucose-lowering agents may favour the development of heart failure through several pathophysiological mechanisms related to the increased insulin levels, water retention and low glucose availability for the heart and muscles. The potential detrimental

effect of the glucose-lowering drugs cannot be dissected by the negative effect of excessive glucose lowering in diabetics. After the United Kingdom Prospective Diabetes Study (UKPDS) the majority of studies in diabetic patients aimed at glycated haemoglobin 1c (HbA1c) <7.5 % or even <7 %, and invariably reported an increased risk of cardiovascular events most often related to heart failure.^{1,14–18} Therefore, an important issue that is still unsolved is the target level of glycated haemoglobin that should be regarded as optimal – the recent Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG) showed a significant reduction in total mortality, morbidity and risk of heart failure despite the achieved HbA1c which was 7.8 %.⁵

A meta-analysis of 13 studies including 34,533 patients showed that intensive glucose lowering is not associated with any significant reduction in cardiovascular risk but conversely results in a 47 % increase in risk of heart failure ($P < 0.001$).¹⁹ A study conducted in a large cohort of heart failure patients with diabetes mellitus showed a U-shaped relationship between HbA1c and mortality, with the lowest risk in patients with moderate glycaemic control (HbA1c 7.1–8.0 %).¹⁴ These results are in agreement with the findings of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, which demonstrated an increase of 21 % in the risk of death from all causes and of 35 % in the occurrence of cardiovascular death with tight control of glucose in patients with diabetes mellitus.²⁰ The importance of hypoglycaemia has also been highlighted by the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) that found a 38 % increased risk of a poorer outcome among patients with hypoglycaemia complicating heart failure post-myocardial infarction (MI).²¹

The glucose-lowering treatment should be carefully evaluated and gradually implemented in diabetic patients with heart failure. Preference in the treatment of diabetic patients with heart failure should be given to metformin and empagliflozin that have shown to be safe and effective.^{5,22,23} Metformin is excreted through the kidney, therefore caution should be exerted in patients with impaired renal function and its use is contraindicated only in patients with severe renal or hepatic impairment. Sulphonylureas may frequently cause hypoglycaemia, although this risk is minimised by the slow release formulations. An increased risk of worsening heart failure has been reported with sulphonylureas in cohort studies including diabetic patients but has never been reported by randomised clinical trials.⁴ These drugs should be used with caution in diabetic patients with heart failure.¹²

Mitiglinides may induce water retention and should be used with caution in patients with heart failure. Alpha-glucosidase inhibitors like acarbose lack any effect on insulin, water and sodium retention, and are safe to use in patients with increased cardiovascular risk and in those with heart failure.

Thiazolidinediones are associated with increased sodium and fluid retention, and increase sympathetic nervous system activity. Randomised clinical trials and meta-analyses have shown that thiazolidinediones increase the risk of heart failure worsening and hospitalisations from heart failure, and they are contraindicated in patients with heart failure.¹³

Dipeptidyl peptidase-4 inhibitors (DPP4is; gliptins) are trendy drugs for the control of glycaemia in patients with diabetes despite their small effect on HbA1c. Large randomised studies with DPP4i have cast doubts about their safety in heart failure showing an increased risk of heart failure hospitalisations, and despite recent data, suggest that they may be safe to use; given their limited clinical benefit and given that there is a lack of data on their effect in patients with heart failure their use is not recommended except under strict cardiology supervision.^{24,25,12,26}

There are no data on the long term safety of glucagon-like peptide-1 (GLP-1) receptor agonists in patients with heart failure. Recently, liraglutide was tested against placebo in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial and showed a significant reduction in the composite primary outcome of the first occurrence of cardiovascular death, non-fatal MI or non-fatal stroke, but no effect on heart failure endpoints. Given the absence of detailed data in patients with heart failure, the use of GLP-1 receptor agonists should be implemented only under strict cardiology supervision.

The sodium-glucose cotransporter 2 inhibitors (SGLT2i) enhance glucose control by increasing the urinary excretion of glucose. Recently, the SGLT2i empagliflozin showed a significant and relevant effect on cardiovascular protection.⁵ The EMPA-REG OUTCOME study conducted in 7,020 patients with type 2 diabetes (glycated haemoglobin level, 7.0–10.0 %) at high risk for cardiovascular events followed for a median of 3.1 years has shown that empagliflozin use led to a significant reduction in the rates of death from cardiovascular causes (38 % relative risk reduction), hospitalisation for heart failure (35 % relative risk reduction) and death from any cause (32 % relative reduction). Empagliflozin reduced by 39 % the hospitalisations for or death from heart failure (2.8 versus 4.5 %; HR 0.61 [0.47–0.79]; $P < 0.001$) and was associated with a reduction in all-cause hospitalisation (36.8 versus 39.6 %; HR 0.89 [0.82–0.96]; $P = 0.003$). The mechanisms responsible for the effects of empagliflozin on cardiovascular endpoints and heart failure are largely unknown. Potential mechanisms to be proven include effect on sodium retention and plasma volume, osmotic diuresis, reduction of insulin levels and insulin response to food intake, modulation of the renin-angiotensin aldosterone system, reduction weight and blood pressure without increases in sympathetic nervous activity.

Insulin is often required for the glucose control of diabetic patients with type 1 diabetes, and of some patients with type 2 diabetes and pancreatic islet beta cell exhaustion. Since insulin induces significant sodium retention precipitating worsening of heart failure, the change in dose, schedule of administration and type of insulin used must be constantly supervised by a cardiologist in patients with chronic heart failure.

Therefore, the heart failure team according to the clinical conditions should make the judgement on the intensity of glycaemic control, the type and dose of glucose-lowering agents, and any change in the glucose-lowering therapy should be closely monitored. ■

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