The Management of Diabetic Patients with Heart Failure

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Introduction

Patients with diabetes mellitus have an increased risk of developing heart failure and diabetes mellitus is highly prevalent amongst patients with heart failure, especially those with HFP EF. Diabetic patients with heart failure have an increased mortality and an increased risk of hospitalisations and the use of certain anti-diabetic agents increase the risk of mortality and hospitalisation in heart failure. Conversely, newer therapeutic agents have shown a significant reduction of mortality, morbidity and risk of developing heart failure in diabetic patients with proven cardiovascular disease. This highly important area is reviewed in this paper.

Abstract

Patients with diabetes mellitus have an increased risk of developing heart failure and diabetes mellitus is highly prevalent amongst patients with heart failure, especially those with HFP EF. Diabetic patients with heart failure have an increased mortality and an increased risk of hospitalisations and the use of certain anti-diabetic agents increase the risk of mortality and hospitalisation in heart failure. Conversely, newer therapeutic agents have shown a significant reduction of mortality, morbidity and risk of developing heart failure in diabetic patients with proven cardiovascular disease.

Epidemiological evidence clearly shows that diabetes mellitus is independently associated with the risk of developing HF. This risk increases by more than two-folds in men and by five-fold in women.[6] In patients with diabetes mellitus the prevalence of HF is reported to be up to 25%, which is 4 times higher than that observed in the general population. The prevalence of diabetes mellitus is even higher in acute heart failure where it reaches 40%. The complex relationship between diabetes mellitus and heart failure is shown by the fact that patients with heart failure and without diabetes have an increased risk of developing heart failure diabetes compared to a matched population (29% vs 18% respectively).[1–3,6]

A meta-analysis of 21 studies including 1,111,569 patients including 507,637 with diabetes mellitus showed that age, diabetes duration, insulin use, ischaemic heart disease, and elevated serum creatinine are independent risk factors for the development of heart failure in diabetics.[7] The relationship between diabetes mellitus and heart failure is not just the result of the sum of the parts since each condition adversely affects the natural course of the other and results in a poorer prognosis than with either disease alone. Since heart failure has a much poorer prognosis than diabetes mellitus is has to be a priority for treatment in patients presenting with the two morbidities.

Altered glucose metabolism of patients with impaired glucose control and diabetes mellitus contribute to structural and functional abnormalities of the heart, culminating in cardiac dysfunction and ultimately CHF, not only via coronary artery disease (CAD), for which altered glucose metabolism is a major and independent risk factor, but also via other multiple pathophysiologic and metabolic abnormalities.[8] Impaired cardiac glucose metabolism has a significant negative effect on cardiac contractility and functioning thereby inducing left ventricular systolic and diastolic dysfunction even in absence of CAD or structural heart disease.[9–10]
The SOLVD trial showed that diabetic patients had higher all-cause and cardiovascular mortality compared to non-diabetic patients. Subsequently, both population studies and clinical trials have demonstrated that diabetes mellitus significantly increases the risk of recurrent HF hospitalizations and hospital stay in patients with heart failure and it is associated with a significantly higher mortality compared to those without diabetes.[11] Diabetes mellitus was the most relevant co-morbidity affecting prognosis of patients with heart failure in the Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity (CHARM) program. In this study the presence of diabetes mellitus was associated with an approximate 2-fold increase of either death or the composite outcome of cardiovascular death or hospitalization for heart failure in insulin users, and a 50% increase risk in non-insulin-treated diabetics.[3]

The increased mortality rate of diabetic patients with heart failure is observed in both patients with reduced and preserved left ventricular ejection fraction as well as in patients with heart failure due to either ischaemic or non-ischaemic origin. However, the interaction between diabetes mellitus and outcomes is weaker in hospitalized patient for acute heart failure suggesting that in hospitalized patients the prognosis depends more on the severity of HF de-compensation rather than on the presence of co-morbidities.

Hyperglycemia 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 utilization 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]

The relevance of glucose lowering agents in patients with heart failure and without diabetes mellitus. Because of the frequent occurrence of diabetic nephropathy the possibility of hyperkalaemia should always be considered and a close surveillance of electrolyte and renal function is recommended. LCZ696, and Ivabradine have been shown to be similarly effective in heart failure patients with and without diabetes. Although non-selective beta blockers may have a negative affect on glycaemic control and increase the risk of future diabetes, these effects should be less frequent with the more selective agents such as bisoprolol, carvedilol and nebivolol.

Glucose lowering treatment in patients with diabetes and HF
The relevance 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 and the USA market because of the evidence of increased risk of cardiovascular events.[13] Although, most of the meta-analyses and the regulatory agencies focused mainly on the risk of coronary events, it was evident that the most significant risk with the use of this drug(s) was related to heart failure.

While the efficacy and safety of the cardiovascular drugs for the treatment of heart failure in diabetic patients are well known those of glucose lowering therapies is uncertain, potentially harmful and not adequately evaluated for most drug classes.[4] Also, the adequate level of glucose control in diabetic patients with heart failure is under debate but higher levels of Hba1c should be recommended for diabetic patients with heart failure.[12] This evidence comes from robust subgroup analyses of the large randomised controlled trials conducted in patients with heart failure in which usually at least 30% of diabetic patients have been enrolled. Beta-blockers and Angiotensin-converting Enzyme Inhibitors are beneficial in patients with diabetes 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 affect on glycaemic control and increase the risk of future diabetes, these effects should be less frequent with the more selective agents such as bisoprolol, carvedilol and nebivolol. There is no reason from the major trials, however, to suggest a preferential use of a beta blocker over another on the basis of the possible negative effect on glucose control. Despite these findings, diabetic patients are still less likely to be discharged from hospital on a β-blocker than non-diabetic patients with HF.[12] Mineralocorticoid receptor antagonists reduce the risk of hospitalization and premature death and they are equally effective in patients with heart failure with and without diabetes mellitus. Because of the frequent occurrence of diabetic nephropathy the possibility of hyperkalaemia should always be considered and a close surveillance of electrolyte and renal function is recommended. LCZ696, and Ivabradine have been shown to be similarly effective in heart failure patients with and without diabetes and should be implemented as appropriate.[12]
One important point in diabetic patients with heart failure but relevant to all patients with dys-glycaemia is the target level of glycated haemoglobin that should be regarded as optimal. From the publication of the UKPDS study onwards almost all studies targeting HbA1c levels <7.5% failed to show a cardiovascular benefit and often demonstrated an increased risk of cardiovascular mortality and morbidity, most often related to heart failure.[1,14–18] In patients with heart failure and co-existing diabetes mellitus maintenance of adequate glycaemic control is a critical issue not only because of the relationship between glucose levels, heart function and outcomes but also because the choice of drugs available to safely manage glucose management in patients with heart failure is limited.[8,9]

A meta-analysis of 13 high quality studies on 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 HF risk (P<0.001).[19] More recently, a study conducted in a large cohort of heart failure patients with T2DM showed a U-shaped relationship between HbA1c and mortality, with the lowest risk in patients with moderate glycemic control (HbA1c 7.1–8.0%) and those treated with insulin sensitizers. Of interest the U-shaped relationship between glucose control and events seems to be present in drug-treated but not in diet-treated diabetic patients.[14]

These findings concur with the results of the ACCORD study, which demonstrated that very tight control of glucose in patients with diabetes mellitus increases by 22% the risk of death from all causes and by 35% the occurrence of cardiovascular death. [20] The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) also found a 38% increased risk of a poorer outcome among patients with hypoglycaemia complicating HF post-MI.[21] In diabetic patients with heart failure a clear difference in the occurrence of adverse outcomes seems also to be related to the type of anti-diabetic medications as patients on drugs with a low risk of hypoglycaemia seem to have a better prognosis than those on medications known to be associated with a high risk of hypoglycaemia risk (secretagogues or insulin).[4,14]

**Treatment of diabetes in patients with heart failure**

The treatment of elevated glucose plasma levels should be carefully evaluated and gradually implemented in diabetic patients with heart failure. In the early stages of diabetes mellitus and throughout patient life preference should be given to metformin that has been shown to be safe and effective.[22,23] Since metformin is excreted though the kidney caution should be exerted in patients with impaired renal function while its use is contraindicated only in patients with severe renal or hepatic impairment. As mentioned above, sulphonylurea derivatives may more frequently induce hypoglycaemia, although this risk is minimised by slow release formulations. An increased risk of worsening heart failure has been reported with sulphonylureas in diabetic patients but has never been proven in prospective randomised clinical trials.[4] Therefore, sulphonylureas should be used with caution in diabetic patients with heart failure.[22]

Metiglinides have a mechanism of action similar to that of sulphonylureas as they bind to an ATP-dependent K+ channel on the membrane of pancreatic beta cells, albeit with a weaker affinity. Because of their effect on insulin secretion, these drugs may induce water retention and should be used with caution in patients with heart failure.

Alpha glucosidase-inhibitors, such as acarbose, inhibit the intestinal alpha glucosidase, an enzyme that releases glucose from larger carbohydrates. Acarbose reduces the rate of digestion of complex carbohydrates and therefore the absorption of glucose, because the carbohydrates are not broken down into glucose molecules. Given the lack of any effect on insulin and water and Na retention, Acarbose is safe to use in patients with increased cardiovascular risk and in those with heart failure.

Thiazolidinediones are a class of drugs that act by activating PPARs (peroxisome proliferator-activated receptors), a group of nuclear receptors, with greatest specificity for PPARγ. These drugs increase the transcription of a number of specific genes and decrease that of others. Their main effect of is a decrease in the amount of free fatty acids present in circulation associated with an increase in the storage of fatty acids in adipocytes and an increased oxidation of carbohydrates. These drugs are associated with an increased fluid retention that results from a reduction in renal excretion of sodium. Furthermore, Thiazolidinediones increase sympathetic nervous system activity, that increases the risk of events in patients with heart failure. Indeed, randomised clinical trials and meta-analyses have shown that Thiazolidinediones increase the risk of heart failure worsening and hospitalisation from heart failure and they are contraindicated in patients with heart failure.[13]

Dipeptidylpeptidase-4 inhibitors (DPP4is; gliptins) and glucagon-like peptide 1 (GLP-1) receptor agonists, are popular drugs for the control of glycaemia in patients with diabetes and they are
widely used despite their effect on HbA1c being relatively modest. These drugs increase incretin (DPP4i) or act as incretin mimetics, thereby improving glycaemic indices. Studies with DPP4i’s have cast doubts about their safety in heart failure since earlier studies have shown an increased risk of heart failure in diabetic patients. [24,25] More recent data suggest that they may be safe to use but 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. [12,26]

Scanty data exist on the long-term safety of GLP1 receptor agonists and no data in patients with heart failure are available. Recently Liraglutide was studied against placebo in the LEADER trial for a period of up to 5 years in more than 9,000 adults with type 2 diabetes at high cardiovascular risk. The trial showed that liraglutide treatment led to a significant reduction in the composite primary outcome of the first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. Given the absence of detailed data in patients with heart failure, the use of liraglutide (as of all GLP1 receptor agonists) should be implemented only under strict cardiology supervision.

The sodium/glucose co-transporter 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.[27] The EMPA-REG OUTCOMEN study conducted in 7020 patients with type 2 diabetes (glycated hemoglobin level, 7.0 to 10.0%) and at high risk for cardiovascular events and 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), hospitalization for heart failure (35% relative risk reduction), and death from any cause (32% relative reduction). Consistent effects of empagliflozin were observed across all pre-defined subgroups including patients with and without heart failure. A consistent effect of empagliflozin was observed across all drug classes used for the treatment of diabetes and/or heart failure. Of notable importance for patients with heart failure, empagliflozin reduced by 39% the rate of hospitalizations for, or death from heart failure [2.8 vs. 4.5%; HR: 0.61 (0.47–0.79); P < 0.001] and was associated with a reduction in all-cause hospitalization [36.8 vs. 39.6%; HR: 0.89 (0.82–0.96); P = 0.003].

Empagliflozin is the first glucose-lowering agent that had been shown to improve heart failure outcomes in patients with type 2 diabetes and in diabetic patients with heart failure. The mechanisms responsible for the effects of empagliflozin on cardiovascular end-points and heart failure are largely unknown. Potential mechanisms to be proven include an 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 in body weight and blood pressure without increases in sympathetic nervous activity. It is possible that the effect of empagliflozin are shared by the drugs in the same class. However, given the recent reports of non-cardiac adverse events with other SGLT2i that had not been observed with empagliflozin and, in the absence of evidence with drugs with similar mechanism of action, the results obtained with empagliflozin cannot be translated to the class of SGLT2i’s.

The safety of the different oral hypoglycaemic options in diabetic HF patients is summarised in Table 1. 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 it can precipitate worsening of heart failure. Although, insulin use in acute patients with heart failure seems safe, in long-term treatment changes in dose, scheduling of administration and the type of insulin used should be constantly supervised by a cardiologist in patients with chronic heart failure to avoid adverse HF-related outcomes. Therefore, the heart failure team according to the clinical conditions should be involved in decisions 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.

Declaration of Interest
The author declares no conflicts of interest.

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