Diabetes and heart failure

Introduction

Heart failure is one of the most common initial presentations of cardiovascular disease in type 2 diabetes. Diabetes is independently associated with the risk of developing heart failure, such that in comparison with individuals without diabetes, the risk is increased more than two-fold in men and more than five-fold in women. The prevalence of heart failure in diabetes is four-fold higher than that in the general population, suggesting that diabetes plays a pathogenic role in the development of the disease and the risk increases with age, duration of diabetes, insulin use, presence of coronary artery disease and elevated serum creatinine.

Patients with diabetes have a 33% greater risk of hospitalisation for heart failure, and the prognosis is extremely poor. Median survival among patients with diabetes and ischaemic heart failure is approximately four years.

KEY MESSAGES

- Heart failure is a common macrovascular complication of type 2 diabetes and is associated with a poor prognosis
- In patients without diabetes, heart failure increases the risk of incident type 2 diabetes
- Both hyperglycaemia and hyperinsulinaemia are associated with increased risk of heart failure
- Of the antidiabetic medications, only metformin and sodium glucose cotransporter-2 (SGLT2) inhibitors have a mechanism of action that is independent of insulin
- In patients with type 2 diabetes at high risk for, or with established cardiovascular disease, SGLT2 inhibitors have been shown to reduce hospitalisation for heart failure.
Pathophysiology of heart failure in diabetes

In patients with diabetes, for every 1% increase in HbA1c, the risk of heart failure increases by approximately 17-20%. However, hyperglycaemia is not the only risk factor for cardiac pathology. Diabetic cardiomyopathy (DCM) was first described nearly 50 years ago based on post-mortem observations of left ventricular (LV) hypertrophy associated with myocardial fibrosis in patients with diabetes and heart failure, but no coronary artery disease or other aetiological conditions to account for heart failure. Subsequently, DCM was defined as the existence of LV dysfunction in diabetic patients without coronary artery disease, hypertension or other potential aetiological conditions to account for heart failure. Subsequently, DCM was defined as the existence of LV dysfunction in diabetic patients without coronary artery disease, hypertension or other potential aetiological conditions. Diabetes has been shown to be associated with an array of pathological mechanisms that lead directly to myocardial fibrosis, myocardial steatosis and increased myocardial cell death (necrosis and apoptosis) (Table 1). In turn, this results in LV remodelling and hypertrophy, longitudinal and radial systolic impairment, alteration of contractile reserve, diastolic dysfunction and overt heart failure.

Advanced glycation end-products activate dendritic cells and upregulate hypertrophy-associated genes in cardiac cells and may be responsible for the hypertrophic and fibrotic heart failure phenotype in individuals with diabetes.

Table 1. Pathological factors associated with DCM

<table>
<thead>
<tr>
<th>Pathological factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired calcium homeostasis</td>
</tr>
<tr>
<td>Alteration of substrates utilisation (increase in lipid use, decrease in glucose oxidation)</td>
</tr>
<tr>
<td>Lipotoxicity</td>
</tr>
<tr>
<td>Glucotoxicity with intervention of advanced glycation end-products</td>
</tr>
<tr>
<td>Mitochondrial dysfunction</td>
</tr>
<tr>
<td>Increased oxidative stress and accumulation of reactive oxygen species affect coronary circulation and cause myocardial hypertrophy and fibrosis</td>
</tr>
<tr>
<td>Increased myocardial levels of cardiotoxic inflammatory cytokines (e.g. tumour necrosis factor α, interleukins)</td>
</tr>
<tr>
<td>Renin-angiotensin-aldosterone system (RAAS) activation</td>
</tr>
<tr>
<td>Cardiac dysautonomy</td>
</tr>
<tr>
<td>Impaired phosphatidylinositol 3-kinases due to hyperinsulinaemia precipitate myocardial dysfunction</td>
</tr>
<tr>
<td>Diabetes increases the risk of other risk factors for heart failure, including coronary artery disease, chronic kidney disease and hypertension.</td>
</tr>
</tbody>
</table>

Furthermore, there appears to be a bidirectional relationship between diabetes and heart failure, in that heart failure itself precipitates the progression of diabetes. In a retrospective analysis of data from the prospective Cardiovascular Health Study among elderly subjects (age ≥65 years) with normal fasting glucose at baseline, the presence of heart failure at baseline was associated with increased odds of developing impaired fasting plasma glucose (odds ratio [OR] 2.18) or overt diabetes (OR 4.78) after 3-4 years. The association between heart failure and worsening diabetes status remained significant after adjustment for age, gender and cardiovascular comorbidities. The risk of developing diabetes may be directly proportional to the severity of heart failure (measured by loop diuretic dose requirements), and there is limited evidence to suggest that improvements in heart failure treatment (e.g. use of RAAS blockers, ventricular assistance devices) may result in better glycaemic control and improvements in the course of diabetes.
There are several postulated mechanisms to account for the relationship between heart failure status and worsening diabetes (Table 2).

<table>
<thead>
<tr>
<th>Table 2. Proposed mechanisms to explain how heart failure might contribute to risk of impaired glucose tolerance and diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increased blood glucose due to increased levels of cortisol and catecholamines</td>
</tr>
<tr>
<td>• Stimulation of gluconeogenesis and glycogenolysis by sympathetic activation</td>
</tr>
<tr>
<td>• Increased catecholamines increase insulin resistance, thereby stimulating pancreatic insulin release</td>
</tr>
<tr>
<td>• Low-grade chronic inflammation (e.g. tumour necrosis factor α, interleukins)</td>
</tr>
<tr>
<td>• Metabolic effects of medication (e.g. diuretics, beta-blockers)</td>
</tr>
<tr>
<td>• Hypoperfusion and congestion of liver and pancreas</td>
</tr>
<tr>
<td>• Decreased physical activity.</td>
</tr>
</tbody>
</table>

It is clear that the relationship between diabetes and heart failure is complex. Without detailed biomarker information on both diseases, it is difficult to discriminate between the pathologies, and whether impaired glucose metabolism leads to worsening heart failure or, conversely, whether worse heart failure status is responsible for greater impairment of glucose metabolism.

**Management of hyperglycaemia in patients with diabetes and heart failure**

Only a few diabetes treatments have specifically been studied in patients with heart failure. However, tighter glycaemic control (i.e. lower HbA1c) has not been shown to decrease the risk of either fatal or non-fatal heart failure-related events. Both glucose and insulin are toxic to the cardiac myocyte and consequently the choice of therapy to improve glucose metabolism in patients with diabetes and heart failure needs to be carefully considered. At a minimum, therapy should not increase the risk of worsening heart failure.

Potentiation of insulin signalling has been shown to contribute to heart failure in type 2 diabetes regardless of glycaemic control. Insulin receptors are abundant in the heart, vasculature, kidneys and adipose tissue. Stimulation by insulin results in activation of intracellular pathways leading to pathological cardiac hypertrophy, remodelling, inflammation and fibrosis; as well as endothelial dysfunction in the vasculature and vascular smooth muscle cell hyperplasia. Insulin increases sodium reabsorption in the proximal and distal tubules of the kidney, promotes the actions of angiotensin II, inhibits the effects of endogenous natriuretic peptides and directly increases the activity of numerous ion transport mechanisms in the renal tubules. Insulin promotes adipogenesis and accumulation and dysfunction of epicardial adipose tissue, causing production of inflammatory cytokines which promote cardiac fibrosis and impaired ventricular function.

The majority of antihyperglycaemic drugs exert their effects by stimulating the release or potentiating the actions of insulin, and treatments that increase insulin signalling increase the risk of heart failure. Insulin use is independently associated with an increased risk of heart failure. Sulphonylureas, which are insulin secretagogues, and thiazolidinediones, which promote insulin signalling by increasing the sensitivity of tissues to its metabolic actions, have both been shown to increase the risk of heart failure in randomised controlled clinical trials. Incretin-based drugs, the dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, stimulate release of insulin from pancreatic beta-cells by potentiating the actions of GLP-1. Members of both of these classes of drugs have been associated with adverse remodelling and
worsening instability of heart failure in patients with type 2 diabetes.13-17

Only two classes of antidiabetic medication, metformin and the sodium glucose cotransporter type 2 (SGLT2) inhibitors, reduce glycaemia by mechanisms that are independent of insulin. Metformin is recommended as first-line pharmacotherapy for patients with type 2 diabetes and is also first-line treatment of choice in those with heart failure.15,18 It is safe and effective in heart failure with preserved or reduced ejection fraction. Retrospective analysis of data in a large population-based cohort study showed that, in comparison to monotherapy with a sulphonylurea, metformin alone, or in combination with a sulphonylurea, was associated with significantly fewer deaths at one year and over long-term follow-up.19 Metformin is contraindicated in patients with severe hepatic or renal impairment.15

Large randomised clinical studies have shown a consistent association between SGLT2 inhibitors and reduced hospitalisation for heart failure in diabetic patients with prior cardiovascular events or at high cardiovascular risk.20-22 In the prospective, randomised EMPA-REG OUTCOME (Empagliflozin, Cardiovascular outcomes, and mortality in Type 2 Diabetes) trial, treatment with empagliflozin was associated with a statistically significant 14% reduction in the primary outcome, a composite of death from cardiovascular causes, nonfatal myocardial infarction (MI) (excluding silent MI) or nonfatal stroke.20 Rates of MI and stroke did not differ between groups, but in comparison with placebo, death from cardiovascular causes, hospitalisation for heart failure and all-cause mortality were reduced by 38%, 35% and 32%, respectively, in the empagliflozin group.

Similar results were observed in the Canagliflozin Cardiovascular Assessment (CANVAS) programme, in which the primary outcome, comprising a composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke, was significantly reduced by 14% in patients randomised to treatment with canagliflozin.21 Hospitalisation for heart failure was reduced by 33%. In both EMPA-REG OUTCOME and CANVAS, patients had a history of atherosclerotic cardiovascular disease or were at high cardiovascular risk at baseline; hospitalisation for heart failure was a predefined exploratory endpoint.21,23

DECLARE-TIMI 58 was a randomised, double-blind, multinational, placebo-controlled phase 3 study in which 17 160 patients with type 2 diabetes and established atherosclerotic cardiovascular disease (secondary prevention: n=6,974) or multiple cardiovascular risk factors (primary prevention: n=10,186) were randomised to dapagliflozin 10mg daily or placebo in addition to treatment as usual.22 The principle primary outcome was to demonstrate the safety of dapagliflozin with respect to major adverse cardiovascular events (MACE: CV death, MI or ischaemic stroke). The rate of MACE was similar in the placebo and dapagliflozin groups, with dapagliflozin meeting the prespecified criteria for noninferiority (P<0.001). Another prespecified primary endpoint was the incidence of cardiovascular death or hospitalisation for heart failure. This was significantly lower in the dapagliflozin group (hazard ratio [HR] 0.83; 95% CI 0.73-0.95), primarily consequent to a lower rate of hospitalisation for heart failure (HR 0.73; 95% CI 0.61-0.88), which remained consistent regardless of the presence or absence of heart failure at baseline.

The mechanisms by which SGLT2 inhibitors may reduce incident heart failure are uncertain. A recent in vitro study showed that exposing cardiomyocytes to high glucose concentrations increases SGLT1 and SGLT2 expression more than seven-fold and expression of GLUT1, which encodes the glucose-regulated glucose transporter 1, almost three-fold.24 Upregulation of SGLT is associated with an increase in sodium influx into cardiomyocytes that increases cytosolic calcium loading via the sodium-calcium exchanger. In patients with diabetes, intracellular calcium overload impairs cell relaxation, causes electrical instability increasing the propensity to tachycardia, and activates a calcium-sensitive hypertrophic signalling pathway. When exposed to high glucose, the cells exhibited markedly impaired contractility with reduced cell shortening and relaxation, reduced re-lengthening velocity and marked hypertrophic changes with increased cell size. Exposure to high glucose also increased expression of NPPB, which encodes the brain-type natriuretic peptide (BNP). When the cardiomyocytes were exposed to empagliflozin, despite no change in cell viability or glycolytic capacity, these high glucose-induced abnormalities were attenuated and the expression of the NPPB, SGLT1, SGLT2 and GLUT1

“Only two classes of antidiabetic medication, metformin and the SGLT2 inhibitors, reduce glycaemia by mechanisms that are independent of insulin.”

EARN FREE CPD POINTS

Join our CPD community at www.denovomedica.com and start to earn today!
Diabetes and heart failure

Diabetes and heart failure

Current evidence for benefit of SGLT2 inhibitor therapy is limited to patients at high risk for or with established cardiovascular disease.

genes were restored to normal levels. These effects were associated with improvements in contractility and relaxation, and in the calcium-handling properties of the cardiomyocytes. This suggests that the clinical benefits of SGLT2 inhibitors in heart failure may arise consequent to downregulation of SGLT1, SGLT2 and GLUT1 gene expression, which is associated with improved functionality of cardiomyocytes. Early (but not late) application of empagliflozin also neutralised an increase in production of caspase 3 protein that occurred in response to high glucose levels. Increased caspase 3 protein may predispose cardiomyocytes to an early apoptotic stage.

It is important to note that current evidence for benefit of SGLT2 inhibitor therapy is limited to patients at high risk for or with established cardiovascular disease. Their effect in heart failure is unknown, but studies to investigate these agents’ utility in these patients are ongoing (Table 3).

Table 3. Large randomised controlled clinical trials of SGLT2 inhibitors in patients with heart failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient population</th>
<th>Intervention</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPEROR-Reduced</td>
<td>2 850 patients with HFrEF</td>
<td>Empagliflozin vs placebo</td>
<td>Cardiovascular death or hospitalisation for heart failure</td>
</tr>
<tr>
<td>EMPEROR-Preserved</td>
<td>4 126 patients with HFrEF</td>
<td>Dapagliflozin vs placebo</td>
<td></td>
</tr>
<tr>
<td>DAPA-HF</td>
<td>4 500 patients with HFrEF</td>
<td>Sotagliflozin vs placebo</td>
<td></td>
</tr>
<tr>
<td>Soloist-WHF</td>
<td>4 000 patients with diabetes plus HFrEF or worsening HF</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HFrEF: Heart failure with reduced ejection fraction; HFrEF: Heart failure with preserved ejection fraction; WHF: Worsening heart failure

Heart failure treatments in people with diabetes

In general, patients with diabetes and heart failure should be treated in the same way as those without diabetes. General principles and recommendations relating to heart failure-specific treatments in people with diabetes are listed in Table 4.

Table 4. Treatment of heart failure in diabetes

- There are no randomised controlled clinical studies to test the effect of cardiovascular interventions (drugs and/or devices) in patients with heart failure and diabetes
- All interventions effective at improving prognosis in patients with heart failure are equally beneficial in patients with and without diabetes
- There is no reason to suggest preferential use of one beta-blocker over another on the basis of possible negative effects on glucose control
- Diabetics are less likely to be discharged from hospital on a beta-blocker than non-diabetic patients with heart failure
- When using a mineralocorticoid receptor antagonist, close surveillance of electrolyte and renal function is recommended in order to exclude hyperkalemia
- Sacubitril/valsartan combination therapy is similarly effective in heart failure patients with and without diabetes
- Metformin is recommended if eGFR >30ml/min/1.73m²
- If eGFR is <60ml/min/1.73m², care should be taken when prescribing a RAAS blocker or sacubitril/valsartan
- Thiazolidinediones and saxagliptin should be avoided.
Conclusions

Heart failure and diabetes are intimately related, each conferring a poorer prognosis on the other. However, in patients with type 2 diabetes, careful consideration of the agent to achieve glycaemic control can help prevent incident heart failure.14

SGLT2 inhibitors are the first class of antidiabetic agents to show a consistent reduction in the incidence of hospitalisation for heart failure in patients with type 2 diabetes. Where they are tolerated and affordable, they may be considered second-line therapy in addition to lifestyle modification and metformin in patients with heart failure, atherosclerotic cardiovascular disease and renal disease as well as for primary prevention of macrovascular complications.18

References


13. Packer M. Potentiation of insulin signalling contributes to heart failure in type 2 diabetes. A hypothesis supported by both mechanistic studies and clinical trials. JACC Basic Transl Sci 2018; 3(3): 415-419.


