

# Diabetes mellitus and heart failure: a deadly duo

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Type 2 diabetes mellitus is alarmingly on the rise and is here to stay. There are an estimated 422 million adults living with it worldwide and the increasing prevalence is primarily due to increases in sedentary lifestyle and obesity (1). Patients with diabetes mellitus are at high risk of developing chronic heart failure (CHF) and when these conditions coexist are at a significantly increased risk of death compared to those without diabetes. The Framingham heart study provided the first observational data in 1979 to suggest that there was an increased risk of CHF in patients with diabetes (2). The incidence of heart failure in men and women suffering from diabetes compared to individuals without the disorder was estimated at four times and seven times greater respectively. Our work has demonstrated that at least 25% of patients with CHF secondary to left ventricular (LV) systolic dysfunction have co-existing type 2 diabetes mellitus (3,4). CHF is a serious complication of diabetes; however, it is often overlooked due to the inability to categorise it precisely as either a microvascular or macrovascular complication.

Our work has demonstrated that over the last fifteen years there has been a significant improvement in the survival of patients with CHF (5). This improvement is primarily due to advancing therapeutic approaches with the use of angiotensin-converting enzyme inhibitors, beta-adrenoceptor antagonists, aldosterone antagonists and resynchronisation therapy in selected patients. Despite these improvements, the prognosis for patients with CHF remains poor with outcomes worse than many cancers. The combination

of CHF and diabetes mellitus is deadly. Our group has shown that diabetes doubles the risk of death in an individual with CHF and that it impacts similarly upon mortality in both ischaemic and non-ischaemic CHF (3). Several clinical trials have similarly demonstrated that diabetes is associated with increased mortality in patients with CHF (6-8). Our work has shown that the risk of heart failure related death is doubled and the risk of sudden cardiac death (SCD) was tripled in those with diabetes (3). Unfortunately, SCD in patients with diabetes and CHF is not addressed in the majority of the major guidelines (9). In another study we have shown that those with diabetes have a higher prevalence of co-morbidities, however diabetes was independently associated with increased mortality (10).

In a recent issue of *JACC*, Johansson *et al.* analysed 35,163 patients in the Swedish Heart Failure Registry (SwedeHF) comparing type 2 diabetes mellitus in both ischaemic and non-ischaemic CHF (11). Similar to our work, the authors found that diabetes was associated with higher all-cause mortality regardless whether patients had ischaemic or non-ischaemic CHF (3). The worst outcomes were seen in those with ischaemic heart disease and type 2 diabetes mellitus, especially in those without previously revascularisation. Most patients with non-ischaemic CHF had other comorbidities associated with heart failure.

Heart failure places a huge burden on the healthcare system and is the leading cause of hospitalisation in the United States and Europe (12). Our work has enabled us to derive and validate a model to identify patients with CHF at low risk

of subsequent heart failure hospitalisation (4). In this study we demonstrated that the presence of diabetes in patients with CHF doubles the risk of heart failure hospitalisation. Similarly, results from the CHARM program showed increased rates of hospitalisation in those patients with CHF and diabetes compared to those without diabetes (8). More recently, we have shown that diabetes is associated with features of adverse structural and functional cardiac remodelling in CHF with reduced ejection fraction (10). In this study, diabetes resulted in worse renal function, lower haemoglobin and more symptomatic heart failure. Patients with diabetes also exhibited echocardiographic evidence of increased left ventricular wall thickness. After one year of contemporary evidence-based therapy we found that individuals with diabetes had less beneficial LV remodelling and required larger diuretic doses. This demonstrates that patients with diabetes and CHF have a poorer response to optimal management compared to those without diabetes.

The pathophysiological link between CHF and type 2 diabetes mellitus is complex and multifactorial. It is well recognised that diabetes is associated with hypertension, dyslipidemia and atherosclerosis however further pathophysiologic mechanisms linking the two conditions have been suggested. Our work offers further insight into the impact that diabetes has on CHF suggesting that recognised prognostic factors like age and renal function do not significantly account for the detrimental effect seen with diabetes (3). This leads us to suggest that there is a myocardial process mediating this due to the greater diuretic requirements, poorer functional capacity and increased cardiovascular death associated with diabetes in those patients with CHF (3). The development of heart failure independent of the severity of coronary artery disease has led researchers to suggest 'diabetic cardiomyopathy' may be contributory via glucotoxicity, microvascular dysfunction and altered collagen disposition (13).

Understanding the pathophysiology is key to tailoring therapies to decrease the unacceptable mortality and hospitalisation rates in patients with both diabetes and CHF. The challenge faced by clinicians is how best to address the needs of a patient with both diabetes and CHF. It is of paramount importance to identify both co-existing conditions and acknowledge that these patients have a very bleak outlook. Currently, clinicians should utilise contemporary therapies to aggressively treat both heart failure and hyperglycaemia associated with diabetes. New therapeutic approaches are needed to tackle this deadly duo to improve the abysmal outcomes currently seen.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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