Original Articles

How diabetes alters the prognosis of patients with heart failure and the impact of therapies

JS Mohal & S Khan

Abstract

The mechanisms causing diabetes and heart failure are inextricably linked, as are the prognostic outcomes seen in these two complex disease processes. Treating both conditions together is absolutely vital to bring about the best long-term outcomes for patients. We have strong evidence-based therapies which have been shown to successfully treat both these conditions with improved prognosis and patient outcomes. The more recent development of SGLT2 inhibitors have further enhanced this clear clinical benefit for heart failure and diabetes combined. This is an exciting area of rapidly expanding research and further trials looking at these benefits are underway.

Introduction

Heart failure carries a significant morbidity and mortality burden and hence is costly to individuals and to healthcare systems around the world. It is well established that the impact of an ageing population and improved survival rates amongst patients with coronary artery disease have contributed to this. Heart failure and diabetes frequently co-exist and between 20-40% of all patients with heart failure also have diabetes[1] The UK Prospective Diabetes Study showed that a 1% elevation in HBA1c led to an 8% increase in heart failure risk.[2] The Framingham Heart Study showed a 5 times increased risk for women and 2.4 times increased risk for men in developing heart failure when diabetes was also present.[3] Traditionally these two conditions have been managed separately however there is a growing acceptance that clinicians are required to be more mindful of the bi-directional impact of both of these conditions.[4]

All of the major risk factors for the development of heart failure also appear in patients who have diabetes, including obesity, hypertension, advanced age, dyslipidaemia, sleep apnoea and chronic kidney disease. The presence of diabetes can also affect the management course of heart failure, just as the management of heart failure can affect the management course of diabetes.[5]

Mechanisms

In diabetics, it is not only coronary artery disease that can lead to the development of heart failure, due to it being an risk factor for ischaemic heart disease. There are also multiple pathophysiological and metabolic abnormalities which are induced by abnormal glucose metabolism which can directly affect cardiac myocytes.[5, 10] Certain mechanisms are more prominent in affecting cardiac structure to bring about heart failure with reduced ejection fraction (HEFrEF). Others can bring about heart failure with preserved ejection fraction (HEFpEF). The exact mechanisms of action are not fully clear however there are a number of putative theories illustrated in Figure 1.

Prognosis & Outcomes

Co-existence of heart failure and diabetes confers a worse prognosis than heart failure alone. Several trials have already shown this.[4] The ALLHAT trial (The Antihypertensives and Lipid-Lowering

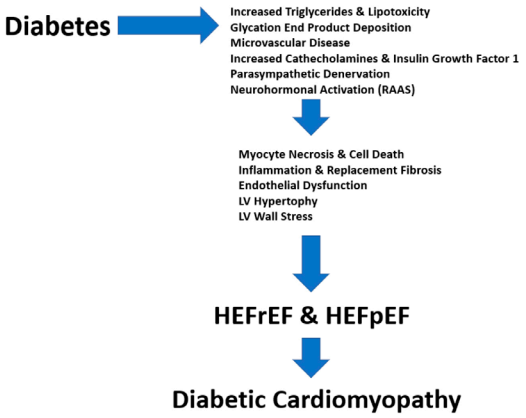

Figure 1. These pathological mechanisms lead to cardiac myocyte loss, the development of left ventricular hypertrophy, perivascular and interstitial fibrosis, stiffening of the myocardium and eventually lead to systolic and diastolic dysfunction. Cumulatively these above changes are often known as 'Diabetic Cardiomyopathy'[5, 6, 7, 8, 9, 10]

Jagdeep Singh Mohal
Department of Cardiology, Imperial College Healthcare NHS Trust, Du Cane Road, London, UK

Sadia Khan
Dept of Cardiology, West Middlesex Hospital, Chelsea & Westminster NHS Foundation Trust, Middlesex, UK

Treatment to Prevent Heart Attack Trial) showed a higher rate of mortality in patients with heart failure and diabetes compared with heart failure alone; 45% versus 24% respectively at 5 years.[16, 17]

The Framingham Heart Study showed 34% of diabetic patients died within 1 year of a diagnosis of heart failure.[5, 18] Furthermore, the CHARM study (Candesartan in Heart Failure: Assessment of Reduction in Morbidity and Mortality) showed that patients with HEFpEF and diabetes had higher rates of cardiovascular death and heart failure hospitalisations when compared to patients with heart failure alone.[19]

A major cohort study carried out in Denmark by Zareini et al[11] investigated 104,000 patients who between 2003 -2014 had a first hospitalisation with heart failure. Following the first hospitalisation, the incidence of new onset diabetes was 2% per year, rising to 3% after 5 years of follow-up. Furthermore, these heart failure patients with new onset diabetes had a markedly elevated risk of death (hazard ratio 1.47, 95% CI 1.42-1.52), compared to heart failure patients without diabetes and also compared with patients with intermediate risk in heart failure patients with prevalent diabetes. This again re-affirms that even when coronary artery disease is absent, there is a substantial relationship between diabetes and the development of heart failure and vice versa and also an increased risk of death.

This is also in line with other studies which showed a graded relationship between blood glucose levels at the time of hospitalisation for heart failure and long-term outcomes for patients without known diabetes.[11, 12] In patients who already have diabetes and develop heart failure, several studies have shown that insulin sensitivity decreases as heart failure progresses. The decreased cardiac output which occurs due to progressive heart failure, leads to reduced impaired blood flow and reduced oxygen distribution to tissues. This in turn increases sympathetic, noradrenaline and adrenaline output which also reduce insulin sensitivity.[13, 14] Interestingly, in patients with advanced heart failure, left ventricular assists device (LVAD) implantation led to better diabetes control.[11, 15] This again supports the notion that improved heart failure management can improve diabetic control and that again these two conditions are inextricably linked. Hence treatment pathways should aim at treating both simultaneously rather than separately . Most of these studies are of patients with type 2 diabetes, however the data suggest that this relationship is likely to hold true in type 1 diabetics as well.

A major 10-year Scottish follow up study examined the incidence and case fatality of heart failure hospitalisations in the entire resident population of Scotland > 30 years old (comprising of 3.25 million people) between 2004 and 2013.[20] This showed that the incidence rates of heart failure hospitalisations were 2.4, 12.4 and 5.6 per 1000 people for those without diabetes, type 2 diabetes and type 1 diabetes respectively. Furthermore, the 30-day case fatality was higher in heart failure patients with type 1 diabetics (for both genders) than in people without diabetes. However, it was similar for type 2 diabetics with heart failure compared to those without diabetes.

The authors commented however that the underlying mechanisms accounting for this case fatality difference are not known. They did however find that people with type 1 diabetes, compared to type 2 diabetics, were less commonly prescribed heart failure prognostic medications such as ACE inhibitors and also those drugs known to reduce the risk of heart disease such as anti-hypertensives and lipid lowering medications. Hence this could be one such reason.

A prospective study by Stoyanova et al[21] compared 290,000 patients from Germany and Austria with type 2 diabetes and heart failure and those without between years 2000 and 2015. Although there are a number of possible mechanisms as shown in Figure 1, data from clinical studies gives insight into some of the underlying mechanisms. This study showed that people with heart failure and type 2 diabetes were more often older and female compared with those without heart failure. Type 2 diabetics with heart failure were more likely to receive insulin, anti-hypertensive medications and lipid lower drugs which in turn meant that they had lower HBA1c's, better metabolic and BP control. The effect on hospitalisation rates and mortality however was not commented upon for this data set and this would be interesting to analyse in further work. That said it does support the earlier mentioned mechanisms that heart failure is linked to higher insulin resistance and hence this could account for more aggressive use of insulin.

A further Swedish National study[22] looked at 266,000 type 2 diabetic patients with and without heart failure and followed them up over a 5.6-year period. They found that of the individuals with type 2 diabetes, 7% were hospitalised with heart failure compared with 3.8% without diabetes. Interestingly this risk of heart failure hospitalisation was twice as high in patients aged < 55 years with good glycaemic control and 4.6 times as high with patients aged < 55 years with poor glycaemic control +/- poor renal function. The risk was five times higher in young women and two times as high in young men. The reasons for this at present are not clear and the study pointed out that further work is needed. However, the risk of heart failure hospitalisation did not change at all for type 2 diabetics aged > 75 years old with HBA1c at target level (< 6.9%) with or without albuminuria when compared to those without diabetes.

Effect of Therapies

An abundance of evidence exists that interventions which are effective at improving prognosis in heart failure are also effective in patients with and without diabetes.[23]

Non glycaemic interventions in HEFrEF patients consist of ACE inhibitors (ACEi)/ Angiotensin Receptor Blockers (ARBs), Beta blockers and Mineralocorticoid Receptor Antagonists (MRA). Dysregulation of the renin-angiotensin-aldosterone system (RAAS) is present in heart failure as well as diabetes and so drugs which block the activity of RAAS are deemed to be beneficial to both conditions. ARBs are recommended when ACE inhibitors are not well tolerated. MRAs are advised as an add on to Beta blockage and ACEi, especially if symptoms persist. It is well documented in several trials (MERIT-HF,

SOLVD, EMPHASIS) that the use of all of these classes of medication lead to significantly reduced mortality and heart failure hospitalisations.[24] It is noted that there is a tendency for under use of Beta blockers in T2DM especially due to the worry about side effects especially causing reduced awareness of hypoglycaemia, however it is important to remember that the benefits of beta blockage in heart failure far out weight the risks in diabetics.

Angiotensin Receptor Neprilysin Inhibitors (ARNIs) such as Sacubitril/Valsartan are advised by the European Society of Cardiology if LVEF < 35% and symptoms persist despite optimum treatment with ACEi/BB and MRA.[26] The PARADIGM-HF Trial showed that use of ARNIs when compared to Enalapril led to a significant reduction (21%) in hospitalisation and cardiovascular death. Importantly this study population 35% of the patients had a diagnosis of T2DM.[24, 26]

In the case of HEFpEF, ACEi/ARBs, Beta Blockers or MRAs have not shown any mortality or reduced hospitalisation benefit and as such the mainstay of treatment remains diuretics to offload fluid and cardiac risk factor control such as BP, lipid levels, weight reduction, optimum diabetic control.[24] Digoxin is used in severe HEFrEF in the setting of sinus rhythm and also for rate control in cases involving atrial fibrillation. It has not been shown to improve mortality, but has been shown to reduce hospitalisations for heart failure.[24]

Ivabradine is recommended in patients who have LVEF < 35% with sinus rhythm and a heart rate of at least 70 bpm, but who cannot tolerate Beta blockers and who are still symptomatic despite ACEi and MRA. The SHIFT trial compared the addition of ivabradine compared to placebo in patients who were already taking ACEi, Beta blockers, MRA and showed a further 18% reduction in risk of cardiovascular death and hospitalisation with those who took Ivabradine.[24, 27] Thirty percent of patients in this study had a diagnosis of diabetes.

Glycaemic interventions include Metformin, Sulphonylureas, GLP-1 receptor agonists (Incretins) and more recently SGLT2 inhibitors. Metformin is currently the first line treatment for type 2 diabetes mellitus but it's use has not currently been shown to bring about any change in heart failure outcomes. Sulphonylureas have had mixed results in their effects on heart failure outcomes with some studies reporting no net benefit but other showing an increased risk of heart failure adverse outcomes. Their safety therefore has not as yet been fully established.[24]

Thiazolidinediones have been associated with increased fluid retention and as such lead to increased heart failure symptoms and hospitalisations, therefore they should be avoided completely.[23, 28] Dipeptidyl Peptidase-4 Inhibitors (DDP4is), also known as Gliptins, bring about a minimal change in HBA1c but do also lead to increased heart failure symptoms and hospitalisations and so their use is also not recommended.[24, 29]

The LEADER trial tested the GLP-1 class drug Liraglutide against a placebo in 9340 patients with type 2 diabetes and cardiovascular disease for just under 4 years. There was a 22% reduction in cardiovascular death, but no significant reduction in non-fatal MI. Liraglutide did not affect heart failure hospitalisations.[30] Hence, it's actual benefit in the context of heart failure has not fully been established as yet.

By far the biggest and most exciting advancement to date has been the introduction of sodium-glucose cotransporter 2 (SGLT2) inhibitors which are in use for type 2 diabetics and are increasingly a fourth pillar in the management of HEFrEF. They work by increasing the secretion of glucose in urine and reducing plasma glucose via insulin independent mechanisms.[31] The exact mechanisms by which SGLT2 inhibitors reduce heart failure hospitalisations and improve LV function are not certain, and more work is needed, however several hypotheses have been put forward. A sustained reduction in intravascular volume reduces the preload and afterload and hence reduces cardiac workload and improves LV function. Furthermore, changes in intravascular volume and blood pressure without changes in heart rate, lead to the suggestion that SGLT2 inhibitors reduce sympathetic reflex activation and also affect other neuro-hormonal pathways.[31]

At present SGLT2 inhibitors are unsuitable for type 1 diabetics, those with a previous history of ketoacidosis or an acute medical illness. Common side effects include urine and genital tract infections, hypotension and can also precipitate euglycaemic ketoacidosis. They can be used in patients with eGFR >30 ml/min/m2.

The large randomised placebo-controlled trials for Empagliflozin (EMPA-REG OUTCOME), Canagliflozin (CANVAS Program) and Dapagliflozin (DECLARE-TIMI 58) showed significant reductions in heart failure admissions within months of SGLT2 inhibitor initiation.[31] However, outcomes related to MI and strokewere not significantly different when compared to placebo. The EMPA-REG OUTCOME trial specifically followed 7020 patients with type 2 diabetes who were at risk for cardiovascular events for 3 years. It showed a 38% relative risk reduction in death from cardiovascular causes and 35% relative risk reduction in heart failure hospitalisations.[23, 32]

The DAPA-HF and EMPEROR-Reduced trials evaluated the impact Dapagliflozin and Empagliflozin respectively on clinical outcomes in patients with HEFrEF who were both type 2 diabetics and non-diabetics. There was a 25% reduction in cardiovascular death and heart failure hospitalisations with the use of these SGLT2 inhibitors compared to placebo.[35]

Mei Q et al.[33] conducted a meta-analysis of seven randomised controlled trials which had evaluated the effects of SGLT2 inhibitors on cardiorenal end points in type 2 diabetic patients. They included EMPA-REG OUTCOME, CANVAS Program, DECLARE-TIMI 58 already mentioned above along with CREDENCE, VERTIS CV, SOLOIST-WHF and SCORED. They concluded that compared with placebo, SGLT2 inhibitors reduced major adverse cardiovascular events (hazard ratio 0.89), heart failure hospitalisation (hazard ratio 0.67), cardiovascular death (hazard ratio 0.86) but did not have any significant impact on stroke or MI and so further assessment of these outcomes is needed.[33]

Furthermore, an analysis of a randomised controlled trial, conducted by Petrie M et al,[34] looked at 4744 patients with HEFrEF with and without diabetes who were given Dapagliflozin vs placebo. The results showed that Dapagliflozin compared with placebo significantly reduced heart failure hospitalisation or an urgent heart failure visit requiring IV treatment and also cardiovascular death in patients with diabetes (hazard ratio 0.75) and also those without diabetes (hazard ratio 0.73). Hence this shows that Dapagliflozin has a role in the treatment of heart failure patients without type 2 diabetes as well as those with diabetes. Taking this further, it is speculated that as subclinical LV diastolic dysfunction is highly prevalent in diabetic patients, a large proportion of patients in the landmark SGLT2 trials may have actually had HEFpEF. Hence by extension SGLT2 inhibitors may actually be beneficial in HEFpEF and not just HEFrEF.[31] At present however SGLT2 inhibitors can be used in patients with HEFpEF and type 2 diabetes, however the EMPEROR-Preserved trial is currently underway to formally assess the benefits of SGLT2 inhibitors in HEFpEF in patients with and without diabetes.[35]

Currently there is significant evidence to suggest that besides their cardiovascular benefits, SGLT2 inhibitors also confer renoprotection as well. The DAPA-CKD trial followed 4304 patients with and without type 2 diabetes over 2.4 years. Patients who were given dapagliflozin compared to placebo demonstrated a reduction in the primary endpoint outcome of decline in eGFR, death from renal causes or cardiovascular death with a hazard ratio of 0.61 (95% CI 0.51-0.72, p<0.001).[35] At present however national guidelines are awaited to formally recommend the use of SGLT2 inhibitors in CKD patients.

In conclusion, it is clear that the mechanisms causing diabetes and heart failure are inextricably linked, as are the prognostic outcomes seen in these two complex disease processes. There is however a solid and strong body of evidence which shows that we have several classes of drugs in our armoury which can effectively treat both these diseases. Treating both conditions together is absolutely vital to bring about the best long-term outcomes for patients. The impressive advances seen with the development of SGLT2 inhibitors have underscored the fact that they have a clear clinical benefit in the treatment of heart failure, diabetes and also renal protective benefits. This is an exciting area of rapidly expanding research and further trials looking at these benefits are underway. There is a specific focus on whether early use of SGLT2 inhibitors may help with prevention of cardiovascular risk factors to thereby delay the development of the later stages of cardiovascular disease, and this will be an exciting frontier to further explore.

How diabetes alters the prognosis of patients with heart failure and the impact of therapies

References

1. McAlister F, Teo K et al. Insights into the contemporary epidemiology and outpatient management of congestive heart failure. ***Am Heart J*** 1999;138 (1):87-94
2. Iribarren C, Karter A et al. Glycaemic control and heart failure among adult patients with diabetes. ***Circulation*** 2001;103:2668-2673
3. Zhou L, Deng W et al. Prevalence, incidence and risk factors of chronic heart failure in the type 2 population: systematic review. ***Curr Diabetes Rev*** 2009;5:171-184
4. Campbell P, Krim S, Ventura H. The Bi-directional Impact of Two Chronic Illnesses: Heart Failure and Diabetes – A review of the Epidemiology and Outcomes. ***Card Fail Rev.*** 2015;1(1):8–10.
5. C. Thomas M. Type 2 Diabetes and Heart Failure: Challenges and Solutions. ***Curr Cardiol Rev.*** 2016 Jul 15;12(3):249–55.
6. Yap J, Yay W et al. Association of Diabetes Mellitus on cardiac remodelling, quality of life and clinical outcomes in heart failure with reduced and preserved ejection fraction. ***J Am Heart Association*** 2019;8:e013114.
7. Seferovic PM, Paulus WJ. Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes. ***Euro Heart J*** 2015;36:1718-1727
8. Paulus WJ, Dal Canto E. Distinct myocardial targets for diabetes therapy in heart failure with preserved or reduced ejection fraction. ***JAAC Heart Failure*** 2018;6:1-7
9. Dimitropoulos G, Tahrani A, Stevens M. Cardiac autonomic neuropathy in patients with diabetes mellitus. ***World J Diabetes*** 2014;5:17-39
10. Bugger H, Abel E. Molecular mechanisms of diabetic cardiomyopathy. ***Diabetologia*** 2014;57(4):660-71
11. Zareini B, Rorth R et al. Heart failure and prognostic impact and incidence of new onset of diabetes mellitus: a nationwide cohort study. ***Cardiovascular Diabetology*** 2019;18:79
12. Zadok O, Kornowski R et al. Admission blood glucose and 10 year mortality among patients with or without pre-existing diabetes mellitus hospitalised with heart failure. ***Cardiovasc Diabetology*** 2017;16:102
13. Schmiegelow M, Anderson C et al. Body mass index is closely correlated to incident diabetes in patients with heart failure or myocardial infarction. ***Eur J Cardiovasc Prevent Rehabil*** 2011;18(2):305-11
14. Paolisso G, De Riu S et al. Insulin resistance and hyperinsulinaemia in patients with chronic congestive heart failure. ***Metabolism*** 1991;40(9)972-7
15. Mohamedali B, Yost G et al. Mechanical circulatory support improves diabetic control in patients with advanced heart failure: improvement in diabetes with LVAD. ***Eur J Heart Fail*** 2014;16(10):1120-4
16. Bertoni A, Hundley W et al. Heart failure prevalence, incidence and mortality in the elderly with diabetes. ***Diabetes care*** 2004;27:699-703
17. David B, Puller L et al. Role of diuretics in the prevention of heart failure. The Antihypertensive and Lipid-lowering treatment to prevent heart attack trial. ***Circ*** 2006;113:2201-10
18. Ho K, Anderson J et al. Survival after the onset of congestive heart failure in Framingham Heart Study Subjects. ***Circ*** 1993;88:107-15
19. MacDonald MR, Petrie MC et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: ana analysis of the Candesartan in Heart Failure: Assessment of Reduction in Morbidity and mortality (CHARM) programme. ***Eur Heart J*** 2008;29:1377-85
20. McAllister D, Read S et al. Incidence of Hospitalisation for Heart Failure and Case-Fatality Among 3.25 Million People) With and Without Diabetes Mellitus. ***Circulation*** 2018;138:2774-2786
21. Stoyanova D, Stratmann B et al. Heart failure among people with type 2 diabetes mellitus: real world data of 289954 people from a diabetes dataset. ***Diabet Med*** 2020;37:1291-1298
22. Rosengren A, Edqvist J et al. Excess risk of hospitalisation for heart failure among people with type 2 diabetes. ***Diabetologia*** 2018;61:2300-2309
23. Rosano G, Vitale C, Seferovic P. Heart failure in patients with diabetes mellitus. Cardiac failure review 2017;3(1):52-55
24. Ofstad A, Atar D et al. The heart failure burden of type 2 diabetes mellitus – a review of pathophysiology and interventions. ***Heart Failure Reviews*** 2018;23:303-323
25. European Society of Cardiology Guidelines 2016 for the diagnosis and treatment of acute and chronic heart failure.
26. McMurray J, Packer M et al. Angiotensin-neprilysin inhibition vs enalapril in heart failure. ***N Eng J Med*** 2014;371(11):993-1004
27. Komajda M, Tavazzi L et al. Efficancy and safety of ivabradine in patients with chronic heart failure and diabetes: an analysis from the SHIFT trial. ***Euro J Heart Fail*** 2015;17(12):1294-1301
28. Home P, Pocock S et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. ***Lancet*** 2009;373:2125-2135
29. Green J, Bethel M et al. Effect of Sitagliptin on cardiovascular outcomes in Type 2 Diabetes. ***N Eng J Med*** 2015;373(3):232-242
30. Marso S, Daniels G et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. ***N Eng J Med*** 2016;375(4):311-322
31. Lan N, Fegan G et al. The effect of sodium-glucose cotransporter 2 inhibitors on the ventricular function current evidence and future directions. ***ESC Heart Failure*** 2019;6:927-935
32. Zinman B, Wanner C et al. Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes. ***N Eng J Med*** 2015;373:2177-2128
33. Mei Q, Liangliang D et al. Effects of SGLT2 inhibitors on cardiovascular and renal outcomes in type 2 diabetes. A meta-analysis with trial sequential analysis. ***Medicine*** 2021;100(10):e25121
34. Petrie M, Verma S et al. Effect of Dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. ***JAMA*** 2020;323(14):1353-1368
35. Gulsin G, Graham-Brown M et al. Benefits of sodium glucose cotransporter 2 inhibitors across the spectrum of cardiovascular diseases. ***Heart*** 2021;10;1136