

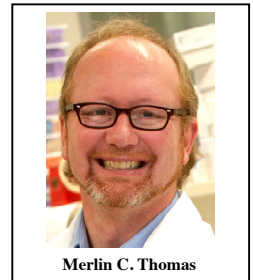
REVIEW ARTICLE

Type 2 Diabetes and Heart Failure: Challenges and Solutions

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Abstract: Increasing numbers of older patients with type 2 diabetes, and their improved survival from cardiovascular events is seeing a massive increase in patients with both diabetes and heart failure. Already, at least a third of all patients with heart failure have diabetes. This close association is partly because all the major risk factors for heart failure also cluster in patients with type 2 diabetes, including obesity, hypertension, advanced age, sleep apnoea, dyslipidaemia, anaemia, chronic kidney disease, and coronary heart disease. However, diabetes may also cause cardiac dysfunction in the absence of overt macrovascular disease, as well as complicate the response to therapy. Current management is focused on targeting modifiable risk factors for heart failure including hyperglycaemia, dyslipidaemia, hypertension, obesity and anemia. But although these are important risk markers, none of these interventions substantially prevents heart failure or improves its outcomes. Much more needs to be done to focus on this issue, including the inclusion of hospital admission for heart failure as a pre-specified component of the primary composite cardiovascular outcomes and new trials in heart failure management specifically in the context of diabetes.



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1. INTRODUCTION

Type 2 diabetes and heart failure are common companions in clinical practice. Between 20% and 40% of all patients with heart failure has diabetes [1]. This is not a modern phenomenon. Indeed, Leyden first reported that heart failure was a 'frequent and noteworthy complication of diabetes mellitus' over 130 years ago [2]. However today, subjects with type 2 diabetes have over twice the risk of incident heart failure than people without diabetes [3-5] and heart failure is the most common initial presentation of cardiovascular disease [6]. This is partly because all the major risk factors for heart failure also cluster in patients with type 2 diabetes, including obesity, hypertension, advanced age, sleep apnoea, dyslipidaemia, anaemia, chronic kidney disease (CKD), and coronary heart disease (CHD). Diabetes itself independently contributes to the development and progression of heart failure. In addition, diabetes complicates the management of heart failure as heart failure complicates the management of diabetes. The prognosis and survival of patients with diabetes and heart failure is approximately half that observed in non-diabetic individuals, even after adjusting for conventional risk factors [7-9]. Death from heart failure is emerging as a leading cause of death in patients with type 2 diabetes [10]. This article will review some of the key

clinical challenges in preventing and managing heart failure in patients with type 2 diabetes, and explore some of the opportunities for improvement.

2.1. Diabetic, Coronary Heart Disease and Heart Failure

Type 2 diabetes mellitus has a negative influence on the prevalence, presentation, severity and prognosis of coronary heart disease (CHD). The burden of cardiovascular disease (CVD) among patients with diabetes is substantial. Between one third to a half of all adults with type 2 diabetes have coronary heart disease, depending on the setting and the methods of diagnosis. In Australian primary care, one in three patients seeing their GP have previously had a heart attack or stroke. Because cardiac events are often silent in diabetes, a diagnosis based on ECG and echocardiographic studies would likely estimate that this prevalence is closer to one in two. Approximately 1-3% of individuals with type 2 diabetes experience CHD events per year; this rate is about twice that in non-diabetic individuals. Moreover, these events occur at a younger age than in non-diabetic individuals. Overall, CHD is the leading cause of early death in patients with type 2 diabetes, accounting for two thirds of all deaths in patients with diabetes. Diabetes is an independent risk factor for all manifestations of CHD. In particular, patients with type 2 diabetes have rates of heart failure, angina pectoris, re-infarction disability and sudden cardiac death that are again at least twice that observed in non-diabetic patients. This is thought to reflect accelerated atherogenesis and increased cardiovascular pathology associated with diabetes (Table 1).

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Table 1. Potential pathogenic contributors to a greater burden of CHD in patients with type 2 diabetes.

- Greater plaque burden
- Greater complexity of lesions
- Greater coronary calcifications
- Greater extent of coronary ischaemia
- More diffuse disease
- More multi-vessel disease
- More significantly-affected vessels
- Fewer normal vessels
- Reduced coronary collateral recruitment
- Reduced coronary vasodilatory reserve

2.2. Diabetic Cardiomyopathy

Even in absence of overt myocardial ischemia and hypertension, it is widely recognized that diabetes is associated with important changes in myocardial structure and function, including a disproportionate left ventricular hypertrophy, perivascular and interstitial fibrosis, leading to stiffening of the heart, diastolic and systolic dysfunction, and an increased the risk of heart failure (Table 2) [11-13]. Cumulatively, these changes are known as “diabetic cardiomyopathy” [11] although they may also be better as considered “cardiac microvascular disease”, as they have more in common with vascular changes in other microvascular beds including the retina, the vaso nevorum and the kidney, than they do with other forms of cardiomyopathy. Many of the same factors implicated in microvascular dysfunction are associated with diabetic cardiomyopathy including hyperglycemia, dyslipidemia, altered energy metabolism, dysregulated insulin signaling, inflammation, endoplasmic reticular stress, mitochondrial dysfunction, oxidative stress and accumulation of advanced glycation end-products (AGEs) and activation of the renin-angiotensin-aldosterone system (RAAS). However, direct effects are also observed in cardiac myocytes including abnormal calcium signalling leading to dysfunctional cardiac relaxation.

Table 2. Potential contributors to diastolic dysfunction associated with diabetic cardiomyopathy.

- Microvascular disease in the heart
- Left ventricular hypertrophy
- Autonomic neuropathy
- Myocardial fibrosis
- Post-translational modification (e.g. AGEs)
- Changes in cardiac muscle metabolism

Dysfunction of the chemical (ion) control of cardiac relaxation.

2.3. Diabetes, Glycaemic Control and Heart Failure

There is strong epidemiological evidence linking poor glycaemic control and the risk of heart failure. For example, in patients with type 1 diabetes from the Swedish National Diabetes Registry the incidence of heart failure increased linearly with HbA1c, and remained significant after adjustment for age, sex, duration of diabetes, cardiovascular risk factors, and baseline or intervening acute myocardial infarction and other co-morbidities [14]. Similarly, in a number of prospective observational studies in type 2 diabetes there is a consistent linear relationship between glycaemic control and heart failure, such that overall adjusted risk ratio (RR) for CHF was 1.15 [95% confidence interval (CI) 1.10-1.21] for each percentage point higher HbA1c [15]. By contrast, the relationship between adverse outcomes and HbA1c in patients with both diabetes and HF appears U-shaped, with the lowest risk of death in those patients with modestly impaired glucose control (HbA1c 7.0-7.8%) and an increased risk of mortality with higher or lower HbA1c levels [16].

In clinical trials testing the utility of glucose lowering in diabetes, intensive treatment is not associated with a reduced risk of new-onset heart failure or a reduction in hospitalisation in patients with established heart disease [17]. This finding appears to be consistent across major trials, even after patients using thiazolidinediones (which increase hospitalization with heart failure by 30-40% [18]) have been excluded. The optimal treatment strategy in patients with diabetes mellitus and heart failure remains controversial. Metformin may be associated with an increased risk of lactic acidosis in patients with heart failure and is often recommended to be discontinued. Insulin and sulphonylureas may cause hypoglycaemia which itself had adverse effects of cardiac function, myocardial perfusion and arrhythmogenicty. Recent data have also questioned whether Dipeptidypetidase 4 (DPP4) inhibitors may increase the risk of hospitalisation from heart failure. However, the absence of a signal from the recently completed Sitagliptin Cardiovascular Outcome Study (TECOS; <http://www.clinicaltrials.gov>; identifier, NCT00790205), study potentially allays some of these concerns. In addition, ongoing studies are also investigating glucagon-like peptide-1 agonists as a treatment for established heart failure.

The recent emergence of inhibitors of the type 2 sodium glucose co-transporter (SGLT2) is also of great interest for the prevention and management of heart failure, as their use is appears to be associated with a lower risk of incident heart failure events, both in the presence or absence of established heart failure or other comorbidities. Moreover, the recently completed EMPA-REG study demonstrated a 38% reduction in cardiovascular death (chiefly sudden death and heart failure deaths) [19]. Whether such benefits may be ascribed to the diuretic effects of SGLT2 inhibition and the persistent contraction of plasma volume associated with these agents is unclear. Other effects on cardiac metabolism, substrate utilization and reduction of ectopic fat in and around the heart may also be important. Additional studies are ongoing and will test these hypotheses, as well as attempt to identify ways to optimize these putative benefits.

2.4. Diabetes, Hypertension and Heart Failure

Lowering blood pressure is widely recommended to reduce vascular risk in individuals with type 2 diabetes. Hypertension, and systolic hypertension in particular is strongly linked to cardiovascular disease and incident heart failure in patients with diabetes. Indeed, hypertension is widely considered to be the single most important modifiable risk factor for heart failure and long-term treatment of hypertension in the general population has been shown to reduce the risk of incident heart failure by approximately half [20, 21]. However, while strong data exists in the general population, there is no clear evidence that blood pressure lowering reduces new-onset heart failure events in patients with diabetes (relative risk reduction 0.86 [95% CI, 0.74-1.00]) [22]. One reason for this paradox may be the differential effects of different antihypertensive agents. For example, while the use of Diuretic-based antihypertensive therapy or RAAS blockers is associated with a lower risk of heart failure, the use of calcium channel agents or α -1-blockade which effectively lower the blood pressure have a modestly increased of heart failure when compared with all other classes of antihypertensive medications [22, 23]. However, the demonstrated benefits with respect to cardiovascular and all cause mortality observed in the ADVANCE study, mean that blood pressure lowering in hypertensive patients with diabetes remains a priority.

2.5. Diabetes, Heart Failure and the Renin Angiotensin Aldosterone System

Activation of the RAAS also contributes the development and progression of heart failure, and diabetes is associated with activation of the RAAS. Blockade of the RAAS is the most widely used antihypertensive strategy in patients with type 2 diabetes and is considered to have vasculo-protective effects beyond blood pressure lowering, including reducing the risk of heart failure [24]. For example, in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) studies, losartan significantly reduced the incidence of first hospitalizations for heart failure versus placebo (hazard ratio 0.74, $p=0.037$). A comparable reduction was also seen in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) and versus atenolol in the LIFE study (hazard ratio 0.57, $p=0.019$) [25]. However, the ADVANCE trial using perindopril and indapamide did not reduce heart failure events, although deaths from cardiovascular causes and total mortality were modestly reduced [26]. Nonetheless, most patients with diabetes and heart failure will receive an agent that blocks the RAAS, unless contraindicated or not-tolerated. Importantly patients with diabetes are more likely to experience postural dizziness or hyperkalemia with RAAS blockade. Each can be a limitation to the use of RAAS blockade in this especially vulnerable population. The recent development of more tolerable oral potassium sequestering agents will be an important adjunct to management in this setting, allowing more patients to take RAAS blockers and potentially in higher doses required for optimal cardioprotection [27].

2.6. Diabetes, obesity and heart failure

Elevated body mass is causally linked to both diabetes and incident heart failure [28, 29]. The greater the elevation in body mass, the greater the risks and the worse the clinical outcomes [30]. These associations appears to be additional an independent to the presence and severity of hypertension, dyslipidemia, obstructive sleep apnoea and cardiovascular disease that also cluster with obesity. Obesity triggers to concentric left ventricular hypertrophy. Visceral adiposity also leads to adverse ventricular remodelling (the 'cardiomyopathy of obesity') due to the impaired sequestration of fats, which can then exert their toxic effects on the heart and other susceptible sites including the pancreas. Neurohormonal activation and the release of pro-inflammatory adipokines may also play a role. In addition, the shear demands of excess body weight on cardiac capacity means that symptoms (such as exertional dyspnoea) and signs (such as ankle edema) are seen earlier and are more marked in obese patients with heart failure.

At the same time, in patients with heart failure, obesity may be associated with improved clinical outcomes when compared to patients with a 'normal' weight. This phenomenon has been termed the "obesity paradox" [31, 32]. This may be partly determined by outcomes in older frailer individuals with non-ischemic disease. It may also be in patients with similar heart failure symptomatology cardiac function is generally better in those patients with obesity, as the extra symptomatic burden imparted by excess fat makes heart failure feel worse and present earlier than in the absence of obesity, leading to misclassification or lead time bias respectively. Another hypothesis is that excess fat is a protective energy reserve against cardiac cachexia.

It is widely recommended that obese patients with diabetes undertake strategies to lose excess weight including regular physical activity, diet and lifestyle modifications. However, it remains to be established whether these measures will reduce new-onset heart failure or improve its outcome should it develop. For example, in the LOOK-AHEAD study substantial improvements in adiposity and increases in physical fitness in patients with diabetes were not associated with any reduction in heart failure [RRR 0.80 (95% CI 0.61-1.04, $p=0.10$) [33]. By contrast, more intensive weight loss achieved following bariatric surgery is associated with regression of cardiac hypertrophy and an increase of stroke volume and contractility [34]. Such interventions may be appropriate for selected patients with diabetes and heart failure, in whom post-operative risk is acknowledged and carefully managed.

2.7. Diabetes, CKD and Heart Failure

Chronic kidney disease (CKD) is also commonly found in patients with diabetes. Around half of all patients with diabetes will develop CKD, defined clinically by a reduction in the estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m², elevated urinary albumin to creatinine ratio or urinary albumin excretion. The presence and severity of CKD identify individuals at increased risk for adverse health outcomes, including heart failure. This so called "cardiorenal syndrome" discussed in detail elsewhere in this edition, so only brief commentary will be made here, specifically in

relation to diabetic kidney disease. Many studies have demonstrated a strong risk association between albuminuria and incident heart failure in patients with type 2 diabetes [28, 35]. Whether heart failure is a consequence of renal dysfunction or a manifestation of the same process going on the both the heart and the kidney is unclear. However, interventions that protect the kidneys in type 2 diabetes appear to also protect the heart.

2.8. Diabetes, Anaemia and Heart Failure

Anaemia is also a common companion to diabetes [36]. This is largely because of the high prevalence of chronic kidney disease in patients with diabetes, leading to functional erythropoietin deficiency [30]. Anaemia is also more common in patients with diabetes than those with renal disease of other causes. For example in the Kidney Early Evaluation Program (KEEP), anaemia was observed in 30% of diabetic patients with stage III CKD, twice the rate seen in non-diabetic patients (14%) [37]. Similarly, the Third National Health and Nutrition Examination Survey (NHANES-III), found people in the general population with diabetes were nearly twice as likely to have anaemia, when compared to people without diabetes, but with a similar degree of renal impairment [38]. Anaemia also develops earlier and is more severe in patients with diabetes than in patients with renal impairment from other causes [39-41]. Like many of the pathophysiological changes of diabetic nephropathy, such as albuminuria, anaemia may be apparent before demonstrable decline in renal function [42]. However, by the time the eGFR declines to less than 60 ml/min, over one in four individuals with diabetes have anaemia [42].

Anaemia has the potential to adversely affect the cardiac function of patients with diabetes in a variety of ways. Patients with heart failure and anaemia generally experience more severe symptoms, have higher rates of hospitalization and reduced survival when compared with patients without anaemia [43, 44]. This is partly because anaemia itself causes symptoms such as lack of energy, breathlessness, dizziness, poor appetite, reduced cognitive function, and reduced exertional capacity which may be readily confused with as well as exacerbate those associated with congestive heart failure [45, 46]. For patients with diabetes, many of whom already have reduced functional capacity, a poor quality of life and a higher prevalence of co-morbid cardiovascular disease, anaemia constitutes an unwelcome additional burden. Anaemia is also potentially significant in determining the outcome of hypoxia-induced organ damage, such as that associated with coronary heart disease or diabetic cardiomyopathy [47]. Chronic anaemia is known to result in increased cardiac output, volume overload, increased heart rate, and ultimately progressive left ventricular hypertrophy (LVH). Anaemia known to be a potent adverse risk factor for new-onset heart failure [28, 48], as well as a marker for poor outcomes in patients with established cardiac dysfunction, even after adjusting for conventional risk factors [49]. In our studies, 94% of diabetic patients with anaemia had evidence of some cardiac abnormality on echocardiography. In contrast, less than 5% of patients with normal cardiac findings were anaemic, suggesting that anaemia is an uncommon finding in patients with a normal heart. Consequently, the identification of anaemia in patients with diabetes and or

CHF is a useful prognostic marker, denoting the patient at increased risk for a range of adverse outcomes, and one in need to careful and close monitoring.

But while there is a strong rationale to correct anaemia, especially in the setting of reduced performance associated with diabetes and heart failure, there is no conclusive current evidence that correcting anaemia significantly improves clinical outcomes beyond palliation. Some small prospective studies performed in diabetic patients with moderate kidney impairment have demonstrated improved cardiac function after the early correction of anaemia [50, 51], some studies have also suggested that the number of hospitalisations may be reduced by correction of anaemia in diabetes [51]. Correction of anaemia may also play a significant role in improving exercise tolerance and patient wellbeing, as well as maintaining patients in a community setting. However, data in patients with heart failure from larger clinical trials seem not to confirm the previous data [52], possibly reflecting the better early management of hypertension and LVH at baseline. The ongoing Reduction of Events with Darbepoetin alfa in Heart Failure trial (RED-HF) is testing the hypothesis that anaemia correction will reduce the composite endpoint of death from any cause or hospital admission for worsening heart failure, and improve other outcomes [53].

2.9. Diabetes, Sympatho-activation and Heart Failure

In patients with diabetes, feedback activation of neuro-hormonal pathways including the sympathetic nervous system (SNS) also contributes to the development and progression of heart failure. SNS over-activity driven by glucose fluctuations in diabetes as well as obesity, renal dysfunction, hyperinsulinaemia, activation of the RAAS, oxidative stress, dysfunctional nitric oxide synthesis and increased circulating non-esterified fatty acids and adipokines [54, 55], each of which may be considered risk factors for heart failure. In addition, progressive damage to autonomic nerve fibres, affecting the longest fibres of the vagus nerve first, results in parasympathetic denervation and early augmentation of sympathetic tone [56]. Other complications of diabetes including obstructive sleep apnoea, depression and stress also feed in to promote and maintain excessive SNS activation in patients with diabetes.

There is a strong relationship between SNS overactivity and prognosis in heart failure [57-59]. This is not simply an epiphenomenon. It is thought that excessive or chronic adrenergic drive leads in the long term to secondary hypertension, vascular stiffening and remodelling, endothelial dysfunction, arrhythmogenicity [60], increased oxygen consumption, left ventricular hypertrophy and fibrosis [61]. In patients with diabetes these negative effects may be exaggerated, while positive actions are diminished. For example, in patients with type 2 diabetes, there may be an impairment of coronary microvascular dilation in response to sympathetic stimulation, even in the absence of macrovascular disease [62]. This imbalance may contribute to increased morbidity and mortality seen in patients with diabetes and heart failure.

Blockade of the SNS is able to improve morbidity and mortality in patients with diabetes and heart failure [63, 64]. For example the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial of patients with type

2diabetes and heart failure was terminated early due to the annual mortality rate in the carvedilol group being reduced by 35% (12.8% vs 19.7%, $p=0.00013$) Participants receiving carvedilol also showed a lower incidence of hospitalisation due to heart failure (17.1% vs 23.7%, $p=0.0001$). However, modulation of SNS is under-utilised as a strategy to protect the diabetic heart. This is partly because of the historically poor tolerability, adverse haemodynamic and metabolic effects of β -blockers in diabetic patients. For example, adverse actions on glucose and lipid control, hypoglycaemic awareness and weight gain [65, 66] limit their acceptability for beta-blockade in patients with diabetes. In addition, some second generation agents like atenolol are cleared by the kidney and may accumulate in diabetic patients with acute-on-chronic renal impairment, like following a heart attack, surgery or angiographic procedure, and precipitate bradycardia, especially if combined with non-dihydropyridine calcium antagonists [67]. Third-generation “vasodilating β -blockers” generally have better tolerability profile than older β -blockers, as well as more favourable effects on renal function and metabolic profiles in patients with diabetes [65]. The advent of radiofrequency renal sympathectomy and baroreflex activation technologies potential offer new exciting new ways to safely tackle the challenge of sympathetic over-activity. However, long term studies with hard outcomes remains to be performed.

2.10. Diabetes, Heart Failure and Anticoagulation

Aspirin is considered to be effective in reducing cardiovascular morbidity and mortality in patients with myocardial infarction or stroke (i.e. in secondary prevention). However, the use of aspirin for use in primary prevention of cardiovascular events is controversial. It may be argued that as the cardiovascular risk of patients with diabetes, and especially those with heart failure as well is at least the same or even greater as those with established cardiovascular disease, they should be treated in the same way. Indeed, American diabetes Association guidelines support the use of low-dose aspirin for the primary prevention of cardiovascular events in selected patients with diabetes with increased cardiovascular risk (10 year risk of CVD events over 10%) and who are not at increased risk for bleeding (previous gastrointestinal bleeding or peptic ulcers, reflux, or concurrent use of other medications that increase the risk of GI bleeding, such as warfarin or NSAIDs). In theory such patients are most likely to have occult atheroma, in which the anti-platelet actions of aspirin may act to prevent coronary thrombosis following plaque erosion or rupture. However, combined data from clinical trials suggests that aspirin has at best a small (<10% risk reduction) to non-significant effect on the risk of CHD events or stroke in diabetic patients who are clinically free of CVD. At the same time low dose aspirin increases the risk of gastrointestinal bleeding. There is also no conclusive evidence that anticoagulation provides any benefits in patients with established heart failure in sinus rhythm [68], although atrial fibrillation and other dysrhythmias are more common individuals with type 2 diabetes as increased filling pressure also results in atrial dilatation, a key risk factor for atrial fibrillation and embolic stroke.

3. CONCLUSION

Increasing numbers of older patients with diabetes, and their improved survival from cardiovascular events will undoubtedly see a massive increase in patients with both diabetes and heart failure. Already a quarter of those with chronic heart failure have diabetes and over 40% of those hospitalized with worsening HF [5]. Current management strategies focusing on known and modifiable risk factors such as glucose, lipids and blood pressure lowering have modest effects at best, and none substantially reduce heart failure or improve its outcomes. Much more needs to be done to address this issue. Recently there has been a call for inclusion of hospital admission for heart failure as a pre-specified component of the primary composite cardiovascular outcomes [69]. This partly follows the excess of events observed following the use of thiazolidinediones. However, a positive strategy to directly address heart failure risk in diabetes is also needed. The potential importance of SGLT2 inhibition to heart failure and its outcomes is perhaps the most important development since the advent of RAAS blockade. It is hoped that new developments in heart failure management, such as inhibition of neprilysin, can also be rapidly explored in the context of diabetes.

CONFLICT OF INTEREST

The author has received honoraria for educational symposia conducted on behalf of Astra-Zeneca, BMS, Abbott, Reata, Abvie, Sanofi Aventis, Boehringer Ingelheim, Takeda Lilly, MSD, Pfizer.

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