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Heart failure: a preventable and treatable complication of type 2 diabetes

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Causes of chronic heart failure in patients with diabetes

Chronic heart failure (CHF) is a complex syndrome in which impaired emptying or filling of the heart results in a clinical picture of fatigue, breathless and fluid retention. CHF is a common, preventable and treatable complication of type 2 diabetes mellitus (T2DM). Diabetes mellitus is highly prevalent amongst patients with CHF, around three to four-fold times higher than in the general population[1, 2]. T2DM is not only a risk factor for the development of CHF, but impaired glucose tolerance might be a consequence of the systemic perturbations of the CHF syndrome[3]. T2DM is an independent risk factor for progressive heart failure and cardiovascular death[3-6] and patients with T2DM have higher New York Heart Association (NYHA) class and symptom burden compared to non-diabetic patients with similar ejection fractions[7].

The most common comorbidities leading to CHF in patients with T2DM are coronary artery disease (CAD) and hypertension. Whilst multivessel CAD is a major cause of CHF in patients with diabetes and a strong adverse predictor of survival[4], the adverse effect of T2DM on outcomes in CHF patients is of a similar magnitude in patients with and without CAD[6]. This suggests an additional direct effect on the myocardium, a ‘diabetic cardiomyopathy’. Although several mechanisms have been proposed, and impaired cardiac glucose metabolism is a strong candidate, the underlying pathogenesis is only partially understood and there is no accepted clinical definition[6, 8, 9]. Overall, the pathophysiology of heart failure and diabetes overlap, both are associated with insulin resistance, impaired glucose metabolism and the metabolic syndrome[10, 11].

Heart failure is classified based upon the presence of reduced left ventricular function as heart failure with preserved (HFpEF) or reduced ejection fraction (HFrEF). In both descriptions, reduced cardiac output and a fall in blood pressure are sensed by baroreceptors and renal afferent arterioles. These in turn trigger the activation of the renin-angiotensin-aldosterone system (RAAS), secretion of anti-diuretic hormone, vasoconstriction, the activation of the sympathetic nervous system and release of epinephrine and norepinephrine. It is these physiological adaptations that result in the clinical syndrome of heart failure. RAAS activation

leads to aldosterone and antidiuretic hormone secretion, promoting sodium and water retention. This augments preload resulting in pulmonary congestion and fluid overload. Vasoconstriction maintains blood pressure to achieve organ perfusion at the expense of excessive afterload which exacerbates pump failure. Sympathetic stimulation increases heart rate and contractility, initially improving ejection fraction but ultimately increasing the heart's metabolic requirements and predisposing to dysrhythmia and sudden cardiac death. On the other hand, natriuretic peptide secretion promotes beneficial structural remodeling, natriuresis, diuresis and reduces sympathetic tone (Figure 1).

Contemporary therapies aim to limit these physiological adaptations, reduce symptoms and improve survival. Diuretics provide symptomatic relief from fluid retention. Angiotensin converting enzyme inhibitors, angiotension II receptor blockers and mineralocorticoid receptor antagonists inhibit the RAAS. Neprilysin inhibitors reduce the degradation of natriuretic peptides to promote structural remodeling, vasodilation and natriuresis. Beta-adrenoreceptor antagonists (beta-blockers) counteract sympathetic activation, reduce heart rate and contractility and. largely by their effect on sympathetic activation and reverse remodeling reduce the risks of dysrhythmia and sudden cardiac death. In those with persistent left ventricular dysfunction and conduction delay, cardiac resynchronization therapy (CRT) improves symptoms and survival, and in selected patients implantable cardiac defibrillators can reduce death due to arrhythmia.

The role of medical therapy

Studies linking diabetes with adverse outcomes, and its influence on therapy in CHF often predate what would now be considered as contemporary therapy. The now more widespread prescription of beta-blockers and uptake of CRT have contributed to the significant improvements in outcomes over recent years[12]. The incidence of sudden cardiac death has diminished over time, but still persists as a major contributor to adverse outcomes, especially in patients with diabetes. In our prospective cohort of 1091 patients, diabetes was associated with higher rates progressive CHF, all-cause and cardiovascular deaths[6] and in clinical trials, although pharmacotherapy and device therapy were effective for both patients with and without

diabetes they remain at higher risk. Most recently, we have demonstrated that patients with diabetes mellitus are in fact more likely to benefit from contemporary heart failure strategies. In a non-randomised prospective cohort of 1797 patients, we described that higher doses of ACE-inhibitor and beta-blocker improved outcomes for all patients but that dose escalation has the greatest effect on mortality in patients with diabetes mellitus, particularly those with the most severely impaired left ventricular function. This observation provides support for the direct role of higher doses of beta-blockers in order to achieve the best outcomes in patients with both CHF and diabetes mellitus[13].

That beta-blockers seem to have additional benefits for diabetic patients may be due to several mechanisms. Firstly, beta-blockade is negatively inotropic and chronotropic, thus reducing cardiac metabolic demands. This might be of particular benefit in the context of CAD, which is highly prevalent in diabetic patients. Secondly, beta-blockers provide prophylaxis against dysrhythmia and sudden cardiac death, which are more common in people with both diabetes mellitus and heart failure[6]. Thirdly, beta-blockers promote structural remodeling of the myocardium. We have shown in a prospective study of 628 patients receiving contemporary heart failure therapy, that patients with diabetes experienced more adverse structural and functional remodeling such that halting of this more rapid progressive change might be even more important in that group[14]. Fourthly, inhibition of the RAAS is not only a crucial treatment for heart failure, but a powerful tool in order to halt the progression of diabetic nephropathy. Finally, beta-blockers suppress sympathetic activation, countering the increased basal sympathetic neural outflow in diabetes mellitus[10].

Historically there has been reluctance to prescribe beta-blockers to those on insulin or sulfonylureas, due to a perceived risk of masking symptoms of hypoglycaemia or prolonging these episodes. However, in clinical trials the rates of hypoglycaemia were similar between groups, and these theoretical risks were far outweighed by the benefits[15].

The role of revascularisation

The role of coronary artery bypass grafting (CABG) is well established for patients with multi-vessel CAD with and without diabetes. Clinical trials have shown a mortality benefit following CABG or percutaneous intervention (PCI) for those with multi-vessel CAD, however those with CHF have often been under-represented. The FREEDOM trial demonstrated that in patients with diabetes, CABG resulted in improved mortality and fewer cardiac events than PCI, but only 3% of these patients had HFrEF[16]. The STITCHES trial showed that CABG was beneficial compared to medical management for patients with HFrEF, but was underpowered to detect whether patients with diabetes derived any additional benefit compared to non-diabetic patients[17]. However, in a large observational study with propensity matching, patients with diabetes and HFrEF treated with CABG had a lower rate of cardiovascular events and death compared to those with multi-vessel CAD treated with PCI[18].

Take home message

CHF patients with diabetes die sooner, have worse symptoms and are more frequently hospitalised. Contemporary heart failure therapies seem to confer additional benefit in those with diabetes. Despite this, there is often a reluctance to prescribe doses achieved in clinical trials, particularly when prescribed by non-cardiologists[19]. That incremental improvements in mortality reduction and hospitalization are observed with increasing doses should provide patients and healthcare professionals confidence in providing these life-saving medications.

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205 **Figure legends**

206 Figure 1

207 Mechanistic framework for diabetes related exacerbation of the heart failure phenotype.