Reducing the risk of heart failure in diabetes mellitus: review of new therapeutics

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ABSTRACT
Diabetes mellitus (DM) and heart failure (HF) are closely related: patients with diabetes have an increased risk of developing HF and those with HF are at higher risk of developing diabetes. When the two diseases are considered individually, HF has a much poorer prognosis than diabetes mellitus; therefore, treatment of HF is a priority in these group of patients. There are many drugs now available to achieve glycemic control in individuals with DM. However, as we enter an era of personalization in the management of DM, the next challenge will be the identification of therapeutic strategies that will not only achieve and maintain glycemic control, but that will also reverse existing complications. Given the high prevalence of HF in DM, there is a strong imperative to advance this field, with the view of identifying robust strategies that will not only improve long-term outcomes in subjects with DM and HF but also limit the likelihood of developing HF in the first place. Newer therapies like sodium-glucose transport protein-2 inhibitors (SGLT-2 I) and sacubitril or valsartan have shown potential benefit for reducing the risk of heart failure in diabetic population. This review will summarize the new therapeutics to reduce the risk of HF in patients with DM.

Keywords: Diabetes mellitus, Heart failure, Metformin, SGLT-2 inhibitors

INTRODUCTION
The prevalence of type 2 diabetes mellitus (T2DM) has risen consistently over the past years. International Diabetes Federation, 2019 reported that India ranks second in the world for the number of diabetes cases (77 million), and has anticipated this number to reach 134.2 million by 2045.¹

Concerns about cardiovascular disease (CVD) in T2DM have traditionally focused on atherosclerotic vasculo-occlusive events, such as myocardial infarction, stroke, and limb ischemia. However, one of the earliest and most serious CVD in patients with diabetes is heart failure (HF). Diabetic patients have an increased risk of developing HF because of the abnormal cardiac handling of glucose and free fatty acids, and because of the effect of the metabolic derangements of diabetes on the cardiovascular system. Following its onset, patients experience a striking deterioration in their clinical course, which is marked by frequent hospitalizations and eventually death. Heart failure and diabetes are linked pathophysiologically. T2DM and HF are each characterized by insulin resistance and are accompanied by the activation of neurohormonal systems (norepinephrine, angiotensin II, aldosterone, and nephrilysin). The two disorders overlap; diabetes is present in 35 to 45% of patients with chronic heart failure (CHF),
whether they have a reduced or preserved ejection fraction.\textsuperscript{2}

A wealth of epidemiological evidences establish that diabetes mellitus (DM) is highly common amongst patients with HF, especially those with heart failure and preserved ejection fraction (HFpEF), and patients with the both conditions have an increased risk of mortality compared with patients without diabetes or HF.\textsuperscript{3} As per the Framingham heart study, HF was shown to be twice as common in men with diabetes and five times more prevalent in women with diabetes between the ages of 45 and 74 years when compared with age-matched non-diabetic controls, and, in those aged ≥65 years, there was a fourfold increase in the prevalence of HF in men with diabetes and an eightfold increase in women with diabetes.\textsuperscript{4} Therefore, an exponential surge has seen in the combined diagnoses of T2DM and HF. On acknowledging these two diseases individually, HF has a much poorer prognosis than diabetes mellitus, therefore HF has to be a priority for treatment in patients presenting with the two conditions.\textsuperscript{3} In this present review we document relationship between HF and T2DM and the potential therapies to both prevent and treat HF are discussed, in addition to the positive effects of newer therapies like sodium-glucose transport protein-2 inhibitors (SGLT-2 i) and sacubitril or valsartan for reducing the risk of heart failure in diabetic population.

ETIOPATHOLOGY OF HF IN DM

The cardio toxic tetrad

The coexistence of coronary artery disease (CAD), left ventricular hypertrophy (LVH) and a specific diabetic cardiomyopathy, normally referred to as the cardiotoxic triad, leads to biochemical, anatomical and functional alterations in cardiomyocytes and cardiac tissues, and was originally thought to be the most appropriate explanation for the development of left ventricular dysfunction; however, the addition of fluid overload, which increases ventricular pressure in a stiffened ventricle, has also been suggested to extend the triad to the cardiotoxic tetrad (Figure 1).\textsuperscript{3,5} The combination of ischaemic heart disease, LVH and diabetic cardiomyopathy in conjunction with an extracellular volume expansion, which may be resistant to the action of atrial natriuretic peptides, initially leads to diastolic dysfunction, which is very common in people with type 2 diabetes.\textsuperscript{6}

Effect of glycemic variability on HF in T2DM

Glucose variability is known as one of the factors associated with adverse CVD outcomes for patients with T2DM. In a prospective, longitudinal study conducted to assess the prognostic impact of long-term glycemic variability (GV) on clinical outcomes in 902 patients with HF and T2DM, HbA1c variability was independently and similarly predictive of combined endpoints of death and HF readmission regardless of ejection fraction.\textsuperscript{7} Yokoto et al assessed the impact of GV on left ventricular (LV) diastolic function in 100 asymptomatic T2DM patients with preserved LV ejection fraction (LVEF) without coronary artery disease. Mitral inflow E and mitral e‘ annular velocities (E/e‘) in patients with high GV ($\geq35.9$ mg/dl) were significantly higher than that in patients with low GV ($<35.9$ mg/dl) (11.3±3.9 vs. 9.8±2.8, \(p=0.03\)). Furthermore, multivariate logistic regression analysis showed that GV $\geq35.9$ mg/dl was an independently associated factor of E/e‘>$14 as well as age. Thus, reducing GV may have a potential for a new therapeutic strategy for the prevention of HF in diabetic patients.\textsuperscript{5}

Figure 1: The cardiotoxic tetrad.\textsuperscript{5}

Poor glycaemic control and risk of HF in DM

Appropriate glycaemic control can reduce the risk of developing HF. UKPDS study showed that every 1% reduction in HbA1c was associated with a 16% decrease in the development of HF in people with new-onset diabetes.\textsuperscript{9} However, intensive glycaemic control in this study did not reduce admissions to hospital with HF.\textsuperscript{10} Tight glycaemic control also did not reduce HF in the action to control cardiovascular risk in type 2 diabetes trial and action in diabetes and vascular disease: preterax and diamicron MR controlled evaluation trial and veterans affairs diabetes trial.\textsuperscript{11-13} In a Swedish prospective case-control study of 33 402 patients with type 1 diabetes, poor glycaemic control significantly increased the risk of hospitalization due HF by fourfold compared to population based controls. HbA1c remained a risk factor for the development of HF even after adjustment for renal disease, showing a steep increase with poor glycaemic control.\textsuperscript{14}

Therapies to reduce the risk of HF in patients with DM

Therapies to reduce the risk of HF in patients with DM can be broadly classified as: oral anti-hyperglycaemic agents (OHA) and non-diabetic medications.

OHA THAT MAY PREVENT OR AMELIORATE HF

Metformin

Metformin, first line OHA for T2DM, and results in a lower risk of death and HF hospitalization compared with
insulin and sulfonylureas.\textsuperscript{15-17} Furthermore, 2019 European Society of Cardiology (ESC) guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the European Association for the Study of Diabetes (EASD) has endorsed the metformin at all stages of HF with preserved or stable moderately reduced renal function (i.e. eGFR >30 ml/min).\textsuperscript{18}

**Table 1: Therapies to reduce the risk of HF in patients with DM.**

<table>
<thead>
<tr>
<th>Therapies to reduce the risk of HF in patients with DM</th>
<th>Drugs</th>
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<tr>
<td>OHA</td>
<td>Metformin</td>
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<tr>
<td></td>
<td>SGLT-2 (i)</td>
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<tr>
<td>Non-diabetic medications</td>
<td>RAAS inhibitors (ACE inhibitors, ARB, MRA, ARNI)</td>
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<td></td>
<td>Beta blocker (metoprolol, carvedilol)</td>
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<tr>
<td></td>
<td>Ivabradine</td>
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<td></td>
<td>Statin (rosuvastatin)</td>
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</table>


**SGLT2-inhibitors**

Hospital admission for heart failure has been shown to significantly reduced by 35%, 33% and 27% with empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients removing excess glucose (EMPA-REG study), canagliflozin cardiovascular assessment study (CANVAS study) and dapagliflozin effect on cardiovascular events-thrombolysis in myocardial infarction (DECLARE-TIMI) 58 trial respectively. The mechanisms by which sodium glucose transporter-2 inhibitors (SGLT-2 \(i\)) mediate these benefits are not understood. However potential mechanisms that have been proposed include increased natriuresis, reduced blood pressure, renal protection and a modest effect to increase circulating ketones, which might improve myocardial energetics.\textsuperscript{19} More recently, reduction in plasma volume without concomitant compensating neurohormonal activation and a mitochondrial protective effect has been postulated as potential mechanism mediating the reduction of heart failure events.\textsuperscript{20} In light of evidence, 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD recommended SGLT2 \(i\) (empagliflozin, canagliflozin, or dapagliflozin) to lower risk of HF hospitalization in patients with DM.\textsuperscript{18} Initial results from empagliflozin comparative effectiveness and safety (EMPRISE) real-world evidence study shows empagliflozin was linked with lower risk for hospitalization for HF compared with DPP-4 inhibitors in people with type 2 diabetes with and without CVD. The full EMPRISE study will deliver a clinical representation of empagliflozin in routine clinical practice comprising comparative effectiveness, safety and healthcare resource utilisation and cost outcomes compared with DPP-4 inhibitors.\textsuperscript{21}

**HF THERAPY IN PATIENTS WITH DM**

**Renin-angiotensin-aldosterone system inhibitors**

Activation of RAAS in diabetes mellitus may also contribute to inflammation, cardiac fibrosis, and oxidative stress which all contribute to cardiac remodeling, and could be reversed or prevented by RAAS blockade. Thus, ACE inhibition and Ang II (angiotensin II) type 1 receptor blockade remain first-line therapy for CVD prevention in patients with diabetes mellitus. Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have similar treatment effects in patients with HF\(rEF\), with and without DM.\textsuperscript{22,23} RAAS blockers should be started at a low dose and up-titrated to the maximally tolerated dose.\textsuperscript{24}

Increased aldosterone signaling has been implicated in HF, diabetic cardiovascular injury including diabetic cardiomyopathy and may also play a role in the pathophysiology of insulin resistance. Inhibition of aldosterone receptor signaling with eplerenone may reduce indices of inflammation and markers of insulin resistance. Thus, it would be of interest to determine metabolic and cardiovascular outcomes (including HF incidence) in high-risk subjects with diabetes mellitus treated with aldosterone receptor antagonists.\textsuperscript{25} Mineralocorticoid receptor antagonist (MRAs) has shown to reduce the death and HF hospitalization in HF\(rEF\).\textsuperscript{26} In, eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS), eplerenone reduced the rate of mortality among patients with acute MI complicated by LV dysfunction and HF symptoms.\textsuperscript{27}

Natriuretic signaling has recently been shown to promote energy expenditure and augment systemic insulin sensitivity. Moreover, reduced adipose tissue natriuretic peptide signaling correlated with insulin resistance. Thus, it is plausible that these mechanisms of action could increase insulin sensitivity and metabolic control in subjects with T2DM and HF. As such, it will be of interest to rigorously determine whether angiotensin receptor-neprilysin inhibitors (ARNI) use could reduce the risk of HF progression in individuals with diabetes mellitus, particularly those at high risk for CVD and HF.\textsuperscript{25} In the prospective comparison of ARNI with ACEI to determine impact on global mortality and in heart failure trial (PARADIGM-HF) trial which included 35% of diabetic population among the patients of heart failure due to reduced EF, the angiotensin receptor neprilysin inhibitor sacubitril/valsartan has shown superior efficacy to enalapril in the reduction of CV death and HF hospitalization in patients with HF\(rEF\) irrespective of glycemic status.\textsuperscript{28} Sacubitril or valsartan therapy has also resulted in a greater reduction in HbA1c levels and a
lower rate of insulin initiation over 3 year follow-up compared with enalapril in patients with DM. This evidence suggests that sacubitril/valsartan might have a metabolic benefit in HFpEF patients and proposes a significant CV benefit of this ARNI, irrespective of the type or etiology of HF. 29

**Beta-blockers**

Although concerns were raised in the past about the potential increase in risk of hypoglycemia, when β-blockade is used in individuals with diabetes mellitus, there is little evidence that this is the case and contemporary clinical guidelines support the use of β-blockade in individuals with diabetes mellitus and HF. Notably, carvedilol (a combined β1/β2 antagonist) improves both glycemic control, LVEF, and decreases oxidative stress in the failing human heart and might be the β-blocker of choice in heart failure in diabetic population.27 Beta-blockers are effective at reducing all-cause death and hospitalization for HFpEF in patients with DM.30 In MERIT-HF study, metoprolol reduced the risk of hospitalization for heart failure by 37% in the diabetic group of CHF.31 Treatment benefits strongly support beta-blocker use in patients with HFpEF and DM.

**Ivabradine**

Increase in resting heart rate is a risk factor for adverse cardiovascular outcome in diabetic patients. Elsewhere, data from ADVANCE trial showed that the risks of new-onset or progressive nephropathy (adjusted HR 1.16 per 10 b.p.m., 95% CI 1.08–1.25) and retinopathy (adjusted HR, 1.11 per 10 b.p.m.; 95% CI, 1.02–1.21) were greater in patients with T2DM and higher resting heart rates.12 Lowering heart rate with ivabradine alleviates ischemia and improves cardiac function by improving coronary filling via the prolongation of diastole and the improvement of cardiac efficiency.32 Systolic heart failure treatment with the I1 inhibitor ivabradine trial (SHIFT) which included 30% of patients with chronic systolic heart failure and diabetes, demonstrated that ivabradine reduces the risk of CV death or HF hospitalization, and HF death or admission for HF, in patients in sinus rhythm with a heart rate ≥70 b.p.m. This analysis confirms the benefits of heart rate reduction with ivabradine are maintained in HF patients with diabetes as well as in those without, as has already been shown for ACE inhibitors, beta-blockers, and MRAs.33

<table>
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<tr>
<th>Drug</th>
<th>Clinical study</th>
<th>Design</th>
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<td><strong>Metformin</strong></td>
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<td>Significantly (p&lt;0.001) reduced incidence of HF with metformin</td>
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<tr>
<td>Dapagliflozin</td>
<td>DECLARE TIMI 58</td>
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<tr>
<td>Canagliflozin</td>
<td>CANVAS</td>
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<td>33% RRR of hospitalization due to HF</td>
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<tr>
<td>ACE I -</td>
<td>SAVE</td>
<td>RCT, CVOT</td>
<td>22% RR of CHF requiring hospitalization</td>
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<tr>
<td>Enalapril</td>
<td>SOLVD</td>
<td>RCT, CVOT</td>
<td>22% RR of deaths attributed to progressive heart failure</td>
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<td>ARB- Valsartan</td>
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<td>RR for Hospital admission for HF= 0.47 (p &lt;0.001)</td>
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<td>ARB- Losartan</td>
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<td>RCT, CVOT</td>
<td>Losartan 150 mg daily versus 50 mg daily; 13% RRR of Hospital admission for HF</td>
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<tr>
<td>ARNI (sacubitril or valsartan)</td>
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<tr>
<td>Ivabradine</td>
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<td>RCT</td>
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</tr>
<tr>
<td>Rosuvastatin</td>
<td>CORONA</td>
<td>RCT</td>
<td>15% RRR for hospital admissions for worsening HF</td>
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</tbody>
</table>

(RRR: relative risk reduction; HR: hazards ratio; RCT: randomized controlled trial; CVOT: cardiovascular outcome trial; SAVE: survival and ventricular enlargement trial; SOLVD: studies of left ventricular dysfunction trial; Val-HeFT: valsartan heart failure trial; HEAAL: heart failure endpoint evaluation of angiotensin II antagonist losartan trial; MERIT HF: metoprolol CR/XL randomised intervention trial in congestive heart failure; SHIFT: systolic heart failure treatment with the I1 inhibitor ivabradine trial; CORONA: controlled rosuvastatin multinational trial in heart failure.)
Lipid-lowering agents

Dyslipidemia is a major risk factor for CVD in T2DM. The characteristics of diabetic dyslipidemia include high plasma TG, high low-density lipoproteins, and low high-density lipoproteins. These changes can be attributed to increased fatty acid flux secondary to insulin resistance in adipocytes, in concert with altered hepatic lipid metabolism. While several classes of pharmacological agents are used to treat dyslipidemia, the controlled rosvuastatin multinational trial in heart failure suggested a reduction in the risk of hospitalization for HF by 15% to 20% in patients on rosvuastatin. The mechanism for the reduction in HF is not clear, but could represent reduced ischemic events or direct effects of the statin on endothelial or microvascular function.34

CONCLUSION

The pathophysiology of HF in diabetes mellitus is complex and represents a cardiovascular complication of diabetes mellitus that contributes importantly to morbidity and mortality. Given the high prevalence of HF in diabetes mellitus, there is a strong imperative to advance this field, with the view of identifying robust strategies that will not only improve long-term outcomes in subjects with diabetes mellitus and HF but also limit the likelihood of developing HF in the first place. For patients with diabetes and HF, metformin and SGLT2 inhibitors are anti-diabetic medications with established excellent cardiovascular safety profiles and that help reduce cardiac readmissions. Non-diabetic drugs which have documented benefits in the management of HF in DM are ACE inhibitors, ARBs, MRAs, ARNI, beta blockers, Ivabradine and lipid lowering agent such as rosvuastatin.

Future research is needed to gain further insight into the pathophysiology and therapeutic options so as to improve the prognosis of this high-risk population.

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