Newer Anti-Diabetic Agents and Heart Failure

Praphulla Koirala[1], Vijay K Chopra[2], Ambrish Mithal[1*]

[1]Department of Endocrinology and Metabolism, Max Super Speciality Hospital, Saket, New Delhi

[2]Department of Cardiology, Max Super Speciality Hospital, Saket, New Delhi

Correspondence:

Ambrish Mithal

E-mail: ambrish.mithal@maxhealthcare.com

According to the International Diabetes Federation (IDF), the burden of diabetes mellitus (DM) in India has been increasing steadily since 1990, growing exponentially in the last decade.[1] At present, diabetes mellitus is highly prevalent in India, affecting 10.1 crore individuals, as reported by the 2023 ICMR INDIAB study.

Almost three-quarters of people with diabetes die due to cardiac causes. Besides myocardial infarction and atherosclerotic cardiovascular disease, studies have now recognised the link between diabetes and heart failure (HF). Although DM and HF are individually associated with considerable morbidity and mortality, they often occur together. The synergy between DM and HF also adversely affects quality of life, patient outcomes and escalates healthcare costs. There is a bidirectional relationship between diabetes and heart failure, where individuals with diabetes have an elevated risk of developing heart failure and those with heart failure are at a greater risk of developing diabetes.[2]

Risk factors

Diabetes mellitus is associated with a nearly two-fold increase in the risk of HF in men and a four-fold increase in women, even after adjustment for other cardiovascular risk factors. In patients with stable coronary artery disease who are free from heart failure at baseline, diabetes and glycaemic control are independent risk factors for new-onset heart failure.[4]

The risk of developing heart failure (HF) in patients with diabetes mellitus (DM) increases with older age, the presence of coronary artery disease (CAD), peripheral arterial disease, nephropathy, retinopathy, longer duration of DM, obesity, hypertension and higher levels of NT-proBNP (N-terminal pro-B-type natriuretic peptide).[5][6][7]

Prevention of HF in patients with Type 2 diabetes mellitus (T2D) should be considered a top priority as the Swedish HF registry has shown a markedly reduced median survival of 3.5 years in patients with HF and T2D, compared with 4.6 years in those with HF alone.[8]

Antidiabetic treatment in patients with diabetes and heart failure

Oral anti-diabetic agents have come a long way since the discovery of biguanides in 1950 A.D. Sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 inhibitors (DPP4i), alpha-glucosidase inhibitors and meglitinides are among the commonly used oral anti-diabetic drugs. Newer drugs like sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon like peptide 1 receptor agonists (GLP1RA) have protective and positive effects on the heart, kidneys and liver besides controlling blood glucose levels and promoting weight loss.

Rosiglitazone, a thiazolidinedione, was withdrawn from the market due to a heightened risk of cardiovascular events, including heart failure. Pioglitazone, currently available thiazolidinedione, is contraindicated in heart failure due to its properties of promoting fluid retention and aggravating heart failure.

A) Sodium-glucose cotransporter-2 inhibitors (SGLT2i)

SGLT-2 inhibitors are a novel class of anti-diabetic drugs that work by inhibiting glucose reabsorption in the renal tubules. They provide an insulin-independent mechanism for glucose control. Notably, they also show favourable effects on body weight, blood pressure, lipid profile, arterial stiffness and endothelial function, as supported by multiple clinical trials and mechanistic studies.

i SGLT2i and prevention of HF in patients with DM:

EMPA-REG OUTCOME trial revealed that empagliflozin significantly reduced rates of death from cardiovascular causes (38% relative risk reduction), hospitalisation for heart failure (35% relative risk reduction) and death from any cause (32% relative risk reduction).[9]

The primary endpoint of MACE and mortality in Declare TIMI-58 was similar in both dapagliflozin and placebo groups but there was a significantly lower rate of CV death or HHF in the dapagliflozin group along with a reduction in adverse renal events in those with and without ASCVD, HF or CKD at baseline.[10]

In the CANVAS trial, treatment with canagliflozin demonstrated primary outcome (composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) was lower than with placebo (hazard ratio, 0.86; P<0.001 for noninferiority; P=0.02 for superiority).[11]

American and European guidelines recommend the use of SGLT2i for the prevention of HF in patients with T2DM.[12][13]

ii SGLT2i and treatment of heart failure in patients with DM

SGLT2 inhibitors are the only proven oral anti-diabetic agents found to be beneficial in patients with established HF, either chronic HF with reduced, mildly reduced, or preserved ejection fraction, or acute decompensated HF.[14]

DAPA-HF trial demonstrated that among patients with heart failure and a reduced ejection fraction (40% or less), the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin 10mg than among those who received placebo, regardless of the presence or absence of diabetes. Dapagliflozin was found to be superior in reducing the primary outcome (a composite of worsening HF, hospitalisation, an urgent visit resulting in intravenous therapy for HF, or CV death), the first worsening HF event (10%), death from CV causes (9.6%) and death from any cause (11.6%).[15]

The EMPULSE trial showed that empagliflozin 10mg was found to be superior to placebo in patients admitted to the hospital with acute heart failure regardless of ejection fraction or diabetes status, in reducing the composite of death, number of heart failure events, time to first heart failure event and change in Kansas City Cardiomyopathy Questionnaire-Total Symptom Score (KCCQ-TSS).[16]

EMPEROR-Preserved Trial, a double-blinded trial done in people with New York Heart Association (NYHA) class II–IV HFpEF (heart failure with a preserved ejection fraction of more than 40%) demonstrated that empagliflozin reduced the combined risk of CV death or HHF by 21% over 26.2 months, mainly related to a lower risk of HHF.

SGLT-2 inhibitors are therefore anti-diabetics of choice for patients with type 2 diabetes at high risk of CV events to reduce HHF, major adverse CV events (MACE), end-stage renal disease and CV death.[17] In addition to improved glycaemic control, diuresis, weight reduction and reduction in blood pressure may be contributors to the observed benefit. At the cellular level, mechanisms proposed to explain these benefits include improved cardiomyocyte calcium handling, enhanced myocardial energetics, induced autophagy and reduced epicardial fat.[18]

B) Glucagon-like peptide 1 receptor agonist (GLP1RA)

In the LEADER trial, the use of liraglutide in patients with type 2 diabetes (T2D) and high cardiovascular (CV) risk was linked to a 13% lower risk than placebo of the composite endpoint involving hospitalisation for heart failure (HHF) or CV death. However, the impact on HHF alone was not found to be statistically significant. Importantly, the observed benefit of liraglutide was consistent across patients, regardless of whether they had a history of heart failure.[19]

However, in the FIGHT trial which investigated the impact of liraglutide on patients with heart failure with reduced ejection fraction (HFrEF) recently hospitalised for decompensation, the results were not favourable. After 6 months of treatment, liraglutide did not show a significantly positive effect on the primary endpoint, the global rank score, which includes death and hospitalisations for heart failure (HF). Additionally, there was a higher risk for heart failure-related events, particularly in patients with type 2 diabetes (T2D).[20]

In patients with HFpEF and obesity, treatment with semaglutide (2.4 SC weekly) appears to result in larger reductions in symptoms and physical limitations, greater improvements in exercise function and greater weight loss compared to a placebo.[21]

However, two small trials showed potential worsening of HF when individuals with existing HF are treated with GLP1RA.[20] [22]

Ferreira et al. suggested that after heart failure (HF) screening, the suggested GLP-1 receptor agonist (GLP-1 RA) treatment decisions are outlined as follows:[23]

1. **T2D without HF:**
   - GLP-1 RAs are recommended for individuals with Type 2 Diabetes (T2D) and without HF.
   - The use of GLP-1 RAs aims to reduce the risk of myocardial infarction and stroke.
   - There is a potential effect to lower the risk of HF hospitalisations.
2. **HF with Preserved Ejection Fraction:**
   - GLP-1 RAs do not appear to reduce HF hospitalisations significantly in patients with HF and preserved ejection fraction.
   - However, considering their potential to reduce atherosclerotic events, the use of GLP-1 RAs may be considered on an individualised basis.
3. **HF with Reduced Ejection Fraction:**
   - Caution is advised in using GLP-1 RAs in patients with HF and reduced ejection fraction.
   - There is concern about the potential risk of worsening HF events and arrhythmias.
   - Decision-making should be based on pending risk–benefit data from further studies.

LIVE Trial, a double-blinded, placebo-controlled multicentre trial in which stable patients on optimal heart failure treatment with reduced left ventricular ejection fraction (LVEF ≤45%), intervention with 1.8 mg Liraglutide once daily showed that serious cardiac events (one death caused by ventricular tachycardia (VT), non-fatal VT, atrial fibrillation requiring intervention, aggravation of ischemic heart disease, and one case of worsening of heart failure) were seen in 12 (10%) patients treated with liraglutide compared with 3 (3%) patients in the placebo group.[24]

Although GLP1RAs have shown effectiveness in reducing cardiovascular events in diabetic patients with preserved ejection fraction, some researchers recommend caution when using GLP1RAs in patients with a reduced ejection fraction till large studies establish further data regarding their efficacy and safety in this condition.

C) Dual Incretin Receptor Agonists

US FDA approved tirzepatide, a novel, once weekly, first dual GLP-1 and GIP receptor agonist for the treatment of T2DM in 2022. Tirzepatide was found to be noninferior and superior to semaglutide resulting in a greater reduction in body weight and glycated hemoglobin levels than semaglutide.[25]

In a pre-specified meta-analysis that incorporated data from all seven randomised controlled trials (RCTs) with a duration of at least 26 weeks from SURPASS, the findings suggest that tirzepatide does not elevate the risk of major cardiovascular events in participants with T2D versus controls, although, data on long term outcome is not available yet.[26]

Conclusion

In individuals with diabetes mellitus, heart failure is prevalent (up to 22%), with risk factors being older age, the existence of coronary artery disease, peripheral arterial disease, nephropathy, retinopathy, longer diabetes duration, obesity, hypertension and elevated NT-proBNP levels. Early diagnosis is facilitated by a lower threshold for advising tests like echocardiography and NT-proBNP measurement.

SGLT2i are the drugs of choice in diabetes with heart failure and are effective in treating heart failure even in the absence of diabetes.

GLP-1 receptor agonists (GLP1RAs) have demonstrated a reduction in cardiovascular events in diabetic patients with preserved ejection fraction. However, caution is advised when using GLP1RAs in patients with a reduced ejection fraction.

Thiazolidinediones are contraindicated in heart failure.

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