Consensus Recommendations for Clinical Practice: Management of Glycemia in a Person with Type 2 Diabetes Mellitus with Heart Failure: An Indian Perspective


### Section 1: The Prevalence and Impact of Heart Failure in Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus (T2DM) is a well-recognized risk-factor for heart failure (HF). Among five modifiable risk factors studied for their influence on the population burden of HF in 14,709 persons in the Atherosclerosis Risk in Community study, namely smoking, elevated low-density lipoproteins, diabetes, hypertension, and obesity, diabetes was associated with the largest incidence rate differences; it was estimated that a 5% reduction in the prevalence of diabetes shall approximately prevent 30,000 incident HF cases in the US population. Among the 5,209 men and women followed for 18 years in The Framingham Heart Study, prior diabetic status resulted in a 2-fold increase in risk of congestive HF (CHF) in men and 5-fold increase in risk in women compared to the non-diabetic cohort. A systematic review of observational studies published in 2013 suggested that each 1% rise in glycated hemoglobin (HbA1c) value led to a 15% increase in the risk of CHF. Among the 34,198 individuals with T2DM in the CALIBER (Cardiovascular disease research using linked bespoke studies and electronic health records) study, 18% individuals had a first cardiovascular disease (CVD) presentation during a median follow-up of 5.5 years. Among the 12 initial manifestations of CVD studied, HF was the second most common first presentation, next only to peripheral arterial disease, and ahead of stable angina, non-fatal myocardial infarction and stroke.

There is limited data on HF burden in people with T2DM in India. However, with the rise in the incidence of various risk factors for HF, in particular hypertension and T2DM, it is clear that the burden of HF in India shall mirror the global picture of substantial overall increase in the future. The international congestive heart failure (INTER-CHF) study was designed to assess the one-year mortality rate in people with HF across China, India, South-East Asia, the Middle-East, South America and Africa. Of the 858 Indian patients with HF, 26% had a known history of diabetes. The one-year mortality rate in the Indian cohort was high at 23%, next only to that in Africa. The United Kingdom progressive diabetes study (UKPDS-83), a prospective observational sub-study that looked into the effect of ethnic differences on long term vascular outcomes in T2DM found that Asian-Indians were at a greater risk of any diabetes-related outcome, which included HF, when compared to White Caucasians. In the ‘I CaRe for Diabetes’ cross-sectional survey, conducted across 250 out-patient departments in India, peripheral edema was observed in 22% of people with T2DM; 11.8% had abnormal 2-dimensional echocardiographic findings, and 6.6% had confirmed HF. The underestimation of prevalence of HF in T2DM in the Indian setting reflects a lack of congruence between existing knowledge and actual clinical practice.

HF and T2DM share a bi-directional clinical relationship. A prospective community-based study over 9 years involving 5314 people with HF without T2DM at onset (mean age 72 years) identified a 2.4-fold higher risk of development of new-onset DM. Moreover, in people with newly detected T2DM and HF, the risk of mortality was increased by 2.5-fold, number of clinic visits by 1.5-fold, and rate of hospitalizations by 1.4-fold; poor glycemic control further worsened these outcomes. HF by itself impairs health-related quality of life (HRQoL), and the co-existence of T2DM and HF further significantly worsens HRQoL.

In the Practice Innovation and Clinical Excellence (PINNACLE) India Quality Improvement Program (PIQIP), a registry for CV quality improvement in India, diabetes was coexistent in 23% of people with HF with reduced ejection fraction (HFrEF). The Trivandrum Heart-Failure Registry assessed clinical outcomes in people hospitalized for HF. DM was a frequent comorbidity, observed in 55% of these hospitalized patients. Despite a younger population, this prevalence of DM is greater in the Trivandrum registry as compared to other registries, suggesting a generally higher prevalence of DM in India. Less than one-fourth of these patients were receiving guideline-based medical treatment.

In a UK-based study of people presenting with their first hospitalization for HF, a greater incidence of diabetes was observed in patients of South Asian ethnicity (46%), as compared to Caucasian patients (18%); patients of South Asian ethnicity had a greater incidence of HF with preserved ejection fraction (HFrEF), and better survival outcomes when compared to Caucasian patients. In another study comparing prospective population based HF cohorts from Sweden and Singapore, people with HF of Southeast Asian ethnicities from Singapore, including 10% of Indian ethnicity, had a 3-fold greater prevalence of DM in HF despite younger age and lesser obesity when compared to Caucasian patients of HF from Sweden. Furthermore, presence of DM was more strongly associated with hospitalization due to HF and all-cause
mortality in the Asian patients when compared to Caucasians.\(^{16}\)

Chronic Kidney Disease (CKD) is a common comorbidity of both T2DM and HF. Over half the people with CKD have concomitant HF or coronary artery disease (CAD), and such patients have exceptionally high rates of CV morbidity and mortality.\(^{17}\) Even modest increases in albuminuria or reduction in estimated glomerular filtration rate (eGFR) strongly predict the risk of CV and HF outcomes.\(^{18}\)

The significance of modifiable risk-factors for HF, which commonly coexist in T2DM, cannot be understated. Obesity, CAD, hypertension, anemia and obstructive sleep apnea contribute to the risk of HF in patients with DM. Community-based studies in India have consistently demonstrated low awareness, inadequate treatment, and poor attainment of targets of CV risk-factors. For hypertension, the rate of awareness and treatment is less than 50% amongst affected patients, and less than a fourth of the hypertensive patients are at target. Nearly half of the patients with diabetes are unaware of their disease, and barely one-third are on target. Less than 5% of patients in urban India attain target cholesterol values.\(^{19}\)

**Consensus Recommendations**

*The Prevalence and Impact of Heart Failure in Type 2 Diabetes Mellitus*

i. Heart failure is a common, yet less recognized, and discussed, complication of type 2 diabetes mellitus.

ii. The co-existence of diabetes mellitus and heart failure has significant clinical and economic implications in terms of clinic visits, hospital admissions, quality of life, morbidity and mortality.

iii. In Indian adults, heart failure and diabetes mellitus occur at a younger age and affect the more productive years of life.

iv. Information on the burden and impact of concomitant heart failure and diabetes mellitus in India is limited.

v. Adequate public-health research and surveillance is necessary to facilitate improved understanding of the burden and impact of heart failure and diabetes mellitus in India.

vi. Increased mortality due to suboptimal therapy of heart failure is a major preventable problem in India.

vii. Significant efforts are required to optimize clinical management approaches in type 2 diabetes mellitus, especially in the presence of cardiovascular and renal comorbidities.

viii. Associated comorbidities in type 2 diabetes mellitus, including coronary artery disease, hypertension, obesity, anemia, obstructive sleep apnea, and/or chronic kidney disease need to be addressed adequately for effective management of heart failure in type 2 diabetes mellitus.

**Section 2: Diagnosis and Classification of Heart Failure**

HF is a complex clinical syndrome that underlines the inability of the heart to perform its circulatory function with the desired efficiency, due to structural and/or functional (systolic or diastolic) alterations.\(^{20}\) HF is a clinical syndrome of symptoms and signs, together with objective evidence of structural or functional abnormality of the heart.

HF may be classified based on left ventricular ejection fraction (LVEF), time-course, or severity of symptoms, as follows:

**Based on Left Ventricular Ejection Fraction:**

- **LVEF <40%:** HF with reduced ejection fraction (HFREF).
- **LVEF ≥50%** with evidence of diastolic dysfunction or structural cardiac changes: HF with preserved ejection fraction (HFpEF).
- **LVEF 40%-49%:** HF with mid-range ejection fraction (HFmrEF). Gray zone between HFREF and HFpEF.

**Based on Time-course:**

- Chronic HF: Present for ≥3 months
- Acute HF: Sudden onset HF or worsening of HF symptoms/signs

**Based on Severity of Symptoms [New-York Heart Association (NYHA) classification]:**

- **Class I:** No limitation in physical activity
- **Class II:** Slight limitation in physical activity. Ordinary activity results in symptoms. Patient is comfortable at rest.
- **Class III:** Marked limitation in physical activity. Daily routine activity results in symptoms. Patient is comfortable at rest.
- **Class IV:** Unable to do physical activity. Symptoms maybe present even at rest.

The American College of Cardiology / American Heart Association classifies the stages of heart failure as follows:

- **Stage A:** High risk, without symptoms (diabetes, hypertension, CAD)
- **Stage B:** Structural heart disease, without symptoms
- **Stage C:** Structural heart disease with previous or current symptoms
- **Stage D:** Structural heart disease with refractory symptoms

**Screening for Heart Failure Risk in Type 2 Diabetes Mellitus:** Routine clinical screening for HF may be considered for all patients of T2DM. Routine electrocardiogram (ECG), as well as measurement of N-terminal pro-B type natriuretic peptide (NT-proBNP) independently adds value to screening assessments.\(^{20}\) Further, the assessment of albuminuria and estimation of eGFR is desirable as they are strong and independent risk-predictors for HF.\(^{16}\)

- Resting ECG: Recommended for all patients of T2DM, at initial visit, and at-least once annually.
- NT-proBNP: May be considered for routine screening of HF in all patients at initial visit, and at-least once annually, whenever possible. NT-proBNP has a greater relevance in ruling out HF, and in prognostic follow-up for HF, but it may not be a useful investigation to help establish the diagnosis of HF. For NT-proBNP, the European Society of Cardiology has recommended a cut-off value of >125 pg/mL for identifying HF in a non-acute setting.
- Albuminuria (urine albumin-creatinine ratio, UACR): Should be considered in all patients of T2DM, at initial visit, and at-least once annually. As per a comprehensive meta-analysis, in patients who have a high-risk of HF events (≥10% risk in 5 years), the number of patients needed to screen...
in order to prevent 1 HF event would be 1,347. If albuminuria is added to the routine screening assessments for HF, the number needed to screen would decrease by 396 patients. This means that if albuminuria is routinely included for screening of HF risk in T2DM, the screening efficiency to prevent 1 additional HF event will improve by 29.4\%.18

- eGFR [based on serum creatinine, using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation]: Estimation of eGFR should be considered for all patients of T2DM, at initial visit, and at-least once annually. If in the earlier example, eGFR is added to the routine screening assessments for HF, the number needed to screen would decrease by 134 patients. This means that if eGFR is routinely included for screening of HF risk in T2DM, the screening efficiency to prevent 1 additional HF event will improve by 9.9\%.18

- Chest X-ray: May be considered in symptomatic HF patients to identify pulmonary venous congestion or edema, and to rule out other diagnoses.

Establishing the Diagnosis of Heart Failure in Type 2 Diabetes Mellitus

It is important to note that all patients of T2DM with HF may not exhibit typical symptoms. On the other hand, not all patients who have symptoms suggestive of HF, actually have HF. Ischemic heart disease and chronic obstructive pulmonary disease can also present with shortness of breath on exertion.

Hence, the optimum diagnosis of HF depends on clinical evaluation of history, physical examination, screening assessments of resting ECG, NT-proBNP (whenever possible), corroborative screening assessments of albuminuria and eGFR, with the confirmatory assessment of doppler echocardiography.

Echocardiography is the cornerstone for confirming the diagnosis of Heart Failure. 2-Dimensional Echocardiography not only provides information on the structure and function of the heart but also helps to differentiate between HFrEF and HFpEF.

Consensus Recommendations: Diagnosis of Heart Failure in Type 2 Diabetes Mellitus

i. Accuracy of the diagnosis of heart failure depends on meticulous clinical assessment (history, physical examination) and accurate interpretation of laboratory parameters.

ii. Routine clinical assessment for Heart Failure (history and physical examination) should be conducted

for all patients of type 2 diabetes mellitus.

iii. Routine serial assessment of resting ECG, UACR, and eGFR (based on serum creatinine, using CKD-EPI equation) should be considered in all patients of type 2 diabetes mellitus to help predict the risk of developing heart failure. Evaluation of NT-proBNP should be considered to assess the probability of heart failure, whenever possible.

iv. Confirmatory Assessment: Echocardiography is an essential laboratory investigation to establish the diagnosis of Heart Failure. Patients should be referred for echocardiography should the clinical or laboratory parameters suggest heart failure. Doppler echocardiography should be conducted in selected patients.

Section 3: Achieving glycemic control in a person with Type 2 Diabetes Mellitus with Heart Failure

Although studies have demonstrated increased risk of HF with worsening glycemic control in people with T2DM, tight glycemic control has not been shown to improve HF outcomes. The evidence pertinent to use of individual anti-diabetic agents in a person with T2DM with HF is reviewed in this section.

3.1. Which Oral Antidiabetic Agents are Contraindicated? Thiazolidinediones (TZDs)

TZDs have a propensity for fluid retention, and the marketed agents have a labelled warning for possible causation or exacerbation of HF.21 People receiving TZDs should be closely monitored for the signs and symptoms of HF. If HF is suspected, TZDs should be discontinued, and HF should be managed as per standards of care. TZDs are not recommended in patients with symptomatic HF, and should not be used in patients with established NYHA Class I-IV HF.

Pioglitazone (15 mg, 30 mg, and 45 mg) has demonstrated a dose-dependent increased risk of developing HF when compared to insulin alone. A post-marketing study in patients of T2DM with HF (NYHA Class II / III) and EF <40% demonstrated.
increased hospitalization for HF with pioglitazone (9.9%) when compared to glyburide (4.7%). The risk was more marked in patients using insulin, and in older patients. In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), which involved patients of T2DM with macrovascular disease, HF events were significantly more common in patients receiving pioglitazone.22

Hospitalization for HF was observed in 5.7% patients receiving pioglitazone, compared to 4.1% patients on placebo; however, the rate of mortality due to HF was not increased with pioglitazone. A post hoc analysis of PROACTIVE revealed an increase in serious HF events (defined as HF that required hospitalization or prolonged hospitalization stay, was fatal or life threatening, or resulted in persistent significant disability or incapacity) in the pioglitazone group (5.7%) when compared to placebo (4.1%) (p = 0.007); however, interestingly, there was no increase in mortality due to HF. On treating 63 patients of T2DM and macrovascular disease with pioglitazone over 3 years, one additional serious HF event can be expected. Edema in the absence of HF was reported in 1 out of 5 patients receiving pioglitazone, compared to 1 out of 8 patients receiving placebo over the study duration of nearly 3 years.22

The Rosiglitazone Evaluated for Cardiovascular Outcomes in oral combination therapy for type 2 diabetes (RECORD) trial demonstrated a 2.1-fold increase in risk of HF-related death or hospitalization with rosiglitazone; moreover, unlike pioglitazone in PROACTIVE, the incidence of HF-related death was increased with rosiglitazone in the RECORD trial. 3

In a meta-analysis of 94 trials (excluding PROACTIVE), where 11,268 patients on pioglitazone were compared with 9,912 patients on other treatments for T2DM for at least 4 weeks, pioglitazone use was associated with a reduction in all-cause mortality and no relevant adverse effect on non-fatal coronary events. Although the odds for non-fatal HF were 38% higher with pioglitazone, it was statistically non-significant.24 A review of evidence suggests that although TZDs may cause fluid and sodium retention, they may improve left ventricle remodeling as well as diastolic performance.25 Further, the CHICAGO (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone) and PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) studies have demonstrated relatively favorable effects of pioglitazone on carotid intima-media thickness (CIMT) and coronary atheroma volume when compared to glimepiride respectively.26 Some physicians use pioglitazone in people with T2DM with cardiac disease with preserved ejection fraction, in order to avail the pleiotropic benefits on the heart.27 A 6-month therapy of pioglitazone in patients of T2DM with left ventricular diastolic dysfunction did not demonstrate any adverse or favorable changes in LV diastolic or systolic function.28 However, a case report does suggest an event of hospitalization for HF and pulmonary edema in a person with diastolic dysfunction who had received pioglitazone therapy over 1 year.29

Dipeptidyl peptidase-4 inhibitors (DPP4-inhibitors)

Evidence from Cardiovascular Outcome Trials (CVOTs) / Other Randomized Controlled Trials (RCTs)

The SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53) trial unexpectedly revealed a statistically significant 27% increase in the risk of hospitalization for HF with saxagliptin; however, there was no increase in the risk for 3-point major adverse CV events (CV death, non-fatal myocardial infarction, non-fatal stroke; 3-P MACE). The increase in risk of hospitalization for HF in the saxagliptin group was attributed partly to presence of background chronic kidney disease (CKD), elevated natriuretic peptide levels, and previous HF.30 Based on an alternative statistical method to calculate the average time before hospitalization for HF (restricted mean survival time), the differences in risk of hospitalization for HF between saxagliptin and placebo remained statistically significant, but not clinically relevant: patients treated with saxagliptin for 720 days would on-average be expected to be free of hospitalization for HF just 4 days less than their counterparts on placebo.31

EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) trial with alogliptin revealed a 19% statistically non-significant increase in risk of hospitalization for HF. These results led to a drug safety communication by the United States Food and Drug Administration (USFDA) in 2016 related to the potential increase in the risk of HF associated with these two DPP-4 inhibitors, despite the fact that a post hoc analysis of EXAMINE trial did not find any increase in risk of hospitalization for HF (HR 1.07; 95% CI 0.79-1.46).32

Secondary analysis of TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) found no increase in the risk of hospitalization for HF or HF-related deaths with sitagliptin.33 CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin) assessed the CV outcomes of linagliptin in nearly seven thousand patients with CV disease, and/or CKD.34 The study population represented patients of T2DM with significantly increased risk for HF, with more than one-fourth with a prior history of HF, and >60% with overt CKD (eGFR <60 mL/min/1.73m² or macroalbuminuria). CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus) revealed that linagliptin therapy was not associated with an increase in risk of hospitalization for HF (HR 0.90; 95% CI 0.74-1.08). Although none of the DPP4-inhibitor CVOTs were designed to evaluate HF outcomes as primary end-point, they did prospectively collect, and centrally adjudicate the events of hospitalization for HF using nearly identical definitions.

In patients with T2DM with HF, the evidence on use of DPP4-inhibitors remains inconsistent. Although, in SAVOR-TIMI 53, patients with prior history of HF and/or elevated baseline levels of NT-proBNP were at a greater risk for hospitalization for HF with saxagliptin (4.2-folds higher in patients with prior HF, and 31% higher in patients belonging to the highest quartile of baseline NT-proBNP),30 a similar trend was not observed with alogliptin in EXAMINE study32, or sitagliptin in TECOS study35. Moreover, in CARMELINA, which included 1,873 patients of T2DM with prior history of HF, linagliptin use was not
associated with an increase in risk of hospitalization for HF (HR 0.88; 95% CI 0.68-1.14).  

Currently, evidence for DPP4-inhibitors in patients with T2DM with diastolic dysfunction is limited. Subgroup analysis of PROLOGUE (Program of Vascular Evaluation under Glucose Control by DPP4 Inhibitor), which studied 115 patients (55 in sitagliptin group and 60 in conventional group), suggested that adding sitagliptin to conventional antidiabetic treatment in patients with T2DM over a period of 2 years attenuated the annual exacerbation in the echocardiographic parameter of diastolic dysfunction [ratio of peak early diastolic transmitral flow velocity (E) to peak early diastolic mitral annular velocity (e′); E/e′ (~0.18 ± 0.55 vs. 1.91 ± 0.53, p = 0.08)], independent of other clinical variables such as blood pressure and glycemic control.  

Similarly, in a small retrospective study including 34 patients with T2DM who presented with acute myocardial infarction (MI), use of DPP4-inhibitors (13 patients) during follow-up resulted in a decrease in echocardiographic parameter of diastolic dysfunction (E/e′) when compared to those not treated with DPP4-inhibitors (21 patients) (-2.53 ± 5.53 vs. 2.58 ± 5.68, p=0.038), suggesting DPP4-inhibitors might be useful in left ventricular diastolic failure. However, conclusive evidence of clinical benefit of any DPP4-inhibitor in patients with T2DM with diastolic dysfunction is presently lacking.

Evidence from Meta-analyses of CVOTs / RCTs

A meta-analysis of three major CVOTs of DPP4-inhibitors (SAVOT-TIMI 53, EXAMINE, TECOS) suggested a marginally significant 12% increase in risk of hospitalization for HF when compared to placebo ([HR 1.12; 95% CI 1.00-1.25); moderate heterogeneity (I² = 44.9, p = 0.16)].

Verma et al. reported a meta-analysis of 100 high quality, placebo-controlled, multi-centric RCTs including the three major CVOTs (SAVOR-TIMI 53, EXAMINE and TECOS) and 97 smaller RCTs; they reported a statistically significant 13% increase in risk of hospitalization for HF with DPP4 inhibitors compared to controls (relative risk [RR] 1.13, 95% confidence interval [CI] 1.01-1.26, I² = 0%; 32 RCTs, n = 54 640, 1244 events). However, an analysis of the three major CVOTs in this study (SAVOR-TIMI 53, EXAMINE and TECOS) suggested a non-significant 14% increase in risk of hospitalization for HF (RR 1.14, 95% CI 0.97-1.32; 3 RCTs, n = 36 543, 1169 adjudicated events). Moreover, this study failed to answer whether DPP4 inhibitors increase the risk of hospitalization for HF overall for the entire class or there are within-class differences. A recent meta-analysis that included all four DPP4-inhibitor CVOTs (SAVOR-TIMI 53, EXAMINE, TECOS, CARMELINA) did not find any increase in risk of hospitalization for HF (fixed model RR 1.06; 95% CI, 0.96–1.17; p = 0.25); moreover, an analysis of all RCTs of ≥52 weeks that specifically looked for hospitalization for HF also did not show any increase in risk of hospitalization for HF (fixed model Peto odd ratio 1.05; 95% CI 0.95-1.15, P = 0.36).

Evidence from Observational Studies

In addition to the information in the previous section gleaned from individual large DPP4-inhibitor CVOTs and meta-analyses including RCTs with or without the large CVOTs, a number of observational studies further confuse the risk of hospitalization for HF posed by DPP4 inhibitors. In a large population based, new-user, retrospective cohort study, saxagliptin use was not associated with an increase in risk of hospitalization for HF when compared to sitagliptin; moreover, the risk of hospitalization for HF was lower with both saxagliptin and sitagliptin when compared to pioglitazone, sulphonylureas, and insulin. In a retrospective cohort study involving 1,203 patients of T2DM after a recent acute MI or acute ischemic stroke, the use of linagliptin (401 patients) was not associated with an increase in risk of all-cause mortality, hospitalization for HF, percutaneous coronary intervention, and coronary artery bypass grafting when compared to 802 matched controls not receiving any DPP4-inhibitor.

In a recently published systematic review in 2019, analysis of 14 observational studies that compared a DPP4-inhibitor with active comparators revealed inconsistent results for hospitalization for HF outcomes.

Miscellaneous Evidence

The VIVIDD (Vildagliptin in Ventricular Dysfunction Diabetes) trial, which included patients of T2DM with HFrEF (LVEF <40%), compared vildagliptin 50 mg twice daily (50 mg once daily if treated with a sulphonylurea) with placebo over a period of one year. Vildagliptin had no major effect on LVEF. However, vildagliptin use was associated with a significant increase in LV end-diastolic volume and a non-significant increase in end-systolic volume. The cause and clinical significance of these observations were unclear. There was a significant increase in stroke volume, but no change in LV wall thickness or mass. There were numerically greater events of CV death and all-cause mortality in the vildagliptin group, but these were not significantly increased when compared to placebo. The authors concluded that there was an urgent need for further studies to assess the safety of DPP4-inhibitors in patients with HF and LV systolic dysfunction.

In a small study, teneligliptin use was associated with improvements in LV and endothelial function, and an increase in serum adiponectin levels. The ongoing TOPLEVEL (Teneligliptin On the Progressive LV Diastolic Dysfunction with Type 2 Diabetes Mellitus study) trial of teneligliptin is designed to assess the long term effect of teneligliptin on cardiac diastolic dysfunction in 936 participants, and might provide further evidence on the long-term effects of teneligliptin on CV and HF outcomes. A truncated data set from the omarigliptin CV outcome trial (OMNEON) did not reveal any increase in hospitalization for HF (HR 0.60; 95% CI 0.35–1.05; p-not reported) with omarigliptin compared to placebo. Sitagliptin, together with granulocyte-colony stimulating factor (G-CSF), was evaluated in 174 patients of T2DM with acute MI who had undergone percutaneous coronary intervention (PCI) in the STITAGRAMI (Randomized comparison of SITAgliptin plus G-CSF versus placebo after early Revascularization in Acute Myocardial Infarction) study. Over a median follow-up of 4.5 years, sitagliptin use was not associated with an increase in risk of major adverse CV events.
Regulatory Warning

In March 2018, the USFDA suggested addition of a warning note in the prescribing information of all the DPP4-inhibitors suggesting consideration of the risks and benefits of DPP4-inhibitors prior to initiating treatment in patients at risk for HF, such as those with a prior history of HF or history of renal impairment, and to observe these patients for signs and symptoms of HF during therapy. Patients must be advised of the characteristic symptoms of HF, and to immediately report such symptoms. If heart failure develops, DPP4-inhibitor should be discontinued.

Consensus Recommendations

Patients of Type 2 Diabetes Mellitus without Heart Failure:

i. Thiazolidinediones (TZDs) can cause, or exacerbate, heart failure in patients of Type 2 Diabetes Mellitus. Patients receiving TZDs should be monitored for symptoms and signs of heart failure. If heart failure is suspected, TZDs should be discontinued, and heart failure should be managed as per standards of care.

ii. Saxagliptin, and possibly alogliptin, may increase the risk of hospitalization for heart failure in patients of type 2 diabetes mellitus with high cardiovascular risk and chronic kidney disease stage 3 & above. Patients should be observed for symptoms and signs of heart failure during therapy. If heart failure is suspected, saxagliptin or alogliptin should be discontinued, and heart failure should be managed as per standards of care.

iii. The choice of a particular DPP4 inhibitor should be based on clinical judgment, guided by pertinent factors related to the patient and the drug. An evidence-based informed decision should be made.

iv. Teneligliptin may cause QT interval prolongation in patients with heart failure.

3.2 Which Oral Antidiabetic Agents are Preferred?

Metformin

At the outset, it should be noted that metformin carries a labelled warning for the risk of lactic acidosis in patients with HF.

In a systematic review of nine observational studies, involving over 34,000 patients of T2DM and HF, metformin use was associated with a significant 20% reduction in mortality in people with diabetes and HF when compared to controls (pooled adjusted risk estimates: 0.80; 95% CI 0.74-0.87; I(2)=15%; P<0.001). There was no increased risk of mortality in subgroups of patients with reduced LVEF (mortality pooled adjusted risk estimate: 0.91; 95% CI 0.72-1.14; I(2)=15%; P=0.001). There was no increased risk of mortality in subgroups of patients with reduced LVEF (mortality pooled adjusted risk estimate: 0.91; 95% CI 0.72-1.14; I(2)=15%; P=0.001). There was no increased risk of mortality in subgroups of patients with reduced LVEF (mortality pooled adjusted risk estimate: 0.91; 95% CI 0.72-1.14; I(2)=15%; P=0.001).

Alternatively, metformin use was associated with a statistically significant reduction in all-cause hospitalizations (pooled adjusted risk estimate: 0.93; 95% CI 0.89-0.98; I(2)=0%; P=0.01; notably, metformin use was not associated with an increase in risk of lactic acidosis.46

In a more recent meta-analysis of 17 observational studies assessing clinical outcomes of metformin use in patients with T2DM and moderate to severe CKD, HF, or chronic liver disease, it was noted that metformin use was associated with a significant 22% reduction in risk of all-cause mortality, and 13% lower risk of readmissions for HF. In patients of T2DM with CKD, metformin use was associated with a statistically significant 22% lower risk of all-cause mortality, as well as 9% lower risk of readmissions for HF.46

The mechanistic studies to assess CV effects of metformin have demonstrated mixed results. In a small RCT involving patients of T2DM without structural heart disease or inducible ischemia, metformin therapy did not improve cardiac diastolic function over 24 weeks; however metformin use decreased cardiac work, which was accompanied by reduced myocardial glucose uptake and fatty acid oxidation.47 In the randomized GIPS (Glycemic Intervention as adjunct to Primary percutaneous coronary intervention in ST-Segment elevation myocardial infarction) III trial, the use metformin 500 mg twice daily in 380 non-diabetic patients who had undergone primary percutaneous coronary intervention for acute MI did not demonstrate an improvement in LVEF over a period of 4 months when compared to placebo.48

Another study involving 105 patients of T2DM without history of cardiac disease suggested that improvement in glycemic control over a period of 12 months leads to an improvement in LV systolic and diastolic function, and metformin use was one among three independent predictors of improvement.49

Despite supportive evidence from observational studies and mechanistic experimental data, confirmatory evidence from a RCT of clinical benefit of metformin use in patients of T2DM and HF is still lacking. ESC 2016 guidelines mention that in patients of T2DM with HF, metformin is a safe first-line therapy for glycemia control.20

Sodium-glucose co-transporter-2 inhibitors (SGLT2-inhibitors)

The Empa-Reg OutCOMe (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients study evaluated the effects of empagliflozin, compared to placebo, on CV outcomes in patients of T2DM with established CVD receiving standard care. The study demonstrated statistically significant improvement in multiple CV outcomes,
Real-world evidence (RWE) has also demonstrated the benefit of SGLT2-inhibitors on HF outcomes in patients with T2DM when compared to other glucose lowering agents.57,58 However, one should be aware of the limitations of real world studies, as was evident from the discordant observations concerning the magnitude of benefit towards reduction in risk of hospitalization for HF seen with canagliflozin from RWE and RCT.59 A number of well-conducted real-world studies have demonstrated consistent benefits with SGLT2-inhibitors in HF related outcomes in patients of T2DM across the spectrum of CVD.60,61 EMPRISE (EMPagliflozin compaRative effectiveness and Safety), a real world study, demonstrated a 49% lower relative risk of hospitalization for HF in patients receiving empagliflozin when compared to matched group of patients receiving sitagliptin.61 A mechanistic study over 16 weeks involving patients of T2DM with CVD and HFrEF has demonstrated improvement in cardiac structural (LV mass index) and functional (early lateral annular tissue Doppler velocity) parameters with empagliflozin.62 Similar observations were made in a 24-week mechanistic study with empagliflozin, demonstrating salutary effects on LV remodeling in patients of T2DM with stable CAD, with normal ejection fraction and without a clear history of HF.63 Unlike the classical diuretic agents, the SGLT2-inhibitors have a more predominant effect on reduction in interstitial volume as compared to blood volume. This might have clinical relevance on certain aspects of HF.64 Unlike the classical diuretic agents, the SGLT2-inhibitors have a more predominant effect on reduction in interstitial volume as compared to blood volume. This might have clinical relevance on certain aspects of HF.64

**Consensus Recommendations**

i. Metformin is a safe anti-diabetic agent for use in eligible patients of type 2 diabetes mellitus with stable heart failure for control of blood glucose.

ii. SGLT2-inhibitors, empagliflozin, canagliflozin and dapagliflozin have demonstrated promising results in reducing the risk of hospitalization for heart failure beyond glycemia control. These agents may be considered for improving heart failure related outcomes beyond glycemia control in patients of type 2 diabetes mellitus, who are at increased risk of heart failure or in those with stable heart failure.

iii. In patients with type 2 diabetes mellitus who are at increased risk of heart failure and who have achieved target glycemic goal without an SGLT2-inhibitor, the inclusion of an SGLT2-inhibitor should be considered in light of the promising results seen with SGLT2 inhibitors in reducing the risk of hospitalization for heart failure beyond glycemia control in this group of patients; if necessary, down-titration of or a change in other antidiabetic agents with empagliflozin in patients with and without T2DM with HFrEF and HFrEF.65 Similarly, DAPA-HF and DELIVER (Dapagliflozin Evaluation to Improve the LIVES of Patients With PReserved Ejection Fraction Heart Failure) trials are evaluating the effect of dapagliflozin on the incidence of worsening heart-failure or CV death in patients with and without T2DM with HF with reduced and preserved ejection fraction respectively.65,66 EMPA-VISION study is evaluating the effects of 10 mg empagliflozin over a period of 12 weeks on cardiac energetics using magnetic resonance imaging technology in patients with HFrEF and HfPEF to investigate mechanisms by which empagliflozin improved HF-related outcomes.67 Two additional EMPERIAL trials will evaluate the effect of empagliflozin in patients with HFrEF and HfPEF on their exercise ability, HF symptoms and quality of life.68 The DAPA-CKD, and EMPA-KIDNEY trials will provide further insights into the renal outcomes with these SGLT2-inhibitors.69,70
should be considered based on appropriate clinical judgment for each individual patient.

iv. Patient-specific and medication-related factors should be considered when selecting a particular SGLT2-inhibitor. The SGLT2-inhibitors should not be used in acute / unstable / dehydrated states. Hydration and volume-status should be monitored during SGLT2-inhibitor therapy. Concomitant use of loop diuretics may result in volume-depletion and based on the clinical situation the dose of loop diuretic might need to be reduced.

v. In patients of type 2 diabetes mellitus in acute decompensated heart failure, metformin or SGLT2-inhibitors should be avoided. Use of insulin may be considered in such situations, despite the fact there is limited supportive evidence for insulin in this scenario.

vi. There is no clear evidence for patients of type 2 diabetes mellitus who have stable heart failure with mid-range ejection fraction (HFrEF); metformin and/or SGLT2-inhibitors may be safe to use in such patients.

### 3.3 Which Antidiabetic Agents are Neutral?

Glucagon-like peptide (GLP) - 1 Receptor Agonists

In patients of T2DM with high CV risk, lixisenatide and exenatide have demonstrated CV-safety as assessed by the 3-point MACE outcome in the ELIXA (Evaluation of cardiovascular outcomes in patients with type 2 diabetes after acute coronary syndrome during treatment with Lixisentide) and EXSCEL (Exenatide Study of Cardiovascular Event Lowering Trial) trials, whereas lixisenatide demonstrated statistically significant reductions in the 3-point MACE and all-cause mortality in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of CV Outcome Results) trial. A significant reduction in 3-point MACE was also observed with semaglutide in the pre-marketing SUSTAIN-6 (Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) trial. However, none of these RCTs demonstrated reduction in the risk of hospitalization for HF; the hazard ratios for hospitalization due to HF was 0.96 (95% CI 0.75–1.23, p=0.63) with lixisenatide, 0.94 (95% CI 0.78–1.13) with once-weekly exenatide, 0.87 (95% CI 0.73–1.05, p=0.14) with lixisenatide, and 1.11 (95% CI 0.77–1.6, p=0.57) with semaglutide. The meta-analysis of the available studies of dulaglutide has not demonstrated an improvement or worsening of hospitalization for HF. The REWIND trial will provide further insights into the CV outcomes with dulaglutide.

The HARMONY (Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease) trial demonstrated a significant 22% reduction in 3-point MACE (HR 0.78; 95% CI 0.68–0.90), which was consistent in the subgroup of patients with prior history of HF (HR 0.70, 95% CI 0.54–0.90). However, albiglutide did not show a reduction in the risk of hospitalization for HF or CV death (HR 0.85; 95% CI 0.70–1.04).

Liraglutide was assessed in 300 recently hospitalized patients with and without T2DM with HFrEF in the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) study. Use of liraglutide did not result in a reduction in rehospitalizations for HF (hazard ratio, 1.30 [95% CI, 0.89–1.88]; P = 0.17) or lead to greater post-hospitalization clinical stability. Further, in patients with T2DM, the use of liraglutide was associated with a non-significant increase in death or hospitalization for HF (HR of 1.54 [95% CI 0.97–2.46], P=0.07). As quoted by the authors, these findings do not support the use of liraglutide in patients with HFrEF.

In another RCT (effect of Liraglutide on left VEntricular function in chronic heart failure patients with and without type 2 diabetes (LIVE)) involving 241 patients of chronic HFrEF with or without T2DM, the possible effect of liraglutide on LV function in patients with chronic HF was assessed. Liraglutide therapy for 24 weeks did not improve LV ejection fraction, or other parameters of systolic function in patients with chronic HF with low EF with or without diabetes. Some of the parameters of diastolic function improved; however, the clinical significance was unclear. The heart-rate increased by 7 beats per minute in the liraglutide group. Serious cardiac events were observed in as many as 10% of patients in the liraglutide group, compared to 3% of patients in the placebo group. However, it is uncertain whether these results are representative of other heart failure populations including patients with HFrEF or diastolic dysfunction. Furthermore, use of liraglutide was not associated with an increase in MACE in the LEADER trial in patients of T2DM with prior HF.

Overall, GLP1-RAs are safe in patients of T2DM who are at risk for HF. The propensity of these agents to increase heart rate needs careful consideration. Moreover, the observations from the FIGHT and LIVE studies suggest a need for further research on the use of GLP-1RA in patients of T2DM with acute or chronic HFrEF respectively.

### Consensus Recommendations

i. None of the GLP-1 receptor agonists have been demonstrated to either worsen or improve the risk of hospitalization for heart failure in patients with type 2 diabetes mellitus.

ii. Further careful research is warranted regarding use of GLP-1 receptor agonists in patients of type 2 diabetes with acute or chronic heart failure with reduced ejection fraction.

### 3.4 Which Oral Antidiabetic Agents are Equivocal?

**Sulphonylureas**

In a recently published meta-analysis of observational studies, sulphonylureas were associated with an increased risk of CV events and mortality. The relative risk for CV event was increased significantly by 13% with the use of sulphonylureas when compared to metformin (RRR of 1.13 [95% CI 1.01–1.27]). For mortality outcome, the relative risk was increased by 20% (RRR 1.20 [95% CI 1.07–1.34]). In another study, propensity matched cohorts of new users of metformin or sulphonylurea were assessed for hospitalization for acute decompensated HF or CV death. In this cohort study, 97% of the patients were male, and 6% patients had history of HF. Sulphonylurea use was associated with a significant 32% increased risk of events, as compared to metformin; the event rates with metformin and sulphonylurea were 8.9 and 12.4 per 1000 patient years.
respectively (adjusted hazard ratio 1.32, 95% CI 1.21, 1.43). Specifically, a statistically significant 30% increase in risk of hospitalization for acute decompensated HF was observed with sulphonylurea use. The findings were consistent in patients with or without prior HF.80 A retrospective assessment of OsMed Health-Db registry database assessed risk of hospitalization for HF in patients with T2DM who were newly initiated on a DPP4 inhibitor or other oral glucose-lowering drugs. Based on propensity matched analysis, DPP4-inhibitors were associated with a lower risk of hospitalization for HF, as compared to sulphonylureas (HR 0.70; 95% CI 0.52-0.94; p=0.018). In the same analysis, when compared to sulphonylureas, TZDs were also associated with a lower risk of hospitalization for HF.81

However, in the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial involving patients of T2DM and significant coronary artery disease, the rate of new HF did not differ significantly between patients receiving insulin-sensitization therapy (metformin and/or TZD) or insulin-provision therapy (sulphonylurea and/or insulin). Peripheral pitting edema was significantly greater in patients receiving insulin-sensitization therapy. However, in a post hoc analysis, in the elderly patients (>75 years of age), insulin-provision therapy was associated with increased overall mortality when compared to insulin sensitization therapy.82

Overall, there is a lack of clear evidence on the risk of hospitalization for HF with the use of sulphonylureas. The data from observational studies suggests an increase in risk of hospitalization for HF with sulphonylureas when compared to metformin, DPP4-inhibitors, or TZDs. However, evidence from a RCT in patients of T2DM with CVD did not suggest an increased risk of HF related events. The CAROLINA trial is evaluating CV outcomes with linagliptin or glimepiride as second-line therapies in T2DM.83

Consensus Recommendations

i. The limited evidence to date points towards possible adverse safety profile of sulphonylureas when compared to other glucose lowering agents for heart failure related outcomes. However, the evidence is inconclusive. A large on-going RCT is looking in to this outcome of interest and shall be reporting it’s finding this year.

3.5 What is the Position of Insulin in type 2 diabetes mellitus with heart failure?

Insulin is known to cause sodium retention that might contribute to development of HF. In a recently published analysis of 24012 patients from four RCTs in patients with HF (mainly HfREF), the use of insulin was associated with a 23% increase in risk of hospitalization for HF [propensity score pooled hazard ratio 1.23 (1.13-1.33)] and a 27% increase in risk for all-cause mortality [propensity score pooled hazard ratio 1.27 (1.16-1.38)].84 Similarly, in a large case-control study nested within a population based cohort study revealed a higher risk of all-cause mortality and hospitalization outcomes with the use of insulin.85 These observations suggest, but do not confirm, the possible increased risk of HF-related hospitalizations with insulin.

The DIGAMI (Diabetes mellitus insulin glucose infusion in acute myocardial infarction) study randomized 306 patients with acute MI and T2DM to intensified glycemic control using insulin-glucose infusion followed by subcutaneous administration of insulin and 314 patients with acute MI and T2DM to conventional therapy. There was a statistically significant 29% relative risk reduction in mortality in the insulin treated group at one year; this study did not report on HF-related outcomes.86 However, the subsequent post-hoc analysis of DIGAMI-2 study suggested that insulin use was associated with a significant increase in risk of non-fatal CV events (OR 1.89; 95% CI 1.35-2.63; p = 0.0002), but not mortality (OR 1.30; 95% CI 0.93-1.81; p = 0.13). This analysis also did not report on HF-related outcomes.87 The BARI 2D study, involving patients of T2DM with coronary artery disease, did not suggest a significant increase in the risk of new-onset HF in the patients receiving insulin or sulphonylureas.82

Furthermore, the ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial did not suggest an increase in risk of hospitalization for HF with the use of insulin glargine. However, low doses of insulin glargine were used in this trial and possible CV effects with higher doses of insulin glargine may not be assumed.88,89

The DEVOTE (Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events) study, involving 7637 patients of T2DM and high risk for CV events, reported on similar CV safety profiles of insulin degludec and insulin glargine as assessed by 3-point MACE. Incidence rate of HF events was 2.34 per 100 patient-years with insulin degludec as compared 2.73 per 100 patient-years with insulin glargine.90

The evidence on CV outcomes with short-acting insulins is limited. A longitudinal cohort study compared the rapid acting insulin analogues for safety outcomes. The overall safety profiles were comparable between insulin lispro, aspart, and glulisine. However, the rates of hospitalization for HF were 28.9, 29.6, 22.6 per 100 patient-years with lispro, aspart and glulisine respectively. Although lesser events of hospitalization for HF were observed with insulin glulisine, this was not statistically significant when compared to insulin lispro (0.76 [0.50, 1.13]) or insulin aspart (0.75 [0.53, 1.08]).91

Although insulin is one of the most widely used anti-diabetic agents in patients with T2DM, particularly in patients with T2DM with decompensated HF, evidence regarding its safety in these patients is meagre; more evidence from well-designed RCTs are needed to assess the CV safety of insulin.

Consensus Recommendations

i. The use of insulin may be indispensable in certain patients with type 2 diabetes mellitus with added co-morbidities, including heart failure.

ii. However, the evidence to support the safety of insulin use in patients with type 2 diabetes mellitus with heart failure is not clearly established.
Executive Summary

Prevalence and Impact of Heart Failure in Type 2 Diabetes Mellitus

i. Heart failure is a common, yet less recognized, and discussed, complication of type 2 diabetes mellitus.

ii. The co-existence of diabetes mellitus and heart failure has significant clinical and economic implications, in terms of clinic visits, hospital admissions, quality of life, morbidity and mortality.

iii. In Indian adults, heart failure and diabetes mellitus occurs at a younger age and affects the more productive years of life.

iv. Information on the burden and impact of concomitant heart failure and diabetes mellitus in India is limited.

v. Adequate public-health research and surveillance is necessary to facilitate improved understanding of the burden and impact of heart failure and diabetes mellitus in India.

vi. Increased mortality due to suboptimal therapy of heart failure is a major preventable problem in India.

vii. Significant efforts are required to optimize clinical management approach in type 2 diabetes mellitus, especially in the presence of cardiovascular and renal comorbidities.

viii. Associated comorbidities in type 2 diabetes mellitus, including coronary artery disease, hypertension, obesity, anemia, obstructive sleep apnea, and/or chronic kidney disease need to be addressed adequately for effective management of heart failure in type 2 diabetes mellitus.

Diagnosis and Classification of Heart Failure in Type 2 Diabetes Mellitus

i. Accuracy of the diagnosis of heart failure depends on meticulous clinical assessment (history, physical examination) and accurate interpretation of laboratory parameters.

ii. Routine clinical assessment for heart failure (history and physical examination) should be conducted for all patients of type 2 diabetes mellitus.

iii. Routine serial assessment of resting ECG, UACR, and eGFR (based on serum creatinine, using CKD-EPI equation), should be considered in all patients of type 2 diabetes mellitus, to help predict the risk of developing heart failure. Evaluation of NT-proBNP should be considered to assess the probability of heart failure, whenever possible.

iv. Confirmatory Assessment: Echocardiography is an essential laboratory investigation to establish the diagnosis of Heart Failure. Patients should be referred for echocardiography and to an appropriate specialist if the clinical or laboratory parameters suggest heart failure. Doppler echocardiography should be conducted in selected patients.

Glycemia Control and Heart-failure

Which Oral Antidiabetic Agents are Contraindicated?

Patients of type 2 diabetes mellitus without Heart Failure:

i. Thiazolidinediones (TZDs) can cause, or exacerbate, heart failure in patients of type 2 diabetes mellitus. Patients receiving TZDs should be monitored for symptoms and signs of heart failure. If heart failure is suspected, TZDs should be discontinued, and heart failure should be managed as per standards of care.

ii. Saxagliptin, and possibly alogliptin, may increase the risk of hospitalizations for heart failure in patients of type 2 diabetes mellitus with high cardiovascular risk and chronic kidney disease stage 3 & above. Patients should be observed for symptoms and signs of heart failure during therapy. If heart failure is suspected, saxagliptin or alogliptin should be discontinued, and heart failure should be managed as per standards of care.

iii. The choice of a particular DPP4 inhibitor should be based on clinical judgment, guided by pertinent factors related to the patient and the drug. An evidence-based informed decision should be made.

iv. Teneligliptin may cause QT interval prolongation in patients with or without history of arrhythmia, severe bradycardia, low serum potassium, congenital prolonged QT syndrome, history of Torsades de pointes, on antiarrhythmic medications.

Patients of type 2 diabetes mellitus with clinically compensated Heart Failure:

v. TZDs are not recommended in patients with symptomatic heart failure, and are absolutely contraindicated in patients with established heart failure.

vi. Saxagliptin may increase the risk of hospitalization for heart failure, and should be avoided in patients with a history of heart failure. Alogliptin might also increase the risk of hospitalization for heart failure.

vii. Sitagliptin and Linagliptin do not increase the risk for hospitalization for heart failure in this group of patients, but more information is required before recommending their routine use in the presence of compensated heart failure. It is prudent to avoid DPP4 inhibitors in a patient of type 2 diabetes mellitus with decompensated heart failure until further information is available, and critically reviewed by various regulatory bodies.

viii. Teneligliptin may cause QT interval prolongation in patients with heart failure.

Which Oral Antidiabetic Agents are Preferred?

i. Metformin is a safe anti-diabetic agent for use in eligible patients of type 2 diabetes mellitus with stable heart failure for control of blood glucose.

ii. SGLT2-inhibitors, empagliflozin, canagliflozin and dapagliflozin have demonstrated promising results in reducing the risk of hospitalizations for heart failure beyond glycemia control. These agents may be considered for improving heart failure related outcomes beyond glycemia control in patients of type 2 diabetes mellitus who are at increased risk of heart failure or in those with stable heart failure.

iii. In patients with type 2 diabetes mellitus who are at increased risk of heart failure and who have achieved target glycemic goal without an SGLT2-inhibitor, the
inclusion of an SGLT2-inhibitor should be considered in light of the promising results seen with SGLT-2 inhibitors in reducing the risk of hospitalizations for heart failure beyond glycemia control in this group of patients; if necessary, down-titration of or a change in other antidiabetic agents should be considered based on appropriate clinical judgment for each individual patient.

iv. Patient-specific and medication-related factors should be considered when selecting a particular SGLT2-inhibitor. The SGLT2-inhibitors should not be used in acute / unstable / dehydrated states. Hydration and volume-status should be monitored during SGLT2-inhibitor therapy. Concomitant use of loop diuretics may result in volume-depletion and based on the clinical situation, the dose of loop diuretic might need to be reduced.

v. In patients of type 2 diabetes mellitus in acute decompensated heart failure, metformin or SGLT2-inhibitors should be avoided. Use of insulin may be considered in such situations, despite the fact there is limited supportive evidence for insulin in this scenario.

vi. There is no clear evidence for patients of type 2 diabetes mellitus who have stable heart failure with mid-range ejection fraction (HFrEF); metformin and/or SGLT2-inhibitors may be safe to use in such patients.

**Which Antidiabetic Agents are Neutral?**

i. None of the GLP-1 receptor agonists have been demonstrated to either worsen or improve the risk of hospitalization for heart failure in patients with type 2 diabetes mellitus.

ii. Further careful research is warranted regarding the use of GLP-1 receptor agonists in type 2 diabetic patients with acute or chronic heart failure with reduced ejection fraction.

**Which Oral Antidiabetic Agents are Equivocal?**

i. The limited evidence to date points towards possible adverse safety profile of sulphonylureas when compared to other glucose lowering agents for heart failure related outcomes. However, the evidence is inconclusive. A large on-going RCT is looking in to this outcome of interest and shall be reporting it’s finding this year.

**What is the Position of Insulin in type 2 diabetes mellitus with heart failure?**

i. The use of insulin may be indispensable in certain patients with type 2 diabetes mellitus with added co-morbidities, including heart failure.

ii. However, the evidence to support the safety of insulin use in patients with type 2 diabetes mellitus with heart failure is not clearly established as yet.

**Algorithm for Selection of Glucose-lowering Therapy in Patients with Type 2 Diabetes Mellitus with Heart Failure**

The choice of therapy should be based on clinical judgment, guided by pertinent factors related to the patient and the medication.

A. In Ambulatory Clinical Setting

1. Patients of type 2 diabetes mellitus at high risk for heart failure:
   - Metformin is a safe therapy for glycemia control.
   - SGLT2-inhibitors reduce the risk of hospitalization for heart failure beyond glycemia control.
   - Thiazolidinediones, saxagliptin, and possibly alogliptin may increase the risk of hospital failure.
   - Teneligliptin may increase the risk of QT-interval prolongation in predisposed patients.
   - Sitagliptin and Linagliptin do not increase the risk of hospitalization in this group of patients but more information is required before recommending their routine use in a patient with type 2 diabetes mellitus at high risk for heart failure.

2. Patients of type 2 diabetes mellitus with Compensated heart failure

Fig. 2: Algorithm for diagnosis of heart failure in type 2 diabetes mellitus
- **Teneligliptin** increases the risk of hospitalization for heart failure beyond glycemia control.
- **SGLT2-inhibitors may reduce the risk of hospitalization for heart failure beyond glycemia control.**
- **Thiazolidinediones**, saxagliptin, and possibly alogliptin increase the risk of hospitalization for heart failure, and should be avoided in the presence of compensated heart failure.
- Teneligliptin increases the risk of QT-interval prolongation, and should be avoided in the presence of compensated heart failure.
- Further research is warranted regarding use of GLP-1 receptor agonists in type 2 diabetic patients with chronic compensated heart failure with reduced ejection fraction. The use of insulin may be considered, but with limited evidence to support its safety in patients of type 2 diabetes mellitus with compensated heart failure.
- The safety profile of sulphonylureas in patients with compensated heart failure is inconclusive at present.

**B. In Hospital Setting**

Patients of type 2 diabetes mellitus with Acute Decompensated heart failure:
- Insulin may be used based on limited supportive evidence.
- Thiazolidinediones, Metformin or SGLT2-inhibitors should not be used.
- Saxagliptin and alogliptin should be avoided. It is best to avoid other DPP4 inhibitors in a patient of type 2 diabetes mellitus with decompensated heart failure. However, an evidence-based informed decision should be made.
- Based on limited available evidence, the use of GLP1-RA is not recommended in acute decompensated heart failure with reduced ejection fraction.
- The safety profile of sulphonylureas for heart failure outcomes in decompensated heart failure is inconclusive at present.

**Acknowledgement(s) and Disclosure(s)**

Dr. Jignesh Ved has helped in the development of this manuscript in his individual capacity. The authors of this manuscript assume full responsibility of the content, in line with ICMJE ethical principles for scientific writing.

**References**


42. Hashikata T, Yamaoka-Tojo M, Kakizaki R, Nemoto T, Fujiyoshi
38. Singh AK, Singh R. Heart Failure Hospitalization with
37. Verma S, Goldenberg RM, Bhatt DL, Farkouh ME, Quan A,
32. Zannad F, Cannon C, Cushman W, Bakris G, Nissen S,
20. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA,
17. Verma S,Early Benefit during Early Stages of Diabetes: Results From the CANVAS Program. Circulation 2018; 137:323-34.
15. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, et al. Cardiovascular Events in Type 2 Diabetes: Results From the CANVAS Program (CIRCULATION). 2018; 137:323-34.
3. Anker SD, Butler J. Empagliflozin, calcium, and SGLT2/2 receptor affinity: another piece of the puzzle. ESC Heart Failure 2018; 5:549.


