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Diabetes Mellitus and Heart Failure: A Consensus Statement

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Word count: 6995
No. of figures: 3
No. of tables: 4

Introduction:

Based on the clinical and epidemiological data, it has been documented that in addition to myocardial infarction (MI) and atherosclerosis-related cardiovascular diseases (CVD), heart failure (HF) is a potential contributor to the morbidity and mortality in patients with diabetes.(1) Type 2 diabetes mellitus (T2DM) is a distinguished predisposing factor for HF(1). The pathophysiology of these two conditions is closely associated. Timely identification and immediate suitable intervention generate to a better outcome. Majority of patients with co-existing T2DM and CVD along with other co-morbidities (e.g., atherosclerotic CVD, HF, chronic kidney disease (CKD), and obesity) augments the need of a specific approach in the selection of appropriate antidiabetic drugs.(2) The present consensus document provides an evidence-based assessment on risk factors, prognosis, and proper management to reduce the morbidity and mortality. It also discusses the management strategies for patients of HF with concomitant T2DM.

Epidemiology of diabetes mellitus and heart failure:

Numerous studies have shown that pre-diabetes is associated with a high risk of HF and suggest an age-adjusted hazard ratio (HR) between 1.2 and 1.7 in different populations of patients with impaired fasting glucose. However, the results are conflicting and hence, no agreement could be established among all studies. As a matter of fact, the risk of developing HF in subjects with pre-diabetes is lower than in subjects with diabetes.(3)

In a systematic review, consisting of 4,549,481 patients with T2DM, documented a 14.9% prevalence of HF, 14.6% of angina, and 10% of myocardial infarction (MI) in patients with T2DM (4). Additionally, in a Swedish and Spanish HF registry data, the prevalence of T2DM in patients with HF were 24% and 45.3% respectively (5). Similarly, in a study which recruited 1082 patients with HF, 490 (45.3%) constituted concomitant diabetes patient. In course of follow-up, it was observed that a total of 151 patients (30.8%) with T2DM died, and 197 patients (40.2%) with T2DM were readmitted because of HF. Increased all-cause mortality (ACM) [hazard ratio (HR) 1.49]; and readmissions [HR 1.39] in T2DM was significantly associated in that study (6). Further, a study by Parry et al., revealed that glycated hemoglobin (HbA 1c) < 6 % (HR 1. 60) as well as HbA1c > 10% (HR 1.80) were independently associated with the risk of HF(6).

A retrospective observational study was conducted in South India by Devarajan A. et al., 2020, among 397 individuals who visited two tertiary care centers. They were classified into 4 groups - DM with HF(DM-HF), DM without HF, non-DM with HF (non-DM-HF) and non-DM without HF. Authors assessed and compared the clinical profile of DM with HF vs. DM without HF and non-DM with HF groups respectively. The parameters such as age, BMI, BP, eGFR showed significant difference between the groups. People with DM-HF were older compared to DM without HF group (58.9 ± 9.2vs.49.5 ± 9.3; $p < 0.001$). An increasing trend was observed in HF prevalence with increasing duration of DM among the DM-HF group. DM-HF showed a higher prevalence of hypertension and coronary artery disease (CAD) by history than DM without HF group. DM-HF group (91.2%) had HF with preserved left ventricular ejection fraction (HFpEF) whereas a high proportion (43.5%) of non-DM-HF group had HF with reduced LV ejection fraction (HFrEF) (7).

Variability in HbA1c has also been found to be associated with HF incidence. It has been postulated that the HbA1c variability augment cell apoptosis and oxidative stress which may lead to HF in patients with diabetes(6). Additionally, CKD increases mortality and the overall progression of CVD as well as HF(5). Further, the prevalence of CKD (eGFR < 60 mL/min/1.73 m in patients with HF was observed to be 63%. This was associated with an 11% increase in hospitalization and a 17% increase in mortality. Renal function abnormality and mortality were prevalent in patients with DM when compared to the reference group (32% vs. 25%) (8). A study conducted by Indian Council of Medical Research the-INDIAB, estimated that approximately 77.2 million people in India are prediabetic. Nearly around 36 million (52%) people comprise undiagnosed DM(9). The most frequent cardiac abnormality associated with asymptomatic DM includes left ventricular (LV) diastolic dysfunction. The other modifiable risk-factors for HF, which commonly coexist in T2DM, are, the obesity, CAD, hypertension (HTN), anemia and obstructive sleep apnea (OSA) (10).

Key take home messages

1. Approximately half (50%) of patients with chronic HF have diabetes in India.
2. The rate of HF in India is expected to increase by 18% annually.
3. HF is more prevalent than MI in patients with T2DM.

4. Variability in HbA1c level, co-morbid CKD, and myocardial ischemia may increase the risk of HF.
5. Both pre-diabetes and undiagnosed diabetes have a high prevalence in India.
6. Early diagnosis and therapeutic interventions will improve morbidity and mortality.
7. Modifiable co-morbidities in T2DM, including CAD, HTN, obesity, anemia, OSA, need to be addressed adequately for effective management of HF in T2DM.

Pathophysiology of DM and HF:

It is evident that T2DM is associated with atherogenic dyslipidemia and endothelial dysfunction suggesting the significance of hyperlipidemia lowering drugs in minimizing HF. A link between glucose levels and HF is well documented. Pathogenic role of insulin resistance and hyperinsulinemia are interrelated to left ventricular hypertrophy (LVH) due to T2DM(11). Hyperglycemia results in cardiac muscle stiffness. Therefore, insulin resistance decreasing antidiabetic drugs that controls the hyperglycemia is the need of the hour to reduce the rate of HF in T2DM. Although, cardiomyopathy in T2DM is independent of atherosclerotic ischemia; there is evidence of cardiomegaly as well in T2DM patients. Hence, the antidiabetic therapy which target such pathology e.g., SGLT2i, have been effective in the treatment modality(12). Further, the HF diagnosis requires signs and symptoms assessment, detailed history, evaluation of differential diagnostic biomarkers such as natriuretic peptides (NPs), and an echocardiogram (ECG). Diagnostic algorithm for heart failure in T2DM is shown in figure 1. Various HF biomarkers utility and their diagnostic accuracy are summarized in table 1 and table 2. A diagrammatic representation of the pathophysiology of HF in T2DM is depicted in figure 2.

Prognosis of Patients with Diabetes Mellitus and Heart Failure:

The most significant clinical end points are CV Death and HHF (Hospitalization with heart failure) and are determined by poor glycemic control.(4)

A study assessed the influence of diabetes on the risk of death in 5491 patients hospitalized with congestive heart failure (CHF) (13). In this study, 16% of patients had diabetes at baseline, and approximately 50% had an ejection fraction <35%, suggesting that both HFrEF and HFpEF were present in the patient population. Almost half (50%) of all HF patients with diabetes died after 3 years- revealed by the mortality analysis of the above-mentioned study (14). The Survival and

Ventricular Enlargement (SAVE) trial, Valsartan in Acute Myocardial Infarction Trial (VALIANT), and the Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) trials together provided an additional data on the prognosis of patients with diabetes and HF (15). All of these studies demonstrated an increased risk of mortality in either gender with diabetes. Further, patients with or without diabetes and HFpEF or HFrEF showed a highest mortality or HHF among HFrEF. This was followed by the patients with diabetes and HFpEF. The collective incidence rate of cardiovascular (CV) death and HHF in patients with diabetes plus HFpEF was equivalent to that in subjects without diabetes but with HFrEF. Also, a similar trend was valid for all-cause mortality (15).

Similarly, in patients with diabetes, the risk for first hospital admission due to HF was 116.6 per 1000 patient-years for those with HFpEF. Whereas the rate was 155.4 per 1000 patient-years for those with HFrEF (16). In the Medanta registry (48.7% had co-morbid DM), it was observed that half of Indian patients had HFrEF (59.1%). Indian data,the Inter-CHF study reported HFrEF prevalence of 53% (with 26% concomitant DM), while the Trivandrum HF Registry (THFR) data reported a prevalence of HFpEF 26% (with 55% concomitant DM) (17). Additionally, a study by Matsue et al., suggested that more than 1/3rd of patients who were hospitalized for HF without a definitive diagnosis of diabetes, exhibited impaired fasting glucose or impaired glucose tolerance (18).

Therefore, among patients with HF, those with concomitant diabetes had a higher risk of mortality and HHF than those without diabetes. Hence, the prevalence of prediabetes and diabetes with heart failure proves as a remarkable predictor of prognosis.(7) Table 3 summarizes characteristics of HF classification based on left ventricular ejection fraction (LVEF), time-course, or severity of symptoms.

Key take home messages

1. Prevalence of heart failure in diabetes is relatively higher, and the prognosis for patients with heart failure is inferior in those with diabetes as compared to those without diabetes.
2. The prevalence of heart failure based on ejection fraction i.e., HFrEF and HFpEF in India is similar (~ 50%) in patients with T2DM.
3. HF phenotype and stage of HF identification can guide the management.

4. Nevertheless, in spite of having no specific therapy for HFpEF, it is clinically relevant to distinguish it from HFrEF and that may lead to the efficient management of risk factors and disease progression.

Heart Failure and Glycemic Control:

Diabetes and HF are directly associated.(4) In other words, patients with diabetes have an increased risk of developing HF and those with HF are at higher risk of developing diabetes. Individually, HF has a much inferior prognosis than DM.(7) Therefore, the HF has to be a main concern for treatment in patients presenting with concomitant DM conditions. Although, there is a paucity of randomized clinical trials conducted to test the effect of cardiovascular drugs in diabetic patients with HF, however, a plethora of evidence suggests that all interventions efficient at improving prognosis in patients with HF are equally beneficial in patients with or without diabetes.(7)

Available guidelines suggest an individualized therapy approach and glycemic goal for every individual patient.(2) In general, all guidelines recommend achieving HbA1c near to a normal glycemic level. Poor glycaemic control increases risk of HF. There is data from observational studies that have calculated the risk for every 1% increase in HbA1c. Regarding the effect of strict glycaemic control on risk of HF, data is conflicting, but in balance, there was no beneficial effect on risk of HF (19). However, achieving glycemic goal is dependent on patient demographic characteristics like age, duration of diabetes, and risk of complications including hypoglycemia and co-morbidities.(20) Therefore, choosing an anti-diabetic drug is very critical and should be individualized based on the patient need.

Even after intensive glycemic control, several studies namely, UKPDS, ADVANCE, ACCORD, and VADT have shown negligible benefit in heart failure(21–23). At the same time, many observational studies have reported that optimal glycemic control is beneficial to patients. Again, an increase in HbA1c more than 8%-10% demonstrated an increase in the risk of HF in some studies.(6)

Key take home messages

1. HF is a common, yet under recognized and under diagnosed, complication of T2DM.
2. Evidence on the burden and impact of concomitant HF and DM in India is limited.
3. HF has a much poorer prognosis than DM alone.
4. Choosing an anti-diabetic drug in co-existing HF patient is very critical and should be individualized based on the patient need.

Effect of Anti-diabetic Drugs on Heart Failure:

While several studies have demonstrated increased risk of HF with worsening glycemic control in people with T2DM, an efficient glycemic control could not be established as a tool to improve HF outcomes. The recent clinical trials conducted in patients with HF who had diabetes showed a diverse response to standard medication.(15) However, these patients are believed to be more susceptible towards the development of side-effects than patients with the same degree of HF but without DM. Therefore, considering cardiovascular safety, a careful selection of antidiabetic therapy becomes imperative in optimizing diabetes treatment modality.(1) The current section reviews the use of individual antidiabetic agents in a person with T2DM plus HF.

Few prominent features of anti-diabetic drugs before considering them for therapy are as follows:

Metformin: FDA in 2006 removed restrictions on use of metformin in patients with medically treated heart failure (24). Metformin users have better outcomes than patients treated with other antihyperglycemic agents as per observational studies. (25). Except renal impairment or another contraindication, metformin is the first line of treatment in glycemic management. Metformin is safe and generally well tolerated. Apart from the observational studies and experimental data, definitive evidence from a randomized controlled trial (RCT) to establish the clinical benefit of metformin in patients of T2DM and HF is still warranted. ESC 2016 guidelines mention that in patients' of T2DM with HF, metformin is a safe first-line therapy for glycemic control. Further, a population-based retrospective cohort study supports a reduced risk of hospitalization for HF associated with metformin use in patients with type 2 diabetes mellitus (26). However, metformin is contraindicated in individuals with severe HF (New York Heart Association, NYHA, classes III –IV), due to concerns of lactic acidosis, with an estimated mortality rate of 50% (27). Additionally, within permissive kidney function limits (eGFR> 30 mL/ min/1.73 m^2),

metformin may be used for the management of hyperglycemia in patients with stable heart failure (28).

Sulfonylurea (SU), thiazolidinediones (TZD), dipeptidyl dipeptidase-4 inhibitor (DPP4i), sodium glucose co-transporter 2 (SGLT-2) inhibitors, and GLP1 agonists constitute second line therapy in case patient fails to achieve glycemic control on first line therapy. This is followed by third line therapy, which include either adding third oral antidiabetic agent or starting insulin.(2)

Thiazolidinediones are insulin sensitizer drug known to cause fluid retention.(2) Use of TZD is contraindicated in patients with HF of class NYHA - III-IV. The safety of sulfonylureas in HF with concomitant T2DM is not fully established. Both TZD and sulfonylureas should be used with utmost care as they might increase the risk of HF worsening.(2) Interestingly, the recent Cardiovascular Outcome Trial of LINAgliptin Versus Glimepiride (CAROLINA) has shown no increase in risk of HHF with glimepiride when compared with linagliptin in T2DM patients without HF[2] (29).

Consensus recommendation

1. ESC 2016 guidelines declare that in patients of T2DM with HF, metformin is a safe first line therapy for glycemic control. Metformin is associated with better short-term and long-term prognosis in patients with HF.
2. The CAROLINA trial evaluating CV outcomes has shown no increase in the risk of HHF with glimepiride in T2DM patients without HF.
3. Reports on effect of TZD on CV safety are conflicting, however, a meta-analysis reported an increased risk of MI with rosiglitazone. Because of the associated side effects such as fluid retention and weight gain with TZD, its use in NYHA III and IV grade HF is avoided.

Glucagon-like peptide (GLP) - 1 Receptor Agonists: Evidence from Cardiovascular Outcome Trials (CVOTs)

GLP-1 receptor agonist belongs to the incretin class of drug having a number of non-glycemic effect including anorexia, hypotension, and increased pulse rate. The accomplished CVOTs with GLP-1 agonist included ‘LEADER’ and ‘SUSTAIN’ studies with liraglutalide and semaglutide

respectively. Trials demonstrated a reduction in MACE (HR 0.87 and 0.74 respectively), and liraglutide exhibited a positive inclination towards reducing the HHF predominantly in high CV risk T2DM patients.(30,31) However, other two studies, 'ELIXA' and 'EXSCEL' with lixisenatide and long acting exenatide respectively failed to establish CV safety.(32,33). A favorable risk benefit ratio for GLP 1 agonists with a reduction in 3- point MACE (HR 0.90; 95% CI: 0.82 -0.99; p = 0.033), CV mortality (HR 0·87; 95% CI: 0·79-0·96; p = 0·007), and ACM (HR 0.88; 95% CI 0.81- 0.95; p = 0·002) were demonstrated in a meta-analysis of 4 CVOTs (LEADER, SUSTAIN-6, ELIXA, and EXSCEL. Albiglutide in 'HARMONY' trial showed a significant decrease in MACE (HR0.78; 95% CI 0.68 to 0.90; p < 0.001) and MI (HR0.75; 95% CI 0.61 to 0.90; p = 0.03), however, did not reduce CV death, ACM, or stroke (34). Yet another, recently published REWIND trial with Dulaglutide also confirmed a reduction in MACE (HR 0.88; 95% CI 0.79 to 0.99; p = 0.026), however, there was no difference in mortality, and conversely, a higher incidence of gastrointestinal adverse events (47.4% vs. 34.1% in placebo) were noted (35).

Consensus recommendation

1. None of the GLP-1 agonist has demonstrated either decreased or increased risk of HHF in patients with T2DM.
2. Certain GLP-1 agonists have shown benefit when compared with placebo in decreasing the risk of composite CV outcomes inT2DM.
3. Current guidelines have changed to recommend GLP-1 agonist as the preferred therapy after metformin in patients with T2DM with established cardiovascular disease.
4. There are ongoing trials of GLP-1 agonist to further understand the cardiovascular benefits in T2DM with acute or chronic HF plus reduced ejection fraction.

Dipeptidylpeptidase-4 (DPP4) inhibitors or gliptins: Evidence from Cardiovascular Outcome Trials (CVOTs)

The class of gliptins (DPP4i) has accumulated evidences on HF with CV outcome trials. Gliptins have exhibited an inconsistent pattern on HHF in CVOTs. Ambiguous results in the

TECOS trial for the HHF end point (3.1% sitagliptin vs. 3.1% placebo) [(HR 1.00; 95% CI 0.83 to 1.20)] were observed with Sitagliptin (36).

In contrary of that, 'SAVOR-TIMI 53' trial revealed an increased risk of HHF (3.5% in saxagliptin vs. 2.8% in placebo) [(HR 1.27; 95% CI 1.07 to 1.51)] with saxagliptin.(37) However, 'EXAMINE' study results conferred an increased HHF trend (3.9% alogliptin vs. 3.3% placebo)[(HR 1.19; 95% CI 0.89 to 1.58)] with alogliptin (38).

The only gliptin trial in HFrEF i.e. vildagliptin in the 'VIVID' study had demonstrated no major effect on ejection fraction (EF), however, caused a statistically significant increase in LV volumes (LV end-diastolic volume by 17.06 ml; 95% CI: 4.62 to 29.51; $p = 0.007$ and LV end-systolic volume by 9.44 ml; 95% CI: − 0.49 to 19.38; $p = 0.062$) (39). However, the significance of this result is yet to decipher. It is important to mention that only saxagliptin and alogliptin have shown increased risk of HHF and not vildagliptin, linagliptin, and sitagliptin. Hence, it is prudent to consider the risk benefit before using these drugs in patients with HF and DM.

Consensus recommendation

1. Certain gliptins, such as, saxagliptin, and possibly alogliptin, may increase the risk of HHF in T2DM patients with high CV risk and CKD.
2. The choice of a particular gliptin should be based on clinical judgment and an evidence-based informed decision should be made.

Sodium-glucose co-transporter-2 inhibitors (SGLT2i): Evidence from Cardiovascular Outcome Trials (CVOTs)

SGLT2i reduce glucose reuptake in the kidney by inhibiting the SGLT-2 transport protein.(40) Thus, it also causes glucosuria and volume loss. There is promising favorable evidence for SGLT2i starting from the initial stages of HF. It has a favorable HHF and mortality outcomes in various CVOTs in T2DM patients. These favorable HF results have been demonstrated both in patients with or without the HF. A recent meta-analysis confirmed statistically significant benefits with SGLT2i on HHF and CV death (HR 0.77; 95% CI 0.71 to 0.84; $p < 0.001$), particularly in patients with or without pre-existing HF, representing benefits in the initial HF stages (40).

The 'EMPA-REG OUTCOME' and 'DECLARE-TIMI 58' studies for empagliflozin and dapagliflozin respectively, revealed a significant reduction in HHF (HR=0.65; 95% CI: 0.50 to 0.85; p = 0.002 and HR=0.73; 95% CI 0.61 to 0.88, respectively) (41,42). The 'CANVAS' database also exhibited a reduction in HHF with canagliflozin vs placebo (HR 0.64; 95% CI: 0.35 to 1.15 vs. HR 0.68; 95% CI: 0.51 to 0.90; interaction p value = 0.91) in the primary and secondary outcome cohort respectively (43). Both 'EMPA-REG OUTCOME' and 'CANVAS' trial demonstrated a significantly decreased nephropathy progression and adverse renal outcomes.(41,43) Empagliflozin and canagliflozin have been approved by US FDA for lowering CV death and MACE in patients with T2DM and established CVD.

In patients with risk factors without baseline CVD or HF, the 'DECLARE-TIMI 58' study results demonstrated a lower incidence of cardiovascular death or HHF (4.9% vs. 5.8%; HR 0.83; 95% CI: 0.73 to 0.95; p = 0.005)(44). DECLARE TIMI results when segregated basis on EF, showed a HHF reduction in patients with (HR 0.64; 95% CI 0.43 to 0.95) and without (HR 0.76, 95% CI 0.62 to 0.92) HFrEF. Also, a reduced mortality (HR 0.55, 95% CI 0.34 to 0.90), and ACM (HR 0.59; 95% CI 0.40 to 0.88) in HFrEF was recorded. Very recently presented DAPA-HF results have exhibited a significant morbidity and mortality benefit with dapagliflozin in HFrEF patients with and without T2DM (with 42% concomitant T2DM) (45).

The EMPEROR-Reduced trial showed that empagliflozin is superior to placebo in improving HF outcomes among patients with symptomatic stable HFrEF (EF ≤40%) on excellent baseline guideline-directed medical therapy (GDMT), irrespective of diabetes status. The primary outcome, cardiovascular death or HF hospitalization, for empagliflozin vs. placebo, was 19.4% vs. 24.7% (hazard ratio [HR]=0.75, 95% CI: 0.65-0.86, p < 0.001). Similarly, cardiovascular death: 10% vs. 10.8% (HR 0.92, 95% CI 0.75-1.12), and HHF were 13.2% vs. 18.3% (HR=0.69, 95% CI 0.59-0.81) (46).

Subgroup analysis of DAPA-HF suggests that Dapagliflozin is effective and safe in patients with heart failure, regardless of Age.(47) Given concerns regarding the safety and efficacy of dapagliflozin in the elderly, the investigators conducted a subgroup analysis to examine the effects of this drug according to age. Patients receiving optimal medical therapy for symptomatic HF (left ventricular EF ≤40%) were included. Patients were randomly assigned to receive 10 mg of dapagliflozin daily or placebo (n = 4,744). Patient ages were as follows: 636 (13.4%) were

<55 years; 1,242 (26.2%) were 55–64 years; 1,717 (36.2%) were 65–74 years; and 1,149 (24.2%) were ≥75 years. The incidence of the primary composite outcome of first episode of worsening HF (hospitalization or an urgent care visit for HF) or CV death was lower in the dapagliflozin group than in the placebo group for each age range. Hazard ratios were as follows: 0.87 (95% CI 0.6–1.28) for <55 years; 0.71 (95% CI 0.55–0.93) for 55–64 years; 0.76 (95% CI 0.61–0.95) for 65–74 years; and 0.68 (95% CI 0.53–0.88) for ≥75 years (P value for interaction = 0.76). There were no differences in treatment discontinuation or adverse events including volume depletion, renal dysfunction, and hypoglycemia between the treatment groups for each age range (47).

In a recent compendium by Singh et al. (48), authors systematically reviewed the literature from Medline, Cochrane Library, and other relevant databases and attempted to provide evidence-based recommendations for the positioning of SGLT2i in the management of diabetes in the Indian population. Executive summary of the compendium is as follows:

- SGLT2i decrease blood glucose concentration by reducing glucose reabsorption from proximal convoluted tubules and by increasing urinary glucose excretion (Grade A, Evidence Level (EL) 1)
- SGLT2i are associated with durable glycaemic efficacy, body weight and blood pressure (BP) reduction with cardiovascular benefits and renoprotective action without a higher risk of hypoglycaemia (Grade A, EL 2)
- Treatment with SGLT2i is associated with side-effects such as genital tract infections (GTIs) and volume depletion-related adverse events; however, these can be minimized with proper education and counselling with close patient monitoring (Grade A, EL 2)
- Body weight, HbA1c and systolic BP are important parameters that can be used to identify non-responders to SGLT2i therapy (Grade B, EL2)
- Treatment with SGLT2i results in persistent calorie loss, which leads to weight loss. There is also some evidence of a reduction in β-cell stress and hyperinsulinaemia, and an increase in insulin sensitivity and the rate of insulin secretion (Grade C, EL 4).

SGLT2i: Indian Phenotype

- SGLT2i are emerging agents that can provide multiple benefits in Indian diabetes patients (Grade B, EL 3).

- The weight reduction associated with SGLT2i is due to loss of fat mass primarily from the abdomen rather than lean mass (Grade A, EL 2).
- The benefits associated with SGLT2i such as improvement of β-cell function and reduction of insulin resistance may be more useful in Indian patients with diabetes (Grade A, EL 2).

On May 5th 2020, the U.S. FDA approved dapagliflozin oral tablets for adults with heart failure with reduced ejection fraction to reduce the risk of CV death and HHF. With the approval, Dapagliflozin was the first among SGLT2 inhibitors, approved to treat adults with New York Heart Association's functional class II-IV heart failure with reduced EF.(49)

In a clinical trial, Dapagliflozin shown improvement in survival and reduced the need for hospitalization in adults with HF with reduced ejection fraction.(50) Safety and effectiveness data were evaluated in a randomized, double-blind, placebo-controlled study of 4,744 participants. The average age of participants was 66 years and more participants were male (77%) than female. After about 18 months, people who received Dapagliflozin had fewer CV deaths, HHF, and urgent HF visits than those receiving the placebo (50).

SGLT2i-Importance of weight loss:

Patients receiving SGLT2 inhibitors steadily experience weight reduction. Meta-analysis had revealed that in comparison to other antidiabetic agents, SGLT2 inhibitors reduced the body weight with a mean difference of 1.8 kg (95% CI: −3.5, −0.1) (51,52). As per European Medicines Agency assessment report, approximately 2–3 kg reduction in body weight was noted in the majority of phase III dapagliflozin studies(53). Early reduction of weight may represent fluid loss because of osmotic diuretic effect of these agents, whereas over consecutive weeks, increasing weight loss is most probably due to caloric loss. The glucose excreted in the urine as a result of SGLT2 inhibition equals to about 200–300 calories each day (54,55).

Plenty of studies have shown added metabolic benefits like improvement in body weight, blood pressure, lipid profile, insulin sensitivity, and cardiac function. SGLT2i has the advantage of efficient glycemic control with added cardiovascular benefit.(55) Needless to say, several mechanisms influence the empagliflozin and canagliflozin towards its inherent positive HF outcome.(55)

Consensus recommendation

1. SGLT2-inhibitors, namely empagliflozin, canagliflozin, and dapagliflozin have demonstrated promising results in reducing the risk of HHF.
2. These anti-diabetic agents may be considered for improving HF related to T2DM patients, who are at increased risk of HF or in those with stable HF.
3. There is clear evidence for patients of T2DM who have stable HF with mid-range ejection fraction (HFrEF); SGLT2-i may be safe to use in such patients.
4. Patient-specific and medication-related factors should be considered when selecting a particular SGLT2-i.

Insulin: Evidence from Cardiovascular Outcome Trials (CVOTs)

Insulin is recognized for sodium retention that might contribute to development of HF.(56) The Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) study, evaluating 7637 patients of T2DM and high risk for CV events, reported to have a similar CV safety profiles of insulin degludec and insulin glargine when assessed by 3-point MACE. Incidence rate of HF events was 2.34 per 100 patient-years with insulin degludec as compared to 2.73 per 100 patient-years with insulin glargine (57).

Consensus recommendation

1. Many patients with T2DM with added co-morbidities, including HF may require addition of Insulin for good glycemic control.
2. CVOT with long-acting insulin analogs do not demonstrate increased HF.
3. However, the evidence to support the safety of insulin use in patients with T2DM with HF is not clearly established.

In a newly published consensus recommendation for clinical practice in Indian scenario for the management of glycemia in a person with T2DM with HF, Mukherjee et al.(58) summarized the OADs that (i) increase the risk for heart failure (ii) contraindicated with clinically compensated heart failure, (iii) preferred in clinically compensated heart failure, (iv) have neutral effect in

clinically compensated heart failure, and (v) are safe for use in people with type 2 diabetes mellitus with acute decompensated heart failure.

Which oral anti-diabetic agents increase the risk for heart failure in people with type 2 diabetes mellitus?

- Thiazolidinediones (TZDs) can cause, or exacerbate, heart failure in patients with 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.
- 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.
- 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.
- 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.

Which oral anti-diabetic agents are contraindicated in people with type 2 diabetes mellitus with clinically compensated Heart Failure?

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

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

Which Oral Antidiabetic Agents are Preferred in people with type 2 diabetes mellitus with clinically compensated Heart Failure?

- 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.
- SGLT2-inhibitors like empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin 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 glycemic control in patients with type 2 diabetes mellitus who are at an increased risk of heart failure. Till date, dapagliflozin and empagliflozin have data supporting their use in people with type 2 diabetes mellitus with heart failure with reduced ejection fraction (HFrEF).
- In patients with type 2 diabetes mellitus who are at increased risk of heart failure and who had 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.
- 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.

- There is no clear evidence favoring the use of any particular oral anti-diabetic agent in people with type 2 diabetes mellitus who have compensated heart failure with mid-range ejection fraction (HFmrEF) or preserved ejection fraction (HFpEF).

Which Antidiabetic Agents are Neutral in people with type 2 diabetes mellitus with clinically compensated Heart Failure?

GLP-1 receptor agonists have NOT demonstrated to either worsen or improve the risk of hospitalization for heart failure in patients with type 2 diabetes mellitus.

- 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 antidiabetic agents are safe for use in people with type 2 diabetes mellitus with acute decompensated heart failure?

- In people with type 2 diabetes mellitus with acute decompensated heart failure, recent evidence suggests that metformin or SGLT2-inhibitors could be considered depending upon the severity of acute heart failure, the prevailing estimated glomerular filtration rate, and absence of specific contraindications for use of these medications. Under most circumstances, insulin is preferred in people with type 2 diabetes mellitus with acute decompensated heart failure, despite the fact that there is limited supportive evidence for use of insulin in this scenario.

Effect of Heart Failure Drugs on Diabetes Mellitus:

The recommended non-glycemic treatment for HF with reduced ejection fraction in patients with T2DM (symptomatic or to prevent HHF and/or death) is similar to the treatment of HF in general and includes angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), angiotensin II receptor blocker neprilysin inhibitor (ARNI), beta-blocker (BB), and Ivabradine.(59–61) Needless to mention, sodium restriction has long been the cornerstone of self-care for patients with heart failure (HF), given the relevance of fluid balance in HF and the potential contribution of dietary sodium to fluid overload.(26) This recommendation persists even though the effects of sodium restriction on quality of life and prognosis of patients with HF

have been consistently questioned over the past decade, owing to the lack of quality evidence to support this practice. In the 2016 ESC guidelines, the salt and fluid restrictions have been modified to 'avoid excessive fluid intake', 'weight-based fluid restriction may cause less thirst', and salt restriction is listed in 'Gaps in evidence' (26,62). ESC guidelines do not provide a specific maximum daily intake of sodium for patients with HF, but advise against excessive intake (defined as > 6000 mg/d of salt, equivalent to 2400 mg/d of sodium). The daily sodium intake recommendations for each stage of heart failure remains similar i.e., no specific maximum daily intake; advise restricting sodium intake to < 6000 mg/d of salt; (2400 mg/d of sodium). Emphasis is currently on the use of diuretics to reduce congestion with intensive management of comorbidities.(26,62)

The Ivabradine or ARNI should be considered in the selected cases with persistent symptoms and EF < 35%.(63) An algorithm for management of heart failure in type 2 diabetes mellitus is depicted in Figure 2.

Renin-angiotensin-aldosterone system (RAAS) inhibitors:

Six studies differentiated by data related to diagnosis of diabetes constituting a meta-analysis (n= 2398 diabetic patients and 10,188 non-diabetic patients) included CONSENSUS, SAVE, 2 SOLVD studies, SMILE, and TRACE studies (64). Meta-analysis demonstrated no difference in mortality among the patients of two different groups. The relative risk (RR) of mortality in patient population with diabetes was 0.84 (95% CI 0.70 to 1.00), while the estimate of the RR in patients without diabetes was 0.85 (95% CI 0.78 to 0.92).(64) However, yet another, large meta-analysis evaluating 47,662 patients demonstrated that, it is the ACEI and not ARBs which contribute to the statistically significant reduction in all-cause mortality (ACM) (RR 0.89; 95% CI 0.83 to 0.96; p = 0.001) and death due to CVD (RR 0.86; 95% CI 0.78 to 0.94; p = 0.001) in HF patients (59). Needless to say, no separate analysis for T2DM in this study was carried out. A subgroup analysis of 'PARADIGM-HF' study in patients of HFrEF was carried out to understand the effect of sacubitril/valsartan combination (ARNI) among diabetic and non-diabetic patients (60). The study revealed a significant reduction in HHF or mortality which was also consistent irrespective of the diabetes [RR 0.87 95% CI: 0.77-0.98] vs non-diabetes status [RR 0.68 95% CI: 0.56-0.83].(60) These results changed the guidelines for the management of HF only 2 months after presented study. Similarly, in a study named CHARM, an equivalent

effect regardless the diabetic status was observed with respect to HHF and mortality when an alternative of ACEI (candesartan) was given(65).

Consensus recommendation

1. The use of RAAS inhibitors exhibits similar efficacy profile in HF patients irrespective of diabetes status.
2. ACEi contributes to the reduction in all-cause mortality (ACM) and CV death

Beta-blockers (BB):

Data classified by diagnosis of diabetes in a meta-analysis evaluated the differential effect of beta-blockers on mortality from HF.(64) Meta-analysis included CIBIS, CPERNICUS, and MERIT-HF studies consisting of 1883 patients with diabetes and 7042 non-diabetic patients. It was observed that patients with diabetes had reduced mortality [0.77 (0.61–0.96)) when given beta-blockers. Further, the RR reduction when compared to non-diabetics was comparatively less [0.65 (0.57–0.74)] (64). Although, the RR comparison yield was not statistically significant, however, the absolute risk reduction in mortality of concomitant diabetes was comparable with non-diabetes.

As a matter of fact, beta blocker led to sharpen the hypoglycemia effect in T2DM patients with HF. In this regard, a study demonstrated that patients with CVD/HF had a higher CV events (HR 1.27; 95% CI, 1.02 to 1.60; p = 0.03), and severe hypoglycemia in patients on BB (HR 1.30; 95% CI, 1.03 to 1.64; p = 0.02).(66)

Consensus recommendation

1. The use of BB demonstrates equivocal safety profile in HF patients irrespective of diabetes status; however, it aggravates the hypoglycemia events in T2DM.

Ivabradine:

Ivabradine, is an inhibitor of the cardiac pacemaker current I_f, which reduces heart rate thereby reducing the cardiac work burden. A reduction in CV death, HHF, and death due to HF was demonstrated by 'SHIFT' study. The results revealed reduction in CV death or HHF (HR 0.82;

95% CI 0.75 to 0.90; p < 0·0001), HHF (HR 0.74; 95% CI 0.66 to 0.83; p < 0·0001) and deaths due to HF (HR 0.74; 95% CI 0.58 to 0.94; p = 0.014). The results of the study were favorable for HFrEF patients with T2DM. Thus, SHIFT results were positive irrespective of the diabetes status (61). The ESC 2016 HF guideline recommends, Ivabradine in HF patients in sinus rhythm with EF ≤ 35% and a resting heart rate (RHR) ≥ 75 bpm), else in those patients who are unable to tolerate BB with RHR ≥ 70 bpm even with maximum tolerated BB dose.(26)

Consensus recommendation

1. Ivabradine is recommended if HF symptoms persist despite treatment with BB, ACEi, and MRA (in patients with sinus rhythm > 70 bpm).

Treatment of HFpEF in T2DM:

The recent published real-world data provides evidence towards increasing prevalence of HFpEF with increased mortality. A meta-analysis revealed that ACM was decreased with BB when compared to placebo (RR 0.78; 95%CI 0.65 to 0.94, p = 0.008), however, there was no effect on HHF (RR 0.67; 95% CI 0.42 to 1.07; p = 0.10) (67).

Again, the ACE inhibitors/ARBs, or other drugs failed to exhibit improvement in HHF or ACM. Even the ARNI could not lower the rate of HHF and ACM among patients with HFpEF as evident by 'PARAGON-HF' study. The percentage death from CV causes was 8.5% in the ARNI group and 8.9% in the valsartan group (HR 0.95; 95% CI 0.79 to 1.16) (68). Table 4 enlists HF outcomes in the various HFpEF/HFrEF trials. Therefore, the current management emphasize on the use of diuretics for aggressive management of associated co-morbidities. Algorithm for management of heart failure in type 2 diabetes mellitus is depicted in Figure 3.

Consensus recommendation for HFpEF

1. For associated co-morbidities, target lipid and blood pressure levels should be achieved.
2. In patients with CAD, coronary revascularization could be a suitable option to adopt.

Therapeutic Targets for Heart Failure in Diabetes:

Apart from SGLT2-i, some novel therapeutic targets for heart failure in diabetes ongoing trials on pharmacological management of HFrEF and HFpEF are as follows:

Ularitide: A synthetic analog of the endogenous urodilatin which is investigated in several phase I and II trials. It is a renal peptide hormone secreted in response to increased pressure. Ularitide causes diuresis, vasodilatation, and inhibition of RAAS by binding to natriuretic peptide receptor (NPR-A) (69).

Levosimendan: It is an inotrope with an added action of vasodilatation and protection against ischemia and reperfusion injury. It increases the cardiac contractility in acute HF (70).

Phosphodiesterase type 5 (PDE-5) inhibitors: They are principally used in the management of pulmonary arterial hypertension and have demonstrated more benefits in HFrEF compared with HFpEF (71).

Omecamtiv: It is a specific cardiac myosin activator to improve cardiac contractility. This has exhibited promising results in phase 2 COSMIC-HF study (72).

Tafamidis: It is primarily used for the management of transthyretin amyloid cardiomyopathy. It binds with the thyroxine-binding sites of transthyretin and has demonstrated a reduction in ACM, CV-related hospitalization (73).

Canakinumab: It is an anti-inflammatory monoclonal antibody targeting IL-1β. Canakinumab has demonstrated a dose dependent reduction in HHF in patients with previous MI and increased hs-CRP (74).

Conclusion:

India registers 14% of deaths due to HF in patients with T2DM. The management of HF is based on its classification. A mixed report on the prognosis of HFrEF and HFpEF in patients with T2DM is available. Research suggests that both HFrEF and HFpEF increase the risk of hospitalization and mortality in patients with T2DM. Furthermore, in patients with newly diagnosed T2DM, the risk of MACE, HF and death increase with a higher number of comorbidities including CKD as the main contributor of mortality. Needless to say, HF diagnosis requires a detailed history, assessment of clinical signs and symptoms, assessment of

diagnostic biomarkers, an ECG, and 2D-Echo. Diabetes can be associated with other endocrine disorders which automatically qualify to classify as HF Stage A. Clinical screening should be done for all patients and TSH, testosterone where clinically indicated. This consensus document was intended to make better patient care, optimize the prognosis by executing the most efficient treatment strategies for the management of HF in T2DM. Additionally, SGLT2i play a major role in the prevention of HF in T2DM patients by its inherent ability to offer protection from CV complications along with best glycemic control. Results with dapagliflozin in DECLARE-TIMI 58 trial generated immense hope by demonstrating a significant reduction in HF in patients with T2DM. Besides the SGLT2i, new innovations may embrace the answer to transform the management of HF, in patients with T2DM.

Appendix-1

Table1: Role of biomarkers in the diagnosis of heart failure

Categories	Specific biomarkers	Recommendations for Diagnostic/Prognostic Value
Myocardial stress/injury	BNP, NT-proBNP	The upper limit of normal BNP value is 35 pg/mL, and for a NT-proBNP value is 125 pg/mL (non- acute settings). BNP >100 pg/mL and NT-pro BNP >300 pg/ml (acute setting) strongly suggests the possibility of HF.
	Troponin	Diagnostic of myocardial infarction, Elevated levels predict HF deaths, suggest ongoing myocyte injury or necrosis in affected patients. Associated with impaired hemodynamics, progressive LV dysfunction.
Remodeling	ST-2	Elevated levels of ST2 have prognostic value in the management of HF. It predicts mortality, and HF events.
	Galectin-3	Predict rehospitalization and death in HFpEF Predict HF events.

ST2: suppressor of tumorigenicity 2; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal- proBNP.

Table 2: Natriuretic peptide cutoff points and diagnostic accuracy

Acute Dyspnea	**To exclude acute HF**	**Cut-off Value**	**Sensitivity**	**Specificity**
	BNP	<30-50 pg/mL	97%	62%
	NT-proBNP	<300 pg/mL	99%	68%
	To identify acute HF			
	BNP	<100 pg/mL	90%	76%
	NT-proBNP	<900 pg/mL	90%	85%
	NT-proBNP, age-stratified approach		90%	84%
		<450 pg/ml for <50y <900 pg/ml for 50–75y <1800 pg/ml for >85y		

Table 3: Characteristics of heart failure classification:

Based on Left Ventricular Ejection Fraction:	**Based on Time-course**	**NHYA classification**	
1. HFrEF: EF < 40%	1. Chronic HF: Present for ≥3 months	Class I	No limitation in physical activity
2. HFmrEF: EF = 40% to 49%	2. Acute HF: Sudden onset HF or worsening of HF symptoms/signs	Class II	Slight limitation in physical activity. (Ordinary activity results in symptoms. Patient is comfortable at rest).
3. HFpEF: EF ≥ 50%		Class III	Marked limitation in physical activity. (Daily routine activity results in symptoms. Patient is comfortable at rest).
		Class IV	Marked limitation in physical activity. (Daily routine activity results in symptoms. Patient is comfortable at rest).

AHA: Stages of heart failure	
Stage A:	High risk, without symptoms (diabetes, hypertension, CAD)
Stage B:	Structural heart disease, without symptoms (previous MI, LV remodeling including LVH and low EF)
Stage C:	Structural heart disease with previous or current symptoms (known structural heart disease and shortness of breath and fatigue)
Stage D:	Structural heart disease with refractory symptoms (patients who have symptoms at rest)

EF: Ejection fraction; HF: Heart failure; HFmrEF: Heart failure with mid-range ejection fraction; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; NYHA: New-York Heart Association; AHA: American Heart Association;

Table 4: HF outcomes in the various HFpEF/HFrEF trials.

4a. Clinical trials in heart failure with preserved ejection fraction			
Drug	**Study**	**Drug/Intervention, Dosage, Median Follow-up**	**HF Outcomes**
ARB	CHARM-Preserve (65)	Candesartan 32 mg vs. placebo FU: 36.6 months	CV death or hospitalization for CHF: 0.86 (0.74-1.0) p = 0.051 CV death: 0·95 (0·76–1·18) p = 0·635 Hospitalization for CHF: 0·84 (0·70–1·00) p = 0·047 CV death, hospitalization for CHF, MI: 0·87 (0·75–1·00) p = 0·051 CV death, hospitalization for CHF, MI, stroke: 0·86 (0·75–0·99) p = 0·037
ACEI	PEP-CHF (75)	Perindopril 4 mg FU- 2.1 year	Death or hospitalization: 0.919 (0.700–1.208) p = 0.545 Hospitalization for HF: 0.86 (0.61–1.20) p = 0.375 Death: 1.09(0.75–1.58) p = 0.665 CV death: 0.98 (0.63–1.53) p = 0.928
	Aldo-DHF (76)	Spironolactone25 mg or placebo FU-12 months	Diastolic function: -1.5 (-2.0 to-0.9) p < 0.001 Maximal exercise capacity: 0.1 (-0.6 to 0.8) p = 0.81 LV ejection fraction: 1.6(0.1–3.1) p = 0.04
BB	SENIORS (77)	Nebivolol up to10 mg vs. placebo FU: 21 months	All-cause mortality or CV hospitalization: 0.86 (0.74–0.99) p = 0.039 All-causemortality:0.88(0.71–1.08) p = 0.21 CV mortality: 0.84 (0.66–1.07) p = 0.17 CV hospitalization:0.90 (0.76–1.06) p = 0.20(
4b. Clinical trials in heart failure with reduced ejection fraction			
Drug	**Study**	**Drug/Intervention, Dosage, Median Follow-up**	**HF Outcomes**
ACEI	SOVLD (78)	Enalapril at doses of 2.5 to 20 mg per day vs placebo	Mortality39.7% vs35.2%, (RRR= 16%, CI: 5 to 26%) p=0.0036)
ARNI	PARADIGM-HF Trial (79)	Enalapril 10 mg twice daily or LCZ696 200 mg	CV death or HHF: HR: 0.80; 95% CI: 0.73 - 0.87; p < 0.001) Death (HR: 0.84; 95% CI: 0.76-0.93; p < 0.001), First HHF (HR: 0.79; 95% CI:0.71-0.89; p < 0.001
Beta blocker	CIBIS II (80)	Bisoprolol 1·25 mg (n=1327) or placebo FU: 1.3 years	All-cause mortality: 11·8% vs 17·3%, HR: 0·66 (95% CI0·54–0·81, p<0·0001) Hospital admission for worsening HF: 18% vs 12%, HR: 0·64 (95% CI: 0·53–0·79), p = 0·0001
	MERIT-HF (81)	Metoprolol 12.5/25 mg or placebo	All-cause mortality: 7.2% vs 11%, HR: 0.66; 95% CI: 0.53-0.81; p = 0.00009

Figure 1: Diagnostic algorithm for heart failure in T2DM.

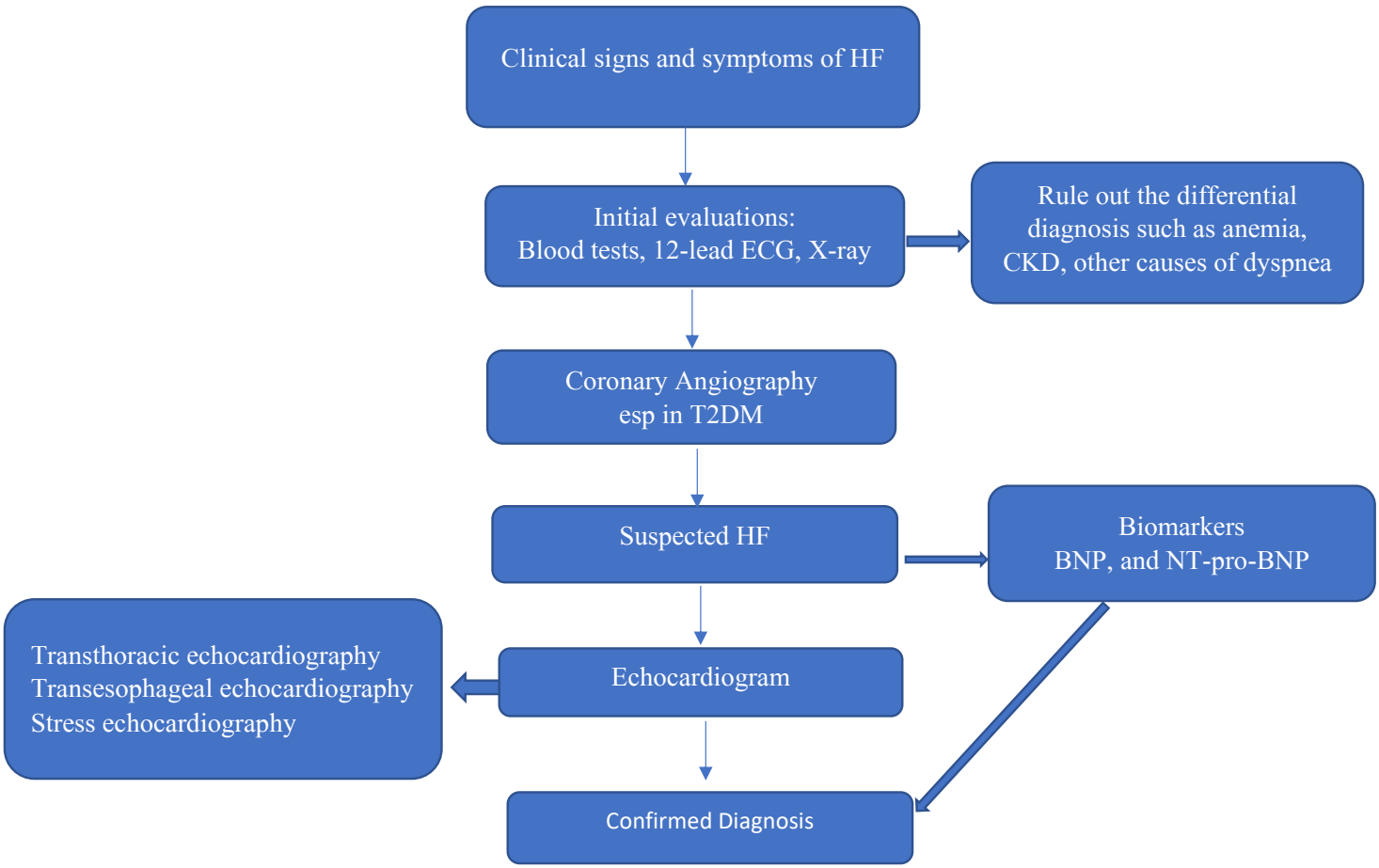
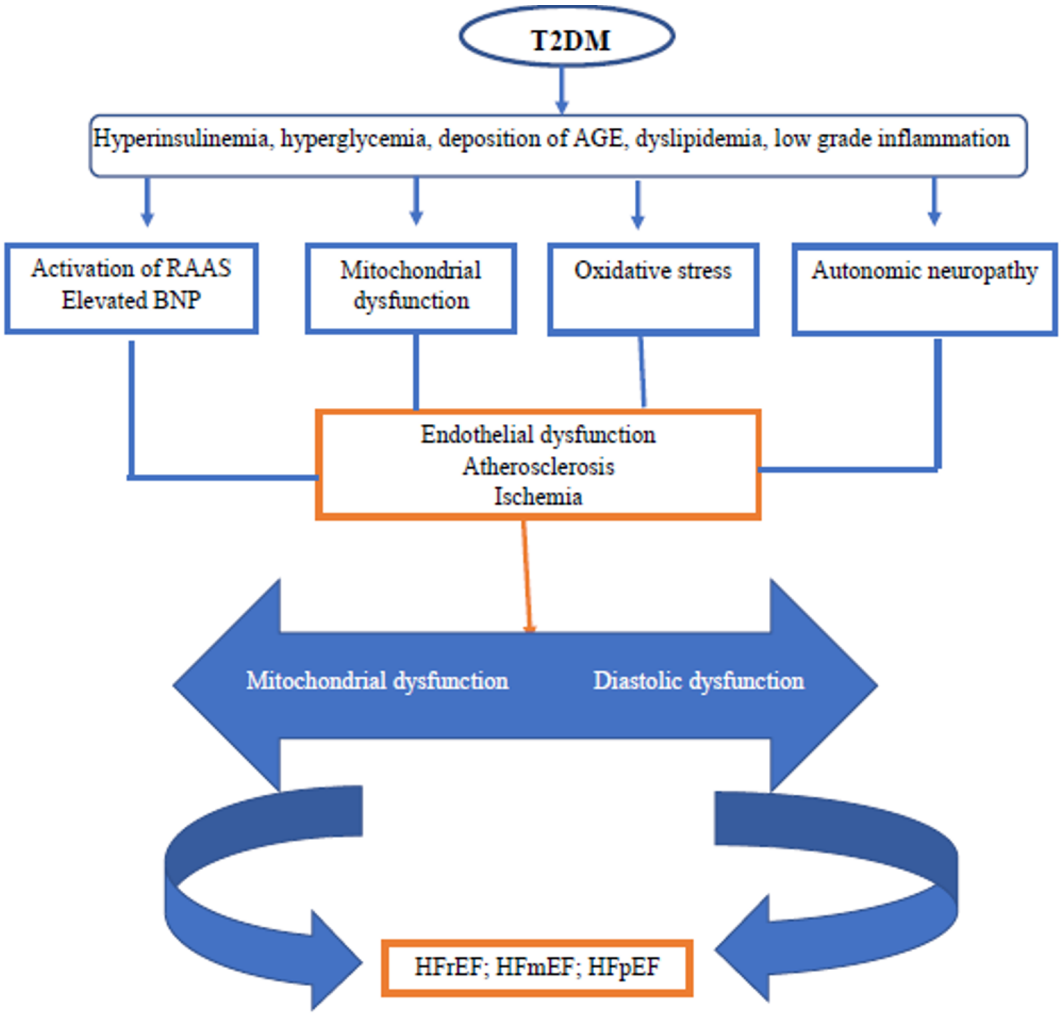
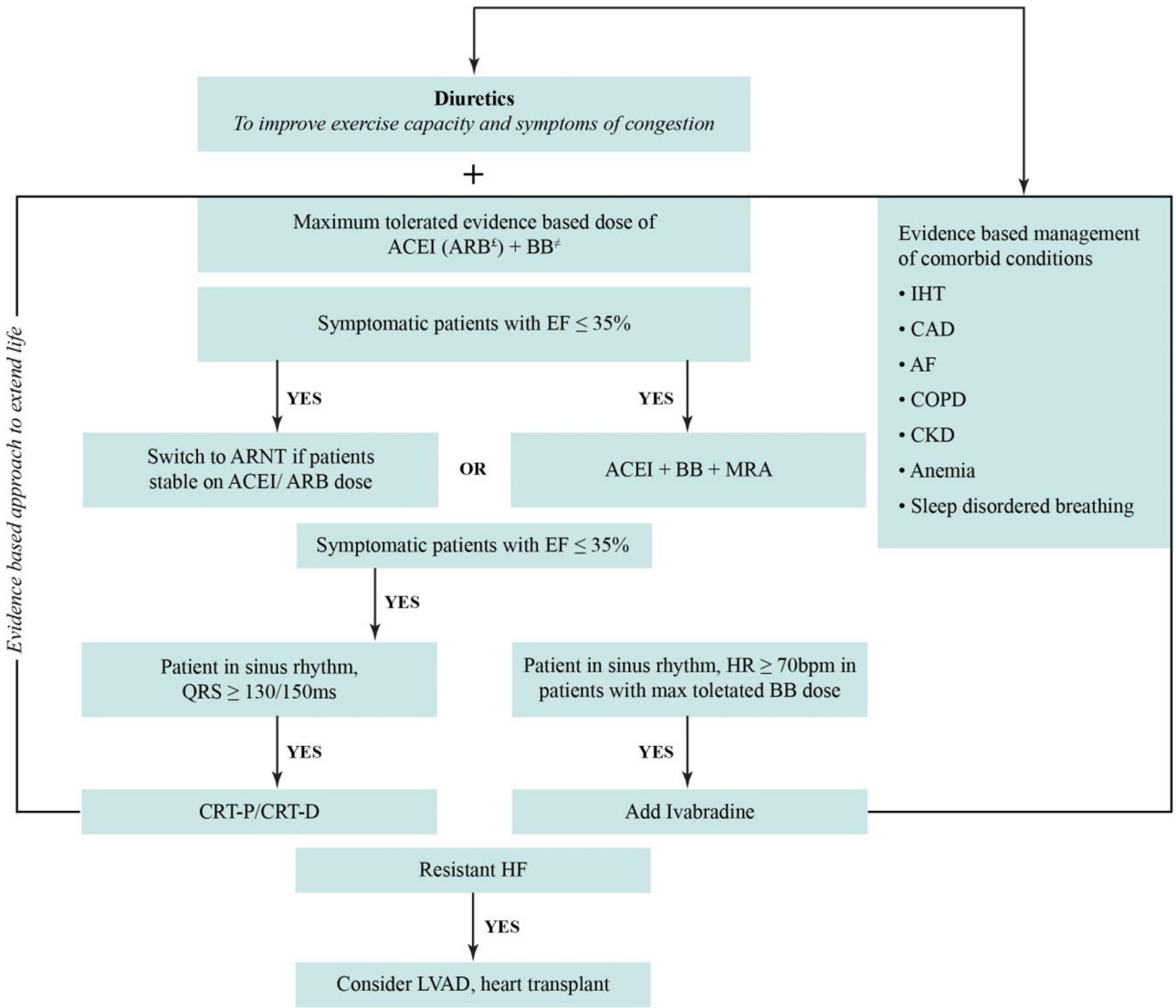


Figure 2: Pathophysiology of heart failure in type 2 diabetes mellitus



AGE: advanced glycation end products; ATP: adenosine triphosphate; BNP: B-type natriuretic peptide; FFA: free fatty acids; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; RAAS: renin-angiotensin-aldosterone system; T2DM: type 2 diabetes mellitus.

Figure 3. Algorithm for management of heart failure in type 2 diabetes mellitus



£If intolerant to ACEI. ≠Select from carvedilol, bisoprolol, metoprolol or nevivolol. *GLP-1 agonist with strongest CVD benifit: liraglutide>semaglutide>exenatide extended release, †SU with no CV risk: gliclazide, glimepiride. ‡Vildagliptin
ACEI: Angiotensin converting enzyme inhibitor; AF: Atrial fibrillation; ARB: Angiotensin II recevtor blocker; ARNI: angiotensin II receptor blocker neprilysin inhibitor; BB: Beta-blocker CAD: Coronary drtery disease; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease, CRT-P: Cardiac synchronization therapy-pace maker CRT-D: Cardiac synchronizapion therapy-defibnllator; EF: Ejection fraction; HF: heart failure; LVAD: ventricular assist device; MRA: Mineralocorticoid receptor antagonist

Adapted from: Kaul, U., Ray, S., Prabhakar, D. et al. Consensus document: management of heart failure in type 2 diabetes mellitus. Heart Fail Rev (2020).

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