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Consensus document: management of heart failure in type 2 diabetes mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is a known predisposing factor for heart failure (HF). The growing burden of these two conditions and their impact on health of the individual and on society in general needs urgent attention from the health care professionals. Availability of multiple treatment choices for managing T2DM and HF may make therapeutic decisions more complex for clinicians. Recent cardiovascular outcome trials of antidiabetic drugs have added very robust evidence to effectively manage subjects with this dual condition. This consensus statement provides the prevalence trends and the impact of this dual burden on patients. In addition, it concisely narrates the types of HF, the different treatment algorithms, and recommendations for physicians to comprehensively manage such patients.

Keywords Type 2 diabetes mellitus · Heart failure · Trials · Diagnosis · Drug

Introduction

Type 2 diabetes mellitus (T2DM) is a well-known predisposing factor for heart failure (HF) and patients with this combination have adverse outcomes, and higher mortality rates compared with those presenting with a single condition [1, 2]. The pathophysiology of both these conditions is closely interlinked [3,4,5]. Early identification and optimal and immediate intervention in such cases result in better outcomes. This consensus document provides evidence-based guidance on risk factors and diagnostic and prognostic factors, which could help in appropriate management to reduce morbidity and mortality. The management strategies for patients with different phenotypes of HF having coexisting T2DM are also discussed.

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The burden of heart failure

Heart failure is a global pandemic affecting an estimated 26 to 37.7 million people worldwide [6, 7]. The burden of HF in India has become an important public health concern because of very high mortality. Table 1 presents the epidemiology and mortality of HF in India.

Heart failure exerts a high economic burden mostly due to hospitalizations [14]. India is the highest spending country on HF in South Asia with a total expenditure of $1186 million, which was 1.10% of global expenditure and 1.7% of total health expenditure of India [15].

Dual burden of heart failure and type 2 diabetes mellitus

A systematic review, analyzing 57 studies and evaluating 4,549,481 patients with T2DM, reported a 14.9% prevalence of HF, 14.6% of angina, 10% of myocardial infarction (MI), and 7.6% of stroke in patients with T2DM [16]. The prevalence of T2DM in patients with HF was 24% and 45.3% in the Swedish and Spanish HF registries respectively [17, 18]. In the latter study enrolling 1082 patients with decompensated HF from 2008 to 2011, 490 (45.3%) had diabetes. A total of 151 patients (30.8%) with T2DM died, and 197 patients (40.2%) with T2DM were readmitted because of HF, during the follow-up period. Type 2 diabetes mellitus was significantly associated with increased all-cause mortality (ACM) (hazard ratio (HR) 1.49; 95% confidence interval (CI) 1.19 to 1.87; $p < 0.001$) and readmissions (HR 1.39; 95% CI 1.15 to 2.69; $p < 0.001$) over the 1-year follow-up [18]. An Asian HF registry reported the prevalence of T2DM as 41.3% in patients with HF [19]. The annual incidence of HF due to diabetes in India has been projected to increase by 18% (73,600 (2000) to 161,000 (2025)) [8]. According to an Indian HF consensus estimate (2018), 50% of patients with chronic HF have diabetes [20]. A recent report from the largest Indian registry documents a prevalence of diabetes to be 49.2% in patients with HF [21].

Key messages
1. Around 50% of patients with chronic HF have diabetes in India.
2. The annual incidence of HF in India is expected to increase by 18%.
3. Heart failure is more prevalent than myocardial infarction in patients with T2DM.

Figure 1 shows the factors associated with HF in T2DM [22, 23] and Table 2 shows the risk score for heart failure in diabetes.

In a study by Parry et al., glycated hemoglobin (HbA1c) < 6% (HR 1.60; 95% CI 1.38 to 1.86; $p < 0.0001$) as well as HbA1c > 10% (HR 1.80; 95% CI 1.60 to 2.16; $p < 0.0001$) were independently associated with the risk of HF. This U-shaped relationship was attributed partly due to the adverse off-target effects of antidiabetic medications like thiazolidinediones (TZDs), or insulin. Glycated hemoglobin variability (HR 0.80, 95% CI 0.74 to 0.85; $p < 0.0001$) has also been found to be associated with HF incidence, with less variability in HbA1c having a protective effect on incident HF. The HbA1c variability is also postulated to enhance cell

Table 1 Epidemiology and mortality of heart failure in India

Author, year	Parameter	Prevalence/Number of patients
Huffman and Prabhakaran, 2010[8]	Heart failure (Overall estimates)	1.3 to 4.6 million
GBD 2017[9]	IHD DALY100,000 population	2679.17
Chaturvedi et al, 2016[10]	Heart failure (hospital attendees)	20.4%
Chaturvedi et al, 2016[10]	Heart failure (General community)	1.2/1000 population
Dokainish et al, 2017[11]	Heart failure mortality (Overall)	23%
Chaturvedi et al, 2016[10]	Heart failure mortality (North India)	0.1 to 0.16 million individuals per year
Chaturvedi et al, 2016[10]	Heart failure mortality (30 days)	12.5%
Harikrishnan et al, 2015[12]	Heart failure mortality (30 days)	12.5%
	Heart failure mortality (90 days)	18.1%
Harikrishnan et al, 2017[13]	Heart failure mortality (1 year)	30.8%

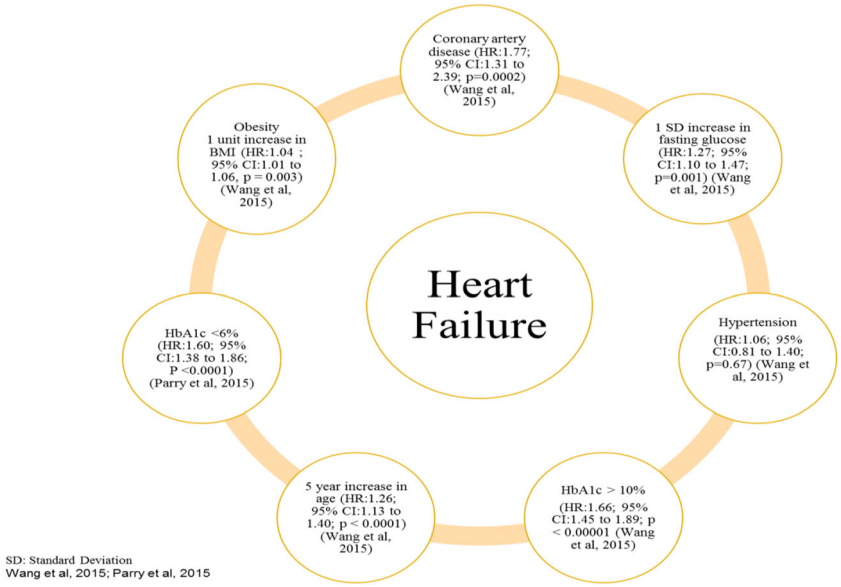


Fig. 1 Factors associated with heart failure

apoptosis and oxidative stress, and thereby lead to HF in patients with diabetes [23]. Moreover, chronic kidney disease (CKD) increases mortality and the overall progression of cardiovascular disease (CVD) and HF [24]. Prevalence of CKD (eGFR < 60 mL/min/1.73 m [2]) in patients with HF was observed to be 63%, which was associated with an 11% increase in hospitalization and a 17% increase in mortality. Worsening of renal function and mortality was more prevalent in patients with diabetes compared with the reference group (32% vs. 25%) [25].

Heart failure in patients with prediabetes

Patients with prediabetes and undiagnosed T2DM represent a vulnerable population who often remain undiagnosed. In the PARADIGM-HF study among 8399 patients with heart failure with reduced ejection fraction (HFrEF), 13% had undiagnosed T2DM (HbA1c ≥ 6.5%) and 25% had prediabetes (HbA1c 6.0–6.4%) [26]. The risk of HF for patients with undiagnosed diabetes mellitus (DM) (HR 1.39; 95% CI 1.17 to 1.64; $p < 0.001$) and prediabetes (HR 1.27; 95% CI 1.10 to 1.47; $p < 0.001$) was higher compared with non-diabetics [26]. India bears a considerable burden of prediabetes and undiagnosed diabetes. The Indian Council of Medical Research-INDIAB study reveals that around 77.2 million people in India are prediabetic [27]. About 36 million (52%) people are known to have undiagnosed DM [28]. The most frequent cardiac abnormality associated with asymptomatic DM includes left ventricular (LV) diastolic dysfunction. Silent myocardial ischemia occurs in T2DM patients due to autonomic neuropathy and increases the probability of HF by a delay in diagnosis and appropriate management [29].

Key messages
1. Glycated hemoglobin variability, TZDs, co-morbid CKD, and silent myocardial ischemia may exacerbate the risk of HF.
2. Prediabetes and undiagnosed diabetes are risk factors for HF and both have a high prevalence in India.

Subclinical heart failure

There is no standard definition for subclinical HF in the current guidelines; however, as per the American Heart Association (AHA) classification of HF, T2DM patients fit under stage A. Nystrom et al. have defined diastolic dysfunction (AHA stage B) as subclinical HF [30]. Another study defined subclinical HF as an absence of signs of overt HF and a B-type natriuretic peptide (BNP) level > 150 ng/mL [31]. Overt HF was considered if patients fulfilled one of the following criteria: NYHA class II–IV, objective signs of HF (pulmonary congestion, ankle edema), history of hospitalization due to HF (HHF), and chronic treatment with diuretics. An Indian study found that 63% of patients with T2DM had diastolic dysfunction, irrespective of the age and the duration of the disease. The study suggests existence of preclinical cardiomyopathy and recommended routine 2D echo in all patients with T2DM to enable early therapeutic interventions [32]. Similar results were seen in patients with T2DM without overt cardiac disease; 68% of patients had asymptomatic LV dysfunction (27% isolated systolic, 16% isolated diastolic, and 25% combined systolic and diastolic) [33]. Subclinical HF being a silent precursor of HF may be underdiagnosed [34], and early

Table 2 TIMI risk score for heart failure in diabetes (TRS-HF_{DM})

Risk Indicator	Points
Prior heart failure	2
Atrial fibrillation	1
Coronary artery disease	1
eGFR <60 mL • min^{-1} • 1.73 m^{-2}	1
Urine albumin-to-creatinine ratio	
>300 mg/g	2
30–300 mg/g	1

therapeutic interventions may improve outcomes and mortality [35, 36].

Key messages
1. Presence of diastolic dysfunction on 2D echo, BNP > 150 ng/mL without overt HF, can be considered to be the signs of subclinical HF.
2. Subclinical HF is underdiagnosed.
3. Early therapeutic interventions will improve mortality and morbidity.

Classification and phenotypes of heart failure

The American College of Cardiology Foundation (ACCF)/AHA [37] classifies patients into four stages based on the risk factors for HF and cardiac structure abnormalities, while the New York Heart Association (NYHA) [38] four stage classification categorizes patients based on their degree of symptomatic limitation of physical activity (Table 3) [39]. Accordingly, DM being a risk factor for HF; patients could be potentially considered STAGE A or NYHA I HF category. Suggesting, patients of T2DM need proactive assessment for HF and managed aggressively in order to prevent morbidity and mortality associated with HF.

Characteristics of heart failure phenotypes

Table 4 describes HF phenotype according to the ejection fraction (EF) [39]. Response to treatment and prognosis of HF differs significantly based on EF, as well as the patient's demographic and comorbidities. Not to mention, patients are being selected to clinical trials based on EF and application of results of such trials to clinical practice should be considered keeping the EF in the background.

The prevalence of both phenotypes based on EF has been observed to be similar. In a Swedish HF registry, 25% and 24% of patients with HF with preserved ejection fraction (HFpEF) and HFrEF, respectively, had diabetes [40]. In 7599 patients with symptomatic chronic HF in the USA, the prevalence of diabetes was 28.3% in patients with HFpEF and 28.5% in those with HFrEF [41]. The Medanta registry (48.7% had comorbid DM) found that most Indian patients had HFrEF (59.1%) [21]. The Inter-CHF study (Indian data) [11] reported an HFrEF prevalence of 53% (26% had comorbid DM), while the Trivandrum HF Registry (THFR) [12] reported a prevalence of HFpEF to be 26% (55% had comorbid DM).

Recommendations
1. The prevalence of HFrEF and HFpEF in India is similar (~ 50%) in patients with T2DM.
2. Identifying the HF phenotype and stage of HF can guide management.
3. Though there is no proven specific therapy for HFpEF, it is clinically important to distinguish it from HFrEF as the latter has proven medical and surgical therapies. Also, identification of HFpEF can direct therapies for efficient management of risk factors and prevent progression.

Table 3 Classification of heart failure (HF)

AHA/ ACCF	**STAGE A** At high risk of HF but without structural heart disease or symptoms of HF	**STAGE B** structural heart disease but without symptoms or signs of HF	**STAGE C** Structural heart disease with prior or current symptoms of HF	**STAGE D** refractory HF requiring specialized interventions
Patients	**Diabetes Mellitus,** hypertension, obesity, metabolic syndrome, atherosclerotic disease	Previous MI, LV remodeling including LVH and low EF, asymptomatic valvular disease	Known structural heart disease and shortness of breath and fatigue	Patients who have symptoms at rest
NYHA	I	I	I, II, III, IV	IV
I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF			
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF			
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF			
IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest			

Pathophysiology of heart failure in type 2 diabetes mellitus

T2DM is associated with more atherogenic dyslipidemia and endothelial dysfunction, clearly suggesting the importance of role of lipid lowering drugs in reducing HF. T2DM is frequently linked to left ventricular hypertrophy largely caused by insulin resistance and hyperinsulinemia [42]. Hyperglycemia results in cardiac muscle stiffness and leading to non-compliance of the myocardium. Therefore, drugs decreasing insulin resistance and aggressively controlling the hyperglycemia should be part of therapy in order to reduce the incidence of HF in T2DM [43].

T2DM could potentially cause cardiomyopathy independent of atherosclerotic ischemia, and there is evidence of cardiomegaly in T2DM patients. Hence, therapy targeting such pathology [44], .e.g., SGLT2i, might be useful [45, 46]. Figure 2 provides a schematic representation of the pathophysiology of HF along with the primary pathways for HF in T2DM.

Diagnosis of HF in type 2 diabetes mellitus

Heart failure diagnosis necessitates a detailed history, assessment of clinical signs and symptoms, assessment of diagnostic biomarkers, and an echocardiogram. The steps to confirm the diagnosis of HF include (1) symptoms and signs of pulmonary and/or systemic venous congestion; (2) identification of any

Table 4 Classification based on ejection fraction (EF)

Ejection Fraction Based	**HFrEF: EF < 40%**
	HFmrEF: EF = 40% to 49%
	HFpEF: EF ≥ 50%
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.	

structural abnormality of atria and/or ventricles or heart valves; (3) evidence of impaired ventricular filling at rest or effort; (4) exclusion of diagnoses with overlapping symptoms; (5) objective documentation of reduced exercise capacity; and (6) evaluation of biomarker levels such as natriuretic peptides (NPs) [20, 53].

Role of biomarkers in the diagnosis of heart failure in type 2 diabetes mellitus

Biomarkers add value as their blood concentrations aid in the diagnosis, determine disease severity, estimate prognosis, evaluate response to therapy, and establish management plans [54, 55]. Largely, B-type natriuretic peptide (BNP) and N-terminal-proBNP are used for the diagnosis and prognosis of HF. However, other biomarkers, cardiac troponin I, could also be used to assist in the diagnosis of HF (Table 5). Biomarkers should be used in conjunction with clinical judgment while making treatment decisions.

Recommendations
1. BNP and NT proBNP are good diagnostic and prognostic markers.
2. ST2 and Galectin-3 are supportive prognostic markers.
3. Elevated cardiac troponin level suggests ongoing cardiac necrosis.
4. High-sensitive troponin is considered quantitative troponin.

The diagnostic algorithm for HF is described in Fig. 3 a and b.

Important diagnostic test in T2DM is the coronary angiography: In India, most common cause of HF is coronary artery disease (CAD), especially in T2DM. Hence, in undiagnosed HF (especially in those aged > 40 years) where the etiology is unclear, it should be mandatory to do a coronary angiography to rule out CAD (in view of the high incidence of CAD, especially in diabetics) [63].

Glycemic management in T2DM and HF-RSSDI [65], ADA [66], and ACE/AACE [67] guidelines

Studies like UKPDS [68], ADVANCE [69], ACCORD [70], and VADT [71]. have shown no improvement in heart failure even after intensive glycemic management. However, many observational studies have reported optimal glycemic control is beneficial to patients. Some studies demonstrated increase in HbA1c more than 8%, 9%, and 10% could potentially increase the risk of worsening of HF [72, 73, 74]. All the guidelines suggest of individualizing therapy and glycemic goal for every patient. Generally, all guidelines recommend being as stringent with HbA1c to near normal glycemic levels (Fig. 4 a and b). However, patient characteristics like age, duration of diabetes, and risk of complications including hypoglycemia and comorbidities should be kept in mind while achieving the glycemic goal. Therefore, choosing a glucose lowering drug is very critical and should be personalized based on the need of the patients.

Few salient points while considering the antidiabetic drug:

- Glycemic management should generally start with metformin unless there is evidence of renal impairment or another contraindication. Metformin is safe and generally well-tolerated. Metformin should be used with caution in patients with estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2 and not to be used in eGFR <30 mL/min/1.73 m^2.
- Second line therapy in case patient fails to achieve glycemic control, may include, sulfonylurea, thiazolidinediones, dipeptidyl dipeptidase-4 inhibitor (DPP4i), sodium-glucose co-transporter 2 (SGLT-2) inhibitors, and GLP1 agonists.
- Third line therapy includes either adding third oral agent or starting insulin.
- Thiazolidinediones and sulfonylureas should be used with caution as they might potentially increase the risk of worsening of heart failure. However, recent study CAROLINA has shown no increase in risk of HHF with glimepiride when compared with linagliptin in T2DM patients without HF [75].
- The completed CVOTs with glucagon-like peptide-1 receptor (GLP-1) agonists include LEADER with liraglutalide [76] and SUSTAIN-6 with semaglutide [77] showed reduction in MACE (HR 0.87 and 0.74 respectively), and liraglutide showed trend towards reducing the hospitalization for HF (HHF) preferably in high CV risk T2DM patients only, whereas ELIXA with lixisenatide [78] and EXSCEL with long acting exenatide [79] failed to demonstrate CV protection. A meta-analysis [80] of these 4 CVOTs (LEADER, SUSTAIN-6, ELIXA, and EXSCEL) (Table 6) demonstrated a favorable risk-benefit ratio for GLP 1 agonists with a reduction in 3-point MACE (HR 0.90; 95% CI 0.82 to 0.99; $p = 0.033$), CV mortality (HR 0·87; 95% CI 0·79 to 0·96; $p = 0·007$), and ACM (HR 0.88; 95% CI 0.81 to 0.95; $p = 0·002$). HARMONY trial [81] showed reduction 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; $p = 0.03$) but did not reduce CV death, ACM, or stroke. The recently published REWIND [82] trial also demonstrated a reduction in MACE (HR 0.88; 95% CI 0.79 to 0.99; $p = 0.026$), though there was no difference in mortality, and a higher incidence of gastrointestinal adverse events (47.4% vs. 34.1% in placebo) were recorded.
- Dipeptidylpeptidase-4 (DPP4) inhibitors or gliptins should be used with caution as they have shown inconsistent effect on HHF in the CVOTs. Sitagliptin showed equivocal results in the TECOS trial [83] for the HHF

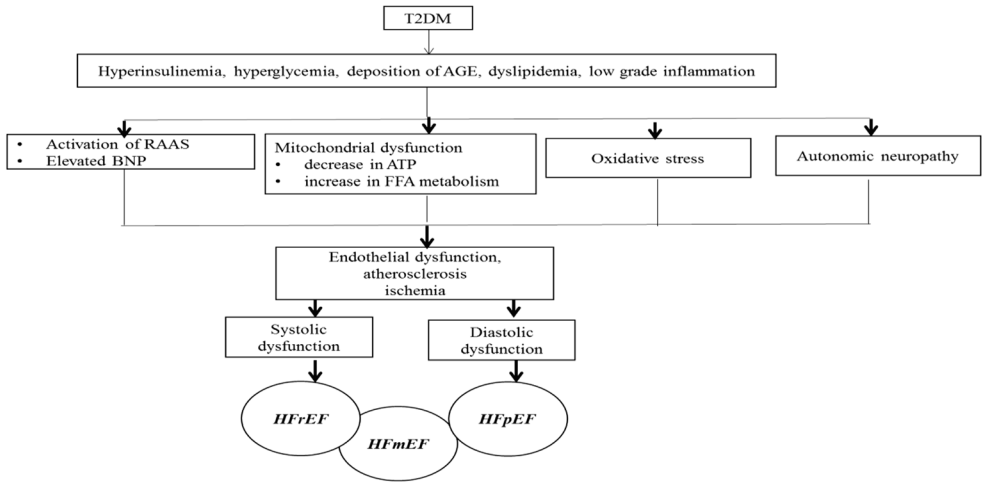


Fig. 2 Schematic representation of pathophysiology of heart failure in type 2 diabetes mellitus. AGE: advanced glycation end products; ATP: adenosine triphosphate; BNP: B-type natriuretic peptide; FFA: free fatty acids; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; RAAS: renin-angiotensin-aldosterone system; T2DM: type 2 diabetes mellitus. Hyperinsulinemia, hypoglycemia, and hyperglycemia with AGE deposition, along with dyslipidemia and low-grade inflammation, result in activation of RAAS, mitochondrial dysfunction, oxidative stress, and autonomic neuropathy (causes silent ischemia-induced myocardial damage). These interlinked pathways lead to endothelial dysfunction, atherosclerosis, and ischemia. The resultant cardiac dysfunction can lead to systolic dysfunction (HFrEF) or diastolic dysfunction (HFpEF), or an intermediate phenotype (HFmrEF) [47,48,49,50,51,52]

end point (3.1% sitagliptin vs. 3.1% placebo (HR 1.00; 95% CI 0.83 to 1.20)). SAVOR-TIMI 53 trial [84] in contrast unveiled 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. EXAMINE [85] results with alogliptin concurred with an increased HHF trend (3.9% alogliptin vs. 3.3% placebo (HR 1.19; 95% CI 0.89 to 1.58)). Vildagliptin in the VIVIDD trial (only gliptin trial in HFrEF) [86] had no major effect on EF, but caused an increase in LV volumes (LV end-diastolic volume 17.06; 95% CI 4.62 to 29.51; $p = 0.007$ and LV end-systolic volume 9.44; 95% CI − 0.49 to 19.38; $p = 0.062$), the significance of which was not clear. Though only saxagliptin and alogliptin have shown increased risk of HHF and not vildagliptin, linagliptin, and sitagliptin, it is advisable to weigh the risk benefit while using these drugs in patients with HF and DM.

Emerging favorable evidence for SGLT2i right from the early stages of heart failure

- Sodium-glucose co-transporter-2 inhibitors (SGLT2i) have had the most favorable HHF and mortality outcomes in multiple CVOTs in T2DM patients. These favorable HF results have been demonstrated in patients with or without a history of HF or atherosclerotic cardiovascular disease (ASCVD). A recent meta-analysis demonstrated robust benefits with SGLT2i on HHF and CV death (HR 0.77; 95% CI 0.71 to 0.84; $p < 0.001$), in patients with and without pre-existing ASCVD or HF, indicating benefits even in the early HF stages [87]. Empagliflozin in the EMPA-REG OUTCOME study [88] and dapagliflozin in DECLARE-TIMI 58 [89] study 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). Analysis of the CANVAS program [90] also showed a reduction in HHF (HR 0.64; 95% CI 0.35 to 1.15 vs. HR 0.68; 95% CI 0.51 to 0.90; interaction $p = 0.91$) in the primary and secondary prevention cohorts, respectively. The US FDA has approved empagliflozin (for lowering CV death) and canagliflozin (for lowering MACE) in patients with T2DM and established CVD. DECLARE-TIMI 58 results showed lower rates of CV death or HHF (4.9% vs. 5.8%; HR 0.83; 95% CI 0.73 to 0.95; $p = 0.005$), and suggested primary prevention of cardiorenal complications, as benefits were shown in patients with risk factors without baseline ASCVD or HF. DECLARE TIMI results when stratified by 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, and reduced CV death (HR 0.55, 95% CI 0.34 to 0.90) and ACM (HR 0.59; 95% CI 0.40 to 0.88) in HFrEF [91]. Numerous studies have shown additional metabolic benefits like improvement in body weight, blood pressure, lipid profile, insulin sensitivity, volume overload, and cardiac function [92,93,94]. Sodium-glucose co-transport-2 inhibitors have the advantage of efficient glycemic control with added cardiometabolic benefits. The recently presented DAPA-

Table 5 Role of biomarkers in the diagnosis of heart failure

Biomarkers	Physiological Actions	Recommendations for Diagnostic/Prognostic Value
B-type natriuretic peptide (BNP) N-terminal-proBNP	In response to abnormal myocardial stretch (as in HF), the ventricular myocyte secretes large amounts of prohormone BNP 1-108. This is quickly cleaved into a biologically active (but less stable) BNP 1-32 and an inert (but more stable) NT-pro-BNP 1-76.	The upper limit of normal BNP value is 35 pg/mL and for a NT-proBNP value is 125 pg/mL(non-acute settings) and BNP >100 pg/ml and NT-pro BNP >300 pg/ml (acute setting) strongly suggests the possibility of HF.[39] Measurement of BNP and NT-proBNP is useful to support the clinical judgement for the diagnosis of ambulatory and acute decompensated patients, especially in the setting of clinical uncertainty.[56,57] Measurement of pre-discharge BNP or NT-proBNP during an HF hospitalization can be useful for establishing a post-discharge prognosis. [58] Partition values for diagnostic criteria of BNP ≥ 100 pg/mL and NT-proBNP ≥ 800 pg/mL have been suggested to support the diagnosis of HFpEF .[54]
Suppressor of tumorigenicity 2 (ST2)	The soluble form of ST2 (sST2), prevents binding of IL-33 to membrane-bound ST2 leading to myocardial death and tissue fibrosis, reduced cardiac function, and acceleration of disease progression	Elevated levels of ST2 have prognostic value in the management of HF. It predicts mortality, and HF events.[59,60,20,54]
Galectin-3	Mediator of tumor growth and metastasis. Promotes cardiac fibroblast proliferation, collagen deposition, and ventricular dysfunction	Predict rehospitalization and death in HFpEF Predict HF events.[61]
Cardiac troponin I	Troponin is an intracellular protein essential in the regulation of muscular contraction. It is made up of three subunits, Troponin I, T, and C. Cardiac troponins I (cTnI) and T (cTnT) are unique to cardiomyocytes. Therefore, increases in circulating cardiac troponins (cTn) are highly specific for ongoing myocardial damage	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,.[62,54]

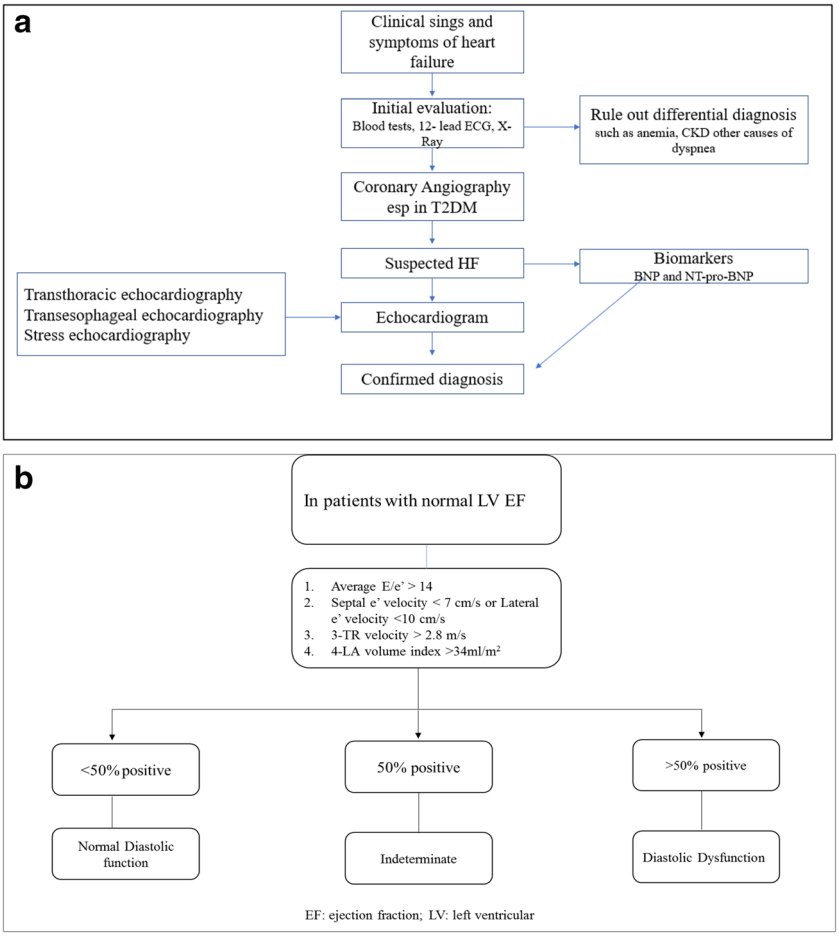


Fig. 3 **a** Diagnostic algorithm for heart failure in T2DM [39, 63]. **b** Algorithm for diagnosis of LV diastolic dysfunction in subjects with normal LVEF [64]. Adapted from Nagueh SF, Smiseth OA, Appleton CP, et al. 2016 [64]

HF [95] results have demonstrated a significant morbidity and mortality benefit with dapagliflozin in HFrEF patients in both with and without T2DM (42% with T2DM). Ongoing studies like EMPEROR with empagliflozin may further suggest whether SGLT2i can be used in patients with baseline HF with or without diabetes to improve mortality and morbidity.

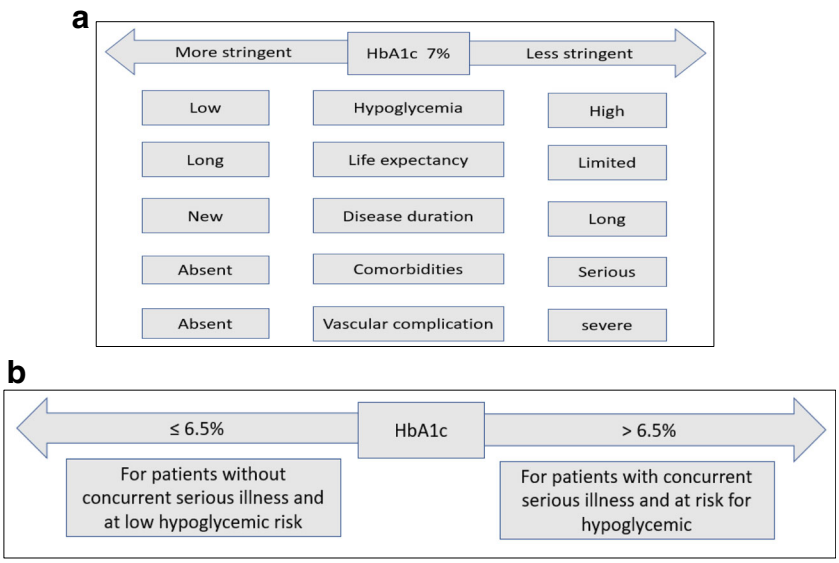


Fig. 4 **a** ADA recommendations for hemoglobin A1c (HbA1c) goals in patients with diabetes mellitus. **b** ACCE recommendations for hemoglobin A1c (HbA1c) goals in patients with diabetes mellitus

Table 6 Antidiabetic cardiovascular outcome trials with positive heart failure outcomes

Drug	Study	Drug, Dosage, Median Follow-up	HF Outcomes
GLP-1 agonist	LEADER[76]	Liraglutide 1.8 mg to maximum tolerable dose vs. placebo FU- 3.8 years	• Death from CV cause: 0.87 (0.78-0.97) $p < 0.001$ • Death: 0.78 (0.66–0.93) $p = 0.007$ • Rate of death from any cause: 0.85 (0.74–0.97) $p = 0.02$ • Hospitalization for HF: 0.87 (0.73–1.05) $p = 0.14$
	SUSTAIN-6[77]	Semaglutide 0.5 mg or 1.0 mg vs. placebo	• Primary end point (CV death, nonfatal MI, nonfatal stroke): 0.74 (0.58-0.95) $p < 0.001$ for noninferiority • Death from CV cause: 0.98 (0.65–1.48) $p = 92$ • Hospitalization for HF: 1.11 (0.77–1.61) $p = 0.57$
SGLT2i	EMPA-REG OUTCOME[88]	Empagliflozin 10 mg or 25 mg vs. placebo FU-3.1 year	• Death from CV causes, nonfatal MI, or nonfatal stroke: 0.86 (0.74 to 0.99) $p = 0.04$ for superiority • Death from CV cause: 0.62 (0.49–0.77) $p < 0.001$ • Hospitalization for HF: 0.65 (0.50–0.85) $p = 0.002$
	CANVAS Program[90]	Canagliflozin 100 mg vs. placebo FU-78 weeks	• Death from CV causes, nonfatal MI, or nonfatal stroke: 0.86 (0.75 to 0.97) $p < 0.001$ for noninferiority; $p = 0.02$ for superiority Death from CV cause: 0.87 (0.72–1.06)
	DECLARE-TIMI 58 [91]	Dapagliflozin vs placebo FU-4.2 years	CV death or hospitalization for HF: 0.83 (0.73–0.95) $p = 0.005$ for superiority • Major adverse CV events: 0.93 (0.84–1.03) $p = 0.17$ for superiority • Hospitalization for HF: 0.73 (0.61–0.88) • Death from any cause: 0.93 (0.82–1.04)

- All the guidelines advise to individualize the therapy based on the characteristics of the patients, e.g., previous history or currently having any form atherosclerotic cardiovascular disease or HF or chronic kidney disease (Fig. 5), preference of weight loss, cost, and etc.

Management of heart failure in type 2 diabetes mellitus

Heart failure treatment needs to be a priority when it coexists with T2DM. Currently, HF management is dependent on EF. The etiology and pathophysiology of HFpEF, HFmrEF, and HFrEF are heterogeneous.

The management of HFpEF and HFmrEF remains empirical and challenging due to scarce evidence as most completed and ongoing studies focus on HFrEF. Identification of the underlying cause of HF is essential to implement a targeted management strategy. The long-term objective is to improve survival, but considering the high morbidity, immediate objectives to reduce hospitalization, improve functional capacity, and achieve a better quality of life (QoL) become highly relevant.

Heart failure with reduced ejection fraction in patients with type 2 diabetes mellitus (Fig. 6)

Pharmacological strategies to improve survival and QoL include angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), angiotensin II receptor blocker neprilysin inhibitor (ARNI), beta-blocker (BB), mineralocorticoid receptor antagonist (MRA), and ivabradine in selected cases. The European Society of Cardiology (ESC) 2016 guidelines do not differentiate treatment protocols based on T2DM status, as HF trial subanalyses in T2DM patients found therapies to be similarly effective [39].

Renin-angiotensin-aldosterone system inhibitors

A meta-analysis [96] of six studies which included CONSENSUS, SAVE, the two SOLVD studies, SMILE, and TRACE with a total of 2398 diabetic patients and 10,188 patients without diabetes showed no difference in mortality among the patients. The RR of mortality in patients with diabetes is 0.84 (95% CI 0.70 to 1.00), whereas the estimate of the RR in patients without diabetes is 0.85 (95% CI 0.78 to 0.92). The CHARM study [97] with candesartan showed matching effects on mortality and HHF when given as an alternative to ACEI, irrespective of the T2DM status. However, a large meta-analysis [98] ($n = 47{,}662$) demonstrated ACEI and not ARBs contribute to the reduction in ACM (RR 0.89; 95% CI 0.83 to 0.96; $p = 0.001$) and CV death (RR 0.86; 95% CI 0.78 to 0.94; $p = 0.001$) in HF patients, though there was no separate analysis in T2DM. Effect of sacubitril/valsartan combination (ARNI) in a subgroup analysis of PARADIGM-HF [99] in patients of HFrEF shows significant reduction in HHF/CV death is consistent irrespective of diabetes status ((no diabetes 0.68 (0.56–0.83) vs. diabetes 0.87 (0.77–0.98)). Last but not the least, benefits with mineralocorticoid receptor antagonists (MRAs) shown in studies such as RALES [100] and EMPHASIS [101] trials were consistent for patients with and without T2DM.

Beta-blockers

Beta-blockers downregulate the hyperactive sympathetic nervous system and has shown to reduce mortality and HHF in multiple trials. A meta-analysis [102] of effect of beta-blockers (CIBIS II, CORPERNICUS, MERIT-HF) (Table 7) on mortality from heart failure reports that patients with diabetes have reduced mortality (0.77 (0.61–0.96)) when given beta-blockers. However, the relative risk reduction when

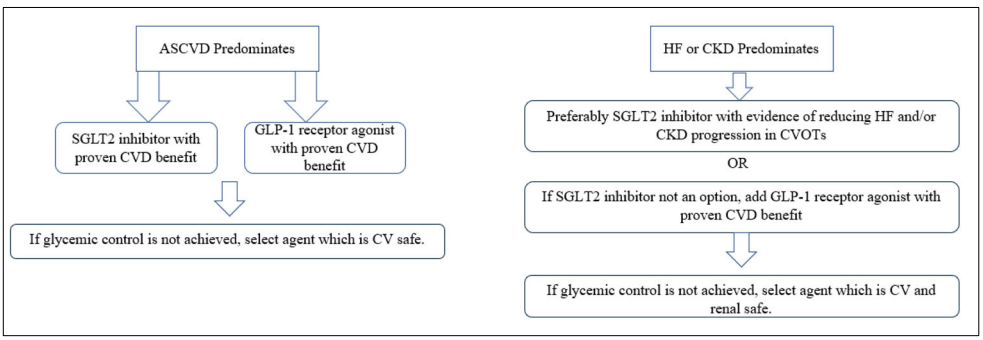
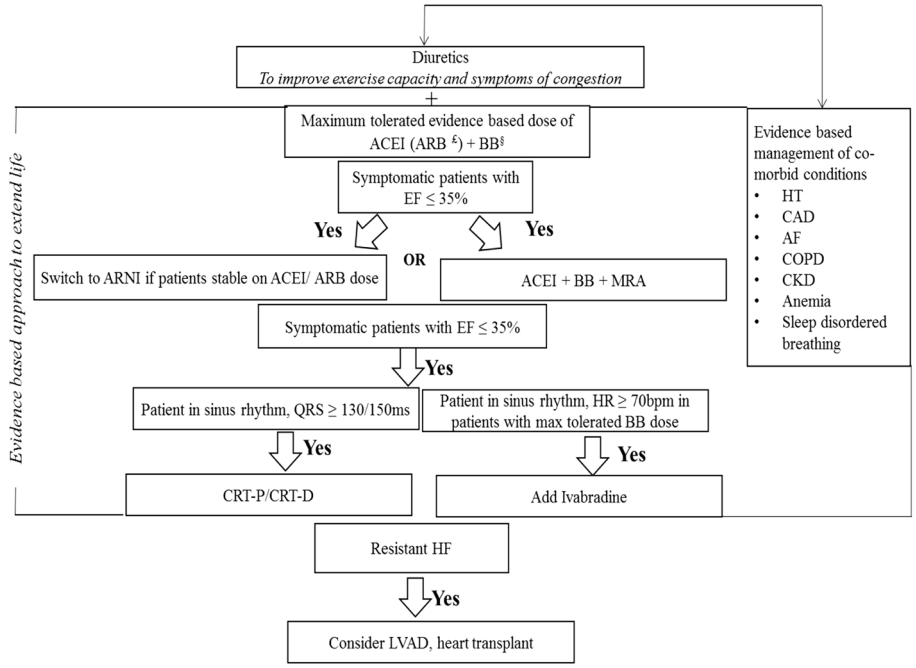


Fig. 5 Choice of antidiabetic drug for T2DM patients with ASCVD or HF or CKD. ASCVD = atherosclerotic cardiovascular disease; HF = heart failure; SGLT2i = sodium glucose co-transporter; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; CVOTs = cardiovascular outcome trials; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA1c = glycated hemoglobin; HF = heart failure



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

Fig. 6 Algorithm for management of heart failure in type 2 diabetes mellitus

compared non-diabetics (0.65 (0.57–0.74)) was less. Nevertheless, looking into the fact that diabetics are at high risk of mortality than non-diabetics, the absolute risk reduction in mortality of diabetics would be comparable with non-diabetics. Blunting of hypoglycemia symptoms is a cause of concern with BB in T2DM patients. A study showed that patients with coronary heart disease or HF had 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; $p = 0.02$) [103].

Ivabradine

Ivabradine is the first I_f channel inhibitor. SHIFT study results showed reduction in CV death or HHF (HR 0.82; 95% CI 0.75 to 0.90; $p < 0{\cdot}0001$), HHF (HR 0.74; 95% CI 0.66 to 0.83; $p < 0{\cdot}0001$) and deaths due to HF (HR 0.74; 95% CI 0.58 to 0.94; $p = 0.014$). SHIFT results were positive for HFrEF patients with T2DM, with a significant primary composite end point reduction (RR 20% and 16%, respectively, in patients with/without diabetes), and benefit was driven by a reduction in HHF (29% and 23%, respectively) [104]. Thus, SHIFT results were positive irrespective of the diabetes status. ESC 2016 HF guidelines recommend ivabradine in HF patients in sinus rhythm with an EF ≤ 35% and a resting heart rate (RHR) ≥ 75 bpm, or in those who do not tolerate BB or with RHR ≥ 70 bpm despite maximum tolerated BB dose [39].

Sodium-glucose co-transporter-2 inhibitor

Dapagliflozin in DAPA-HF trial [99] significantly reduced composite of HHF/CV death/urgent HF visit (HR 0.74; 95% CI 0.65 to 0.85; $p < 0.00001$), HHF (HR 0.70; 95% CI 0.59 to 0.83; $p = 0.00004$) CV death (HR 0.82; 95% CI 0.69 to 0.98; $p = 0.029$) when compared with placebo in HFrEF patients which included both diabetic and non-diabetic subjects. Dapagliflozin was added to the standard of care. The quality of life was also significantly improved as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) score [99]. The results were positive in both T2DM and non-T2DM patients. All cause death was reduced as well (HF 0.83; 95% CI 0.71 to 0.97; $p = 0.022$). Dapagliflozin is the only sodium-glucose co-transporter-2 inhibitor (SGLT2i) to date to have such data on HFrEF patients in both diabetic and non-diabetic patients.

Recommendations
1. Neurohormonal activation plays a key role in the pathogenesis of HFrEF; therefore, triple-therapy with ACEI (ARB, if ACEI intolerant), BB, and MRA should be used.
2. ACEI and not ARBs contributes to the reduction in all-cause mortality and CV death.
3. The combination of ACEI with ARBs can cause an increased risk of adverse events like hypotension, hyperkalemia, and renal dysfunction.
4. BB therapy has a better outcome in non-diabetics compared with diabetic patients. They should be used cautiously in T2DM patients, as they may blunt symptoms of hypoglycemia.
5. MRAs should generally be prescribed irrespective of ejection fraction.
6. ACEI and ARBs should be replaced by ARNI to reduce morbidity and mortality.
7. Dapagliflozin has significantly reduced morbidity and mortality in HF patients and could be considered early in the therapy of such patients.

Heart failure with preserved ejection fraction in patients with type 2 diabetes mellitus

Real-world data indicate a rising HFpEF prevalence [109], and more so diabetes in HFpEF with high mortality equivalent to HFrEF and thus necessitating to target this population for treatment. DM was associated with longer length of stay and lower likelihood of being discharged home. The 30-day all-cause mortality and readmissions to hospital are also more with HFpEF and DM [110]. DM in HFpEF is responsible for alteration hemodynamic changes in patients and hence leading to volume overload and more congestion and increased chances of rehospitalization [111]. In general, DM patients are young and have high body mass index (BMI), high incidence of ischemic event, and hypertension vis-à-vis non-DM patients [112, 113].

These changes indicate importance of treatment of such patients with great attention. Recent meta-analysis, in HFpEF the all-cause mortality was decreased by beta-blockers compared with placebo (RR 0.78, 95%CI 0.65 to 0.94, $p = 0.008$) but surprisingly has no effect on HHF (RR 0.67; 95% CI 0.42 to 1.07; $p = 0.10$). However, ACE inhibitors/ARBs, MRAs, or other drugs failed to show improvement in either HHF or all-cause mortality [114].

In PARAGON-HF study [115], ARNI also could not significantly lower the rate of total HHF and death from CV causes among patients with HFpEF. There were 894 primary events (composite of total hospitalizations for HF and death from CV causes) in 526/2407 patients in the ARNI group and 1009 primary events in 557/2389 patients in the valsartan group (rate ratio 0.87; 95% CI 0.75 to 1.01; $p = 0.06$). The incidence of 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); there were 690 and 797 total HHFs, respectively (rate ratio 0.85; 95% CI 0.72 to 1.00). Table 8 enlists HF outcomes in the various HFpEF trials. Emphasis is currently on the use of diuretics to reduce congestion with intensive management of comorbidities.

Recommendations for HFpEF
1. In patients with CAD, coronary revascularization could be considered.
2. Target lipid and blood pressure levels should be achieved.
3. Mineralocorticoid receptor antagonists can be considered to decrease hospitalizations for heart failure.

Role of devices in the management of heart failure

Device therapy is indicated for patients with advanced HF or in the presence of comorbid conditions.

Established and guideline-recommended devices in use

Implantable cardioverter defibrillator (ICD) therapy decreased risk of death (HR 0.77; 97.5% CI 0.62 to 96; $p = 0.007$) in both ischemic and nonischemic HF in the SCD HeFT trial [123]. The MADIT-II trial similarly showed a reduction in death (HR 0.69; CI 0.51 to 0.93; $p = 0.016$) in patients with prophylactic ICD implantation (Table 9). Cardiac resynchronization therapy (CRT) can correct electrical and mechanical disharmony and improve ventricular efficiency in patients of HF associated with left bundle branch block. The two types of CRT devices include cardiac resynchronization therapy-pace maker (CRT-P), a special pacemaker, and cardiac resynchronization therapy-defibrillator (CRT-D), a pacemaker with an in-built ICD [124]. Cardiac resynchronization therapy is recommended for HFrEF with EF < 35% and a QRS duration of ≥ 130 ms (CRT-P), ≥ 150 ms (CRT-D) [38, 39].

Recommendations
1. Implantable cardioverter defibrillator should be considered in patients with NYHA II to III and LVEF < 35%.
2. Cardiac resynchronization therapy should be considered in patients with NYHA II to III, LVEF < 35%, QRS ≥ 150 ms with left bundle branch block.

What does the future hold for HF patients?

Most current and ongoing studies in HF may not have included a T2DM cohort; however, as many patients may have T2DM as comorbidity, there is a rationale for extending these benefits for T2DM patients as well.

The failure after a promise

Serelaxin, a synthetic analog of endogenous relaxin, worked to improve plasma volume and cardiac output while

Table 7 Clinical trials in heart failure with reduced ejection fraction

Drug	Study	Drug/Intervention, Dosage, Median Follow-up	HF Outcomes
ACEI	SOVLD[105]	Enalapril at doses of 2.5 to 20 mg per day vs placebo	• Mortality 39.7% vs 35.2%, (RRR= 16%, CI: 5 to 26%) p=0.0036)
ARNI	PARADIGM-HF trial[80]	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[106]	Bisoprolol 1·25 mg (n=1327) or placebo FU: 1.3 years	• All-cause mortality: 11·8% vs 17·3%, HR: 0·66 (95% CI 0·54–0·81, 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[107]	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

decreasing blood pressure and peripheral resistance. Unfortunately, after very promising early phase results, the phase-3 RELAX-AHF 2 trial did not meet the end points of CV death and worsening HF in patients with acute HF. Tolvaptan, an oral vasopressin type 2 receptor antagonist, worked to improve symptoms of congestion in HF. The EVEREST study [127] results showed an improvement in dyspnea but with no improvement in the QoL. Similarly, the QUEST study [128] showed an improvement in HF symptoms, but with a risk of hypernatremia at higher doses.

Next 10 years; what to expect?

Tables 10 and 11 enlist ongoing trials on pharmacological management of HFrEF and HFpEF.

Ularitide is being investigated in several phase 1 and II trials for acute HF [129]. It is a synthetic analog of the endogenous urodilantin, a renal peptide hormone secreted in response to increased pressure. It causes diuresis, vasodilation, and inhibition of RAAS by binding to natriuretic peptide receptor (NPR-A). Levosimendan is an inotrope with additional actions of vasodilation and protection against ischemia and reperfusion injury. It enhances cardiac contractility in acute HF and may be considered in patients with hypotension and hypoperfusion [130]. Phosphodiesterase type 5 (PDE-5) inhibitors like sildenafil, treprostinil, and udenafil are pulmonary vasodilators with a positive effect on LV remodeling. They are primarily used in the management of pulmonary arterial hypertension and have shown more benefits in HFrEF compared with HFpEF [131]. Oral nitrite is considered a novel agent for HFpEF with pulmonary arterial hypertension. After the success of a single dose of inhaled nitrite (phase 2 trial) in increasing pulmonary artery compliance, a single oral dose also achieved improved cardiac hemodynamics [132]. Omecamtiv mecarbil is a specific cardiac myosin activator, which aims to improve cardiac contractility. It showed promising results in phase 2 COSMIC-HF study [133] with an improvement in stroke volume, systolic ejection time, and biomarkers. The ongoing phase 3 GALACTIC-HF trial is

Table 8 Clinical trials in heart failure with preserved ejection fraction

Drug	Study	Drug, Dosage, Median Follow-up	HF Outcomes
ARB	CHARM-Preserved[116]	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
	I-PRESERVE[117]	Irbesartan 300 mg vs. placebo FU: 49.5 months	• Death from any cause or hospitalization for a CV cause: 0.95 (0.86–1.05) p = 0.35 • Death: 1.00 (0.88 to 1.14) p = 0.98 • Hospitalization for CV cause: 0.95 (0.85 to 1.08) p = 0.44 • Hospitalization for worsening HF: 0.95 (0.81–1.10) p = 0.50
ACEI	PEP-CHF[118]	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[119]	Spironolactone 25 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[120]	Nebivolol up to 10 mg vs. placebo FU: 21 months	• All-cause mortality or CV hospitalization: 0.86 (0.74–0.99) p = 0.039 • All-cause mortality: 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
	J-DHF [121]	Carvedilol up to 10 mg twice-daily vs. control FU- 3.2 years	• CV death and unplanned HHF: 0.902 (0.546–1.488) p = 0.6854 • All-cause mortality: 0.990 (0.526– 1.864) p = 0.9747 • Worsening of symptoms: 0.879 (0.470– 1.643) p = 0.8337 • CV death, or unplanned hospitalization: 0.768 (0.504–1.169) p = 0.2178 • All-cause death, or unplanned hospitalization for HF: 0.990 (0.627– 1.564) p = 0.9655
Sildenafil (Liu et al, 2017)[122]	Effects of sildenafil on cardiac structure and function, cardiopulmonary exercise testing and health-related QoL measures in HFpEF and pulmonary hypertension	Sildenafil 60 mg three times a day vs. placebo FU-12 weeks	• Peak heart rate: 8 bpm (-14.97 to -1.03) • Peak blood pressure: 13.8 mmHg (-22.04 to -5.47)/7.3 mmHg (-13.60 to -1.07)

Table 9 Device RCTs with positive heart failure outcomes

Study	Device	Patient population	Outcomes
COMPANION[125]	CRT-P, CRT-D, or medical therapy	NYHA III–IV QRS ≥120 ms	• In DM patients with advanced HF, there was a substantial benefit from device therapy with significant improvement in all end points. • All-cause mortality or all-cause hospitalization (HR = 0.77, 95% CI 0.62-0.97), • All-cause mortality or cardiovascular hospitalization (HR = 0.67, 95% CI 0.53-0.85), • All-cause mortality or HHF (HR = 0.52, 95% CI 0.40-0.69) • All-cause mortality (HR = 0.67, 95% CI 0.45-0.99)
SCD-HeFT[123]	ICD vs amiodarone vs placebo	NYHA II–III EF ≤35%	• Reduction in death with ICD in non-DM was 0.67 (97.5% CI, 0.50–0.90) vs 0.95 (97.5% CI, 0.68–1.33) in DM
MADIT-II[126]	ICD	Prior MI EF ≤30%	• The risk of death in patients treated with the ICD compared with conventional therapy was similar in DM (HR 0.61; 95% CI 0.38 to 0.98) and non-DM (HR 0.71; 95% CI 0.49 to 1.05)

expected to conclude in 2021. CT-1 is considered a novel drug based on gp130, which forms a part of cytokine receptors. Cytokines like IL-6, IL-11, and CT-1 along with their receptors are associated with inflammation. CT-1is said to induce a beneficial physiological cardiac hypertrophy and retard the pathological hypertrophy [134]. Tafamidis is specifically used for the management of transthyretin amyloid cardiomyopathy. It binds to the thyroxine-binding sites of transthyretin with high affinity and selectivity and has shown a reduction in ACM, CV-related hospitalization, and retarded exercise capacity decline [135]. Canakinumab, an anti-inflammatory monoclonal antibody targeting IL-1β, demonstrated a dose-dependent reduction in HHF in patients with previous MI and elevated high sensitivity C-reactive protein (hsCRP). However, it was complicated by a high risk of serious infections [136].

Gene therapy is a promising approach to rejuvenate the failing cardiomyocytes. Although most preclinical studies demonstrated highly promising results, their translation into improved clinical outcomes has not occurred. Gene therapy could play a role in restoring depleted membrane proteins, or by balancing the intracellular calcium concentration [134]. Genes for SERCA2a are said to restore intracellular calcium concentration. Studies have shown a reduction in CV events and the average hospitalization time [137, 138], but the improvement in patient outcomes has not been substantial. Percutaneous insertion of genes into the heart using adeno-associated virus 1 (AAV1), AAV6, and AAV9 as vectors is another development under study. New gene targets with improved gene delivery systems may pave the way for keeping the promise of successful management of HF. Stem cell therapy has generated interest, as it can potentially regenerate or replace damaged cardiomyocytes, but the response has been a mix of optimism and disappointment due to inconsistent results [139,140]. Human pleuripotent stem cells (hPSCs) are replacing embryonic stem cells because of lack of ethical issues or fear of rejection [140]. A heart transplant is the preferred therapy for patients with end-stage HF and has better

Table 10 Ongoing trials in HFrEF (pharmacological approach)

Drug	Study Name (Title)	Drug	Primary Objective
SGLT2i	EMPEROR-Reduced (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction) NCT03057977 [141]	Empagliflozin vs. placebo	• Time to first event of adjudicated CV death or adjudicated HHF • A heart of adjudicated HHF • Time to first adjudicated HHF • Time to all-cause mortality • Time to onset of DM • Occurrence of all-cause hospitalization
	EMPERIAL-reduced (Effect of 12 Weeks Treatment of Once Daily) EMPagliflozin 10 mg Compared With Placebo on ExeRcise Ability and Heart Failure Symptoms, In Patients With Chronic HeArt FaiLure With Reduced Ejection Fraction (HFrEF) NCT03448419[142]	Empagliflozin vs placebo	• Change from baseline to week 12 in CHQ-SAS dyspnea score • Change from baseline in PGI-S of HF symptoms at week 12 • PGI-C in HF symptoms at week 12
	DETERMINE-reduced (Dapagliflozin Effect on Exercise Capacity Using a 6-minute Walk Test in Patients With Heart Failure With Reduced Ejection Fraction) NCT03877237 [143]	Dapagliflozin vs placebo	• To determine whether dapagliflozin is superior to placebo in increasing exercise capacity in patients with chronic heart failure NYHA functional class II-IV and preserved ejection fraction • To determine whether dapagliflozin is superior to placebo in improving patient-reported HF symptoms

survival rates due to advances in immunosuppression, better rejection diagnostic methods, and expansion of donor pool due to the inclusion of donation after circulatory death [129].

Conclusion

Heart failure and T2DM are the major public health threats globally. In India, 14% of deaths are due to HF in patients with T2DM. Heart failure classification forms the basis of its management. There are mixed reports about the prognosis of HFrEF and HFpEF in patients with T2DM. However, research suggests that both equally increase the risk of hospitalization and death in patients with T2DM. Moreover, in patients with a new diagnosis of T2DM, the risk of MACE, HF, and death increased incrementally with a greater number of comorbidities with CKD being the main driver of mortality. Heart failure diagnosis necessitates a detailed history, assessment of clinical signs and symptoms, assessment of diagnostic biomarkers, an electrocardiogram, and 2D-Echo. Biomarkers can decide prognosis and treatment trajectory in patients with T2DM having HF. This consensus document was aimed to ensure better patient care, optimize prognosis, and reduce the cost burden by implementing the most efficient treatment strategies for the management of HF in T2DM. SGLT2i may play a role in the prevention of HF in T2DM patients by its ability to offer

Table 11 Ongoing trials in HFpEF (pharmacological approach)

Drug	Study Name (Title)	Drug	Primary Objective
ARNI	PARALLAX (A Randomized, Double-blind Controlled Study Comparing LCZ696 to Medical Therapy for Comorbidities in HFpEF Patients) NCT03066804 [144]	LCZ696 vs sacubitril/valsartan LCZ696 vs Enalapril LCZ696 vs Valsartan LCZ696 vs placebo to match sacubitril/valsartan LCZ696 vs placebo to match enalapril LCZ696 vs placebo to match valsartan.	• Change from baseline in N-terminal pro-brain natriuretic peptide (NT-proBNP) at week 12 • Change from baseline in NYHA functional class at week 24
	PERSPECTIVE (Efficacy and Safety of LCZ696 Compared to Valsartan on Cognitive Function in Patients with Chronic HFpEF) NCT02884206 [145]	LCZ696 vs Valsartan. LCZ696 vs placebo of LCZ696. LCZ696 vs placebo of Valsartan	NA
Trepostinil	A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Oral Treprostinil in Subjects With Pulmonary Hypertension (PH) in HFpEF NCT03037580 [146]	Oral treprostinil vs placebo	• Change in NT-proBNP Levels from baseline to Week 24 • Time to the first clinical worsening event over the 24-week treatment period
Udenafil	ULTIMATE-HFpEF (A Randomized Trial of Udenafil Therapy in Patients With HFpEF) NCT01599117 [147]	Udenafil (Zydena) vs placebo	• Admission for HF • Composite clinical endpoints • Change of symptomatic status expressed as NYHA functional class • Cardiac death
Inorganic nitrite	INABLE-Training (Inorganic Nitrite to Amplify the Benefits and Tolerability of Exercise Training in HFpEF NCT02713126 [148]	Oral Sodium Nitrite vs placebo	• Change in symptoms of HF

Table 11 (continued)

Drug	Study Name (Title)	Drug		Primary Objective
SGLT2i	EMPEROR-Preserved (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction) NCT03057951 [149]	Empagliflozin	vs placebo	• Time to first event of adjudicated CV death or adjudicated HHF in patients with HFpEF • Occurrence of adjudicated HHF (first and recurrent) • Time to first adjudicated HHF • Time to adjudicated CV death • Time to all-cause mortality • Time to onset of DM • Change from baseline in clinical summary score (HF (CHF) symptoms and physical limitations domains) of the KCCQ • Occurrence of all-cause hospitalization
	EMPERIAL- Preserved (12 Weeks Treatment of Once Daily) EMPagliflozin 10 mg Compared With Placebo on ExeRcise Ability and Heart Failure Symptoms, In Patients With Chronic HeArt FaiLure With Preserved Ejection Fraction (HFpEF) NCT03448406 [150]	Empagliflozin	vs placebo	• Change from baseline to week 12 in CHQ-SAS dyspnea score • Change from baseline in PGI-S of HF symptoms at week 12 • PGI-C in HF symptoms at week 12
	PRESERVED-HF; (Dapagliflozin in PRESERVED Ejection Fraction Heart Failure) NCT03030235 [151]	Dapagliflozin vs placebo Dapagliflozin vs placebo		Change from baseline in NTproBNP at 6 and 12 weeks Change from baseline to week 12 in KCCQ overall summary score
	DETERMINE-preserved – (Dapagliflozin Effect on Exercise Capacity Using a 6-minute Walk Test in Patients With Heart Failure With Preserved Ejection Fraction) NCT03877224 [152]			• Change from baseline in 6-minute walking distance at Week16 • Change from baseline in the KCCQ Total symptom score at Week16

Table 11 (continued)

Drug	Study Name (Title)	Drug	Primary Objective
	DELIVER- Dapagliflozin (Evaluation to Improve the LIVEs of Patients With Preserved Ejection Fraction Heart Failure) NCT03619213 [153]	Dapagliflozin vs placebo	• Time to the first occurrence of any of the components of this composite: 1) CV death; 2) Hospitalization for HF; 3) Urgent HF visit • Total number of (first and recurrent) hospitalizations for HF and CV death • Proportion of patients with worsened NYHA class from baseline to 8 months • Time to the occurrence of death from any cause
	ERADICATE-HF (ERtugliflozin triAl in DIabetes With Preserved or Reduced ejeCtion FrAcTion mEchanistic Evaluation in Heart Failure trials) NCT03416270 [154]	Ertugliflozin vs placebo	• Heart rate • Echocardiography for markers of systolic and diastolic function, cardiac output • Arterial stiffness • Systolic blood pressure • Diastolic blood pressure • Cardiac output • Systemic vascular resistance

protection from CV complications in addition to optimum glycemic control. DECLARE-TIMI 58 results with dapagliflozin generated hope by showing a significant reduction in HF in patients with T2DM, with no prior ASCVD or HF. Along with SGLT2i, new innovations in device design and delivery, gene therapy, and stem cell therapy may hold the key to revolutionize the management of HF, especially in patients with T2DM. Whether this will help to achieve the ideal long-term objective of extending the life span of patients with T2DM with HF, only time and more path-breaking studies will tell.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Kannel W, McGee D (1979) Diabetes and cardiovascular risk factors: the Framingham study. Circulation. 59:8–13
2. Ofstad AP, Atar D, Gullestad L, Langslet G, Johansen OE (2018) The heart failure burden of type 2 diabetes mellitus—a review of pathophysiology and interventions. Heart Fail Rev 23:303–323
3. Ingle L, Reddy P, Clark AL, Cleland JG (2006) Diabetes lowers six-minute walk test performance in heart failure. J Am Coll Cardiol 47:1909–1910
4. Egstrup M, Kistorp CN, Schou M, Høfsten DE, Møller JE, Tuxen CD, Gustafsson I (2013) Abnormal glucose metabolism is associated with reduced left ventricular contractile reserve and exercise intolerance in patients with chronic heart failure. Eur Heart J Cardiovasc Imaging 14:349–357
5. Kristensen SL, Mogensen UM, Jhund PS, Petrie MC, Preiss D, Win S, Køber L, McKelvie R, Zile MR, Anand IS, Komajda M, Gottdiener JS, Carson PE, McMurray J (2017) Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-Preserve trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). Circulation. 135:724–735

6. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basáñez MG, Baxter A, Bell ML, Benjamin EJ, Bennett D, Bernabé E, Bhalla K, Bhandari B, Bikbov B, Bin Abdulhak A, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bolliger I, Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F, Chen H, Cheng AT, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahiya M, Dahodwala N, Damsere-Derry J, Danaei G, Davis A, de Leo D, Degenhardt L, Dellavalle R, Delossantos A, Denenberg J, Derrett S, Des Jarlais DC, Dharmaratne SD, Dherani M, Diaz-Torne C, Dolk H, Dorsey ER, Driscoll T, Duber H, Ebel B, Edmond K, Elbaz A, Ali SE, Erskine H, Erwin PJ, Espindola P, Ewoigbokhan SE, Farzadfar F, Feigin V, Felson DT, Ferrari A, Ferri CP, Fèvre EM, Finucane MM, Flaxman S, Flood L, Foreman K, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabbe BJ, Gabriel SE, Gakidou E, Ganatra HA, Garcia B, Gaspari F, Gillum RF, Gmel G, Gosselin R, Grainger R, Groeger J, Guillemin F, Gunnell D, Gupta R, Haagsma J, Hagan H, Halasa YA, Hall W, Haring D, Haro JM, Harrison JE, Havmoeller R, Hay RJ, Higashi H, Hill C, Hoen B, Hoffman H, Hotez PJ, Hoy D, Huang JJ, Ibeanusi SE, Jacobsen KH, James SL, Jarvis D, Jasrasaria R, Jayaraman S, Johns N, Jonas JB, Karthikeyan G, Kassebaum N, Kawakami N, Keren A, Khoo JP, King CH, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lalloo R, Laslett LL, Lathlean T, Leasher JL, Lee YY, Leigh J, Lim SS, Limb E, Lin JK, Lipnick M, Lipshultz SE, Liu W, Loane M, Ohno SL, Lyons R, Ma J, Mabweijano J, MacIntyre M, Malekzadeh R, Mallinger L, Manivannan S, Marcenes W, March L, Margolis DJ, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty J, McDermott M, McGill N, McGrath J, Medina-Mora ME, Meltzer M, Mensah GA, Merriman TR, Meyer AC, Miglioli V, Miller M, Miller TR, Mitchell PB, Mocumbi AO, Moffitt TE, Mokdad AA, Monasta L, Montico M, Moradi-Lakeh M, Moran A, Morawska L, Mori R, Murdoch ME, Mwaniki MK, Naidoo K, Nair MN, Naldi L, Narayan KM, Nelson PK, Nelson RG, Nevitt MC, Newton CR, Nolte S, Norman P, Norman R, O'Donnell M, O'Hanlon S, Olives C, Omer SB, Ortblad K, Osborne R, Ozgediz D, Page A, Pahari B, Pandian JD, Rivero AP, Patten SB, Pearce N, Padilla RP, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Phillips MR, Pierce K, Pion S, Polanczyk GV, Polinder S, Pope CA 3rd, Popova S, Porrini E, Pourmalek F, Prince M, Pullan RL, Ramaiah KD, Ranganathan D, Razavi H, Regan M, Rehm JT, Rein DB, Remuzzi G, Richardson K, Rivara FP, Roberts T, Robinson C, de Leòn FR, Ronfani L, Room R, Rosenfeld LC, Rushton L, Sacco RL, Saha S, Sampson U, Sanchez-Riera L, Sanman E, Schwebel DC, Scott JG, Segui-Gomez M, Shahraz S, Shepard DS, Shin H, Shivakoti R, Singh D, Singh GM, Singh JA, Singleton J, Sleet DA, Sliwa K, Smith E, Smith JL, Stapelberg NJ, Steer A, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Syed S, Tamburlini G, Tavakkoli M, Taylor HR, Taylor JA, Taylor WJ, Thomas B, Thomson WM, Thurston GD, Tleyjeh IM, Tonelli M, Towbin JA, Truelsen T, Tsilimbaris MK, Ubeda C, Undurraga EA, van der Werf M, van Os J, Vavilala MS, Venketasubramanian N, Wang M, Wang W, Watt K, Weatherall DJ, Weinstock MA, Weintraub R, Weisskopf MG, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams SR, Witt E, Wolfe F, Woolf AD, Wulf S, Yeh PH, Zaidi AK, Zheng ZJ, Zonies D, Lopez AD, Murray CJ, AlMazroa M, Memish ZA (2012) Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the global burden of disease study 2010. Lancet. 380:2163–2196
7. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CSP, Sato N, Shah AN, Gheorghiade M (2014) The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 63:1123–1133
8. Huffman MD, Prabhakaran D (2010) Heart failure: epidemiology and prevention in India. Natl Med J India 23:283–288
9. Institute of Health Metrics and Evaluation (2017) GBD compare. https://vizhub.healthdata.org/gbd-compare/ [Accessed 6th June 2019]
10. Chaturvedi V, Parakh N, Seth S, Gupta N, Misra P, Rai SK, Anand K et al (2016) Heart failure in India: the INDUS (INDiaUkieri Study) study. J Pract Cardiovasc Sci 2:28–35
11. Dokainish H, Teo K, Zhu J et al (2017) INTER-CHF Investigators. Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. Lancet Glob Health 5: e665–e672
12. Harikrishnan S, Sanjay G, Anees T et al (2015) Trivandrum Heart Failure Registry. Clinical presentation, management, in-hospital and 90-day outcomes of heart failure patients in Trivandrum, Kerala, India: the Trivandrum Heart Failure Registry. Eur J Heart Fail 17:794–800
13. Harikrishnan S, Sanjay G, Agarwal A, Kumar NP, Kumar KK, Bahuleyan CG, Vijayaraghavan G, Viswanathan S, Sreedharan M, Biju R, Rajalekshmi N, Nair T, Suresh K, Jeemon P (2017) One-year mortality outcomes and hospital readmissions of patients admitted with acute heart failure: data from the Trivandrum Heart Failure Registry in Kerala, India. Am Heart J 189:193–199
14. Lesyuk W, Kriza C, Kolominsky-Rabas P (2018) Cost-of-illness studies in heart failure: a systematic review 2004-2016. BMC Cardiovasc Disord 18:74
15. Cook C, Cole G, Asaria P, Jabbour R, Francis DP (2014) The annual global economic burden of heart failure. Int J Cardiol 171:368–376
16. Einarson TR, Acs A, Ludwig C, Panton UH (2018) Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol 17:83
17. Lawson CA, Solis-Trapala I, Dahlstrom U et al (2018) Comorbidity health pathways in heart failure patients: a sequences-of-regressions analysis using cross-sectional data from 10,575 patients in the Swedish Heart Failure Registry. PLoS Med 15:e1002540a
18. Carrasco-Sánchez FJ, Gomez-Huelgas R, Formiga F et al (2014) RICA investigators. Association between type-2 diabetes mellitus and post-discharge outcomes in heart failure patients: findings from the RICA registry. Diabetes Res Clin Pract 104:410–419
19. Tromp J, Tay WT, Ouwerkerk W et al (2018) ASIAN-HF authors. Multimorbidity in patients with heart failure from 11 Asian regions: a prospective cohort study using the ASIAN-HF registry. PLoS Med 15:e1002541
20. Mishra S, Mohan JC, Nair T, Chopra VK, Harikrishnan S, Guha S, Ramakrishnan S, Ray S, Sethi R, Samal UC, Sarat Chandra K, Hiremath MS, Banerjee AK, Kumar S, Das MK, Deb PK, Bahl VK (2018) Management protocols for chronic heart failure in India. Indian Heart J 70:105–127

21. Chopra VK, Mittal S, Bansal M, Singh B, Trehan N (2019) Clinical profile and one-year survival of patients with heart failure with reduced ejection fraction: the largest report from India. Indian Heart J. https://doi.org/10.1016/j.ihj.2019.07.008
22. Wang Y, Negishi T, Negishi K, Marwick TH (2015) Prediction of heart failure in patients with type 2 diabetes mellitus-a systematic review and meta-analysis. Diabetes Res Clin Pract 108:55–66
23. Parry HM, Deshmukh H, Levin D, van Zuydam N, Elder DH, Morris AD, Struthers AD, Palmer CN, Doney AS, Lang CC (2015) Both high and low HbA1c predict incident heart failure in type 2 diabetes mellitus. Circ Heart Fail 8:236–242
24. Schefold JC, Filippatos G, Hasenfuss G, Anker SD, von Haehling S (2016) Heart failure and kidney dysfunction: epidemiology, mechanisms and management. Nat Rev Nephrol 12:610–623
25. Lawson CA, Testani JM, Mamas M, Damman K, Jones PW, Teece L, Kadam UT (2018) Chronic kidney disease, worsening renal function and outcomes in a heart failure community setting: a UK national study. Int J Cardiol 267:120–127.b
26. Kristensen SL, Preiss D, Jhund PS et al (2016) PARADIGM-HF Investigators and Committees.. Risk related to pre-diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction: insights from prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial. Circ Heart Fail 9:e002560.a
27. Anjana RM, Pradeepa R, Deepa M et al (2011) ICMR–INDIAB Collaborative Study Group. Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: phase I results of the Indian Council of Medical Research-INdia DIABetes (ICMR-INDIAB) study. Diabetologia 54:3022–3027
28. Patel S, Nanda R, Abraham J, Sahoo S, Ganguly A, Mohapatra E (2017) Prediabetes and undiagnosed diabetes mellitus: the hidden danger. Indian J Med Biochem 21:91–95
29. Serhiyenko VA, Serhiyenko AA (2018) Cardiac autonomic neuropathy: risk factors, diagnosis and treatment. World J Diabetes 9: 1–24
30. Nyström T, Santos-Pardo I, Hedberg F et al (2017) Effects on subclinical heart failure in type 2 diabetic subjects on liraglutide treatment vs. glimepiride both in combination with metformin: a randomized open parallel-group study. Front Endocrinol (Lausanne) 8:325
31. König P, Mayer O, Bruthans J et al (2019) The prognostic importance of subclinical heart failure in stable coronary heart disease patients. Acta Cardiol 3:1–8
32. Rajput R, Jagdish SSB, Rattan A (2002) Echocardiographic and Doppler assessment of cardiac functions in patients of non-insulin dependent diabetes mellitus. JIACM 3:164–168
33. Faden G, Faganello G, De Feo S et al (2013) The increasing detection of asymptomatic left ventricular dysfunction in patients with type 2 diabetes mellitus without overt cardiac disease: data from the SHORTWAVE study. Diabetes Res Clin Pract 101:309–316
34. Schocken DD, Benjamin EJ, Fonarow GC et al (2008) American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Cardiovascular Nursing; American Heart Association Council on High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; Functional Genomics and Translational Biology Interdisciplinary Working Group. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. Circulation 117:2544–2565
35. Shindler DM, Kostis JB, Yusuf S, Quinones MA, Pitt B, Stewart D, Pinkett T, Ghali JK, Wilson AC (1996) Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. Am J Cardiol 77:1017–1020
36. Wang TJ (2003) Natural history of asymptomatic left ventricular systolic dysfunction in the 3746 community. Circulation. 108: 977–982
37. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW (2009) 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 119:e391–e479
38. Yancy CW, Jessup M, Bozkurt B, American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines et al (2013) 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 62:e147–e239
39. Ponikowski P, Voors AA, Anker SD et al (2016) Authors/Task Force Members; Document Reviewers.. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 18:891–975
40. Johansson I, Dahlström U, Edner M, Näsman P, Rydén L, Norhammar A (2018) Type 2 diabetes and heart failure: characteristics and prognosis in preserved, mid-range and reduced ventricular function. Diab Vasc Dis Res 15:494–503
41. MacDonald MR, Petrie MC, Varyani F et al (2008) CHARM Investigators. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. Eur Heart J 29: 1377–1385
42. Levelt E, Mahmod M, Piechnik SK, Ariga R, Francis JM, Rodgers CT, Clarke WT, Sabharwal N, Schneider JE, Karamitsos TD, Clarke K, Rider OJ, Neubauer S (2016) Relationship between left ventricular structural and metabolic remodeling in type 2 diabetes. Diabetes. 65:44–52
43. Basta G, Schmidt AM, De Caterina R (2004) Advanced glycation end products and vascular inflammation: implications for accelerated atherosclerosis in diabetes. Cardiovasc Res 63:582–592
44. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A (1972) New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol 30:595–602
45. Verma S, Mazer CD, Yan AT, Mason T, Garg V, Teoh H, Zuo F, Quan A, Farkouh ME, Fitchett DH, Goodman SG, Goldenberg RM, al-Omran M, Gilbert RE, Bhatt DL, Leiter LA, Jüni P, Zinman B, Connelly KA (2019) Effect of empagliflozin on left ventricular mass in patients with type 2 diabetes mellitus and coronary artery disease: the EMPA-HEART CardioLink-6 randomized clinical trial. Circulation. 140(21):1693–1702
46. Brown AJM, Lang C, McCrimmon R, Struthers A et al (2019) A randomised controlled trial of dapagliflozin on left ventricular hypertrophy in patients with type two diabetes. The DAPA-LVH Trial. Circulation 140:A10643

47. Schilling JD (2015) The mitochondria in diabetic heart failure: from pathogenesis to therapeutic promise. Antioxid Redox Signal 22:1515–1526
48. Kayama Y, Raaz U, Jagger A, Adam M, Schellinger IN, Sakamoto M, Suzuki H, Toyama K, Spin JM, Tsao PS (2015) Diabetic cardiovascular disease induced by oxidative stress. Int J Mol Sci 16:25234–25263
49. Verma SK, Garikipati VNS, Kishore R (1863) Mitochondrial dysfunction and its impact on diabetic heart. Biochim Biophys Acta Mol basis Dis 2017:1098–1105
50. Chong CR, Clarke K, Levelt E (2017) Metabolic remodelling in diabetic cardiomyopathy. Cardiovasc Res 113:422–430
51. Orsborne C, Chaggar PS, Shaw SM, Williams SG (2017) The renin-angiotensin-aldosterone system in heart failure for the non-specialist: the past, the present and the future. Postgrad Med J 93: 29–37
52. Maack C, Lehrke M, Backs J, Heinzel FR, Hulot JS, Marx N, Paulus WJ, Rossignol P, Taegtmeyer H, Bauersachs J, Bayes-Genis A, Brutsaert D, Bugger H, Clarke K, Cosentino F, de Keulenaer G, Dei Cas A, González A, Huelsmann M, Iaccarino G, Lunde IG, Lyon AR, Pollesello P, Rena G, Riksen NP, Rosano G, Staels B, van Laake L, Wanner C, Farmakis D, Filippatos G, Ruschitzka F, Seferovic P, de Boer RA, Heymans S (2018) Heart failure and diabetes: metabolic alterations and therapeutic interventions: a state-of-the-art review from the Translational Research Committee of the Heart Failure Association-European Society of Cardiology. Eur Heart J 39:4243–4254
53. Yancy CW, Jessup M, Bozkurt B et al (2017) 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 136:e137–e161
54. Chow SL, Maisel AS, Anand I, American Heart Association Clinical Pharmacology Committee of the Council on Clinical Cardiology; Council on Basic Cardiovascular Sciences; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Epidemiology and Prevention; Council on Functional Genomics and Translational Biology; and Council on Quality of Care and Outcomes Research et al (2017) Role of biomarkers for the prevention, assessment, and management of heart failure: a scientific statement from the American Heart Association. Circulation 135:e1054–e1091
55. Nadar SK, Shaikh MM (2019) Biomarkers in routine heart failure clinical care. Card Fail Rev 5:50–56
56. Maisel AS, Krishnaswamy P, Nowak RM et al (2002) Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 347:161–167
57. Januzzi JL Jr, Camargo CA, Anwaruddin S et al (2005) The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol 95:948–954
58. Omar HR, Guglin M (2016) Discharge BNP is a stronger predictor of 6-month mortality in acute heart failure compared with baseline BNP and admission-to-discharge percentage BNP reduction. Int J Cardiol 221:1116–1122
59. Boisot S, Beede J, Isakson S, Chiu A, Clopton P, Januzzi J, Maisel AS, Fitzgerald RL (2008) Serial sampling of ST2 predicts 90-day mortality following destabilized heart failure. J Card Fail 14:732–738
60. Bayes-Genis A, Pascual-Figal D, Januzzi JL, Maisel A, Casas T, Valdés Chávarri M, Ordóñez-Llanos J (2010) Soluble ST2 monitoring provides additional risk stratification for outpatients with decompensated heart failure. Rev Esp Cardiol 63:1171–1178
61. Gehlken C, Suthahar N, Meijers WC, de Boer RA (2018) Galectin-3 in heart failure: an update of the last 3 years. Heart Fail Clin 14:75–92
62. Stelzle D, Shah ASV, Anand A, Strachan FE, Chapman AR, Denvir MA, Mills NL, McAllister D (2018) High-sensitivity cardiac troponin I and risk of heart failure in patients with suspected acute coronary syndrome: a cohort study. Eur Heart J Qual Care Clin Outcomes 4:36–42
63. Mishra S et al (2018) Indian Heart J 70:105–127
64. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T et al (2016) Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 29(4):277–314
65. Bajaj S (2018) RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2017. Int J Diabetes Dev Ctries 38(Suppl 1):1–115
66. ADA (2020) Standards of medical care in diabetes—2020. Available from: https://care.diabetesjournals.org/content/diacare/suppl/2019/12/20/43.Supplement_1.DC1/DC_43_S1_2020.pdf. Accessed 20 Feb 2020
67. AACE/ACE (2020) Consensus statement by The American Association Of Clinical Endocrinologists And American College Of Endocrinology on the comprehensive type 2 diabetes management algorithm–2020 executive summary. Available from: https://www.aace.com/pdfs/diabetes/algorithm-exec-summary.pdf. Accessed 20 Feb 2020
68. UK Prospective Diabetes Study (UKPDS) Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [published correction appears in Lancet. 1999;354:602]. Lancet 352:837–853
69. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M et al (2008) ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 358:2560–2572
70. The Action to Control Cardiovascular Risk in Diabetes Study Group (2008) Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 358:2545–2559
71. Hayward RA, Reaven PD, Wiitala WL, Bahn GD, Reda DJ, Ge L, for the VADT Investigators et al; Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes [published correction appears in N Engl J Med. 2015;373:198]. N Engl J Med 2015;372:2197–2206
72. Skrtic S, Cabrera C, Olsson M, Schnecke V, Lind M (2017) Contemporary risk estimates of three HbA1c variables in relation to heart failure following diagnosis of type 2 diabetes. Heart. 103: 353–358
73. Lind M, Olsson M, Rosengren A, Svensson AM, Bounias I, Gudbjornsdottir S (2012) The relationship between glycaemic control and heart failure in 83,021 patients with type 2 diabetes. Diabetologia. 55:2946–2953
74. Blecker S, Park H, Katz SD (2016) Association of HbA1c with hospitalization and mortality among patients with heart failure and diabetes. BMC Cardiovasc Disord 16:99
75. Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ et al (2019) Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA 322(12):1155–1166
76. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF (2016) Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 375:311–322a

77. Marso SP, Bain SC, Consoli A et al (2016) SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 375:1834–1844b
78. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, ELIXA Investigators et al (2015) Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 373(23):2247–2257
79. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N, Maggioni AP, Marso SP, Öhman P, Pagidipati NJ, Poulter N, Ramachandran A, Zinman B, Hernandez AF, EXSCEL Study Group (2017) Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 377(13):1228–1239
80. Bethel MA, Patel RA, Merrill P, EXSCEL Study Group et al (2018) Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. Lancet Diabetes Endocrinol 6:105–113
81. Hernandez AF, Green JB, Janmohamed S, Harmony Outcomes committees and investigators et al (2018) Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 392:1519–1529
82. Gerstein HC, Colhoun HM, Dagenais GR, REWIND Investigators et al (2019) Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 394:121–130
83. Green JB, Bethel MA, Armstrong PW, TECOS Study Group et al (2015) Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 373:232–242
84. Scirica BM, Braunwald E, Raz I, SAVOR-TIMI 53 Steering Committee and Investigators* et al (2014) Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation 130:1579–1588
85. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL et al (2013) EXAMINE: alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 369: 1327–1335
86. McMurray JJV, Ponikowski P, Bolli GB, VIVIDD Trial Committees and Investigators et al (2018) Effects of vildagliptin on ventricular function in patients with type 2 diabetes and heart failure: a randomized placebo-controlled trial. JACC Heart Fail 6: 8–17
87. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire D, Wilding JPH, Sabatine MS (2019) SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 393:31–39
88. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE, EMPA-REG OUTCOME Investigators (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 373:2117–2128
89. Wiviott SD, Raz I, Bonaca MP, DECLARE–TIMI 58 Investigators et al (2019) Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 380:347–357
90. Mahaffey KW, Neal B, Perkovic V et al (2018) CANVAS Program Collaborative Group. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS program (Canagliflozin Cardiovascular Assessment Study). Circulation. 137:323–334
91. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RHM, Kuder J, Murphy SA, Bhatt DL, Leiter LA, McGuire D, Wilding JPH, Bonaca MP, Ruff CT, Desai AS, Goto S, Johansson PA, Gause-Nilsson I, Johanson P, Langkilde AM, Raz I, Sabatine MS, Wiviott SD (2019) Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation. 139:2528–2536
92. Singh AK, Unnikrishnan AG, Zargar AH, Kumar A, Das AK, Saboo B, Sinha B, Gangopadhyay KK, Talwalkar PG, Ghosal S, Kalra S, Joshi S, Sharma SK, Sriram U, Mohan V (2019) Evidence based consensus on positioning of SGLT2i in type 2 diabetes mellitus in Indians. Diabetes Ther 10:393–428
93. Solini A, Giannini L, Seghieri M et al (2017) Dapagliflozin acutely improves endothelial dysfunction, reduces aortic stiffness and renal resistive index in type 2 diabetic patients: a pilot study. Cardiovasc Diabetol 16:138
94. Sattar N, McLaren J, Kristensen SL, Preiss D, McMurray JJ (2016) SGLT2 inhibition and cardiovascular events: why did EMPA-REG outcomes surprise and what were the likely mechanisms? Diabetologia. 59:1333–1339
95. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets D, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM, DAPA-HF Trial Committees and Investigators (2019) DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 381(21):1995–2008
96. Shekelle PG, Rich MW, Morton SC, Atkinson CS, Tu W, Maglione M, et al Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. J Am Coll Cardiol 2003;41(9):1529–1538
97. Granger CB, McMurray JJ, Yusuf S, CHARM Investigators and Committees et al (2003) Effect of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM Alternative trial. Lancet 362:772–776
98. Tai C, Gan T, Zou L, Sun Y, Zhang Y, Chen W (2017) Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular events in patients with heart failure: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord 17:257
99. Kristensen SL, Preiss D, Jhund PS, Squire I, Cardoso JS, Merkely B, PARADIGM-HF Investigators and Committees et al (2016) Risk related to pre-diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction: insights from prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial. Circ Heart Fail 9(1): e002560
100. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341(10):709–717
101. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B, EMPHASIS-HF Study Group (2011) Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 364(1):11–21
102. Shekelle PG, Rich MW, Morton SC, Atkinson CS, Tu W, Maglione M, Rhodes S, Barrett M, Fonarow GC, Greenberg B, Heidenreich PA, Knabel T, Konstam MA, Steimle A, Warner Stevenson L (2003) Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. J Am Coll Cardiol 41(9): 1529–1538

103. Tsujimoto T, Sugiyama T, Shapiro MF, Noda M, Kajio H (2017) Risk of cardiovascular events in patients with diabetes mellitus on β-blockers. Hypertension. 70:103–110
104. Komajda M, Tavazzi L, Francq BG, SHIFT Investigators et al (2015) Efficacy and safety of ivabradine in patients with chronic systolic heart failure and diabetes: an analysis from the SHIFT trial. Eur J Heart Fail 17:1294–1301
105. Investigators SOLVD, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN (1991) Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 325(5):293–302
106. (1999) The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. Lancet 353(9146):9–13
107. MERIT-HF Study Group (1999) Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). Lancet 353:2001–2007
108. Eichhorn EJ, Bristow MR (2001) The carvedilol prospective randomized cumulative survival (COPERNICUS) trial. Curr Control Trials Cardiovasc Med 2:20–23
109. Dunlay SM, Roger VL, Redfield MM (2017) Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 14:591–602
110. Smaha LA, American Heart Association (2004) The American Heart Association get with the guidelines program. Am Heart J 148(Suppl):S46–S48
111. McHugh K, DeVore AD, Wu J, Matsouaka RA, Fonarow GC, Heidenreich PA, Yancy CW, Green JB, Altman N, Hernandez AF (2019) J Am Coll Cardiol 73(5):602–611
112. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, Swedberg K, Yusuf S, Granger CB, Pfeffer MA, McMurray J, Solomon SD (2018) Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail 20: 1230–1239
113. Aguilar D, Deswal A, Ramasubbu K, Mann DL, Bozkurt B (2010) Comparison of patients with heart failure and preserved left ventricular ejection fraction among those with versus without diabetes mellitus. Am J Cardiol 105:373–377
114. Zheng SL, Chan FT, Nabeebaccus AA, Shah AM, McDonagh T, Okonko DO, Ayis S (2018) Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Heart. 104(5):407–415
115. Solomon SD, JV, Anand IS et al (2019) Angiotensin-Neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 381(17):1609–1620
116. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J (2003) CHARM Investigators and Committees Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 362:777–781
117. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A (2008) Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 359:2456–2467
118. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J, PEP-CHF Investigators (2006) The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 27:2338–2345
119. Edelmann F, Wachter R, Schmidt AG et al (2013) Aldo-DHF Investigators Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA 309:781–791
120. Flather MD, Shibata MC, Coats AJ et al (2005) SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 26: 215–225
121. Yamamoto K, Origasa H, Hori M, J-DHF Investigators (2013) Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). Eur J Heart Fail 15:110–118
122. Liu LC, Hummel YM, van der Meer P, Hoendermis ES et al (2017) Effects of sildenafil on cardiac structure and function, cardiopulmonary exercise testing and health-related quality of life measures in heart failure patients with preserved ejection fraction and pulmonary hypertension. Eur J Heart Fail 19:116–125
123. Bardy GH, Lee KL, Mark DB et al (2005) Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter–defibrillator for congestive heart failure. N Engl J Med 352:225–237
124. Moss AJ, Zareba W, Hall WJ et al (2002) Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 346:877–883
125. Ghali JK, Boehmer J, Feldman AM, Saxon LA, Demarco T, Carson P, Yong P, Galle EG, Leigh J, Ecklund FL, Bristow MR (2007 Nov) Influence of diabetes on cardiac resynchronization therapy with or without defibrillator in patients with advanced heart failure. J Card Fail 13(9):769–773
126. Wittenberg SM, Cook JR, Hall WJ, McNitt S, Zareba W, Moss AJ (2005) Multicenter Automatic Defibrillator Implantation Trial. Comparison of efficacy of implanted cardioverter-defibrillator in patients with versus without diabetes mellitus. Am J Cardiol 96(3): 417–419
127. Konstam MA, Gheorghiade M, Burnett JC, Grinfeld L, Maggioni AP, Swedberg K (2007) Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. 297:1319–1331
128. Matsuzaki M, Hori M, Izumu T, Fukunami M (2011) Efficacy and safety of tolvaptan in heart failure patients with volume overload despite the standard treatment with conventional diuretics: a phase III, randomized, double-blind, placebo-controlled study (QUEST study). Cardiovasc Drugs Ther 25(Suppl 1):S33–S45
129. Choi HM, Park MS, Youn JC (2019) Update on heart failure management and future directions. Korean J Intern Med 34:11–43
130. Gustafsson F, Guarracino F, Schwinger RHG (2017) The inodilator levosimendan as a treatment for acute heart failure in various settings. Eur Heart J Suppl 19(Suppl C):C2–C7
131. Hutchings DC, Anderson SG, Caldwell JL, Trafford AW (2018) Phosphodiesterase-5 inhibitors and the heart: compound cardioprotection? Heart. 104:1244–1250
132. Levine AR, Helbling NL, Chien N, Bachman TN, Simon MA, Gladwin MT (2018) Abstract 17077: acute hemodynamic effects of oral nitrite in pulmonary hypertension related to heart failure with preserved ejection fraction (PH-HFpEF). Circulation 138: A17077
133. Teerlink JR, Felker GM, McMurray JJV, COSMIC-HF Investigators et al (2016) Chronic oral study of myosin activation to increase contractility in heart failure (COSMIC-HF): a phase 2, pharmacokinetic, randomised, placebo-controlled trial. Lancet 388:2895–2903
134. Machaj F, Dembowska E, Rosik J, Szostak B, Mazurek-Mochol M, Pawlik A (2019) New therapies for the treatment of heart failure: a summary of recent accomplishments. Ther Clin Risk Manag 15:147–155
135. Maurer MS, Schwartz JH, Gundapaneni B et al (2018) ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 379:1007–1016

136. Ridker PM, Everett BM, Thuren T, MacFadyen J, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ, CANTOS Trial Group (2017) Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 377:1119–1131
137. Jessup M, Greenberg B, Mancini D, Cappola T, Pauly DF, Jaski B, Yaroshinsky A, Zsebo KM, Dittrich H, Hajjar RJ, Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID) Investigators (2011) Calcium upregulation by percutaneous administration of gene therapy in cardiac disease (CUPID) a phase 2 trial of intracoronary gene therapy of sarcoplasmic reticulum Ca2+-ATPase in patients with advanced heart failure. Circulation. 124:304–313
138. Zsebo K, Yaroshinsky A, Rudy JJ, Wagner K, Greenberg B, Jessup M, Hajjar RJ (2014) Long-term effects of AAV1/SERCA2a gene transfer in patients with severe heart failure: analysis of recurrent cardiovascular events and mortality. Circ Res 114:101–108
139. Tompkins BA, Rieger AC, Florea V et al (2018) Comparison of mesenchymal stem cell efficacy in ischemic versus nonischemic dilated cardiomyopathy. J Am Heart Assoc 7:e008460
140. Park M, Yoon YS (2018) Cardiac regeneration with human pluripotent stem cell-derived cardiomyocytes. Korean Circ J 48:974–988
141. Available at https://clinicaltrials.gov/ct2/show/NCT03057977 [Accessed on 5th June 2019]
142. Available at https://clinicaltrials.gov/ct2/show/NCT03448419[Accessed on 5th June 2019]
143. Available at https://clinicaltrials.gov/ct2/show/NCT03877237 [Accessed on 5th June 2019]
144. Available at https://clinicaltrials.gov/ct2/show/NCT03066804 [Accessed on 5th June 2019]
145. Available at https://clinicaltrials.gov/ct2/show/NCT02884206 [Accessed on 5th June 2019]
146. Available at https://clinicaltrials.gov/ct2/show/NCT03037580 [Accessed on 5th June 2019]
147. Available at https://clinicaltrials.gov/ct2/show/NCT01599117 [Accessed on 5th June 2019]
148. Available at https://clinicaltrials.gov/ct2/show/NCT02713126 [Accessed on 5th June 2019]
149. Available at https://clinicaltrials.gov/ct2/show/NCT03057951 [Accessed on 5th June 2019]
150. Available at https://clinicaltrials.gov/ct2/show/NCT03448406 [Accessed on 5th June 2019]
151. Available at https://clinicaltrials.gov/ct2/show/NCT03030235 [Accessed on 5th June 2019]
152. Available at https://clinicaltrials.gov/ct2/show/NCT03877224 [Accessed on 5th June 2019]
153. Available at https://clinicaltrials.gov/ct2/show/NCT03619213 [Accessed on 5th June 2019]
154. Available at https://clinicaltrials.gov/ct2/show/NCT03416270 [Accessed on 5th June 2019]