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Review Article

Evaluation and Management of Patients With Diabetes and Heart Failure: A Korean Diabetes Association and Korean Society of Heart Failure Consensus Statement

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ABSTRACT

Diabetes mellitus is a major risk factor for the development of heart failure. Furthermore, the prognosis of heart failure is worse in patients with diabetes mellitus than in those without it. Therefore, early diagnosis and proper management of heart failure in patients with diabetes mellitus are important. This review discusses the current criteria for diagnosis and screening tools for heart failure and the currently recommended pharmacological therapies for heart failure. We also highlight the effects of anti-diabetic medications on heart failure.

Keywords: Heart failure; Diabetes mellitus

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome with cardinal symptoms (for example, dyspnea, ankle swelling, and fatigue) and/or signs (for example, elevated jugular venous pressure, pulmonary congestion, lung crackles, and peripheral edema) caused by structural or functional cardiac abnormalities that lead to reduced cardiac output and/or elevated intracardiac pressure.[1-3] Globally, the prevalence of HF and diabetes mellitus (DM) is

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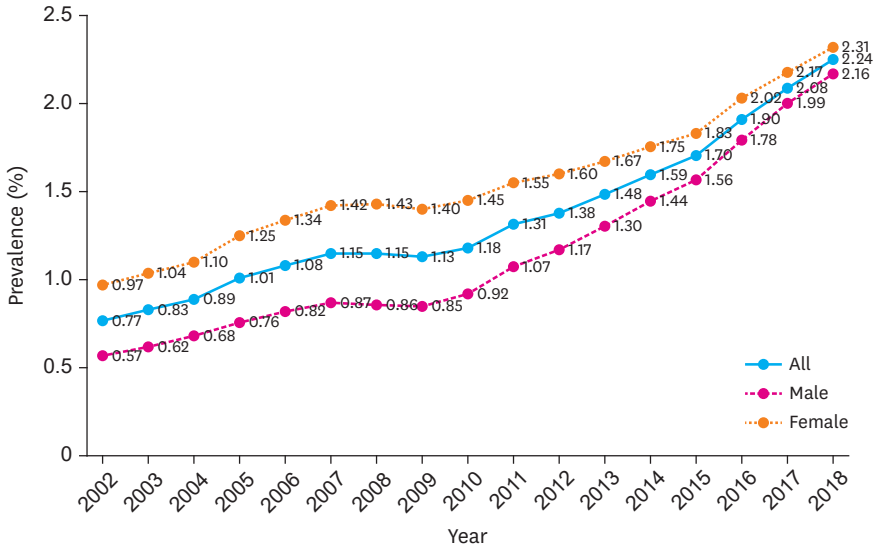

Figure 1. Estimated prevalence of HF from 2002 to 2018 in Korea. The estimated prevalence of HF was 2.24% in 2018. Regarding the sex, the prevalence of HF was 2.31% in women and 2.16% in men. Furthermore, there has been a continuous increase in the HF prevalence from 0.77% in 2002 to 2.24% in 2018. Data are modified from the Heart failure statistics in Korea, 2020 and obtained permission to use the data from International Journal of Heart Failure.[7]
HF = heart failure.

increasing with the aging of the population.[1,4] Among Korean adults aged 30 years or older, 16.7% (19.2% in men and 14.3% in women) had DM according to the Diabetes Fact Sheet published by the Korean diabetes association in 2020.[5] The prevalence of HF ranges from 1% to 3% in the general adult population in industrialized countries.[6] In Korea, the prevalence of HF has continuously increased from 0.77% in 2002 to 2.24% in 2018 (**Figure 1**).[7] The prevalence of HF according to age and sex also gradually increased between 2002 and 2018 (**Supplementary Figure 1**).[7] Obesity and diabetes have been identified as important risk factors for the development and poor prognosis of HF.[8] In this review, we highlight the current criteria for the diagnosis and screening tools for HF and the currently recommended pharmacological therapies for HF. We also discuss the effects of anti-diabetic medications on HF and the management of type 2 diabetes mellitus (T2DM) in patients with HF.

EPIDEMIOLOGY AND PROGNOSIS

Prevalence of HF in patients with DM

HF is a common comorbidity and a fatal complication of DM. The prevalence of HF was reported to range from 19% to 26% in patients with DM.[9,11] The hospitalization rates due to HF in the Korean population with DM increased from 72 to 146 and 124 to 161 per 10,000 men and women, respectively, based on data from the Korean National Health Insurance Service-National Sample Cohort from 2006 to 2015.[12]

The Framingham Heart Study demonstrated an increased risk of HF in patients with DM, a 2-fold higher incidence of HF in men, and five times high for women with DM than in age-matched non-diabetic controls.[13] In observational studies, each 1% increase in glycated hemoglobin A1c (HbA1c) was associated with a 30% increase in risk of HF in type 1 DM

(T1DM),[14] and each 1% increase in HbA1c levels was associated with an 8% increase of risk in T2DM, independent of other risk factors, including obesity, smoking, hypertension, dyslipidemia, and coronary heart disease.[15] These results suggest that chronic hyperglycemia is an aggravating factor for HF in patients with both T1DM and T2DM.

Prevalence of DM in patients with HF

Although there was heterogeneity between epidemiological studies on HF due to different study populations and different data sources, the prevalence of DM ranged from 20% to 36% in patients with HF in Korea.[4] The prevalence of comorbid DM in patients with HF continuously increased from 2002 to 2018 in Korea.[7] HF-related trials and registries in Western countries have reported that the prevalence of DM ranges from 25% to 45%.[16-23]

Diabetic cardiomyopathy

In 1972, Rubler et al.[24] proposed the existence of a unique type of cardiomyopathy in patients with DM termed diabetic cardiomyopathy. These patients had congestive HF in the absence of coronary artery disease (CAD), hypertension, valvular heart disease, or alcoholism. This concept was confirmed by the Framingham Heart Study, in which higher rates of HF in women (5-fold) and men (2.4-fold) with DM were shown to be independent of other risk factors, such as age, coronary heart disease, and hypertension. Many epidemiological studies have also confirmed a significantly increased prevalence of ventricular dysfunction in patients with diabetes, independent of the influence of relevant covariates. According to these studies,[11,13,24] the American College of Cardiology Foundation[25] and the European Society of Cardiology[26] described diabetic cardiomyopathy as a clinical condition of cardiac dysfunction without atherosclerotic coronary vascular diseases and hypertension in patients with DM.

The pathophysiology of diabetic cardiomyopathy is complex and not clearly understood. Multiple mechanisms have been suggested to explain diabetic cardiomyopathy development. These include 1) alterations in mitochondrial fatty acid oxidation; 2) impaired mitochondrial Ca2+ handling; 3) cardiac insulin resistance, which causes impaired signaling of insulin receptor substrate, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), and downstream pathways; 4) activated renin-angiotensin-aldosterone system (RAAS) in genesis; 5) cardiac autonomic neuropathy; 6) microvascular dysfunction; and 7) inflammatory pathways that result in myocardial fibrosis, stiffness, and hypertrophy.[27,28]

The clinical effects of diabetic cardiomyopathy progress from asymptomatic diastolic dysfunction to systolic dysfunction and symptomatic HF. Many potential novel therapies for diabetic cardiomyopathy, including antioxidants, coenzyme 10, PI3K gamma inhibitors, miRNA-based therapies, and stem cell therapies, are being developed to target the pathophysiology of diabetic cardiomyopathy.[29]

Prognosis of DM in patients with HF

Patients with HF and DM have worse clinical outcomes, including death, hospitalization, and health-related quality of life, than those without DM.[30-33] DM in patients with HF was associated with a greater relative risk of cardiovascular death or HF hospitalization, ranging from 1.6-fold to 2-fold compared to those without DM, regardless of left ventricular ejection fraction (LVEF).[23,34]

EVALUATION AND DIAGNOSIS OF HF

Screening and diagnosing HF in patients with DM

HF often manifests as the first cardiovascular event in patients with DM.[35] Therefore, it is important to evaluate HF in symptomatic patients with DM. The most common and typical symptoms include dyspnea with orthopnea, fatigue, and swelling of the legs or ankles. A careful and detailed history and physical examination are essential for the assessment of HF in symptomatic patients with DM. However, symptoms and signs lack sufficient accuracy to be used alone to diagnose HF.[36,37] In addition to the symptoms and signs, an essential diagnostic work-up includes a 12-lead electrocardiogram (ECG), chest radiography, and initial laboratory tests. ECG provides important information regarding arrhythmia, heart rate, QRS morphology and duration, and ischemic signs, such as ST-elevation or ST depression. Chest radiography provides information on cardiomegaly, pulmonary congestion, and other lung diseases that can cause dyspnea.

Initial laboratory testing should include a complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, iron status profile tests, and thyroid function tests. Among these laboratory tests, troponin-I should be included because it is useful for the detection of acute coronary syndrome.

The measurement of natriuretic peptides (NPs); B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is recommended as an initial diagnostic test in patients with symptoms suggestive of HF, if available. Elevation of the plasma NPs concentration (chronic HF: BNP ≥35 pg/mL or NT-proBNP ≥125 pg/mL, acute HF: BNP ≥100 pg/mL, NT-proBNP ≥300 pg/mL) supports a diagnosis of HF.[38]

Transthoracic echocardiography (TTE) is recommended as the initial diagnostic test to assess cardiac structure and function after a complete history, physical examination, and laboratory tests, including NPs. The determination of LVEF is a fundamental step in classifying HF (**Table 1**) and guiding evidence-based pharmacological and device-based therapies.

In addition to LVEF, evidence supporting increased LV filling pressures (for example, hemodynamic measurement by invasive test or diastolic function on imaging, NP by non-invasive test) is required for HF diagnosis. HF is more likely in patients with a history of myocardial infarction (MI), arterial hypertension, CAD, atrial fibrillation, alcohol misuse, chronic kidney disease, cardiotoxic chemotherapy, and in those with a family history of cardiomyopathy or sudden death.[1] The initial diagnostic tests recommended in the guidelines for the assessment of patients with suspected HF are summarized in **Table 2**.

Table 1. Classification of HF

Type of HF	HFrEF	HFmrEF	HFpEF
Diagnostic criteria			
1	Symptoms ± signs*	Symptoms ± signs*	Symptoms ± signs*
2	LVEF ≤40%	LVEF 41–49%	LVEF ≥50%
3	-	-	1. Elevation of natriuretic peptide 2. Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/ or increased LV filling pressure

HF = heart failure; EF = ejection fraction; HFrEF = HF with reduced EF; HFmrEF = HF with mildly reduced EF; HFpEF = HF with preserved EF; LVEF = left ventricular ejection fraction.
*Sings of HF may not be present and/or nonspecific in the early stage of HF (especially in HFpEF) and/or in patients treated with optimal medical treatment, including diuretics.

Table 2. Initial tests for screening and diagnosing HF

Tests	Recommendations
Natriuretic peptide (BNP or NT-proBNP)	BNP or NT-proBNP is recommended as an initial diagnostic test in patients with symptoms and signs suggestive of HF to rule out the diagnosis of HF. *Cutoff value: BNP ≥35 pg/mL or NT-proBNP ≥125 pg/mL
ECG	The ECG may reveal abnormalities such as ST elevation, ST depression, atrial fibrillation, Q wave, LV hypertrophy, and a widened QRS complex (for example, LBBB) that increase the likelihood of a diagnosis of HF.
Chest X-ray	A chest X-ray is recommended to evaluate the presence or absence of pulmonary congestion and cardiomegaly in patients with suspected HF.
Echocardiography	LVEF, chamber size, degree of wall thickness, regional wall motion abnormalities, valvular function, RV function, pulmonary hypertension, and parameters of diastolic function
Standard blood tests	CBC, serum urea, electrolytes, creatinine, thyroid, and liver function tests, fasting glucose, HbA1c, lipids, and iron statuses (TSAT and ferritin)

HF = heart failure; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro B-type natriuretic peptide; ECG = electrocardiogram; LBBB = left bundle branch block; LV = left ventricular; LVEF = left ventricular ejection fraction; RV = right ventricular; CBC = complete blood count; HbA1c = hemoglobin A1c; TSAT = transferrin saturation.
*Cutoff values may have lower specificity, especially in older patients or those with atrial fibrillation or chronic kidney disease. Usually, higher cutoff values are recommended for the diagnosis of HF in these patients.

The most common cause and a factor related to the development of HF in patients with DM is CAD.[39] Furthermore, DM is a risk factor for CAD. However, diabetic patients present more often with atypical chest pain, or they may have no symptoms even if they have extensive CAD ("silence ischemia"). Therefore, coronary computed tomography angiography or functional stress tests (exercise ECG, stress echocardiography, single photon emission computed tomography, and positron emission tomography) should be considered for the assessment of myocardial ischemia in diabetic patients with typical, atypical cardiac symptoms or abnormal findings on resting ECG even without symptoms. Furthermore, invasive coronary angiography is recommended in patients with angina or may be considered in patients with HF reduced ejection fraction (HFrEF) with an intermediate to high pre-test probability of CAD and the presence of ischemia in non-invasive stress tests.[1,40-42] The diagnostic algorithm for symptomatic patients with suspected HF and DM is shown in **Figure 2**.

Patients with DM as at-risk for HF or pre-HF

DM-related pathophysiological factors, such as insulin resistance, oxidative stress, and inflammation, can contribute to the development of structural heart disease and HF via systemic, myocardial, and cellular mechanisms.[43] Therefore, even if patients with DM do not currently have symptoms associated with HF, it is important to recognize patients with DM who are at risk of developing HF; therapeutic strategies to prevent HF in these patients are also important. The HF guidelines emphasize at-risk for HF (stage A) and pre-HF (stage B).[2] The recent consensus statement of the universal definition and classification of HF classifies patients with DM into stage A category.[3] Even if patients with DM have no symptoms or signs of HF, they are classified as stage B if any of evidence of subclinical abnormalities exists (**Supplementary Table 1**).

TREATMENT ALGORITHM FOR HF IN PATIENTS WITH DM, FOCUSING ON GUIDELINE-DIRECTED MEDICAL THERAPY (GDMT)

Patients at-risk for HF

The primary treatment goal for patients at risk of HF is to prevent the development of HF. Recent guidelines recommend the following for the primary prevention of HF[2]: 1) In patients with hypertension, blood pressure (<130/80 mmHg) should be controlled by GDMT for hypertension to prevent symptomatic HF. 2) In patients with T2DM and either established

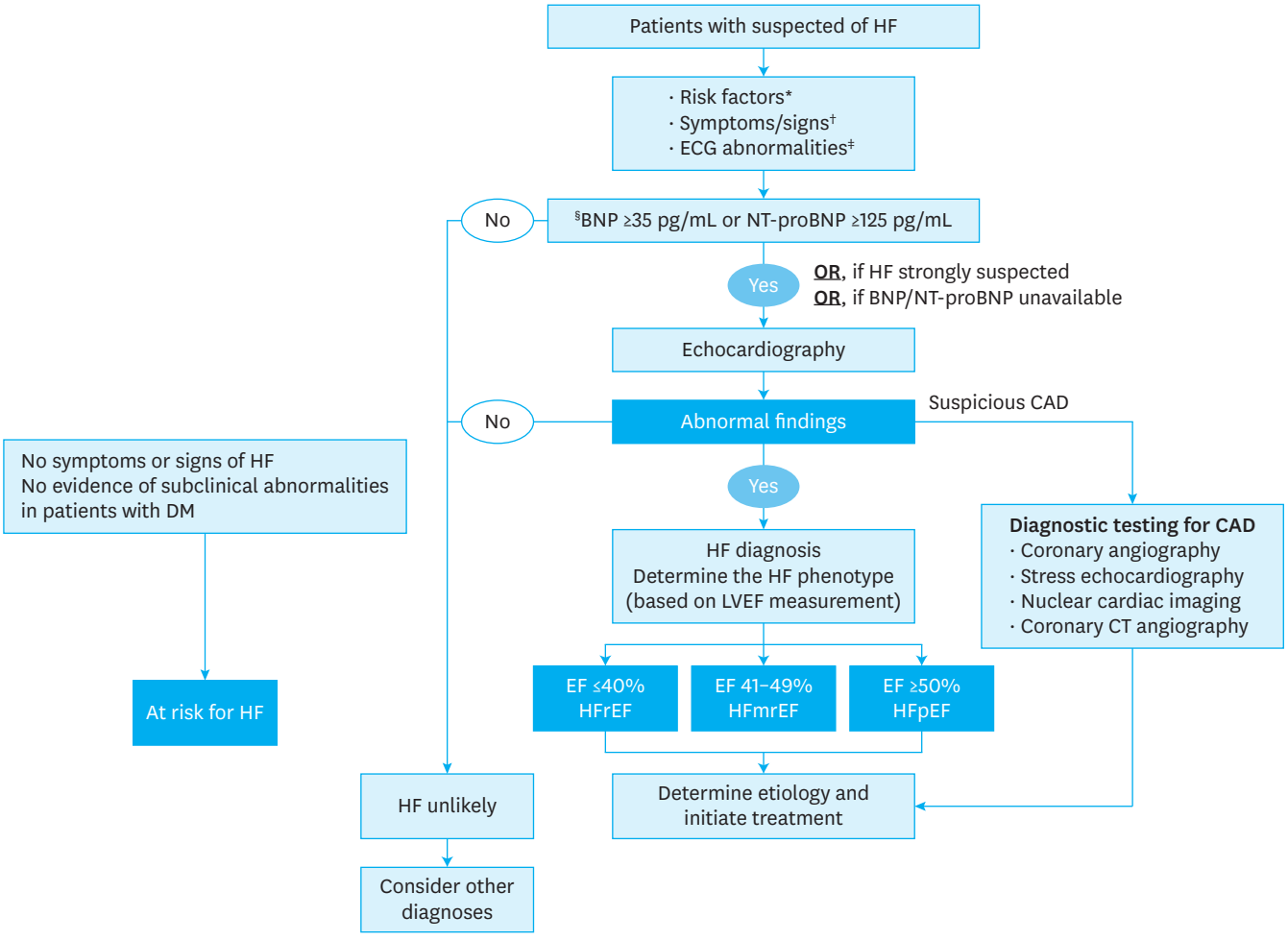

Figure 2. The diagnostic algorithm for patients with suspected HF. Adopted and modified from 2022 Korean Society of Heart Failure Guideline for the Management of Heart Failure (https://www.kshf.or.kr/news/news_01.php?boardid=ksnotice&mode=view&idx=55).
HF = heart failure; ECG = electrocardiography; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro B-type natriuretic peptide; CAD = coronary artery disease; DM = diabetes mellitus; LVEF = left ventricular ejection fraction.
*Risk factors for HF include CAD, DM, dyslipidemia, hypertension, chest radiation, cardiotoxic drugs, infections, excessive alcohol intake, obesity, and cigarette smoking; †Typical symptoms of HF include breathlessness, orthopnea, paroxysmal nocturnal dyspnea, reduced exercise tolerance, fatigue, tiredness, and ankle swelling; ‡Abnormal ECG findings include atrial fibrillation, Q waves, LV hypertrophy, and a widened QRS complex that increases the likelihood of a diagnosis of HF and may also guide therapy; §Values for the diagnosis of acute HF: BNP ≥100 pg/mL, NT-proBNP ≥300 pg/mL and rule-in values of NT-proBNP (age-adjusted threshold) for the diagnosis of acute HF: >450 pg/mL if aged <55 years, >900 pg/mL if aged between 55 and 75 years, and >1,800 pg/mL if aged >75 years.

cardiovascular disease or at high cardiovascular risk (**Supplementary Table 2**), sodium-glucose co-transporter 2 (SGLT2) inhibitors should be used to prevent hospitalization for HF.[33-45] 3) Healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful in reducing the future risk of HF.

Patients with HFrEF

General principle of pharmacotherapy

Recent HF guidelines recommend GDMT medication classes, including RAAS inhibitors (angiotensin receptor-neprilysin inhibitor [ARNI], angiotensin-converting enzyme inhibitor [ACEI] or angiotensin II receptor blocker [ARB]), beta-blockers (BB), mineralocorticoid receptor antagonist (MRA), and SGLT2 inhibitors as first-line therapy to reduce cardiovascular death and hospitalization in patients with HFrEF and NYHA (New York Heart Association) class II-III symptoms.[1,2]

The quadruple therapy with ARNI, evidence-based BB, MRA, and SGLT2 inhibitors may reduce the risk of death by 73% over 2 years.[47] However, the achievement of the target doses of each drug class before initiating treatment with the next may require 6 months or more. Furthermore, each of these foundational drugs has been shown to reduce morbidity and mortality within 30 days of treatment initiation.[48] Recently, strategies for the initiation and titration of comprehensive disease-modifying therapy have been proposed to obtain the early clinical benefit of each individual therapy (**Supplementary Figure 2**).[45,49]

In recent randomized trials, the proportion of patients with DM varies from 20% to almost 50%.[50,51] However, the benefit of GDMT in patients with HFrEF was observed between those with and without DM. The algorithm for the treatment strategy, including guideline-direct medication and devices in patients with HFrEF, is shown in **Figure 3**. Evidence-based doses

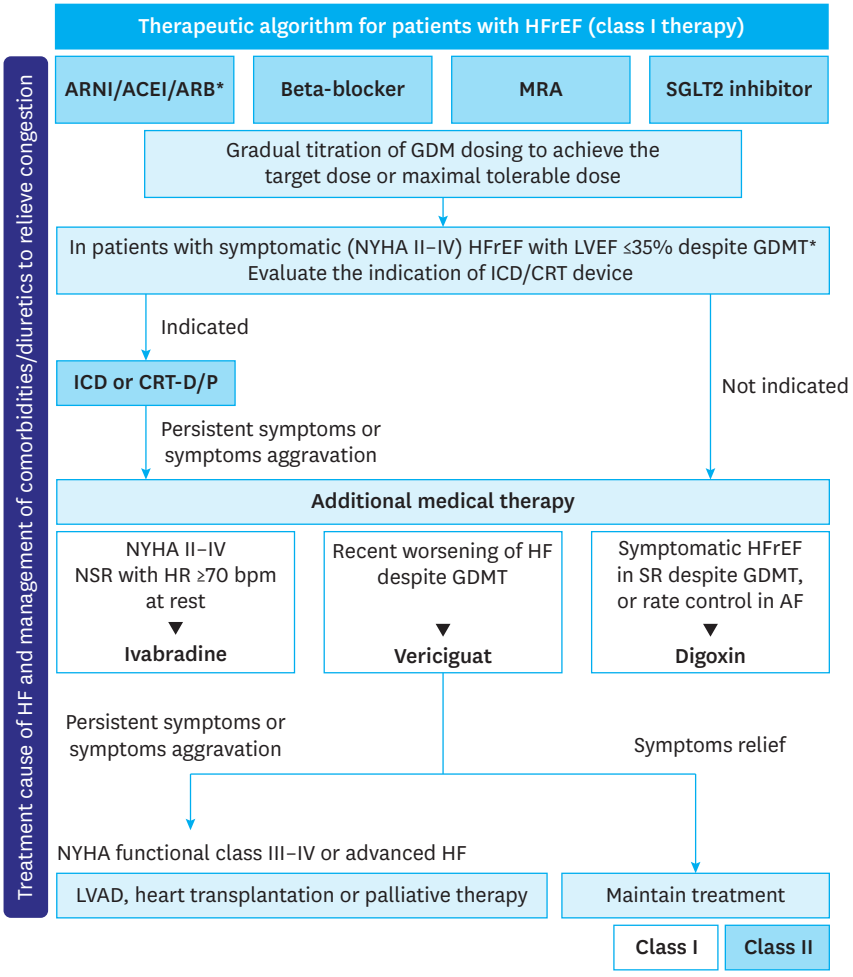

Figure 3. Therapeutic algorithm for patients with HFrEF. Adopted and modified from 2022 Korean Society of Heart Failure Guideline for the Management of Heart Failure (https://www.kshf.or.kr/news/news_01.php?boardid=ksnotice&mode=view&idx=55).
HFrEF = heart failure reduced ejection fraction; ARNI = angiotensin receptor-neprilysin inhibitor; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist; SGLT2I = sodium-glucose co-transporter 2 inhibitors; GDM = guideline-directed medication; NYHA = New York Heart Association; ICD = implantable cardioverter-defibrillator; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; NSR = normal sinus rhythm; HR = heart rate; GDMT = guideline-directed medical treatment; SR = sinus rhythm; AF = atrial fibrillation; LVAD = left ventricular assist device.
*ARB is recommended as a replacement if patients are unable to tolerate ACE-I or ARNI. Strategies for the initiation and titration of disease-modifying therapy are described in more detail in **Supplementary Figure 2**.

and contraindications or cautions of disease-modifying drugs for patients with HFrEF are summarized in **Table 3** and **Supplementary Table 3**.

ARNI

Sacubitril/valsartan, an ARNI, significantly reduced hospitalization for worsening HF, CV mortality, and all-cause mortality in patients with HFrEF compared with enalapril.[18] ARNI also reduces CV death or HF hospitalizations in hospitalized patients due to acute decompensated HF or in ACEI naïve (i.e., de novo) patients with HFrEF.[52,53] Recent evidence suggests that ARNI could reduce the reliance on diuretics in HFrEF patients[54] and promotes reverse cardiac remodeling and improves outcomes in patients with HFrEF.[55] Based on these results, guidelines recommend the use of ARNI in symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. ARNI is also recommended as a replacement for ACEIs or ARBs in patients with HFrEF to reduce the risk of hospitalization for HF and death (if patients tolerate an ACEI or ARB).

ACEIs/ARBs

ACEI is recommended for all patients with HFrEF, unless contraindicated or not tolerated, to reduce the risk of hospitalization and death due to HF. To improve clinical outcomes, ACEIs should be up-titrated to the maximum tolerated recommended doses. ARBs are recommended as a replacement for ACEI or ARNI in patients with HFrEF to reduce the risk of

Table 3. Evidence-based doses of disease-modifying drugs in patients with heart failure with reduced ejection fraction

Drug	Starting dose	Target dose
ACEI		
Captopril	6.25 mg t.i.d.	50 mg t.i.d.
Enalapril	2.5 mg b.i.d.	10–20 mg b.i.d.
Lisinopril	2.5–5 mg q.d.	20–35 mg q.d.
Ramipril	2.5 mg b.i.d.	5 mg b.i.d.
Trandolapril	0.5 mg q.d.	4 mg q.d.
ARNI		
Sacubitril/Valsartan	49/51 mg b.i.d.	97/103 mg b.i.d.
Beta-blockers		
Bisoprolol	1.25 mg q.d.	10 mg q.d.
Carvedilol	3.125 mg b.i.d.	25 mg b.i.d.
Metoprolol	12.5–25 mg q.d.	200 mg q.d.
Nebivolol	1.25 mg q.d.	10 mg q.d.
MRAs		
Eplerenone	25 mg q.d.	50 mg q.d.
Spironolactone	25 mg q.d.	50 mg q.d.
SGLT2 inhibitors		
Dapagliflozin	10 mg q.d.	10 mg q.d.
Empagliflozin	10 mg q.d.	10 mg q.d.
ARBs		
Candesartan	4 mg q.d.	32 mg o.d.
Losartan	50 mg q.d.	150 mg q.d.
Valsartan	40 mg b.i.d.	160 mg b.i.d.
Other agents		
Ivabradine	5 mg b.i.d.	7.5 mg b.i.d.
Vericiguat	2.5 mg q.d.	10 mg q.d.
Digoxin	62.5 mcg q.d.	250 mcg q.d.

Sacubitril/valsartan may have an optional lower starting dose of 24/26 mg b.i.d. for patients with a history of symptomatic hypotension; Spironolactone has an optional starting dose of 12.5 mg in patients with renal impairment or hyperkalemia.
ACEI = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium-glucose co-transporter 2; ARB = angiotensin receptor blocker; q.d. = quaque die (once daily); b.i.d. = bis in die (twice daily); t.i.d. = ter in die (three times a day).

hospitalization and death due to HF (if patients are unable to tolerate an ACEI or ARNI). Only three ARBs (valsartan, candesartan, and losartan) were proven to be beneficial for reducing HF hospitalization or death in large randomized controlled trials (RCTs).[56-59]

BBs

Beta-blockers are recommended for all patients with HFrEF to reduce the risk of hospitalization for HF, improve symptoms, and prevent death. Beta-blockers should be initiated in a clinically stable, euvolemic status, and from a low dose and gradually titrated to the maximum tolerated dose. Three beta-blockers (bisoprolol, carvedilol, and metoprolol succinate-controlled release/extended release [CR/XL]) have been proven to be beneficial for reducing HF hospitalization and mortality in patients with HFrEF.[60-62]

MRA

MRA is recommended for all patients with HFrEF to reduce the risk of hospitalization and death due to HF.[63] To improve clinical outcomes, MRA should be up-titrated to the maximum tolerated recommended dose. Patients at risk of renal dysfunction or hyperkalemia require close monitoring of potassium levels and renal function during MRA treatment.

SGLT2 inhibitors

Dapagliflozin and empagliflozin reduce the risk of cardiovascular death or HF hospitalization by approximately 26% and by 25% in patients with symptomatic stable HFrEF.[19,51,64] Furthermore, empagliflozin can reduce the diuretic need in outpatient HF patients.[65] For this cardiovascular benefit of SGLT2 inhibitors, dapagliflozin and empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death regardless of diabetes status.

Patients with HF with improved ejection fraction (HFimpEF)

Although there is little data to guide the management of patients with HFimpEF (previous LVEF ≤40%, a 10-point increase from baseline LVEF, and a second measurement of LVEF >40%), TRED-HF trial demonstrated that withdrawal of GDMT in patients with dilated cardiomyopathy who had recovered their LV functions resulted in high rate of relapse of HF (44%) within 6 months.[66] Therefore, guidelines recommend that GDMT should be continued to prevent the relapse of HF and LV dysfunction, even in asymptomatic patients.

Patients with HF with mid-range ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF)

Until recently, despite the large number of studies performed in patients with HFpEF and HFmrEF, including a significant proportion with diabetes, no current therapies have been proven to reduce CV endpoints except for SGLT2 inhibitors. Two large-scale trials, EMPEROR-preserved and DELIVER, assessed the CV effect of SGLT2 inhibitors in patients with HFpEF and HFmrEF. These trials have shown that SGLT2 inhibitors (empagliflozin, dapagliflozin) significantly reduced the risk of CV death or hospitalization for worsening HF regardless of diabetic status.[67,68]

Recent prespecified meta-analyses of the several clinical trials testing SGLT2 inhibitors confirmed the robust effect of SGLT2 inhibitors in reducing the risk of CV death and hospitalizations for worsening HF, irrespective of LVEF.[69,70] Taken together, SGLT2 inhibitors will be the foundational therapy to reduce CV death and hospitalization for HF in a broad range of patients with HF, irrespective of diabetes status or LVEF.

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Furthermore, diuretics are recommended to reduce congestion symptoms in these patients. Reducing body weight in obese patients and increasing exercise may further improve symptoms and exercise capacity and should be considered in appropriate patients. It is important to identify and treat the underlying risk factors, etiology, and coexisting comorbidities in HFpEF and HFmrEF (for example, hypertension, atrial fibrillation, valvular heart disease, and amyloidosis).

FOLLOW-UP AND MONITORING

Patients with chronic HF, even if symptoms are well-controlled and stable, require follow-up to ensure continued optimization of therapy to detect asymptomatic progression of HF. Guidelines recommend follow-up at intervals of no longer than 6 months to check symptoms, heart rate and rhythm, blood pressure, full blood count, electrolytes, and renal function. TTE is also recommended 3–6 months after optimizing the GDMT for HFrEF to determine the requirement for the addition of new pharmacological agents and implanted devices. Furthermore, TTE should be repeated in patients with worsening HF. Although measurements of BNP or NT-proBNP provide prognostic information, routine monitoring of NPs is not recommended to adjust GDMT in patients with HF.[1,2)]

WHEN TO REFER TO HF CARDIOLOGIST

Timely and appropriate referral to HF cardiologists in selected patients is very important to evaluate new-onset HF and optimize treatment strategies to prevent the progression of HF. **Table 4** summarizes the clinical cases that should be referred to cardiologists or HF specialists.

PHARMACOTHERAPY OF DM IN PATIENTS WITH HF

Drug-specific factors to consider when using antihyperglycemic agents in patients with T2DM and HF are described in **Table 5**.

Table 4. Clinical cases for referral of patients with HF to a HF cardiologist

Clinical scenario	When/why
1. New-onset (*de novo*) HF	For evaluation of etiology, guideline-directed evaluation, and management of recommended therapies
2. Chronic HF with high-risk features	i) Need for intravenous inotropic therapy due to sustained NYHA functional class III-IV symptoms of congestion or profound fatigue or systolic blood pressure less than 90 mmHg and/or symptomatic hypotension ii) New onset of atrial fibrillation, ventricular arrhythmias, or repetitive ICD shocks iii) Two or more emergency department visits or hospitalizations for worsening HF in the prior 12 months iv) Inability to tolerate optimally dosed beta-blockers and/or ACEI/ARB/ARNI and/or aldosterone antagonists v) Clinical deterioration, as indicated by worsening edema, rising biomarkers (BNP, NT-proBNP, others), worsened exercise testing, decompensated hemodynamics, or evidence of progressive remodeling on imaging
3. Persistently reduced LVEF ≤35% despite guideline-directed medical therapy for 3 months	For consideration of device therapy in patients without prior placement of ICD or CRT
4. Second opinion is needed regarding the etiology of HF	i) Coronary ischemia and the possible value of revascularization ii) Valvular heart disease and the possible value of valve repair iii) Suspected myocarditis iv) Established or suspected specific cardiomyopathies (for example, hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, restrictive cardiomyopathy, cardiac sarcoidosis, and amyloidosis)

HF = heart failure; NYHA = New York Heart Association; ICD = implantable cardioverter-defibrillator; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro B-type natriuretic peptide; CRT = cardiac resynchronization therapy.

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Table 5. Drug-specific factors to consider when using antihyperglycemic agents in patients with type 2 diabetes and HF

Agents	Effect on HF	Effect on ASCVD	Effect on renal function	Hypoglycemia (monotherapy)	Weight change	Additional considerations
SGLT2 inhibitors	Benefit: dapagliflozin, empagliflozin, canagliflozin, ertugliflozin	Benefit: Empagliflozin, canagliflozin	Benefit: empagliflozin, canagliflozin, dapagliflozin	No	Loss	· Polyuria and frequent urination · Risk of dehydration, standing hypotension, and acute renal injury if a sufficient water supply is not accompanied · Risk of genital infections, urinary tract infections, Fournier's gangrene, and euglycemic DKA · Should be discontinued before scheduled surgery to prevent potential DKA
Metformin	Neutral	Potential benefit	Neutral	No	Neutral	· Contraindication: severe hepatic failure, eGFR <30, dehydration, sepsis, hypoxia, acute or unstable HF · Risk of GI side effects, and B12 deficiency
GLP-1 RAs	Neutral	Benefit: liraglutide, dulaglutide, semaglutide	Benefit: liraglutide, dulaglutide, semaglutide	No	Loss	· Contraindication: discontinue if pancreatitis is suspected · Risk of GI side effects · Risk of thyroid C-cell tumors in rodents
DPP4 inhibitors	Neutral, Potential risk: saxaglipitin	Neutral	Neutral	No	Neutral	· Contraindication: discontinue if pancreatitis is suspected · Risk of joint pain
2nd generation SU	Neutral	Neutral	Neutral	Yes	Gain	· Higher risk of hypoglycemia
Insulin	Neutral	Neutral	Neutral	Yes	Gain	· Higher risk of hypoglycemia
TZDs	Increased risk	Potential benefit: pioglitazone	Neutral	No	Gain	· Contraindication: congestive HF · Risk of fluid retention, edema, bone fractures, and bladder cancer · Benefit in NASH

HF = heart failure; ASCVD = atherosclerotic cardiovascular disease; SGLT2 = sodium-glucose cotransporter 2; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; GLP-1 RAs = glucagon-like peptide receptor agonists; DPP4 = dipeptidyl peptidase-4; SU = sulfonylurea; TZDs = thiazolidinedione; NASH = nonalcoholic steatohepatitis.

SGLT2 inhibitor

SGLT2 inhibitors reduce blood glucose levels by inhibiting glucose reabsorption in the proximal tubules of the kidneys in patients with T2DM. Clinical trials evaluating the CV outcomes of SGLT2 inhibitors have revealed that SGLT2 inhibitors reduce the risk of HF hospitalization in patients with T2DM.[71-73] Furthermore, recent trials have demonstrated that SGLT2 inhibitors have beneficial effects on HF in non-diabetic patients. DAPA-HF trial evaluated the effect of dapagliflozin on the risk of worsening HF or death from CV causes in patients with NYHA class II–IV HF and ejection fraction ≤40%.[19] After a median of 18.2 months, dapagliflozin treatment showed a 26% risk reduction in HF hospitalization or CV death (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.65–0.85). The beneficial effects of dapagliflozin were similar between patients with and without DM. Similar results were reproduced in the EMPEROR-Reduced trial.[51] During a median follow-up of 16 months, the primary outcomes of CV death and HF hospitalization were reduced by 25% in the empagliflozin group (HR, 0.75; 95% CI, 0.65–0.86). These effects were observed regardless of DM presence. In a retrospective observational study using the National Health Insurance Service claims database in Korea, use of SGLT2 inhibitors was associated with a lower risk of HF compared with use of DPP-4 inhibitors or sulfonylurea as add-on therapy to metformin in Korean patients with T2DM.[74] Based on these results, SGLT2 inhibitors are recommended as first-line glucose-lowering agents for patients with T2DM with HF, independent of HbA1c.

SGLT2 inhibitors cause osmotic diuresis by increasing urinary glucose excretion and predisposing patients to dehydration and postural hypotension, especially in older patients or those taking diuretics. The volume depletion caused by SGLT2 inhibitors may lead to renal impairment. Acute kidney injury has been reported in patients treated with SGLT2 inhibitors. Volume status should be assessed, and sufficient water intake should be included in parallel during SGLT2 inhibitor therapy. SGLT2 inhibitors increase the risk of urinary tract infections

(UTIs) and genital infections, especially in females. Signs and symptoms of UTIs and genital infections should be monitored and treated properly. Ketoacidosis with euglycemia or modestly elevated blood glucose levels (<250 mg/dL) has been reported in patients receiving SGLT2 inhibitor therapy.[75] It should be discontinued in situations of prolonged fasting owing to acute illness or before scheduled surgery to avoid the potential risk of diabetic ketoacidosis.

Metformin

Although metformin has been contraindicated in patients with HF due to the potential risk of lactic acidosis, a recent analysis suggests that metformin has favorable effects in patients with diabetes with HF by improving insulin sensitivity.[76] In a meta-analysis of nine cohort studies, metformin therapy was associated with reduced in all-cause mortality compared to any other antidiabetic therapy: 23% vs. 37% (aOR, 0.80; 95% CI, 0.73–0.88) in patients with diabetes with HF.[76] In that study, metformin was not associated with an increased risk of metabolic acidosis. Most evidence supports the safety of metformin in patients with diabetes with HF. However, metformin in patients with acutely decompensated HF, sepsis, or hypoperfusion should be stopped to avoid lactic acidosis.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)

GLP-1 receptor agonists are effective for glycemic control and weight loss. In CV outcome trials of GLP-1 RA, some GLP-1 RA showed CV benefits but did not demonstrate the effects on HF in patients with T2DM. The CV outcome trial of liraglutide (LEADER) revealed a significant reduction in the composite endpoint of death from CV causes, nonfatal MI, or nonfatal stroke in patients with T2DM with an increased CV risk.[77] In SUSTAIN-6 trial, treatment with semaglutide showed a 24% reduction in major adverse CV events.[78] In the REWIND trial, dulaglutide was also associated with a 12% reduction in CV events.[79] However, the risk of hospitalization for HF evaluated as a secondary outcome in these studies did not differ between the treatment and control groups. In a meta-analysis of eight randomized trials, GLP-1RA reduced the risk of hospitalization for HF by 10% (HR, 0.90; 95% CI, 0.83–0.98).[80] Furthermore, in the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) trial with 300 advanced patients with HF (NYHA III-IV) with and without DM, there was no impact of liraglutide on post-hospitalization clinical stability or HF readmission.[81] Thus, GLP-1 RA may be safe for use in patients with HF, although it has not shown beneficial effects.

Sulfonylureas (SUs)

While some observational studies comparing SUs with other anti-diabetic medications showed weak associations between SU treatment and CV risk, the results of RCTs suggest a neutral effect of SUs on adverse CV outcomes. In the United Kingdom Prospective Diabetes Study (UKPDS), no difference was observed between SUs and insulin treatments in HF events in newly diagnosed participants with DM.[82] A meta-analysis of 47 RCTs showed neutral outcomes of SUs for CV key outcomes, such as all-cause death, CV death, MI, or stroke.[83] Recently, the CAROLINA trial showed no difference in CV outcomes, including HF hospitalizations, between treatments with DPP4 (dipeptidyl peptidase-4) inhibitor (linagliptin) and SU (glimepiride).[84] The suggested potential mechanism of the adverse CV effects of SUs is the inhibition of ischemic conditioning and hypoglycemia. There is no clear evidence of an association between SU use and adverse CV outcomes.

Insulin

In observational studies, the prevalence of HF and cardiac mortality risk increased in patients with T2DM receiving insulin treatment.[85] A meta-analysis of patients with HF and

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DM using dataset of RCTs and population-based cohort studies revealed that insulin use was associated with a higher risk of all-cause mortality (OR, 2.02; 95% CI, 1.87–2.19) and rehospitalization for HF (OR, 1.42; 95% CI, 1.32–1.53).[86] However, evidence from RCTs has consistently indicated no increase in CVD risk with insulin use. The ORIGIN trial evaluated the CV safety of the basal insulin analog glargine in participants with prediabetes or early T2DM and a high CV risk in 6.2 years of follow-up.[87] In this trial, the risks of initial and recurrent HF hospitalizations were similar in the insulin-glargine and standard care groups. In the Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE), 4.9% of patients experienced HF hospitalization, and there was no significant difference in the risk of HF hospitalization between treatments.[88] Further studies evaluating the CV safety of insulin therapy in patients with HF are needed.

DPP4 inhibitors

Most trials examining the effects of DPP4 inhibitors (alogliptin, sitagliptin, and linagliptin) on CV safety have indicated that DPP4 inhibitor treatment is safe for CV outcomes, including major CV events, CV death, all-cause mortality, and HF hospitalization.[89-91] However, the SAVOR-TIMI 53 trial reported that the risk of HF hospitalization increased in patients with type 2 diabetic patients treated with saxagliptin compared to placebo (OR, 1.27; 95% CI, 1.07–1.51).[92] The mechanisms responsible for these observations are not yet fully understood. It is recommended that saxagliptin be used with caution in patients with high CV risk because of the potential risk of HF hospitalization.

Thiazolidinediones (TZDs)

TZDs can cause fluid retention and weight gain, and may increase the risk of HF. The RECORD trial found an increased risk of HF death or hospitalization associated with rosiglitazone (HR, 2.10; 95% CI, 1.35–3.27).[93] In the DREAM study, rosiglitazone reduced the development of DM and renal disease but increased new-onset HF (HR, 7.03; 95% CI, 1.60–30.9) in patients with prediabetes.[94] In the PROACTIVE trial, although pioglitazone resulted in a 16% risk reduction in the secondary endpoint of all-cause mortality, non-fatal MI, and stroke (HR, 0.84; 95% CI, 0.72–0.98), risk of HF was increased (HR, 1.41; 95% CI, 1.10–1.80) compared to placebo.[95] TZDs are contraindicated in patients with NYHA class III–IV HF and should be used with caution in patients with signs or symptoms or those at high risk of HF.

Glycemic target in patients with HF

While several RCTs have performed addressing the effects of intensive glycemic control on CV end points, optimal glycemic targets in HF patients with DM have not been evaluated yet.[96] Current Korean Diabetes Association guidelines recommend an HbA1c goal of <6.5% for most adults with T2DM but emphasize the individualization based on patient characteristics and comorbidities.[97]

CONSENSUS STATEMENT

1. In general, the evaluation and management for heart failure (HF) are similar between people with and without diabetes. Patients with diabetes are at higher risk of HF development and face a poorer prognosis. Therefore, a more comprehensive approach to HF is needed in patients with diabetes.

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2. The measurement of B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) for the diagnosis or exclusion of HF is recommended in patients with DM presenting with symptoms (dyspnea, chest discomfort, or typical chest pain) and/or signs (pulmonary congestion or peripheral edema).

3. Functional stress tests or coronary CT angiography should be considered for the assessment of myocardial ischemia and to determine whether HF originated from coronary artery disease in diabetic patients presenting with symptoms (dyspnea, chest discomfort, or typical chest pain) and/or ischemic signs on ECG (ST-segment deviations, T-wave inversion, or Q waves).

4. Transthoracic echocardiography (TTE) should be performed during initial evaluation to assess cardiac structure and function in patients with strongly suspected HF or elevated natriuretic peptide levels (chronic HF: BNP ≥35 pg/mL or NT-proBNP ≥125 pg/mL, acute HF: BNP ≥100 pg/mL, NT-proBNP ≥300 pg/mL).

5. Renin-angiotensin-aldosterone system (RAAS) inhibitors, including angiotensin receptor-neprilysin inhibitor (ARNI), angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB), beta-blocker (BB), mineralocorticoid receptor antagonist (MRA), and sodium-glucose co-transporter 2 (SGLT2) inhibitor, are recommended as a first-line therapy to reduce cardiovascular death and hospitalization in patients with HFrEF and NYHA class II-III symptoms.

6. SGLT2 inhibitors are recommended in patients with HFpEF and HFmrEF regardless of diabetes status for decreasing HF hospitalization and cardiovascular death.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Stages of HF

Click here to view

Supplementary Table 2
Definition of high risk of cardiovascular events in clinical trials

Click here to view

Supplementary Table 3
Contraindications or cautions of disease-modifying agents in patients with HFrEF

Click here to view

Supplementary Figure 1
The prevalence of HF according to age and sex between 2002 and 2018. The prevalence of HF according to age in men (A) and women (B) gradually increased between 2002 and 2018. Data are modified from the Heart failure statistics in Korea, 2020 and obtained permission to use the data from International Journal of Heart Failure.[7]

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Supplementary Figure 2

Proposed strategies for initiation of disease-modifying therapy in patients with HF. (A) McMurray and their colleague proposed "new sequence" algorithm that involves three steps.[49] (B) Strategy and timeline for Simultaneous or Rapid Sequence initiation of Quadruple therapy in patients with HF are shown.[47]

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