Clinical Practice Guideline

2022 HFCT Focused Update of the 2019 HFCT Heart Failure Guidelines: Part 1 - Heart Failure Classification and Pharmacological Treatment for Heart Failure with Reduced Ejection Fraction (HFrEF)

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Received 27 June 2022 | Revised 17 August 2022 | Accepted 1 September 2022

J Med Assoc Thai 2022;105(11):1153-9

Website: http://www.jmatonline.com

Since the publication of the 2019 Heart Failure Council of Thailand (HFCT) Heart Failure Guidelines, new evidence from key clinical trials have resulted in considerable changes in management of patient with heart failure (HF), which led to adoption of new recommendations in various international guidelines and consensus statements (Table 1)[1-4]. Due to these practice-changing new evidence, it is necessary to update the previously published 2019 Guidelines for the Management of HF.

Rather than comprehensive revision of the guidelines, this is a focused update of selected section of the previous guideline. The 2022 HFCT Focused Update of the 2019 HFCT Heart Failure Guidelines will be published in two parts. This part 1 publication is focused on terminology, classification, and pharmacologic treatment of heart failure with reduced ejection fraction (HFrEF). The part 2 publication will be focused on diagnosis and management of heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF).

Of note, other recommendations from the 2019 HFCT heart failure guideline not mentioned here are considered unchanged.

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How to cite this article:

Ariyachaipanich A, Buakhamsri A, Phrommintikul A, Chirakarnjanakorn S, Krittayaphong R, Senthong V, et al. 2022 HFCT Focused Update of the 2019 HFCT Heart Failure Guidelines: Part 1 - Heart Failure Classification and Pharmacological Treatment for Heart Failure with Reduced Ejection Fraction (HFrEF). J Med Assoc Thai 2022;105:1153-9.

DOI: 10.35755/jmedassocthai.2022.11.13702

Terminology and classification

In 2021, for the first time, major cardiac societies endorsed a new Universal Definition and Classification of HF. This 2022 HFCT focused update introduced the summary of terminology of HF staging and classification in Figure 1.

There are three significant updates in terminology and classification of HF:

1. Significance of biomarker in diagnosis of stage B HF: The abnormal level of natriuretic peptide in patients at risk for HF will make that patient classified into the stage B HF. It is important to note that the elevated level of natriuretic peptide must not be explained by other causes. This conclusion is based on knowledge that the patients with abnormal biomarker have higher risk to develop HF even with or without structural abnormalities on imaging evaluation. The term "pre-heart failure" is now recommended to be used synonymously with stage

Table 1. Updated international guidelines and consensus statements

Recent international guidelines and consensus statement in heart failure
• 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
• 2021 Universal Definition and Classification of Heart Failure
• 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment
• 2019 ACC Expert Consensus Decision Pathway on Risk Assessment, Management, and Clinical Trajectory of Patients Hospitalized with Heart Failure

ACC=American College of Cardiology; ESC=European Society of Cardiology

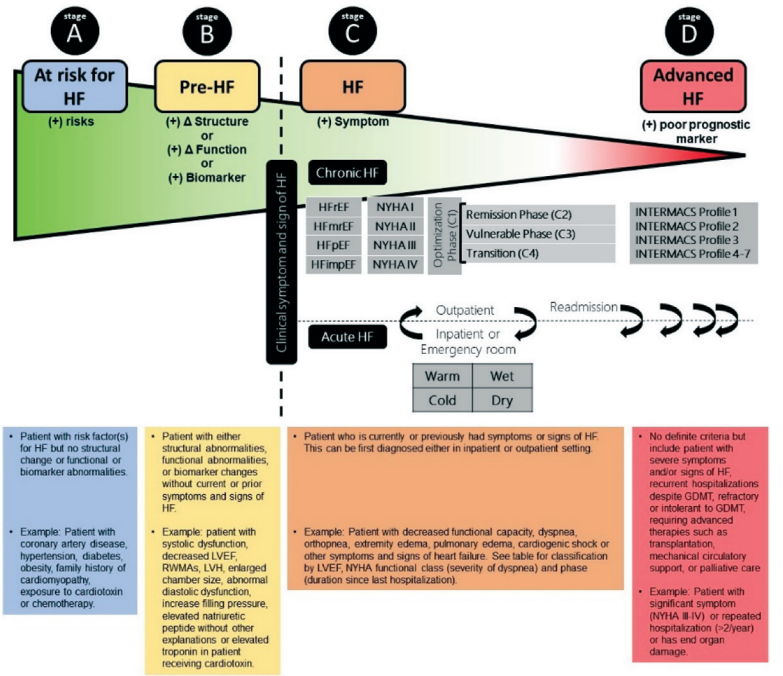

Figure 1. Terminology of HF staging and classification.

GDMT=guideline directed medical therapy; HF=heart failure; HFimpEF=heart failure with improved ejection fraction; HFmrEF=heart failure with mildly reduced ejection fraction; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; LVEF=left ventricular ejection fraction; LVH=left ventricular hypertrophy; NYHA=New York Heart Association; RWMA=reginal wall motion abnormalities

B HF.

2. Terminology of classification based on left ventricular ejection fraction: In patient with HF (stage C), the left ventricular ejection fraction (LVEF) is one of the most important parameters for selecting pharmacologic treatment and cardiac implantable electric device. Other than commonly known HFrEF with LVEF of 40% or less and HFpEF with LVEF of 50% or more, two important updates are:

- HF with mildly reduced EF (HFmrEF): With more evidence of patient characteristics and response of treatment closely related to HFrEF, now the patient with LVEF 41% to 49% is called HF with mildly reduced EF. Management and recommendation for patients with HFmrEF is discussed in the 2022 HFCT Focused Update of the 2019 HFCT Heart Failure Guidelines: Part 2.

- HF with improved EF (HFimpEF): The patient with history of HFrEF or LVEF of 40% or less, whose EF has increased by 10% or more points to more than 40%, such as LVEF at the time of diagnosis of 35% and later increased to 45%, are classified into HFimpEF. The patients with HFimpEF have better prognosis than HFrEF but GDMT should be continued. There are no other specific recommendations.

3. Classification based on duration since last admission - Phase of HF: For the first time, this focused update introduces a new terminology to facilitate strategy to optimize guideline-directed medical therapy by classifying patient into phases. This may be considered as a sub-classification of chronic stable HF (stage C) who is not hospitalized.

There are four phases of chronic stable outpatient HF-1. Optimization Phase, Remission Phase,

Table 2. Classification based on duration since last admission - Phase of HF

Phase	Name	Definition	Suggested goal	Suggested follow up
C1	Optimization	Not optimally on GDMT, usually recently diagnosed HF	Intensive HF education, up titrate pharmacologic treatment to maximally tolerated doses or as tolerate within 3-6 months.	2-4 weeks
C2	Remission	Already on OMT and no HF hospitalization for >6 months	Surveillance for alteration in symptoms. Consider reducing diuretic if possible. Evaluation for CIED if needed. Routine functional capacity assessment.	2-6 months
C3	Vulnerable	Recent hospitalization within 6 months, but not within 30 days	Similar to optimization phase with more urgency. Consider medications that can reduce HF hospitalization.	2-8 weeks
C4	Transition	Recent hospitalization within 30 days	Transition of care from inpatient to outpatient.	1-2 weeks

CIED=cardiac implantable electronic devices; GDMT=guideline-directed medical therapy; OMT=optimal medical therapy

Table 3. Updated definition, classification, terminology, and medication

Recommendations	COR	LOE
Patients are classified as the stage B heart failure (pre-HF) if having either structural abnormalities, functional abnormalities, or biomarker changes without current or prior symptoms and signs of HF.	I	B
Chronic HF patients should be classified based on LVEF, NYHA functional class and duration since last hospitalization (phase of heart failure).	I	C
Initiation and up titration of any 4 classes of medication (RASi, BB, MRA, SGLT2i) in any order with no fixed hierarchical sequence which simultaneous and rapid up titrating strategy should be considered.	IIa	C

BB=beta-blockers; LVEF=left ventricular ejection fraction; MRA=mineralocorticoid receptor antagonist; NYHA=New York Heart Association; RASi=renin-angiotensin aldosterone inhibitors/modulators; SGLT2i=sodium-glucose co-transporter-2 inhibitor

Vulnerable Phase, and Transition Phase, so-called C1, C2, C3 and C4, respectively. There are different goals and resource utilizations for each phase. Definition and management are shown in Table 2. Traditionally, classification of chronic HF patient is done by NYHA functional class or LVEF. If heart failure hospitalization is considered a major HF event that affect qualities of life (QoL), morbidity, mortality, and prognosis, phase of HF will help further optimization of management. Of note, unlike stage of HF, each patient can shift back and forth between phases. The goal is to maintain the patient into remission phase (C2).

Recommendation regarding the terminology and classification of HF are shown in Table 3.

Main figure

The pharmacologic treatment of chronic HF in the previously published Central Illustration of the 2019 HFCT guideline was updated as shown in Figure 2. These changes include new evidence of angiotensin receptor neprilysin inhibitor (ARNI) in HF, role of sodium-glucose co-transporter 2 inhibitors (SGLT2i), treatment of HFmrEF, and evidence of vericiguat in HFrEF.

The figure simplified the pharmacologic treatment of HF in many ways. For HFrEF, a renin-angiotensin system inhibitor/modulator (RASi), beta-blockers (BB), mineralocorticoid receptor antagonist (MRA), and SGLT2i are considered class I recommendation for treatment of HFrEF.

It is likely that the four classes of medication are synergistic. Rather than specific sequential initiation of each medication, the focus should be on patient characteristics, indication, contraindications, cautions, and accessibilities with goal to initiate in any order. The patient will benefit the most with the best possible outcomes if all four classes of medication were being used.

The angiotensin receptor-neprilysin inhibitor (ARNI) is consider a prefer RASi over angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blocker (ARB). Depending on clinical setting, initiation, and up titration these medications, in any order, with the goal to achieve recommended or maximum tolerated dose should be achieved within three to six months.

The pharmacologic treatment of HFmrEF are the same medical classes as HFrEF but lower class of recommendation and level of evidence. For HFpEF, other than MRA and ARB, which have been previously recommended, ARNI and SGLT2i are added.

Digoxin, hydralazine/isosorbide dinitrate and vericiguat may be considered in patients with recent HF hospitalization, within six months, or with persistently significant symptoms burden.

Specific recommendations of each medication

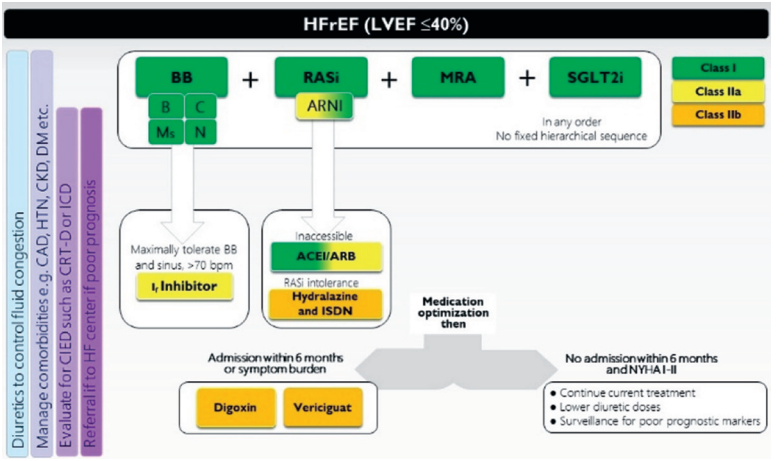

Figure 2. Pharmacologic therapy for chronic HF.

ACEI=angiotensin-converting enzyme inhibitors; ARB=angiotensin receptor blocker; ARNI=angiotensin receptor-neprilysin inhibitor; BB=beta-blockers; B=bisoprolol; C=carvedilol; CAD=coronary artery disease; CIED=cardiac implantable electronic devices; CKD=chronic kidney disease; CRT=cardiac re-synchronization therapy-defibrillator; DM=diabetes mellitus; HTN=hypertension; ICD=implantable cardioverter defibrillator; ISDN=isosorbide dinitrate; Ms=metoprolol succinate; MRA=mineralocorticoid receptor antagonist; N-nebivolol; RASi=renin-angiotensin aldosterone inhibitors/modulators; SGLT2i=sodium-glucose co-transporter-2 inhibitor

Table 4. Angiotensin-neprilysin inhibitor (ARNI) for HFrEF

Recommendations	COR	LOE
An ARNI (sacubitril/valsartan) is recommended as a replacement for an ACEI or ARB to reduce the risk of HF hospitalization and death.	I	B
An ARNI (sacubitril/valsartan) should be considered in patients with ACEI or ARB naïve.	IIa	C
Low-dose ARNI should be carefully initiated and gradually up-titrated to the target dose in patients with vulnerable characteristics (Table 5).	I	C

ACEI=angiotensin-converting enzyme inhibitors; ARB=angiotensin receptor blocker; ARNI=angiotensin receptor-neprilysin inhibitor

class are discussed below.

ARNI for HFrEF

An ARNI, sacubitril/valsartan, was tested in PARADIGM-HF[5] trial against enalapril in patients with symptomatic HFrEF. This study demonstrated superior benefit of ARNI in reduction of the primary outcome of CV death or HF hospitalization when compared to enalapril. With these significant clinical benefits, sacubitril/valsartan is then recommended to timely replace ACEI or ARB in patients who have been treated with ACEI or ARB for HFrEF therapy (Table 4). It is important to note that in patients who have been treated with ACEI, ACEI needed to be stop 36 hours prior to switching to ARNI. This "wash out period" is necessary to limit risk of angioedema.

Initiation of an ARNI in patients with de novo HFrEF or ACEI/ARB naïve, rather than a pretreatment of ACEI or ARB, appears to be safe and clinically effective in recent studies. PIONEER-HF[6] was an in-hospital study, where clinically stable patients with de novo HFrEF were randomized to sacubitril/valsartan or enalapril. Patients treated with sacubitril/valsartan had a higher reduction in natriuretic peptide levels and improved early clinical outcomes compared with those on enalapril. Both medications showed similar safety profiles.

PROVE-HF[7] was an open-label study conducted in patients who were eligible for ARNI therapy. Sacubitril/valsartan were initiated and titrated up to maximum tolerated dose. Drug was safe and well tolerated. Patients were followed for one year and showed significant improvement in LVEF and evidence of reversed cardiac remodeling. Target dose of sacubitril/valsartan was also achieved in most patients with low blood pressure at baseline by using gradual dose titration as demonstrated in TRITATION study[8].

With these clinical evidence and data from PARADIGM-HF, initiation of sacubitril/valsartan should be considered in patients with HFrEF and ACEI or ARB naïve to obtain early benefits without delay (Table 4). There is no plausible scientific concept to support initiation of ACEI or ARB before

Table 5. Cautions and contraindications before start angiotensin-neprilysin inhibitor (ARNI)

Vulnerable clinical characteristics/cautions in initiation of ARNI
1. Renal impairment:
- Mild-to-moderate (eGFR 30-59 mL/minute/1.73 m^2): no starting dose adjustment required.
- Severe* (eGFR <30 mL/minute/ 1.73 m^2): reduce starting dose to 24/26 mg twice daily; double the dose every 2-4 weeks to target maintenance dose of 97/103 mg twice daily, as tolerated.
2. Hepatic impairment:
- Mild (Child-Pugh A): no starting dose adjustment required.
- Moderate (Child-Pugh B): reduce starting dose to 24/26 mg twice daily; double the dose every 2 to 4 weeks to target maintenance dose of 97/103 mg twice daily, as tolerated
3. Systolic blood pressure <100 mm Hg
4. Serum potassium >5.2 mEq/L
5. Volume depletion: consider reduction in diuretic requirement if needed
Contraindications of ARNI
1. Within 36 hours of ACEI use
2. History of angioedema with or without an ACEI or ARB
3. Pregnancy
4. Bilateral renal artery stenosis
5. Lactation (no data)
6. Severe hepatic impairment (Child-Pugh C)
7. Concomitant aliskiren use in patients with diabetes
8. Known hypersensitivity to either ARBs or ARNIs

ACEI=angiotensin-converting enzyme inhibitors; ARB=angiotensin receptor blocker; ARNI=angiotensin receptor-neprilysin inhibitor; eGFR=estimated glomerular filtration rate

* This population was not studied in PARADIGM-HF. The statement is consistent with FDA-approved labeling indications.

switching to ARNI in patients with ACEI or ARB naïve. Care should be taken during dose titration of sacubitril/valsartan in patients with vulnerable clinical characteristics (Table 5).

SGLT2i for HFrEF

The benefits of cardiovascular events reduction of SGLT2i in HFrEF have been shown in ambulatory HF patients receiving optimal guidelines-directed medical therapy (GDMT). DAPA-HF and EMPEROR-Reduced enrolled patients NYHA II-IV, LVEF of 40% or less and elevated NT-proBNP despite optimal medical therapy[9,10]. Treatment with dapagliflozin in DAPA-HF trial and empagliflozin in EMPEROR-Reduced trial resulted in a 26% and 25% risk reduction in the primary outcomes, which is a composite of worsening HF or CV death, respectively. The magnitude of benefits was not different between patients with or without diabetes. In addition, SGLT2i improved HF symptoms, physical function, and quality of life. Although cardiovascular death was significantly reduced in DAPA-HF study but not in EMPEROR-Reduced, the meta-analysis of both trials did not show significant heterogeneity in CV death between these studies[11].

In addition to ambulatory HF patients, diabetic patients who were hospitalized with HF has been recruited in the SOLOIST-WHF study. Treatment with the combined SGLT-1 and 2 inhibitors, sotagliflozin, before or shortly after discharge resulted in 33% lower number of deaths from cardiovascular causes and hospitalizations and urgent visits for HF. The median LVEF in the study population was 35% and 79% had LVEF of less than 50%. There was no difference between patients with LVEF above or below 50%.

The meta-analysis of SGLT2 inhibitors in diabetic patients demonstrated an 11% reduction of major cardiovascular events reduction as combined cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, in established atherosclerotic cardiovascular disease[12]. In diabetic patients, SGLT2i reduced the risk of cardiovascular death or hospitalization for HF by 23% with a similar benefit in patients with and without atherosclerotic cardiovascular disease and with and without a history of HF[12].

Dapagliflozin or empagliflozin are recommended for symptomatic patients with HFrEF (Table 6). The medication is recommended to be started in ambulatory patients with HFrEF or may be considered in acute HF patients who are stabilized before discharge or early after discharge.

The adverse effects of SGLT2i including a small but reversible reduction in eGFR following initiation, dehydration, or genitourinary tract infection. Risk of hypoglycemia may be increased in diabetic patients receiving other anti-diabetic agents[9-11].

Table 6. SGLT2i for HFrEF

Recommendations	COR	LOE
Dapagliflozin or empagliflozin are recommended for symptomatic patients with HFrEF to reduce the risk of heart failure hospitalization and death	I	A
SGLT2i are recommended for diabetic patients who are at risk for heart failure and asymptomatic left ventricular systolic dysfunction	I	A

HFrEF=heart failure with reduced ejection fraction; SGLT2i=Sodium-glucose co-transporter-2 inhibitor

Table 7. Vericiguat for HFrEF

Recommendations	COR	LOE
Vericiguat may be considered in addition to optimal HF therapies for high risk HFrEF patients with worsening symptoms or recent hospitalization to reduce the risk of subsequent heart failure hospitalization and cardiovascular death.	IIb	B

HFrEF=heart failure with reduced ejection fraction

Table 8. Executive summary of updated recommendations for HFrEF

Recommendations	COR	LOE	Note
Terminology and classification			
Patients are classified as the stage B heart failure (pre- heart failure) if having either structural abnormalities, functional abnormalities, or biomarker changes without current or prior symptoms and signs of HF.	I	B	NEW
Chronic HF patients should be classified based on LVEF, NYHA functional class and duration since last hospitalization (phase of heart failure).	I	C	UPDATE
Initiation and up titration of any 4 classes of medication (RASi, BB, MRA, SGLT2i) in any order with no fixed hierarchical sequence which simultaneous and rapid up titrating strategy should be considered.	IIa	C	NEW
ARNI for HFrEF			
An ARNI (sacubitril/valsartan) is recommended as a replacement for an ACEI or ARB to reduce the risk of HF hospitalization and death.	I	B	SAME
An ARNI (sacubitril/valsartan) should be considered in patients with ACEI or ARB naïve.	IIa	C	UPDATE
Low-dose ARNI should be carefully initiated and gradually up-titrated to the target dose in patients with vulnerable characteristics (Table 5).	I	C	UPDATE
SGLT2i for HFrEF			
Dapagliflozin or empagliflozin are recommended for symptomatic patients with HFrEF to reduce the risk of heart failure hospitalization and death	I	A	NEW
SGLT2i are recommended for diabetic patients who are at risk for HF and asymptomatic left ventricualr systolic dysfunction	I	A	NEW
Vericiguat for HFrEF			
Vericiguat may be considered in addition to optimal HF therapies for high risk HFrEF patients with worsening symptoms or recent hospitalization to reduce the risk of subsequent heart failure hospitalization and CV death.	IIb	B	NEW

ACEI=angiotensin-converting enzyme inhibitors; ARB=angiotensin receptor blocker; ARNI=angiotensin receptor-neprilysin inhibitor; BB=beta-blockers; CIED=cardiac implantable electronic devices; HFrEF=heart failure with reduced ejection fraction; LVEF=left ventricular ejection fraction; MRA=mineralocorticoid receptor antagonist; NYHA=New York Heart Association; RASi=Renin-angiotensin aldosterone inhibitors/modulators; SGLT2i=Sodium-glucose co-transporter-2 inhibitor

Vericiguat for HFrEF

Vericiguat is an oral soluble guanylate cyclase (sGC) stimulator with mechanism of action at NO-cGMP axis. In VICTORIA study, vericiguat is associated with reduction in the composite of HF hospitalization or cardiovascular death when using in patient with worsening chronic HF patient defined by recent hospitalization or need for intravenous diuretics. The efficacy in general HF patient is not established yet. This new medication with novel mechanism of action is not available in Thailand at the time of publication but once approved, is likely be valuable medication class that may be considered in patients with chronic HF in vulnerable phase (Table 7)[13].

Pharmacologic treatment of HFrEF and consideration factors

The profile of HF patients such as presence of congestion, heart rate, blood pressure, renal function, potassium level, and comorbidities should be taken into consideration when prioritizing GDMT (Figure 3). Beta-blockers should be used with caution or avoided in the patients with overt congestion and symptomatic bradycardia. The beta1-selective beta-blocker as bisoprolol or metoprolol succinate, may be considered rather than carvedilol or nebivolol to avoid hypotension in patients who have borderline blood pressure. RASi in the patients with hyperkalemia, especially in the setting of impaired renal function should be used judiciously and started with lowest dose with close follow-up.

What is already known on this topic?

Since the publication of the 2019 HFCT Heart Failure Guidelines, new evidence from key clinical trials have resulted in considerable changes in management of patient with HF, which led to adoption of new recommendations in various international guidelines and consensus statements.

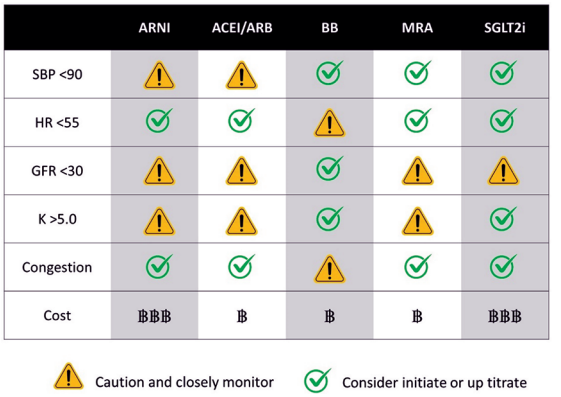

Figure 3. Pharmacologic treatment of HFrEF according to various consideration factors.

ACEI=angiotensin-converting enzyme inhibitors; ARB=angiotensin receptor blocker; ARNI=angiotensin receptor-neprilysin inhibitor; BB=beta-blockers; eGFR=glomerular filtration rate (unit in mL/minute/1.73 m^2); HR=heart rate (unit in bpm); K=serum potassium level (unit in mEq/mL); MRA=mineralocorticoid receptor antagonist; SBP=systolic blood pressure; SGLT2i=Sodium-glucose co-transporter-2 inhibitor

฿฿฿ represent higher cost of medication

What does this study add?

This part 1 publication is focused on terminology, classification, pharmacologic treatment of heart failure with reduced ejection fraction (HFrEF), especially new recommendation of RASi, ARNI, and SGLT2i.

Conflicts of interest

The authors declare no conflict of interest.

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