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Consensus
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2023 Consensus of Taiwan Society of Cardiology on the Pharmacological Treatment of Chronic Heart Failure

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The prevalence of heart failure is increasing, causing a tremendous burden on health care systems around the world. Although mortality rate of heart failure has been significantly reduced by several effective agents in the past 3 decades, yet it remains high in observational studies. More recently, several new classes of drugs emerged with significant efficacy in reducing mortality and hospitalization in chronic heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). To integrate these effective therapies and prioritize them in the management of Asian patients, Taiwan Society of Cardiology has recently appointed a working group to formulate a consensus of pharmacological treatment in patients with chronic heart failure. Based on most updated information, this consensus provides rationales for prioritization, rapid sequencing, and in-hospital initiation of both foundational and additional therapies for patients with chronic heart failure.

Key Words: Asia • Chronic heart failure • Consensus • Foundational therapy • Left ventricular ejection fraction

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Abbreviations

ACEI	Angiotensin converting enzyme inhibitor
A-HeFT	African-American Heart Failure Trial
aHR	Adjusted hazard ratio
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
ATLAS	Assessment of Treatment with Lisinopril and Survival
CI	Confidence interval
cGMP	Cyclic guanosine monophosphate
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival
DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
DELIVER	Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure
DIG	Digitalis Investigation Group
EMPEROR-Preserved	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction
EMPHASIS-HF	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
EMPULSE	Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure
HEAAL	Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan
HFimpEF	Heart failure with improved EF
HFmrEF	Heart failure with mildly reduced ejection fraction
HFnEF	Heart failure with normal ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFsrEF	Heart failure with severely reduced ejection fraction
IMPACT-HF	Initiation Management Pre-Discharge: Assessment of Carvedilol Therapy for Heart Failure
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left ventricular ejection fraction
MRA	Mineralocorticoid receptor antagonist
NYHA	New York Heart Association
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PARADIGM-HF	Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
PARAGON-HF	Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction
PEP-CHF	Perindopril in Elderly People with Chronic Heart Failure
PIONEER-HF	Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode
RALES	Randomized Aldactone Evaluation Study
SGLT2	Sodium-glucose co-transporter 2
SHIFT	Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial
SOLOIST-WHF	Effect of Sotagliflozin on Cardiovascular Eventsin Patients with Type 2 Diabetes Post Worsening Heart Failure
SOLVD	Studies of Left Ventricular Dysfunction
STRONG-HF	Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
V-HeFT	Vasodilator Heart Failure Trial
VICTORIA	Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction
WHF	Worsening heart failure

1. INTRODUCTION

Heart failure is a clinical syndrome characterized by cardinal symptoms of shortness of breath, ankle swelling, and fatigue, and commonly accompanied by typical signs of elevated jugular venous pressure, lung rales, and peripheral edema.[1] The prevalence of heart failure is around 1-2% in adults, but the clinical course of heart failure is grave, characterized by repetitive hospitalization and high cardiovascular mortality.[1] Mortality rate of heart failure has been significantly reduced by several effective drugs in the past 3 decades,[2-4] but it remains high in observational studies.[5] More recently, several new classes of drugs emerged with significant efficacy in reducing mortality and hospitalization in chronic heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF).[6-12] How to integrate these effective therapies and prioritize them is unclear in recent heart failure guidelines and consensuses.[1,13] Taiwan Society of Cardiology has recently appointed a working group to formulate a consensus of pharmacological treatment in patients with chronic heart failure.

2. BURDEN OF HEART FAILURE IN ASIA AND TAIWAN

The incidence of heart failure in developed countries has been stabilized and ranges from 1% to 14%.[14] Although the global age-adjusted incidence of heart failure is decreasing, the absolute number and heart failure prevalence is increasing[15,16] (Figure 1). Heart failure mortality remains high, approximately 50% at 5 years in recent years.[17] With significant regional and ethnic heterogeneity, the reported 6-month and 12-month crude mortality rates were 6.9% and 9.6%, respectively, among heart failure patients in Asia.[16]

The incidence of heart failure in Taiwan in 2016 was 2.19 per 1000 person-years with a stepwise increase with age, with an overall temporal trend of slightly decreased incidence from 2001 to 2016 (2.44 to 2.19 per 1,000 person-years, respectively).[18] The prevalence increased from 0.63% in 2001 to 1.40% in 2016, with a 2.22-fold increase over the 16 years. The projected prevalence rate was estimated to be 1.99% in 2025, and would step up every 5 years to 2.44%, 2.88%, 3.36%, 3.89%, and 4.45% (803,401 patients estimated) in 2050.[18] The lifetime risk of heart failure was 1 in 5 for Taiwanese adults aged ≥ 20 years, being higher for males (1 in 4) compared to females (1 in 5). The incident mortality after newly diagnosed heart failure during follow-up was estimated to be 38.5%, 52.2%, 62.1%, 69.6% and 75.5% at 2-year, 4-year, 6-year, 8-year and 10-year follow-up, respectively. The annual rate of all-cause death was 16.53%, higher than those without heart failure [adjusted hazard ratio (aHR): 1.80, 95% confidence interval (CI): 1.38-2.36, $p < 0.01$].[18]

Consensus statements

- Despite a decrease in the incidence rate of heart failure in Taiwan in the recent 2 decades, the prevalence rate is increasing, similar to current Asia status.
- For adult Taiwanese, the lifetime risk of heart failure is 1 in 5 for women and 1 in 4 for men.
- The all-cause death rate of heart failure in Taiwan is very high, around 50% in 4 years and 75% in 10 years.

3. PROPOSED RE-CLASSIFICATION OF HEART FAILURE

Classification of heart failure based on left ventricu-

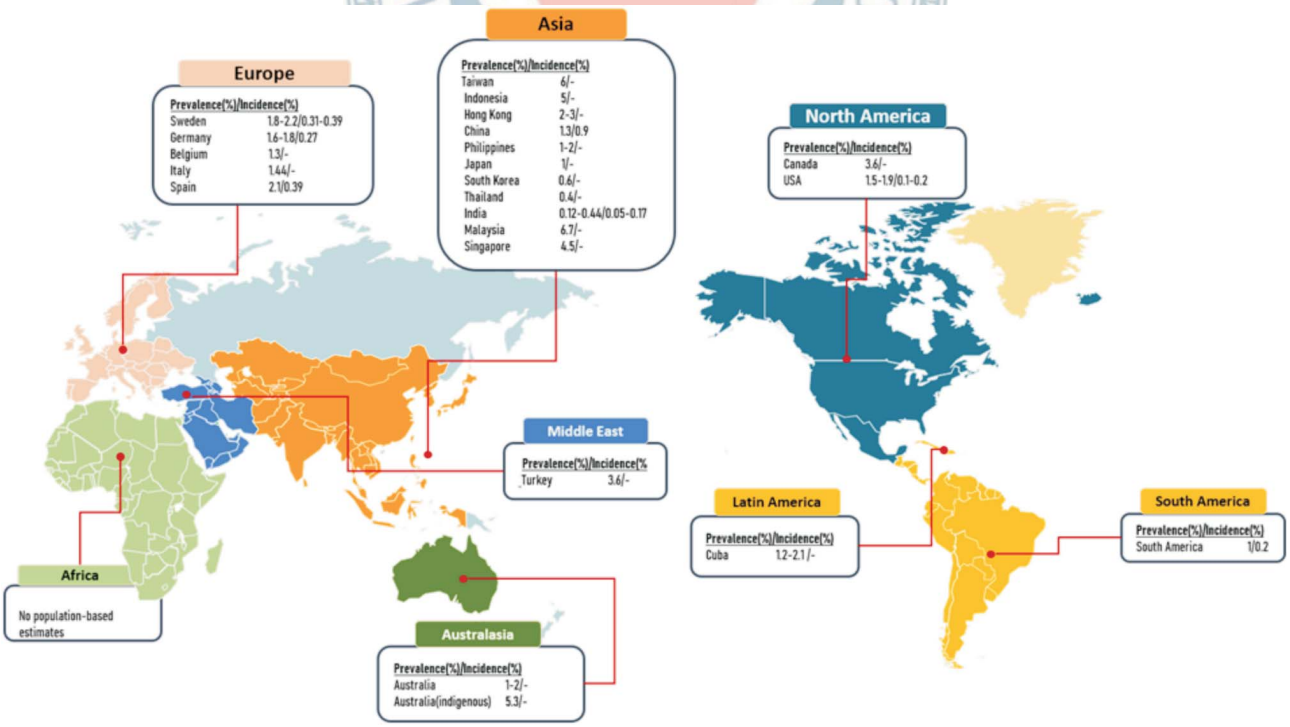


Figure 1. *Prevalence and incidence of heart failure in population-based studies around the world.*

lar ejection fraction (LVEF) is the most practical approach because it relates to prognosis and response to treatment. More importantly, almost all clinical trials enrolled patients accordingly to individual LVEF. Previously, HFrEF and HFpEF were defined as LVEF ≤ 40% and ≥ 50%, respectively, and LVEF 41-49% was defined as heart failure with mildly reduced EF (HFmrEF).[1,19] It seems somewhat awkward to classify patients with LVEF < 50% into HFrEF and HFmrEF. Are patients with HFrEF more severe than and responding to therapy differently to patients with HFmrEF? Several analyses suggested that patients with HFmrEF were less severe than HFrEF, but benefit from, though to a lesser degree, mineralocorticoid receptor antagonist (MRA),[20,21] beta-blockers,[22] angiotensin receptor blocker (ARB),[21,23] angiotensin receptor-neprilysin inhibitor (ARNI),[21,24] and, most recently, sodium-glucose co-transporter 2 (SGLT2) inhibitor.[25] A more straightforward way is to classify patients with LVEF < 50% as HFrEF, and further classify HFrEF into HFmrEF (LVEF 41%-49%) and heart failure with severely reduced EF (HFsrEF) (LVEF ≤ 40%) (Figure 2 and Table 1). It is also reasonable to name those patients with LVEF ≥ 60% as heart failure with normal EF (HFnEF).[26,27] There is an argument that male, when compared with female, have a lower cutoff EF (EF ≥ 55% vs. ≥ 60%) for HFnEF.[26] We did not propose different cutoff of LVEF for gender, as the efficacy of heart failure treatment was similar between genders in more recent trials,[11,12] though in the only ARNI trial we did observe a difference.[28] In a subgroup analysis of the DELIVER trial, patients with HFnEF got similar degree of benefits from SGLT2 inhibitor.[12,29] Nevertheless, other underlying causes, such as amyloidosis and hypertrophic cardiomyopathy, need to be thoroughly investigated in patients with HFnEF.

Heart failure patients with an initial LVEF ≤ 40%, but that improved to > 40% or even ≥ 50%, are classified as heart failure with improved EF (HFimpEF). Patients with HFimpEF can be looked at as a subgroup of HFsrEF, who have baseline characteristics similar to HFsrEF but different from those with HFpEF.[30] The DELIVER trial is the first to enroll this particular type of patients and confirmed that patients with HFimpEF obtained similar magnitude of benefits compared with that for HFrEF.[12]

Additionally, objective evidence of cardiac structural and functional abnormalities consistent with spontane-

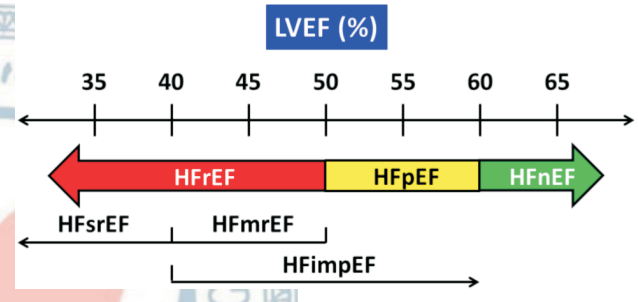


Figure 2. *Proposed new classification of heart failure. HFimpEF, HF with improved ejection fraction (previous LVEF < 40% that improved by 10% in LVEF and now > 40%); HFimpEF,heart failure with improved EF; HFmrEF, heart failure with mildly reduced ejection fraction; HFnEF, heart failure with normal ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFsrEF, heart failure with severely reduced ejection fraction; LVEF, left ventricular ejection fraction.*

Table 1. Classification of heart failure based on LVEF

Type of HF	HFrEF		HFpEF	HFnEF
	HFsrEF	HFmrEF		
CRITERIA				
1	Symptoms ± signs	Symptoms ± signs	Symptoms ± signs	Symptoms ± signs
2	LVEF ≤ 40%	LVEF 41-49%	LVEF 50-59%	LVEF ≥ 60%
3	–	–	Objective evidence of cardiac structural and functional abnormalities consistent with spontaneous or provokable increased LV filling pressures; and elevated natriuretic peptides*	Objective evidence of cardiac structural and functional abnormalities consistent with spontaneous or provokable increased LV filling pressures; and elevated natriuretic peptides*

HF, heart failure; HfmrEF, heart failure with mildly reduced ejection fraction; HfnEF, heart failure with normal ejection fraction; HfpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HfsrEF, heart failure with severely reduced ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction.

* B-type natriuretic peptide ≥ 35 pg/mL and/or N-terminal pro-B type natriuretic peptide ≥ 125 pg/mL.

ous or provocable increased LV filling pressures, and elevated natriuretic peptides, are required to define HFpEF and HFnEF (Table 1).

Consensus statements

- Based on LVEF, Taiwan Society of Cardiology has proposed a new classification of heart failure.
- Heart failure with LVEF ≤ 40%, 41%-49%, 50%-59%, and ≥ 60% are classified as HFsrEF, HFmrEF, HFpEF, and HFnEF, respectively.
- Patients with HFrEF include those with HFsrEF and HFmrEF.
- Heart failure with an initial LVEF ≤ 40%, but that improves to > 40% or even ≥ 50%, are classified as HFimpEF.
- Objective evidence of cardiac structural and functional abnormalities, combined with elevated natriuretic peptides, is required to define HFpEF and HFnEF.
- For patients with HFnEF, underlying causes, such as amyloidosis and hypertrophic cardiomyopathy, should be thoroughly investigated.

4. CLASSIFICATION OF MEDICATIONS FOR HFrEF

4.1. Diuretics

Given the central role of volume expansion in the pathogenesis of congestion, diuretics are among the cornerstones of treatment of heart failure, though the effects of diuretics, except MRAs, on morbidity and mortality are uncertain. Despite that the recent OPTIMIZE-HF registry with diuretic use compared with no diuretic use after discharge for heart failure demonstrated reductions in all-cause death and hospitalization for heart failure,[31] diuretics should not be used in isolation, since they need to be combined with other evidence-based therapy. Loop diuretics are the mainstays of diuretic agents in most patients with heart failure, irrespective of LVEF.

4.2. Foundational therapy and additional therapy

In this consensus, we classify medications for HFrEF into two groups: foundational therapy and additional therapy. We consider a drug to be foundational therapy if it reduces cardiovascular death and/or all-cause death, and the risk of hospitalization for heart failure in large-scale clinical trials.[32] This group includes angiotensin converting enzyme inhibitor (ACEI), ARB, beta-blocker, MRA, ARNI, and SGLT2 inhibitor. Additional therapy includes digoxin, hydralazine/isosorbide dinitrate, ivabradine, and vericiguat, because the magnitude of the overall treatment effects has been modest, the strength of evidence (the level of statistical significance) is not robust, or the benefits are limited to specific subgroups.[32] In general, foundational therapy should be used first, whereas additional therapy can be added when patients still have symptoms despite of foundational therapy, or in certain conditions when foundational therapy cannot be applied or contraindicated. The characteristics, inclusion criteria, and event reductions of major placebo-controlled HFsrEF trials for both the foundational therapies and additional therapies are shown in Table 2.

Asian patients were not included in some remote trials, and only recent trials of ARNI,[6] SGLT2 inhibitors,[7,8] and vericiguat enrolled Asian patients.[10] In general, the efficacy in Asian subgroup did not differ from other races and the main trial.[6-8,10]

4.3. ACEI/ARB/ARNI

4.3.1. ACEI

ACEIs are the first class of foundational therapy that could reduce all-cause death, cardiovascular death, and hospitalization for heart failure[33,34] (Table 2). They should be used in patients with systolic blood pressure ≥ 90 mmHg.[1] Patients with severely impaired renal function (serum creatinine level > 3.7 mg/dL) were excluded.[33] Based on one important study in Asians, ACEI can be used in patients with an estimated glomerular filtration rate of 20 mL/min.[35] The major issue of ACEI in Asian population is higher prevalence of cough compared with Caucasians. The starting doses, target doses, and the mean doses achieved in clinical trials are shown in Table 3.

In the Studies of Left Ventricular Dysfunction (SOLVD) trial,[34] HRs for all-cause death, heart failure hospitalization, and the combined endpoint of heart failure hospitalization or all-cause death at 14 days after randomization were 0.80 (95% CI: 0.32-2.03), 0.63 (95% CI: 0.35-1.12), and 0.65 (95% CI: 0.39-1.06), respectively. Corresponding HRs at 30 days were 0.82 (95% CI: 0.41-1.67), 0.43 (95% CI: 0.27-0.68), and 0.43 (95% CI: 0.27-0.68), respectively[36] (Table 3). The magnitude of these early

Table 2. Characteristics, inclusion criteria, and efficacy of major trials of HFsrEF

Characteristics	Inclusion/exclusion criteria									Events			
Class of drug	Name of trial	Drug name	Number of patient	EF (%)	SBP (mmHg)	HR (bpm)	Cr (mg/dL)	eGFR (mL/min)	K (meq/L)	All-cause death	CV death + HHF	CV death	HHF
Foundational therapy													
ACEI	CONSENSUS[33]	Enalapril	253	NR	NR	NR	≤ 3.7	NR	NR	↓	NR	↓	NR
	SOLVD[34]	Enalapril	2,569	≤ 35	NR	NR	≤ 2	NR	NR	↓	↓	↓	↓
ARB	Val-HeFT[39]	Valsartan	5,010	≤ 40	≥ 90	NR	≤ 2.5	NR	NR	↔	↓	↔	↓
	CHARM-Alternative[40]	Candesartan	2,028	≤ 40	NR	NR	< 3	NR	< 5.5	↔	↓	↓	↓
BB	US Carvedilol[49]	Carvedilol	1,094	≤ 35	≥ 85	≥ 68	NR	NR	NR	↓	↓	↓	↓
	MERIT-HF[3]	Metoprolol succinate	3,991	≤ 40	≥ 100	≥ 68	NR	NR	NR	↓	↓	↓	↓
	CIBIS-II[51]	Bisoprolol	2,647	≤ 35	≥ 100	≥ 60	NR	NR	NR	↓	↓	↓	↓
	COPERNICUS[50]	Carvedilol	2,289	≤ 25	≥ 85	≥ 68	≤ 2.8	NR	3.5-5.2	↓	↓	↓	↓
	SENIORS[52]	Nebivolol	2,128	≤ 35	≥ 90	≥ 60	NR	NR	NR	↔	↓	↔	↔
MRA	RALES[4]	Spironolactone	1,663	≤ 35	NR	NR	≤ 2.5	NR	≤ 5	↓	↓	↓	↓
	EMPHASIS-HF[55]	Eplerenone	2,737	≤ 35	NR	NR	NR	≥ 30	≤ 5	↓	↓	↓	↓
ARNI	PARADIGM-HF[6]	Sacubitril/valsartan	8,442	≤ 40	≥ 100	NR	NR	≥ 30	≤ 5.2	↓	↓	↓	↓
SGLT2 i	DAPA-HF[7]	Dapagliflozin	4,744	≤ 40	≥ 95	NR	NR	≥ 30	NR	↓	↓	↓	↓
	EMPEROR-Reduced[8]	Empagliflozin	3,730	≤ 40	≥ 100	NR	NR	≥ 20	NR	↔	↓	↔	↓
	SOLOIST-WHF[9]	Sotagliflozin	1,222	NL	≥ 100	NR	NR	≥ 30	NR	↔	↓	↔	↓
Additional therapy													
Digoxin	DIG[72]	Digoxin	6,800	≤ 45	NR	NR	NR	NR	NR	↔	NR	↔	↓
Vasodilator	V-HeFT I[76]	Hydralazine/ isosorbide dinitrate	642	< 45	NR	NR	NR	NR	NR	↓	NR	NR	NR
	A-HeFT[78]	Isosorbide/ hydralazine	1,050	≤ 35	NR	NR	NR	NR	NR	↓	NR	NR	↓
Sinus node inhibitor	SHIFT[79]	Ivabradine	6,558	≤ 35	≥ 85	≥ 70	NR	NR	NR	↔	↓	↔	↓
sGC stimulator	VICTORIA[10]	Vericiguat	5,050	≤ 45	≥ 100	NR	NR	≥ 15	NR	↔	↓	↔	↓

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; bpm, beat per minute; Cr, serum creatinine; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HFsrEF, heart failure with severely reduced ejection fraction; HHF, heart failure hospitalization; HR, heart rate; K, potassium; MRA, mineralocorticoid receptor antagonist; NL, no limit; NR, not reported; SBP, systolic blood pressure; sGC, soluble guanylate cyclase; SGLT2 i, sodium-glucose co-transporter 2 inhibitor.

Table 3. Doses and early effects of foundational therapies in randomized controlled trials

Drug name	Trial name	Ref. #	Starting dose	Steps of titration	Target dose	Mean dose achieved in RCTs	Proportion reaching target dose	Mean dose at earliest time of efficacy (% of target dose)	Earliest time of efficacy
Enalapril	SOLVD	34,36	2.5-5 mg BID	2-3	10 mg BID	16.6 mg/day	49%	NR	30 days
Candesartan	CHARM-low LVEF	41,42	4-8 mg QD	2-3	32 mg QD	24 mg/day	60%	8.5 mg QD (26.6%)	28 days
Carvedilol	COPERNICUS	50,54	3.125 mg BID	4	25 mg BID	37 mg/day	65%	6.5 mg BID (26%)	28 days
Eplerenone	EMPHASIS-HF	42,55	25 mg QD	2	50 mg QD	42 mg/day	85%	27.6 mg QD (55.2%)	28 days
Eplerenone	EPHESUS	58,59	25 mg QD	2	50 mg QD	42.6 mg/day	NR	25 mg QD (50%)	30 days
Sacubitril/valsartan	PARADIGM-HF	6,48	49/51 mg BID	2	97/103 BID	182 mg/193 mg/day	NR	NR (Most patients maintained at target dose)	30 days
Dapagliflozin	DAPA-HF	7,69	10 mg QD	1	10 mg QD	9.8 mg/day	98.1%	10 mg QD (100%)	28 days
Empagliflozin	EMPEROR-Reduced	8,70	10 mg QD	1	10 mg QD	NR	NR	10 mg QD (100%)	28 days

BID, twice daily; NR, not reported; QD, once daily; Ref, reference.

effects of starting doses of enalapril is similar to its previously reported long-term effects at the target dose.[36] These data prompt early initiation of ACEI in HFsrEF. Given that enalapril have been safely initiated in-hospital in the Comparison of Sacubitril-Valsartan versus Enalapril on Effect on N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF) trial,[37] ACEI can be initiated before discharge to provide maximal protection, if patients are in the convalescent phase with hemodynamic stability.

The effect of ACEI extending to patients with HFmrEF was shown in the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial.[38] Patients with LVEF 41-49% (i.e. HFmrEF) were enrolled to compare perindopril versus placebo. Perindopril did not reduce the primary endpoint (composite of all-cause death and heart failure hospitalization) (HR: 0.919, 95% CI: 0.700-1.208; p = 0.545), due to lower enrollment and event rates. Moreover, many patients withdrew from perindopril (28%) and placebo (26%) after 1 year and started taking open-label ACEI. Interestingly, there were reductions in hospitalization for heart failure (HR: 0.63, 95% CI: 0.41-0.97; p = 0.033) (Table 4). Functional class (p < 0.030) and 6-minute corridor walk distance (p = 0.011) improved in those assigned to perindopril. Though uncertainty remains about the effects of perindopril on long-term morbidity and mortality in this clinical setting (HFmrEF), improved symptoms and exercise capacity and fewer hospitalizations for heart failure were observed for perindopril in the first year.[38]

4.3.2. ARB

ARBs reduced cardiovascular death and hospitalization for heart failure, but not all-cause death[39,40] (Table 2). They should be used in patients with systolic blood pressure ≥ 90 mmHg.[39] It is reasonable to have the similar lower limit of estimated glomerular filtration rate as ACEI (20 mL/min). Patients who are intolerant to ACEI because of cough or angioedema should be started on or changed to an ARB.

Early efficacy of ARB was shown in a pre-defined sub-analysis of patients with low LVEF in the CHARM Program.[41,42] Treatment with candesartan led to a significant reduction in the composite of all-cause death and heart failure hospitalization within 28 days of randomization (HR: 0.61, 95% CI: 0.43-0.86) when the daily dose was only 8.5 mg daily, 26.6% of the target dose (Table 3).

The effect of ARB extending to patients with HFmrEF was demonstrated by in an analysis of 7,598 patients in the whole CHARM Program[23] (Table 4). Patients with HFmrEF were similar to those with HFsrEF with respect to some characteristics, and intermediate between HFsrEF and HFpEF with respect to others.[23] The incidence of primary endpoint (cardiovascular death and heart failure hospitalization) for candesartan vs. placebo were 14.4 versus 17.5%/y in HFsrEF (HR: 0.82, 95% CI: 0.75-0.91; p < 0.0010), 7.4 vs. 9.7%/y in HFmrEF (HR: 0.76, 95% CI: 0.61-0.96; p = 0.02), and 8.6 vs. 9.1 %/y in HFpEF (HR: 0.95, 95% CI: 0.79-1.14; p = 0.57). For recurrent hospitalization due to heart failure, the incidence rate ratios were 0.68 in HFsrEF (95% CI: 0.58-0.80; p < 0.001), 0.48 in HFmrEF (95% CI: 0.33-0.70; p < 0.001),

Table 4. Evidence of foundational therapies in patients with HFmrEF

Drug class/ drug name	Trial name	Number of patients	Inclusion LVEF (patient number)			Primary endpoints	Effect on primary endpoint by LVEF HR (95% CI) (p value)			P_{int}	Effect on HHF by LVEF HR (95% CI) (p value)			P_{int}
ACEI/ perindopril	PEP-CHF[38]	850	< 40% (0)	41-49% (850)	≥ 50% (0)	All-cause death + HHF	< 40% –	**41-49% HR: 0.69 (0.47-1.01) (p = 0.055)**	≥ 50% –	–	< 40% –	**41-49% HR: 0.63 (0.41-0.97) (p = 0.033)**	≥ 50% –	–
ARB/ candesartan	CHARM-Program[23]	7,598	< 40% (4,323)	41-49% (1,322)	≥ 50% (1,953)	CV death + HHF	< 40% HR: 0.82 (0.75-0.91) (p < 0.001)	**41-49% HR: 0.76 (0.61-0.96) (p = 0.02)**	≥ 50% HR: 0.95 (0.79-1.14) (p = 0.57)	0.27	< 40% HR: 0.68* (0.58-0.80) (p < 0.001)	**41-49% HR: 0.48* (0.33-0.70) (p < 0.001)**	≥ 50% HR: 0.78* (0.59-1.03) (p = 0.08)	0.60
ARNI	PARADIGM/ PARAGON Pooled[24]	13,195	32.5-42.5% (3,143)	42.5-52.5% (1,427)	52.5-62.5% (2,166)	CV death + HHF	**32.5-42.5% HR: 0.81 (0.69-0.94) (p = 0.005)**	**42.5-52.5% HR: 0.89 (0.73-1.10) (p = 0.28)**	52.5-62.5% HR: 0.89 (0.74-1.06) (p = 0.05)	0.05	**32.5-42.5% HR: 0.81 (0.69-0.94) (p = 0.005)**	**42.5-52.5% HR: 0.89 (0.73-1.10) (p = 0.28)**	52.5-62.5% HR: 0.89 (0.74-1.06) (p = 0.05)	0.15
Beta-blocker	11 trials/ Meta-analysis[22]	14,262	–	41-49% (5,750)	≥ 50% (244)	All-cause death or CV death	–	**41-49% HR: 0.59 (0.34-1.03) (p = 0.066)**	≥ 50% HR: 1.79 (0.78-4.10) (p = 0.17)	NR	–	**41-49%[#] HR: 0.48 (0.24-0.97) (p = 0.04)**	≥ 50%[#] HR: 1.77 (0.61-5.14) (p = 0.29)	NR
MRA/ eplerenone	TOPCAT[20]	1,766	45 to < 50% (197)	50 to 55% (289)	55 to 60% (422)	CV death + HHF	**45 to < 50% HR: 0.55 (0.33-0.91)**	50 to 55% HR: 0.83 (0.56-1.25)	55 to 60% HR: 0.85 (0.60-1.21)	0.069	**45 to < 50% HR: 0.60 (0.32-1.10)**	50 to 55% HR: 0.80 (0.65-1.06)	55 to 60% HR: 0.70 (047-1.06)	0.037
SGLT2 inhibitor/ empagliflozin	EMPEROR-Preserved[11]	5,988	< 50% (1,983)	50 to < 60% (2,058)	≥ 56% (1,947)	CV death + HHF	**< 50% HR: 0.71 (0.57-0.88)**	50 to < 60% HR: 0.80 (0.64-0.99)	≥ 56% HR: 0.87 (0.69-1.10)	NR	NR	NR	NR	NR
SGLT2 inhibitor/ empagliflozin	EMPEROR-Reduced/EMPEROR-Preserved pooled[25]	9,718	35-44% (1,272)	45-54% (2,260)	55-64% (2,092)	CV death + HHF	**35-44% HR: 0.82 (0.63-1.05)**	**45-54% HR: 0.74 (0.61-0.91)**	55-64% HR: 0.78 (0.62-0.97)	NR	**35-44% HR: 0.72 (0.52-0.98)**	**45-54% HR: 0.66 (0.50-0.86)**	55-64% HR: 0.70 (0.53-0.92)	0.32
SGLT2 inhibitor/ dapagliflozin	DELIVER[12]	6263	< 49% (2,116)	50 to 59% (2,256)	≥ 60% (1,891)	CV death + WHF	**< 49% HR: 0.87 (0.72-1.04)**	50 to 59% HR: 0.79 (0.65-0.97)	≥ 60% HR: 0.78 (0.62-0.96)	> 0.05	**> 44% and ≤ 51%[†] HR: 0.83 (0.64-1.07)**	> 51% and ≤ 60%[†] HR: 0.66 (0.51-0.84)	≥ 60%[†] HR: 0.88 (0.64-1.22)	> 0.05
SGLT1+2 inhibitor/ sotagliflozin	SOLOIST-WHF[9]	1,222	< 50%	≥ 50%		CV death + total HHF + urgent HF visit	**< 50% HR: 0.72 (0.56-0.94)**	≥ 50% HR: 0.48 (0.27-0.86)						

* Recurrent heart failure hospitalization; [#] Cardiovascular death; [†] Data from Jhund et al.[29] Data shown in bold characters are for HFmrEF.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; CV, cardiovascular; HF, heart failure; HfmrEF, heart failure with mildly reduced ejection fraction; HHF, heart failure hospitalization; HR, hazard ratio; int, interaction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NR, not reported; SGLT2 I, sodium-glucose co-transporter 2 inhibitor; WHF, worsening heart failure (heart failure hospitalization + urgent heart failure visit).

and 0.78 in HFpEF (95% CI: 0.59-1.03; p = 0.08) (Table 4). With EF as a continuous spline variable, candesartan significantly reduced the primary outcome until LVEF well over 50% and recurrent HF hospitalizations until LVEF well over 60%.[23] These findings were confirmed by a recent pooled analysis of individual patient-level data from the CHARM-Program.[21] An ARB may be of benefit beyond the upper limit of LVEF eligibility used in contemporary HFrEF trials (40%) and may extend to HFmrEF (LVEF 41-49%) and even to the lower part of the LVEF range currently categorized as HFpEF (LVEF ≥ 50%).[21]

4.3.3. ARNI

An ARNI is comprised of an ARB and a neprilysin inhibitor. In the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial,[6] sacubitril/valsartan, when compared with enalapril, reduced the primary endpoint (composite of cardiovascular death and heart failure hospitalization) by 20% (HR: 0.80, 95% CI: 0.73-0.87; p < 0.001) (Table 2). Cardiovascular death (HR: 0.80, 95% CI: 0.71-0.89, p < 0.001), heart failure hospitalization (HR: 0.79, 95% CI: 0.71-0.89, p < 0.001), and all-cause death (HR: 0.84, 95% CI: 0.76-0.93, p < 0.001) were all reduced. Based on a putative placebo analysis of the PARADIGM-HF trial, sacubitril/valsartan significantly reduced cardiovascular death by 34% (p < 0.0001) and heart failure hospitalization by 49% (p < 0.0001).[43]

Additional benefits of sacubitril/valsartan included an improvement in symptoms and quality-of-life,[6] a reduction in the incidence of diabetes requiring insulin treatment,[44] and a reduction in the decline in renal function,[45] as well as a reduction in hyperkalemia.[46] We recommend that an ACEI or ARB can be replaced by sacubitril/valsartan in ambulatory patients with HFsrEF, who remain symptomatic despite optimal treatment. Symptomatic hypotension was more common in patients treated with sacubitril/valsartan.[6] Sacubitril/valsartan should be used in patients with systolic blood pressure ≥ 100 mmHg.[6] It is reasonable to have the lower limit of estimated glomerular filtration rate at 20 mL/min.[47]

In the PARADIGM-HF trial,[6] the reduction in heart failure hospitalization with ARNI was evident within the first 30 days (HR: 0.60, 95% CI: 0.38-0.94),[48] suggesting a benefit of early initiation of ARNI (Table 3). This was supported by the PIONEER-HF trial that enrolled in-hospital patients.[37] The time-averaged reduction in NT-proBNP concentration was significantly greater in the sacubitril/valsartan group than in the enalapril group (percent change, -46.7% vs. -25.3%; ratio of change with sacubitril/valsartan vs. enalapril, 0.71; 95% CI: 0.63 to 0.81; p < 0.001).[37] The greater reduction in the NT-proBNP concentration with sacubitril/valsartan was evident as early as week 1 (ratio of change, 0.76; 95% CI: 0.69 to 0.85). Rehospitalization for heart failure was also reduced (HR: 0.56, 95% CI: 0.37 to 0.84). It should be noted that before randomization patients were required to be hemodynamically stable, defined by maintenance of a systolic blood pressure of at least 100 mmHg for the preceding 6 hours, with no increase in the dose of intravenous diuretics and no use of intravenous vasodilators during the preceding 6 hours and no use of intravenous inotropes during the preceding 24 hours.[37]

The effect of ARNI in patients with HFmrEF was demonstrated in a recent pooled analysis from PARADIGM-HF and Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON-HF)-HF trial.[24] A total of 13,195 patients were re-classified into six LVEF categories: ≤ 22.5% (n = 1269), > 22.5% to 32.5% (n = 3987), > 32.5% to 42.5% (n = 3143), > 42.5% to 52.5% (n = 1427), > 52.5% to 62.5% (n = 2166), and > 62.5% (n = 1202). The effect of sacubitril/valsartan on the primary endpoints (cardiovascular death and heart failure hospitalization) was modified by LVEF (treatment-by-continuous LVEF interaction p = 0.02), and benefit appeared to be present for individuals with LVEF primarily below the normal range, including patients with HFmrEF, although the treatment benefit for cardiovascular death diminished at a higher ejection fraction[21,24] (Table 4).

4.4. Beta-blocker

Carvedilol,[49,50] metoprolol succinate,[3] and bisoprolol[51] consistently reduced all-cause death, cardiovascular death, and hospitalization for heart failure (Table 2). Both sudden death and death due to progressive heart failure were reduced. In the SENIORS trial,[52] nebivolol reduced the primary composite endpoints of all-cause death plus hospitalization for heart failure and the secondary composite endpoints of cardiovascular death plus heart failure hospitalization, though all-cause death and cardio-

vascular death were not reduced (Table 2). Beta-blockers should be used in patients with heart rate ≥ 60/min, and systolic blood pressure ≥ 85 mmHg, but renal function and serum potassium level did not impose limitation for their use (Table 2).

The safety and efficacy of early initiation of beta-blocker was demonstrated in the Initiation Management Pre-Discharge: Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) trial.[53] Early initiation of carvedilol in stabilized patients hospitalized for HF improved the use of beta-blocker at 60 days without increasing side effects or length of stay. The early effects of beta-blocker in patients with severe heart failure was shown in a subanalysis of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial that enrolled patients with very high risk, defined by 1 or more of the following: the presence of pulmonary rales, ascites, or edema at randomization; 3 or more hospitalizations for heart failure within the last year; hospitalization at the time of screening or randomization; need for intravenous positive inotropic agent or vasodilator drug within 14 days before randomization; or left ventricular ejection fraction of 15%.[54] Kaplan-Meier curves suggested that the all-cause death separated as early as 14-21 days among all randomized patients (HR: 0.75, 95% CI: 0.41-1.35), especially in very-high risk group (HR: 0.20, 95% CI: 0.06-0.70).[54] It is noteworthy that 21 days of treatment is at a time when patients were generally receiving a dosage of only 6.25 mg of carvedilol twice a day, 26% of the target dose (Table 3).

The efficacy of beta-blocker in patients with HFmrEF was demonstrated in a recent individual patient-level meta-analysis.[22] Among 14,262 patients in sinus rhythm, median LVEF was 27%, including 575 patients with LVEF 40-49% and 244 ≥ 50%. Beta-blockers reduced all-cause and cardiovascular death compared to placebo in sinus rhythm, an effect that was consistent across LVEF strata, except for those in the small subgroup with LVEF ≥ 50%. For LVEF 40-49%, death occurred in 7.2% patients randomized to beta-blockers compared to 12.4% with placebo (aHR: 0.59, 95% CI: 0.34-1.03). Cardiovascular death occurred in 4.5% with beta-blockers and 9.2% with placebo (aHR: 0.48, 95% CI: 0.24-0.97) (Table 4). Over a median of 1.0 year following randomization (n = 4,601), LVEF increased with beta-blockers in all groups in sinus rhythm except those with LVEF ≥ 50%. For patients in atrial fibrillation at baseline (n = 3,050), beta-blockers increased LVEF if baseline LVEF was < 50%, but did not improve prognosis. These data support the efficacy of beta-blockers in patients with HFmrEF.[22]

4.5. MRA

MRAs consistently reduced all-cause death, cardiovascular death, and heart failure hospitalization (Table 2). Both sudden death and death due to progressive heart failure were reduced.[4] In patients with a baseline serum potassium level greater than 5 meq/L, MRA is contraindicated or should be used with caution.[4,55] In regarding to renal function, patients with advanced chronic kidney disease, defined by estimated glomerular filtration rate < 30 mL/min in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial[55] or serum creatinine > 2.5 mg/dL (≈ glomerular filtration rate < 20-26 mL/min) in the Randomized Aldactone Evaluation Study (RALES) trial, were excluded.[4] Given that MRAs provide huge benefits in the reduction in mortality, it is generally accepted that they can be used cautiously in patients with an estimated glimerular filtration rate ≥ 20 mL/min if the dose can be properly reduced and the risk of hyperkalemia and acute kidney injury be carefully monitored.[56]

In a subanalysis of the RALES trial, patients with baseline estimated glomerular rate < 60 mL/min exhibited similar relative risk reductions in all-cause death and the combined endpoint of death plus heart failure hospitalization as those with an estimated glomerular rate ≥ 60 mL/min, but with greater absolute risk reduction (10.3% vs. 6.4%).[57] Moreover, worsening renal function (defined as a 30% reduction in estimated glomerular filtration rate from baseline to 12 weeks post-randomization) was associated with an increased adjusted risk of death in the placebo group (HR: 1.9, 95% CI: 1.3 to 2.6) but not in those randomized to spironolactone (HR: 1.1, 95% CI: 0.79 to 1.5, p for interaction = 0.009). The risk of hyperkalemia and renal failure was higher in the spironolactone arm, but the substantial net clinical benefit remained.[57]

The early benefits of MRA were described in both the EMPHASIS-HF trial[55] and the EPHESUS trial.[58] In the EMPHASIS-HF trial, eplerenone reduced the primary endpoint (composite of cardiovascular death and heart failure hospitalization) within 28 days (HR: 0.51, 95% CI:

0.30-0.87) when the daily dose was only 27.6 mg, 55.2% of the target dose[42,55] (Table 3). In a subanalysis of EPHESUS,[58] eplerenone reduced the risk of all-cause death by 31% (HR: 0.69, 95% CI: 0.54-0.89, p = 0.004) and cardiovascular death by 32% (HR: 0.68, 95% CI: 0.53-0.88, p = 0.003) at 30 days after randomization, when patients were treated with eplerenone 25 mg/day, 50% of the target dose[59] (Table 3). The benefits of predischarge administration of MRA was confirmed by another study from Asia.[60]

The effect of MRA in patients with HFmrEF was demonstrated in a recent sub-analysis of patients from America in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial.[20] Patients were categorized into four groups according to their LVEF: < 50%, 50-55%, 55-60%, and ≥ 60%. The efficacy (HRs and 95% CI) for the primary endpoint (cardiovascular death, aborted cardiac arrest, and heart failure hospitalization) were 0.55 (95% CI: 0.33-0.91), 0.83 (0.56-1.25), 0.85 (0.60-1.21, and 0.89 (0.69-1.15) (p for interaction 0.069); for cardiovascular death (0.46, [0.23-0.94]; 0.76 [0.40-1.45]; 0.97 [0.57-1.64], and 0.73 [0.49-1.10] (p for interaction 0.93); for heart failure hospitalization (0.60 [0.32-1.10]; 0.80 [0.51-1.25]; 0.70 [0.47-1.06]; and 0.85 [0.71-1.26] (p for interaction 0.037); for all-cause death (0.58 [0.34-0.99]; 0.92 [0.56-1.50]; 1.12 [0.75-1.66], and 0.75 [0.55-1.03] (p for interaction 0.54) (Table 4). Therefore, MRA was effective in patients with HFmrEF. These findings were supported by a recent meta-analysis of individual patient-level data from the three MRA trials:[21] RALES,[4] EMPHASIS-HF,[55] and the TOPCAT trials.[61] MRA are benecifial not only in HFsrEF patients (≤ 40%), but in HFmrEF patients (LVEF 41-49%) and even to patients with lower part of LVEF range currently categorized as HFpEF (LVEF 50-59%).[21]

4.6. SGLT2 inhibitor

SGLT2 inhibitors consistently reduced the composite endpoints of cardiovascular death plus heart failure hospitalization (Table 2). Sotagliflozin inhibits both SGLT1 and SGLT2, but the Effect of Sotagliflozin on Cardiovascular Eventsin Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial only enrolled diabetic patients.[9] Interestingly, only dapagliflozin reduced all-cause death and cardiovascular death.[7] Dapagliflozin also reduced the risk of any serious ventricular arrhythmia, cardiac arrest, or sudden death.[62] SGLT2 inhibitors can be safely used in patients with systolic blood pressure ≥ 95 mmHg and an estimated glomerular filtration rate ≥ 20 mL/min. For patients with baseline systolic blood pressure < 110 mmHg, dapagliflozin increased systolic blood pressure with time.[63] SGLT2 inhibitors increase hematocrit,[64] decrease MRA-induced severe hyperkalemia,[65] and prevent new-onset diabetes.[66] Asian patients seem to benefit more from the use SGLT2 inhibitors, compared with Caucasian patients.[67] In a recent Asian-subanalysis of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial,[68] dapagliflozin reduced the risk of the primary endpoint (cardiovascular death plus heart failure hospitalization) to the same extent in patients from Asia (HR: 0.65, 95% CI: 0.49 to 0.87) as elsewhere (HR: 0.77; 95% CI: 0.66 to 0.89; p for interaction = 0.32). The absolute risk reduction, however, was numerically greater in Asians (5.8%/year vs. 3.5%/year) that translated to number-need-to-treat of 18 vs. 29. East-Asian patients (China, Japan, and Taiwan) when compared with South-East Asians and South Asians, seem to benefit the most (HRs: 0.61, 95% CI: 0.43-0.86; 0.69, 95% CI: 0.26-1.85; 0.87, 95% CI: 0.45-1.72, respectively; p for interaction 0.72) with an absolute risk reduction of 8.1%/year and a number-need-to-treat of only 13.[68]

The efficacy of SGLT2 inhibitors appeared within 30 days of initiation[69,70] (Table 3). The safety and efficacy of initiation of SGLT2 before discharge has been shown in the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure (EMPULSE) trial.[71] Patients were randomized in the hospital when they were clinically stable (median time from hospital admission to randomization, 3 days) and were treated for up to 90 days. The primary outcome of the trial was clinical benefit, defined as a hierarchical composite of death from any cause, number of heart failure events and time to first heart failure event, or a 5 point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire (KCCQ) Total Symptom Score at 90 days, as assessed using a win ratio.[71] When compared with placebo, more patients treated with empagliflozin had clinical benefit (stratified win ratio: 1.36; 95% CI: 1.09-1.68; p = 0.0054), meeting the primary endpoint. Clinical benefit was observed for both acute de

novo and decompensated chronic heart failure and was observed regardless of ejection fraction or the presence or absence of diabetes. These findings indicate that initiation of SGLT2 inhibitor in patients hospitalized for acute heart failure was well tolerated and resulted in significant clinical benefit within 90 days after starting treatment.[71]

The information regarding SGLT2 inhibitor in patients with HFmrEF was provided by the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) trial and the Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER) trial.[11,12] SOLOIST-WHF trial also contained patients with HFmrEF.[9] In the EMPEROR-Preserved trial, patients with LVEF > 40%, including HFmrEF, HFpEF, and HFnEF, were enrolled.[11] The primary endpoint (cardiovascular death and heart failure hospitalization) was reduced by empagliflozin (HR: 0.79, 95% CI: 0.69-0.90, p < 0.001), mainly driven by a significant reduction in heart failure hospitalization (0.71, 95% CI: 0.60-0.83).[11] Cardiovascular death was not reduced (HR: 0.91, 95% CI: 0.76-1.09). The HRs and 95% CI for patients with HFmrEF, HFpEF, and HFnEF were 0.71 (0.57-0.88), 0.80 (0.64-0.99), and 0.87 (0.69-1.10), supporting the effectiveness of empagliflozin in patients with HFmrEF. In a pooled analysis of both the EMPEROR-Reduced trial and EMPEROR-Preserved trials, patients were grouped based on LVEF: < 25%, 25-34%, 35-44%, 45-54%, 55-64%, and ≥ 65%.[25] The HRs and 95% CI were 0.73 (0.55-0.96), 0.63 (0.50-0.78), 0.72 (0.52-0.98), 0.66 (0.50-0.86), 0.70 (0.53-0.92), 1.05 (0.70-1.58), respectively. These data re-confirm that empagliflozin was effective in patients with HFmrEF and HFpEF, but the efficacy attenuated in patients with HFnEF.

In the DELIVER trial, patients with LVEF > 40%, including HFmrEF, HFpEF, and HFnEF, were enrolled.[12] The primary endpoint was worsening heart failure (heart failure hospitalization and urgent heart failure visit) and cardiovascular death. Dapagliflozin reduced the primary endpoint by 18% (HR: 0.82, 95% CI: 0.73-0.92, p < 0.001), mainly driven by a significant reduction in worsening heart failure (0.79, 95% CI: 0.69-0.91).[12] Cardiovascular death was not significantly reduced (HR: 0.88, 95% CI: 0.74-1.05). The HRs and 95% CI for patients with HFmrEF, HFpEF, and HFnEF were 0.87 (0.72-1.04), 0.79 (0.65-0.97), and 0.78 (0.62-0.96) (p for interaction > 0.05), supporting the effectiveness of dapagliflozin in patients with HFmrEF, HFpEF, and HFnEF (Table 4). Of note, in the pre-defined pooled analysis of DAPA-HF and the DELIVER trials, the efficacy of dapagliflozin was demonstrated across the full-spectrum of LVEF, without attenuation in patients with HFnEF.[29]

In the SOLOIST-WHF trial, 79% patients have LVEF < 50% that include patients with HFmrEF and HFsrEF.[9] The primary end point was cardiovascular death and total number of heart failure hospitalizations and urgent visits. Though the trial ended early because of loss of funding from the sponsor, sotagliflozin reduced primary endpoint (HR: 0.67, 95% CI: 0.52 to 0.85; p < 0.001), mainly driven by reduction in total number of heart failure hospitalizations and urgent visits (HR: 0.64, 95% CI: 0.49-0.83, p < 0.001). Cardiovascular death was not significantly reduced (HR: 0.84, 95% CI: 0.58-1.22). Patients with LVEF < 50% and ≥ 50% obtained benefits in the reduction of primary endpoint (HR: 0.72, 95% CI: 0.56-0.94; HR: 0.48, 95% CI: 0.27-0.86; respectively) (Table 4). These data suggested that sotagliflozin was effective in patient with HFmrEF and HFpEF, though the trial only enrolled patients with type 2 diabetes.

4.7. Digoxin

In the main trial of Digitalis Investigation Group (DIG) that enrolled patients with sinus rhythm and an LVEF ≤ 45%,[72] digoxin did not reduce all-cause death, nor cardiovascular death, but the combined endpoints of all-cause death plus heart failure hospitalization (HR: 0.85, 95% CI: 0.79-0.91, p < 0.001) and heart failure hospitalization alone (HR: 0.72, 95% CI: 0.66-0.79, p < 0.001) were decreased (Table 2). The details of inclusion and exclusion were not reported, but it is generally accept that digoxin should not be used in patients with end-stage renal disease[73] and heart rate less than 60/min.

In the ancillary DIG trial that enrolled patients with sinus rhythm and an LVEF > 45%,[74] digoxin did not significantly reduced the primary endpoint (death and hospitalization due to heart failure) (HR: 0.82, 95% CI: 0.63-1.07; p = 0.136). In a retrospective analysis of the DIG trial, the effects of digoxin were examined in three groups according to LVEF: < 40% (HFsrEF), 40-49% (HFmrEF), and ≥ 50% (HFpEF).[75] Digoxin reduced primary endpoint in patients with HFsrEF (HR: 0.74, 95% CI: 0.68-0.81),

but not in patients with HFmrEF (HR: 0.83, 95% CI: 0.66-1.05) and HFpEF (HR: 0.88, 95% CI: 0.65-1.19).[75]

4.8. Vasodilator

In the Vasodilator Heart Failure Trial (V-HeFT) I, patients with LVEF < 45% were enrolled.[76] Vasodilator therapy with hydralazine/isosorbide dinitrate reduced all-cause death by 34% (p < 0.028) (Table 2). The effect on cardiovascular death and heart failure hospitalization was not reported. The detailed inclusion criteria regarding blood pressure and renal function were not mentioned either. It is generally agreed that vasodilator therapy should be used in patients with systolic blood pressure ≥ 100 mmHg. In the V-HeFT II trial, patients with LVEF < 45% were randomized to enelaptril or hydralazine/isosorbide dinitrate.[77] Enalapril was more effective than hydralazine/isosorbide dinitrate in reducing all-cause death by 28% (p = 0.016). Interestingly, in the African-American Heart Failure Trial (A-HeFT), hydralazine/isosorbide dinitrate significant reduced all-cause death by 43% (p = 0.01) and heart failure hospitalization by 33% (p = 0.001).[78] The data for vasodilator in patients with HFmrEF was lacking. Vasodilator therapy with hydralazine/isosorbide dinitrate might be considered in patients with HFsrEF who are intolerant to ACEI or ARB.

4.9. Ivabradine

The Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT) trial demonstrated the efficacy of ivabradine, a sinoatrial node modulator that selectively inhibits I_f current, in reducing the composite endpoint of cardiovascular death and heart failure hospitalization (HR: 0.82, 95% CI: 0.75-0.90, p < 0.0001) in patients with LVEF ≤ 35% and sinus rhythm[79] (Table 2). The effects were mainly driven by a reduction in heart failure hospitalization (HR: 0.74, 95% CI: 0.66-0.83; p < 0·0001), whereas the cardiovascular death was not significantly reduced (HR: 0.91, 95% CI: 0.80-1.03). Ivabradine should be used in patients with systolic blood pressure ≥ 85 mmHg and sinus rhythm with a baseline heart rate ≥ 70/min despite the use of beta-blocker at maximally tolerated doses. The effect of ivabradine in patients with HFmrEF is unknown.

4.10. Vericiguat

Vericiguat stimulates soluble guanyl cyclase and increases cyclic guanosine monophosphate (cGMP) production. In the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) trial,[10] vericiguat reduced primary composite endpoint (cardiovascular death or heart failure hospitalization) (HR: 0.90, 95% CI: 0.82-0.98), mainly driven by a reduction in heart failure hospitalization (HR: 0.90, 95% CI: 0.81-1.00). Cardiovascular death was not reduced (HR: 0.93, 95% CI: 0.81-1.06) (Table 2). Intesteringly, the VICTORIA trial in the first large-scale trial that enrolled patients with worsening heart failure (WHF) who had recently been hospitalized within 6 months or had received intravenous diuretic therapy within 3 months. According to its inclusion/exclusion criteria, vericiguat can be used in patients with an estimated glomerular filtration rate ≥ 15 mL/min, but not in patients with systolic blood pressure < 100 mmHg, though the blood pressure change throughout the trial was minimal.[10]

In a pre-defined subgroup analysis of the VICTORIA trial, vericiguat was effective in patients with LVEF < 40% (HR: 0.88, 95% CI: 0.80-0.97),[10] but not in patients with LVEF ≥ 40% (HR: 1.05, 95% CI: 0.81-1.36). Therefore, vericiguat can be used in patients with HFsrEF, but its effect in HFmrEF is not clear.

Consensus statements

- Loop diuretics are the mainstays of diuretic agents in most patients with heart failure, irrespective of LVEF.
- Foundational therapies include ACEI, ARB, beta-blocker, MRA, ARNI, and SGLT2 inhibitor. They reduce cardiovascular death and/or all-cause death, and the risk of hospitalization for heart failure in large-scale clinical trials.
- Additional therapies include digoxin, hydralazine/isosorbide dinitrate, ivabradine, and vericiguat, because the magnitude of the overall treatment effects has been modest, the strength of evidence is not robust, or the benefits are limited to specific subgroups.
- Additional therapy can be added when patients still have symptoms despite of foundational therapy, or in certain conditions when foundational therapy cannot be applied or contraindicated.
- Asian patients were not included in some remote trials, and only recent trials of ARNI, SGLT2 inhibitors, and vericiguat enrolled Asian patients. In general, the efficacy in Asian subgroup did not differ from other races and the main trial.

- Before prescribing heart failure medications, the following parameters should be examined: systolic blood pressure, heart rate, renal function, and serum potassium level.

5. DOSE OF FOUNDATIONAL THERAPY

Clinical practice guidelines recommened using the same target doses defined by randomzied controlled trials.[1,19] Previously, the foundational therapies were started at a low dose and the dose was then increased in steps over several weeks or months to a target dose if each dose increment was tolerated. However, the mean doses that were achieved in trials were lower than the target doses defined by individual trials (Table 3). The achieved doses were approximately 50-70% of the target doses for ACEI/ARB, and 60-70% for beta-blockers. Given that all the foundational therapies at the achieved doses were proven to be effective in reducing mortality and heart failure hospialization, "**maximally tolerated dose**" seems a better term than "**target dose**" when we define the adequacy of doses.

One misconception is that only target doses or maximally tolerated doses can provide efficacy. This is probably not true. As shown in Table 3, many foundational therapies were effective at the doses that were far lower than the target doses. More importantly, the efficacy appeared very early, generally within the first 30 days of initiation (Table 3). For instance, in the CHARM-Low LVEF analysis, candesartan reduced the composite of all-cause death or heart failure hospitalizaiton within 28 days of randomization (HR: 0.61, 95% CI: 0.43-0.86) at a dose of 8.5 mg/day, 26.6% of the target dose.[41,42] Similarly, in the EMPHASIS-HF trial, eplerenone reduced all-cause death and heart failure hospitalization within 28 days of randomization (HR: 0.51, 95% CI: 0.30-0.87) at a dose of 27.6 mg/day, 55.2% of the target dose.[42,55] In the PARADIGM-HF trial,[6] those receiving 50% to < 100% and < 50% of target dose of sacubitril/valsartan obtained similar efficacy (HR: 0.79, 95% CI: 0.67-0.92; HR: 0.79, 95% CI: 0.58-1.07; respectively) compared with those receiving 100% target dose (HR: 0.79, 95% CI: 0.71-0.88).[80] There are two randomzied trials comparing low dose and high dose therapy in HFrEF, the Assessment of Treatment with Lisinopril and Survival (ATLAS) and the Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL) trials.[81,82] The high dose regimen reduced heart failure hospitalization, but did not further reduce mortality, when compared with the low dose regimen.

Consensus statements

- The mean doses that were achieved in trials were lower than the target doses defined by individual trials.
- Because all the foundational therapies at the achieved doses were effective in reducing mortality and heart failure hospialization, "**maximally tolerated dose**" is a better term than "**target dose**" when we define the adequacy of doses.
- The efficacy of foundational therapy appears very early, generally within the first 30 days of initiation.

6. EFFECTS OF FOUNDATIONAL THERAPY ACCORDING TO EVIDENCE-BASED BACKGROUND THERAPIES

When considering combination therapy for HFsrEF, it is important to ensure that the beneficial effect of a new drug are truly additive to the those obtained from other foundational therapies, across different doses and different combinations. Taken SGLT2 inhibitors as examples, consistent benefits have been shown on the primary endpoint of cardiovascular death and heart failure hospitalization irrespective of background use of other foundational therapies at less than 50% or 50% or more of target dose, and in various clinical relevant dual and triple combinations[7,8,83,84] (Table 5). Similar findings have been reported for ARNI in the PARADIGM-HF trial.[85] These data provide a rationale for early combination of foundational therapies, well before the maximally tolerated dose being achieved.

Consensus statement

- Early combination of foundational therapies can be started before the maximally tolerated dose being achieved.

7. RAPID SEQUENCING STRATEGY OF FOUNDATIONAL THERAPIES

Previously, guidelines suggested initiating founda-

tional therapies in patients with HFsrEF in a conventional sequence that follows the chronological order in which trials were conducted, typically requiring ≥ 6 months. We propose "rapid sequencing" strategy to obtain maximal benefits in shortest duration for the management of HFsrEF. This strategy was based on 5 principles: First, ARNI is a replacement for ACEI/ARB.[6] Second, patients should be started on all four foundational therapies within 2-4 weeks because drugs act rapidly to reduce mortality and heart failure hospitalization (Table 3). Third, low starting doses of foundational therapy have substantial therapeutic benefits (Table 3), and achievement of low doses of all four classes of drugs should take precedence over up-titration to target doses.[32] Fourth, the efficacy of each foundational therapy is independent of type and doses of other foundational therapies (Table 5). Fifth, the agents that started earlier could enhance the safety of other agents that were started simultaneously or later in the sequence. For instance, early initiation of SGLT2 inhibitor decreased the risk of MRA-induced hyperkalemia,[65] increased blood pressure favoring the subsequent use of ARNI,[63] and reduced fluid overload that facilitate the addition of a beta-blocker.[54]

A recent modelling study using data from six pivotal

Table 5. Effect of SGLT2 inhibitor on primary endpoints by background therapy

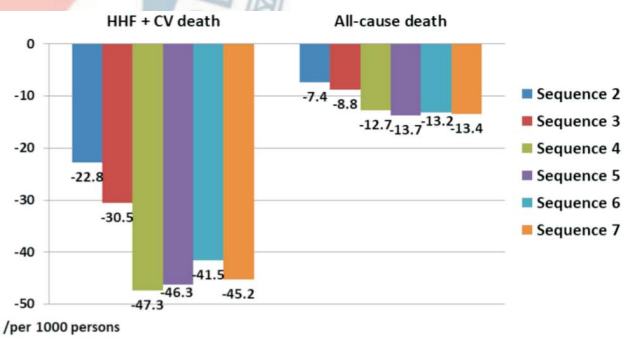
Trial name	DAPA-HF[7,83]		EMPEROR-reduced[8,84]	
Drug name	Dapagliflozin		Empagliflozin	
	HR (95% CI)	p for interaction	HR (95% CI)	p for interaction
Overall effect	0.74 (0.65-0.85)		0.75 (0.65-0.86)	
ARNI		1.00		NR
Yes	0.75 (0.50-1.13)		0.64 (0.45-0.89)	
No	0.74 (0.65-0.86)		0.77 (0.66-0.90)	
ACEI/ARB target dose		0.21		0.18
< 50%	0.78 (0.65-0.94)		0.85 (0.69-1.06)	
≥ 50%	0.64 (0.50-0.82)		0.67 (0.52-0.88)	
Beta-blocker target dose		0.76		0.15
< 50%	0.71 (0.59-0.86)		0.66 (0.54-0.80)	
≥ 50%	0.74 (0.60-0.90)		0.81 (0.66-1.00)	
MRA target dose		0.82		0.96
< 50%	0.71 (0.45-1.12)		0.77 (0.22-2.63)	
≥ 50%	0.74 (0.63-0.88)		0.75 (0.63-0.88)	
ACEI/ARB ≥ 50% target dose + beta-blocker ≥ 50% target dose		0.40		0.96
Yes	0.66 (0.48-0.91)		0.74 (0.54-1.03)	
No	0.77 (0.66-0.89)		0.75 (0.64-0.87)	
ACEI, ARB, or ARNI + beta-blocker (all at any dose)		NR		0.64
Yes	NR		0.68 (0.60-0.77)	
No	NR		0.73 (0.56-0.94)	
ARNI + beta-blocker + MRA (all at any dose)		0.86		0.15
Yes	0.70 (0.41-1.19)		0.55 (0.35-0.86)	
No	0.74 (0.65-0.85)		0.77 (0.67-0.89)	
ACEI/ARB + beta-blocker + MRA (all ≥ 50% target dose)		0.65		0.71
Yes	0.70 (0.48-1.01)		0.80 (0.55-1.17)	
No	0.75 (0.65-0.87)		0.74 (0.64-0.86)	
ACEI, ARB, or ARNI + beta-blocker + MRA (all at any dose)		NR		0.73
Yes	NR		0.68 (0.58-0.79)	
No	NR		0.70 (0.59-0.84)	

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; HF, heart failure; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; NR, not reported; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

trials in HFrEF provided us the rationale for the strategy to accelerate foundational therapies.[86] The investigators compared (i) more rapid up-titration of therapies used in the conventional order (based on the chronology of the trials), and (ii) accelerated up-titration and using treatments in different orders than the conventional ones. The best sequence for reducing the composite of heart failure hospitalization and cardiovascular death was the accelerated sequence of SGLT2 inhibitor/MRA/ARNI/beta-blocker within 12 weeks that could reduced 47 events per 1000/year than the conventional sequence of ACEI (ARB)/beta-blocker/ARNI/SGLT2 inhibitor in 24 weeks (Figure 3A and 3B).[86] The investigators further studied the possibility of starting two drugs simultaneously, followed by the remaining two drugs (Figure 3C and 3D). Compared with sequence 3 (ARNI/BB/MRA/SGLT2 inhibitor in 12 weeks) in Figure 3A, the greatest incremental reduction in the composite of heart failure hospitalization and cardiovascular death was with the sequence starting with the combination of SGLT2 inhibitor plus MRA, followed by an ARNI and then beta-blocker (the sequence of SGLT2 inhibitor plus MRA as the same initial, followed by a beta-blocker, and then an ARNI, was almost as effective) (Figure 3C and 3D).[86] More recently, the investigators of the Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF) trial adopted a more aggressive strategy in patients with heart failure irrespective of LVEF.[87] Patients allocated to the high-intensity care group received 3 foundational therapy (beta-blocker, ACEI/ARB/ARNI, MRA) up to at least half the optimal doses before discharge. These medications were up-titrated to 100% of the recommended doses within 2 weeks of discharge. The primary endpoint (180-day heart failure readmission or all-cause death) was reduced by 34% (HR: 0.66, 95% CI: 0.50-0.86, p = 0.0021) in the high-intensity group compared to the usual care group.[87] We recommend rapid sequencing, instead of conventional sequencing strategy, for patients with HFsrEF (Figure 4).

Sequence	Medication order	Duration of titration (weeks)
1	RASi/BB/MRA/ARNI/SGLT2i	24
2	RASi/BB/MRA/ARNI/SGLT2i (accelerated)	16
3	ARNI/BB/MRA/SGLT2i	12
4	SGLT2i/MRA/ARNI/BB	12
5	SGLT2i/MRA/BB/ARNI	12
6	SGLT2i/BB/MRA/ARNI	12
7	MRA/SGLT2i/BB/ARNI	12

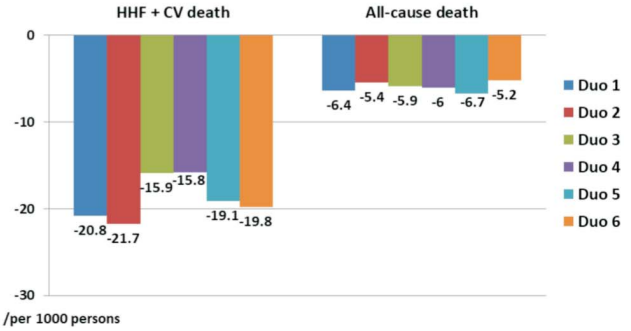
A



B

Sequence	Medication order	Duration of titration (weeks)
Duo 1	SGLT2i + MRA/BB/ARNI	11
Duo 2	SGLT2i + MRA/ARNI/BB	11
Duo 3	SGLT2i + BB/MRA/ARNI	11
Duo 4	BB + ARNI/SGLT2i/MRA	8
Duo 5	BB + MRA/SGLT2i/ARNI	10
Duo 6	MRA + ARNI/SGLT2i/BB	10

C



D

Figure 3. *Comparison of different rapid sequencing strategies of foundational therapies. (A) Seven different sequencing strategies. (B) The best sequence for reducing the composite of heart failure hospitalization and cardiovascular death was the accelerated sequence of SGLT2i/MRA/ARNI/beta-blocker within 12 weeks. (C) Six different sequencing strategies starting with combination therapy. (D) The best sequencing for reducing the composite endpoints was the sequence starting with the combination of SGLT2i plus MRA, followed by an ARNI and then beta-blocker. * ARNI can be prescribed when systolic blood pressure ≥ 100 mmHg. ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; CV, cardiovascular; HHF, heart failure hospitalization; MRA, mineralcorticoidreceptor antagonist; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose co-transporter 2 inhibitor.*

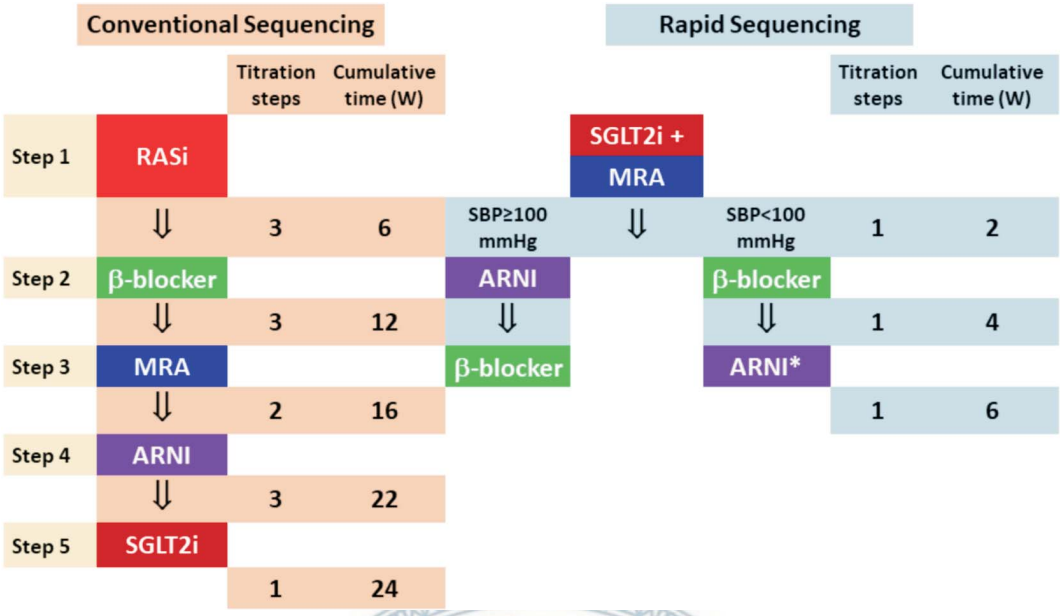


Figure 4. *Conventional sequencing and rapid sequencing strategies for HFsrEF. With the rapid sequencing strategy, all 4 classes of foundational therapies can be provided in 4 weeks. SBP, systolic blood pressure; W, week; other abbreviations as in Figure 3.*

Consensus statements

- We propose "rapid sequencing" strategy, instead of conventional sequencing strategy, to obtain maximal benefits in shortest duration for the management of HFsrEF.
- Patients should be started on all four foundational therapies within 2-4 weeks.
- ACEI/ARB should be replaced by ARNI to achieve better efficacy.
- We suggest starting with combination of SGLT2 inhibitor and MRA, followed by an ARNI and then beta-blocker (or beta-blocker first, followed by ARNI depending on systolic blood pressure), to achieve maximal benefits.
- The most recent data suggested that all the foundational therapies with half doses could be applied before discharge and were increased to full doses within 2 weeks after discharge.

8. IN-HOSPITAL INITIATION

A quarter of patients hospitalized for worsening HFrEF are either rehospitalized or dead within 30 days of discharge.[88] On the other hand, hospitalization for heart failure provides a key opportunity to improve utilization of foundational therapy. Mounting evidence supports hospitalized and ambulatory patients with HFrEF as a common pathophysiology on a continuum,[89] and deferring in-hospital initiation of foundational therapies exposes patients to excess risk of early post-discharge deterioration and death,[90] and the possibility of never having the medication prescribed.[91] Table 6 shows recent trials evaluating in-hospital initiation of foundational therapies for patients with HFrEF. In general, in-hospital initiation of foundational therapies was associated with better primary outcome and/or secondary outcome without an increase in adverse events. The data supporting SGLT2 inhibitors for in-hospital initiation are most robust. The safety data in the hospitalized patients with COVID-19 in the recent DARE-19 (Dapagliflozin in patients with cardiometabolic risk factors hospitalized with COVID-19) trial supported the safety of in-hospital initiation of SGLT2 inhibitor, though patient populations were different.[92] Intiation of foundational therapies requires relative stability in hospitalized patients. Supplemental Table 1 shows the timing of in-hospital initiation and definitions of hemodynamically stable conditions in different trials. We propose that patients should fulfill all the following four conditions to be qualified for in-hospital initiation of SGLT2 inhibitor or ARNI: 1) systolic blood pressure ≥ 90 mmHg, 2) intra-

Table 6. Recent trials evaluating in-hospital initiation of foundational therapies in HFrEF

Drug class	Trial name	Number of patients	Design	Primary endpoint	Results (95% CI)	Secondary or tertiary or exploratory endpoints	Results (95% CI)
β-blocker	IMPACT-HF[53]	363	Pre-discharge vs. post-discharge	Persistence of medication at 60 days	91.2% vs. 73.4% p < 0.0001	Composite of death, HHF, and urgent HF visit	45.4% vs. 46.1% (-0.09-0.11)
ARNI	PIONEER-HF[37]	884	ARNI vs. enalapril	Change of NT-proBNP at 4, 8 weeks	-46.7% vs. 25.3% HR: 0.71 (0.63-0.81)	Composite of death, HHF, LVAD, list on heart transplantation	9.3% vs. 16.8% HR: 0.54 (0.37-0.79)
SGLT2i	EMPA-RESPONSE-AHF[108]	80	Empagliflozin vs. placebo	1. Change in VAS score 2. Diuretic response 3. Change in NT-proBNP 4. Length of stay	1. VAS: 1264 vs. 1650 2. -0.35 vs. -0.12 kg 3. -46% vs. -42% 4. 8 vs. 8 days (All p > 0.05)	In-hospital worsening HF, HHF and death at 60 days	10% vs. 33% (p = 0.014)
	SOLOIST-WHF[9]	596 (1,222*)	Sotagliflozin vs. placebo	Total HHF and urgent HF visit, and CV death	52.1% vs. 76.6 %/y HR: 0.71 (0.51-0.99)	Total HHF and urgent HF visit	40.4% vs. 63.9% HR: 0.64 (0.49-0.83)
	EMPULSE[71]	530	Empagliflozin vs. placebo	Win ratio of the composite (death, HHF, time to HF event, KCCQ-TSS ≥ 5 points) at day 90	53.9% vs. 39.7% Win ratio 1.36 (1.09-1.68) p = 0.0054	KCCQ-TSS change from baseline to day 90	36.19 vs. 31.73 Difference = 4.45 (0.32-8.59)
GDMT	STRONG-HF[87]	1,078	High-intensity care vs. usual care	180-day HF readmission and all-cause death	15.2% vs. 23.3% HR: 0.66 (0.50-0.86) p = 0.0021	1. All-cause death 2. 90-day HF readmission and all-cause death	1. HR: 0.84 (0.56-1.26) 2. 0.73 (0.53-1.02)

* Total patient number in the SOLOIST-WHF trial.

ARNI, angiotensin receptor neprilysin inhibitor; CI, confidence interval; CV, cardiovascular; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HHF, heart failure hospitalization; HR, hazard ratio; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire-Total Symptom Score; LVAD, left ventricular assisted device; NT-proBNP, N-terminal pro B type natriuretic peptide; SGLT2i, sodium-glucose co-transporter 2 inhibitor; VAS, Visual Analogue Scale.

venous diuretic being stopped or unchanged in the recent 6 hours, 3) intravenous vasodilator being discontinued ≥ 6 hours, and 4) intravenous inotrope being stopped for more than 24 hours.

Consensus statements

- Deferring in-hospital initiation of foundational therapies exposes patients to excess risk of early post-discharge deterioration and death, and the possibility of never having the medication prescribed.
- In-hospital initiation of foundational therapies was associated with better primary outcome and/or secondary outcome without an increase in adverse events.
- Intiation of foundational therapies requires relative stability in hospitalized patients.
- Clinical stability for in-hospital initiation of SGLT2 inhibitor or ARNI includes all the followings: 1) systolic blood pressure ≥ 90 mmHg, 2) intravenous diuretic being stopped or unchanged in the recent 6 hours, 3) intravenous vasodilator being discontinued ≥ 6 hours, and 4) intravenous inotrope being stopped for more than 24 hours.

9. TREATMENT ALGORITHM FOR HFrEF

Efficacy of foundational therapies across the full spectrum of LVEF was shown in the Figure 5. Pharmacological treatment of HFsrEF starts with in-hospital initiation with 2-drug combination followed by the third drug in 2 weeks. The fourth drug is applied after another 2 weeks and the four foundational therapies can therefore be put together in 4 weeks. For patients with HFsrEF, vericiguat, ivabradine, and digoxin can be added upon the foundational therapies under different conditions, or when foundational therapies are contraindicated (Figure 5).

10. TREATMENT OF HFpEF

All foundational therapies for HFrEF, except ACEI[38] and beta-blocker,[22] have some evidence to support their efficacy in reducing heart failure endpoint in patients with HFpEF (Table 3, Figure 5). The efficacy of MRA remained persistent, though with less effect, in the lower range of LVEF of HFpEF (up to 55%).[20] ARNI decreased heart failure endpoints in the range of HFpEF until LVEF around 57%.[24,93] Data for SGLT2 inhibitors are the most robust with their efficacy in the spectrum of LVEF from 25% to 65%,[25] even to LVEF of 70%.[29] A recent individual patient-level meta-analysis also demonstrated efficacy of cardesartan, MRA, and ARNI extending to the lower part of the LVEF range of HFpEF.[21]

In the recent DELIVER trial, starting dapagliflozin during or shortly after heart failure hospitalization in patients with HFmrEF or HFpEF appears safe and effective.[94] Time to first statistical significance for the primary end point was 13 days after randomization (HR: 0.45; 95% CI: 0.20-0.99; p = 0.046).[95] These data suggested that foundational therapies should be initiated very early, best before discharged for patients with HFpEF, similar to what we have observed for patients with HFrEF.

The benefit of combination therapy for HFpEF was recently reported, based on individual patient-level analysis from MRA, ARNI, and SGLT2 inhibitor.[96] Switching to ARNI from ACEI/ARB, adding an MRA, and empagliflozin reduced cardiovascular death and heart failure hospitalization in the subgroups with LVEF 45% to 54% (HR: 0.49, 95% CI: 0.32-0.74) and LVEF 55% to 64% (HR: 0.54, 95% CI: 0.37-0.80) but not in those with LVEF ≥ 65% (HR: 1.17, 95% CI: 0.65-2.10).[96]

In-hospital initiation of combination therapy for HFpEF was recently reported in the STRONG-HF trial that contained 15% patients with HFpEF.[87] The efficacy in the high-intensity care group was consistent in patients with LVEF ≥ 50% vs. those < 50%. Therefore, we recommend rapid sequencing, instead of conventional sequencing strategy, for HFpEF. Figure 6 shows the treatment algorithm for HFpEF.

Consensus statements

- All foundational therapies for HFrEF, except ACEI and beta-blocker, have evidence in reducing heart failure endpoint in patients with HFpEF.
- SGLT2 inhibitors have the strongest evidence in patients with HFpEF, followed by ARNI, whereas MRA and ARB are only effective in the lower end of LVEF in patients with HFpEF.
- We recommend rapid sequencing strategy for patients with HFpEF, starting with SGLT2 inhibitor and combining it with ARNI or MRA depending on systolic blood pressure.

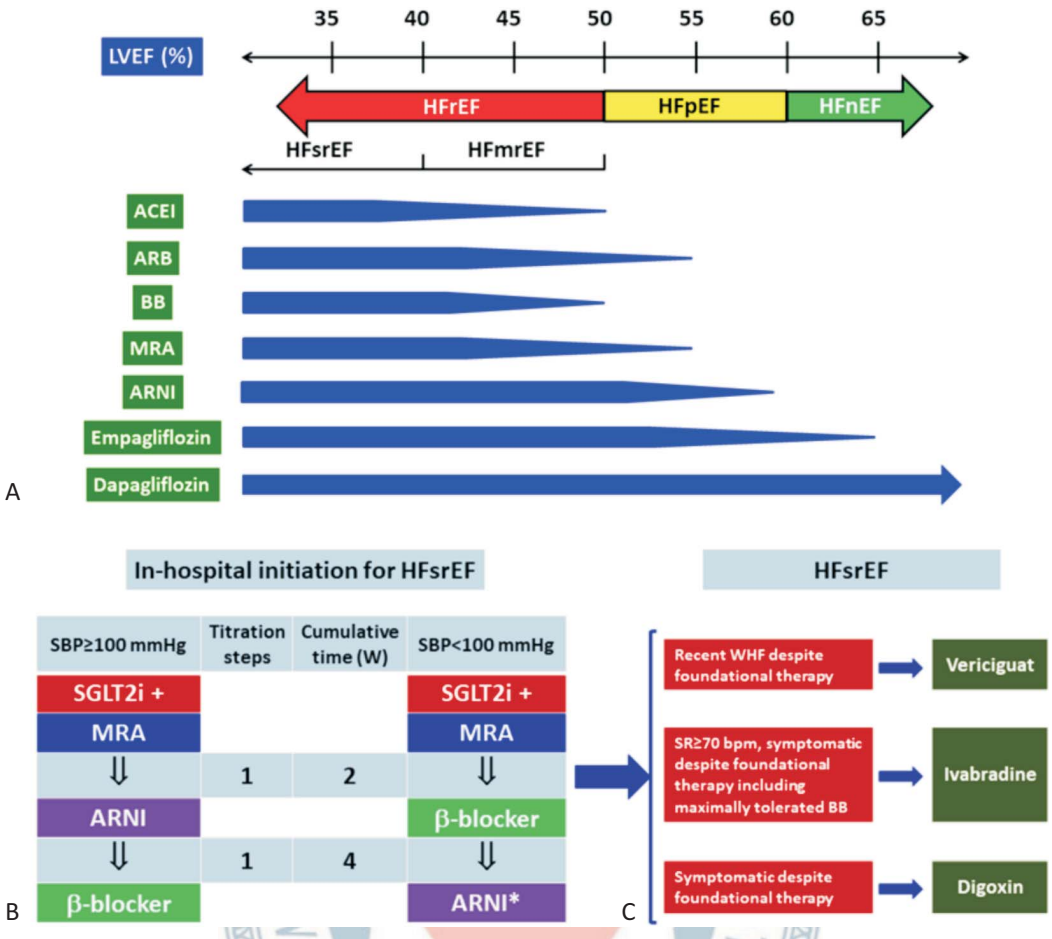


Figure 5. *Treatment algorithm for HFrEF. (A) Efficacy of foundational therapy in full spectrum of LVEF. The tapering of the horizontal blue bar suggests decreasing in efficacy in reducing heart failure endpoint. (B) Strategy for in-hospital initiation of foundational therapies for HFsrEF. (C) Role of additional therapy for HFsrEF. Abbreviations as in Figure 2 and 3.*

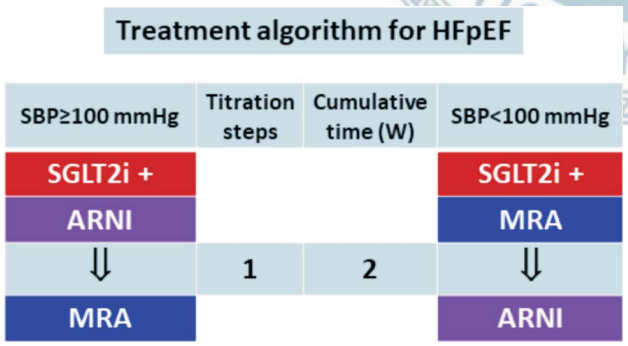


Figure 6. *Treatment algorithm for HFpEF. We recommend in-hospital initiation with combination therapy. Abbreviations similar to those in Figure 3 and Figure 4.*

11. TREATMENT OF HFnEF

The only class of drug that is effective in patients with HFnEF is SGLT2 inhibitors. Empagliflozin's effect can extend to LVEF of 65%,[25] whereas dapagliflozin can extend its efficacy to LVEF of 70% or above.[29]

Consensus statements

- The only class of drug that is effective in patients with HFnEF is SGLT2 inhibitor.
- In contrast to empagliflozin, the efficacy of dapagliflozin did not attenuate in the range of high LVEF up to 70% or above.

12. WORSENING HEART FAILURE

WHF is traditionally defined by progressive signs and symptoms of heart failure in patients with chronic heart failure, presented with either an unplanned hospitalization or an urgent visit resulting in inravenous di-

uretic management in the emergency or outpatient setting, despite previously stable therapy[97] (Figure 7). After each episode of WHF, the cardiac function does not completely recover to the level before WHF, and the interval between each episode of WHF becomes shorter, resulting in more frequent heart failure hospitalization or urgent heart failure visit[97,98] (Figure 7). WHF should be differentiated from the following three conditions: 1) Poor adherence to foundational theapy; 2) Acute heart failure due to other secondary causes; 3) De novo heart failure.[97]

WHF is not uncommon in patients with HFrEF, affecting 1/6 in the real world setting and 1/8 in clinical trial in a follow-up period of 18 months.[99,100] The prognosis of patients with WHF is poor. In a recent registry, patients with WHF had an increased risk of both death (22.5% in 2 years) and heart failure readmission (56% in 30 days).[99] The number of heart failure hospitalization is also a strong predictor of mortality in patients with heart failure.[101] Based on a health care database, median survival after the first, second, third, and fourth hospitalization was 2.4, 1.4, 1.0, and 0.6 years.[101] On the other hand, WHF provides a great opportunity to modify or escalate diuretics and foundational therapy to reduce further deterioration of cardiac function. Interesingly, only a few trials put WHF as a component of the primary endpoint (Supplemental Table 2).

WHF is increasing in numbers in the recent decade. Based on the electronic health recorda from a large, integrated health care system in the US, the annual incidence (events per 100 person-years) of WHF increased from 25.2 in 2010 to 33.0 in 2019, primarily caused by increases in outpatient encounters (from 7 to 10) and ED visits/observation stays (from 4 to 7).[102] Altogether, 50.0% of WHF was due to heart failure hospitalization, 22.5% from emergency department visit, and 27.6% from outpatient encounter. In a sub-analysis from the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy Post Approval Registry (MADIT-CRT) trial, patients with WHF who received intravenous diuretic therapy during urgent outpatient clinic visits had similar all-cause death to patients who were hospitalized (15.9 vs. 18.5 per 100 patient-years).[103] Similar results were observed in the PARADIGM-HF trial.[104] Moreover, in the sub-analyses of PARADIGM-HF and DAPA-HF trials patients with WHF who

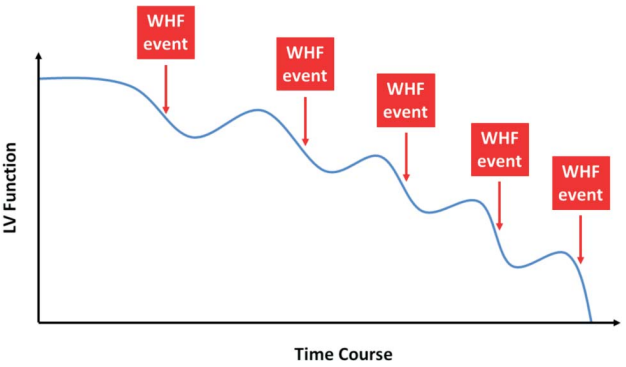


Figure 7. *Clinical course of worsening heart failure. After each episode of worsening heart failure (WHF), the left ventricular function does not completely recover to the level before WHF, and the interval between each episode of WHF becomes shorter, resulting in more frequent heart failure hospitalization or urgent heart failure visit. LV, left ventricle.*

received only outpatient drug intensification not limiting to intravenous diuretic also experienced a significant increase in all-cause death compared to those without WHF (PARADIGM-HF: aHR: 5.2, 95% CI: 4.2-6.3; DAPA-HF: aHR: 3.14, 95% CI: 2.40-4.11).[100,104] Therefore, the definition of WHF might need to be modifed to include patients who receive intensification of any foundational therapy, not limiting to intravenous diuretic, in outpatient clinic. These patients should be closely monitored and foundational therapy and diuretics should be escalated.

WHF is generally preceded by gradual progressive "subclinical worsening", and a subclinical high-risk state that follows an apparent clinical recovery and discharge[97] (Figure 7). Early detection of the subclinical worsening might be useful to reduce the future risk of WHF. On the other hand, this silent worsening can be unrecognized as patients might limit their daily activity and mask heart failure symptoms. More recently, severel studies have suggested that patient-reported health status such as KCCQ score might have more prognostic value than physician-assessed health status changes in New York Heart Association (NYHA) class.[105,106] Regular check of KCCQ score may be useful to detect the subclinical worsening. Moreover, biomarker levels could disclose ongoing cardiac structural and funcitonal deterioration, such as NT-proBNP levels that elevated weeks to months before clinical worsening.[107]

Consensus statements

- WHF is defined by progressive signs and symptoms of

heart failure in patients with chronic heart failure, presented with either an unplanned hospitalization, or an urgent visit requiring intravenous diuretic management in the emergency, or outpatient visit with modification of therapy, not limiting to diuretic, despite previously stable therapy.

- WHF should be differentiated from the following three conditions: 1) Poor adherence to foundational theapy; 2) Acute heart failure due to other secondary causes; 3) De novo heart failure.
- After each episode of WHF, the cardiac function does not completely recover to the level before WHF, and the interval between each episode of WHF becomes shorter, resulting in more frequent heart failure hospitalization or urgent heart failure visit.
- WHF is not uncommon in patients with HFrEF, affecting 1/8 to 1/6 patients in 18 months.
- Patients with WHF have a poor prognosis, with a 2-year mortality rate of more than 20% and a readmission rate above 50% in 30 days.
- WHF, however, also provides a great opportunity for health care providers to modify or escalate diuretics and foundational therapy to reduce further deterioration of cardiac function.
- WHF is generally preceded by gradual progressive "subclinical worsening". Early detection of the subclinical worsening with subsequent initiation or modification of medications is important.
- Patient-reported health status such as KCCQ score is more important than physician-assessed health status in NYHA class for the early detection of WHF.
- Biomarker levels, such as NT-proBNP, elevate weeks to months before clinical events, and may be useful for the early detection of WHF.

13. FUTURE PERSPECTIVES

Though foundational therapies significantly improve outcomes in patients with heart failure, the residual risk of cardiovascular death and heart failure hospitalization is still high. Several neuromormonal modulators and novel drugs with new mechanisms are now being tested in clinical trials. Table 7 shows ongoing phase 2 and 3 drug trials for patients with HFrEF and HFpEF.

DECLARATION OF CONFLICT OF INTEREST

Dr. C.-E. Chiang has received honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Menarini, MSD, Novartis, Pfizer, and Sanofi. Dr. C.-L. Hung has received honorarium from Astrazeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Pfizer, and Sanofi. Dr. Y.-W. Wu has received honorarium from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, MSD, Novartis, Pfizer, Sanofi, and Takeda. Dr. T.-H. Lin has received honorarium from Astrazeneca, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, MSD, Novartis, Pfizer, Sanofi, Bayer, Viatris, Menariri, Tanabe, and Takeda. Dr. K.-C. Ueng has received honorarium from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Merck Sharp and Dohme, Novartis, Pfizer, and Sanofi. Dr. S.-H. Sung has received honorarium from Astrazeneca, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Novartis, Pfizer, Sanofi, Abbott, and Edward. Dr. C.-K. Wu has received honorarium from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Novartis, Pfizer, Sanofi, and Abbott. Dr. T.-H. Chao has received honorarium from Bayer, AstraZeneca, Eli Lilly, Boehringer Ingelheim, Daiichi-Sankyo, Tanabe Taiwan, and Novartis. Dr. Y.-H. Lin has received honorarium from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Novartis, Pfizer, and Sanofi. Dr. M. YC Chen has received honorarium from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, and Pfizer. Dr. P.-L. Lin has received honorarium from AstraZeneca, Abbott, Boehringer Ingelheim, Bayer, Daiichi-Sankyo, Eli Lilly, Novartis, Novo Nordisk, Pfizer, and Sanofi. Dr. T.-F. Chao has received speaker honorarium from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Novartis, Pfizer, and Sanofi. Dr. H.-M. Cheng has received honorarium from AstraZeneca, Pfizer, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Novartis, SERVIER, Sanofi, Takeda, and Eli Lilly. Dr. M.-E. Liu has received honorarium from Abbott, AstraZeneca, Bayer, Biotronik, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Medtronic, MSD, Novartis, Pfizer, and Sanofi. Dr. H.-I. Yeh has received honorarium from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, MSD, Novartis, Novo Nordisk, Pfizer, and Sanofi. Dr. Y.-H. Li has received honorarium from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Novartis, Pfizer, and Sanofi. Dr. I.-C.

Table 7. Ongoing drug trials in chronic heart failure/acute myocardial infarction

Class of drug	Trial name (NCT#)	Drug name	Phase	Patient number	Comparison	Primary endpoint	Estimated completion date
SGLT2 i	A Study to Test Whether Empagliflozin Can Lower the Risk of Heart Failure and Death in People Who Had a Heart Attack (EMPACT-MI) (NCT04509674).	Empagliflozin	3	6500	vs. placebo	All-cause death + HHF	March 31, 2023
	Dapagliflozin Effects on Cardiovascular Events in Patients With an Acute Heart Attack (DAPA-MI) (NCT04564742).	Dapagliflozin	3	6400	vs. placebo	CV death + HHH	September 22, 2023
	Effect of Ertugliflozin on Cardiac Function in Diabetes (ERTU-GLS) (NCT03717194)	Ertugliflozin	3	120	vs. placebo	Change of global longitudinal strain after 24 weeks' treatment	December 31, 2022
	Ertugliflozin in Chronic Heart Failure (NCT04438213).	Ertugliflozin	2	90	Ertugliflozin, metolazone, or a placebo	Change in urine sodium concentration and total body water from baseline to day 7 to 6 weeks	July 2023
GLP1 RA	Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity (STEP-HFpEF) (NCT04788511).	Semaglutide	3	516	vs. placebo	Changes in KCCQ clinical summary score and body weight	April 25, 2023
	Research Study to Look at How Well Semaglutide Works in People Living With Heart Failure, Obesity and Type 2 Diabetes (STEP HFpEF DM) (NCT04916470).	Semaglutide	3	610	vs. placebo	Changes in KCCQ clinical summary score and body weight	August 8, 2023
GLP1 RA/GIP	A Study of Tirzepatide (LY3298176) in Participants With Heart Failure With Preserved Ejection Fraction and Obesity (SUMMIT) (NCT04847557).	Tirzepatide	3	700	vs. placebo	Composite of all-cause death, heart failure events, 6MWD and KCCQ Clinical Summary Score	November 22, 2023
ARNI	Changes in NT-proBNP, Safety, and Tolerability in HFpEF Patients With a WHF Event (HFpEF Decompensation) Who Have Been Stabilized and Initiated at the Time of or Within 30 Days Post-decompensation (PARAGLIDE-HF) (NCT03988634).	Sacubitril/ valsartan	3	450	Sacubitril/ valsartan vs. valsartan	Proportional change in NT-proBNP from baseline to the average of weeks 4 and 8	October 31, 2022
MRA	Study to Evaluate the Efficacy and Safety of Finerenone on Morbidity & Mortality in Participants With Heart Failure and Left Ventricular Ejection Fraction Greater or Equal to 40% (FINEARTS-HF) (NCT04435626).	Finerenone	3	5500	vs. placebo	CV death + HHF	May 2, 2024
	Efficacy, Safety and Tolerability of AZD9977 and Dapagliflozin in Participants With Heart Failure and Chronic Kidney Disease (MIRACLE) (NCT04595370).	AZD9977	2	500	AZD9977 + dapagliflozin vs. dapagliflozin	Percent change from baseline in UACR at 12 weeks	June 26, 2023

Table 7. Continued

Class of drug	Trial name (NCT#)	Drug name	Phase	Patient number	Comparison	Primary endpoint	Estimated completion date
sGC activator	Vericiguat in Participants With Chronic Heart Failure With Reduced Ejection Fraction (HFrEF) (VICTOR) (NCT05093933).	Vericiguat	3	6000	vs. placebo	CV death + HHF	June 15, 2025
Myeloperoxidase (MPO) inhibitor	Study to Evaluate the Efficacy and Safety of AZD4831 in Participants With Heart Failure With Left Ventricular Ejection Fraction > 40% (ENDEAVOR) (NCT04986202).	AZD4831	2b and 3	1485	vs. placebo	1. KCCQ-Total Symptom Score change from baseline at 16 and 24 weeks 2. 6MWD change from baseline at 16 and 24 weeks	November 13, 2024
Others	A Study of Mavacamten in Participants With HFpEF and Elevation of NT-proBNP With or Without Elevation of cTnT (EMBARK-HFpEF) (NCT04766892).	Mavacamten	2	35	Single arm	NT-proBNP and cTnT levels at 26 weeks	April 30, 2023
	A Study of Ponsegromab in People With Heart Failure (GARDEN TIMI 74) (NCT05492500).	Ponsegromab (growth differentiation factor 15)	2	416	vs. placebo	Change from baseline in KCCQ 23 Clinical Summary Score	September 13, 2024
	Effectiveness of CRD-740 in Heart Failure (CARDINAL-HF) (NCT05409183).	CRD-740 (a PDE9 inhibitor)	2	660	vs. placebo	Part A: The change in plasma cGMP at Week 4 Part B: The change in NT-proBNP at Week 12	January 2024
	REGN5381 in Adult Heart Failure Patients With Elevated Pulmonary Capillary Wedge Pressure and Reduced Left Ventricular Ejection Fraction.	REGN5381 (Natriuretic peptide receptor 1 agonist)	2	80	vs. placebo	Incidence and severity of treatment-emergent adverse events (TEAEs)	November 22, 2023
	Study to Assess Efficacy and Safety of CDR132L in Patients With Reduced Left Ventricular Ejection Fraction After Myocardial Infarction (HF-REVERT) (NCT05350969).	CDR132L (Cardiac miR-132 inhibitor)	2	280	vs. placebo	Percent change in Left Ventricular End-Systolic Volume (LVESVI) at Month 6	November 30, 2024
	Exploratory Ph 2A, Double-Blind, Placebo-Controlled Dose Escalation Study of Safety, Tolerability, PD, & PK of HU6 for Subjects With Obese HFpEF (NCT05284617).	HU6 (Controlled Metabolic Accelerator)	2	62	vs. placebo	Calculating the PK parameter Cmax	October 30, 2023
	A Study to Assess the Hemodynamic Effects, Safety, Tolerability, and Pharmacokinetics of Intravenous APD418 in Adult Participants With Heart Failure With Reduced Ejection Fraction.	APD418 (beta$_3$-Adrenergic Receptor Antagonist)	2	80	vs. placebo	Change from baseline in cardiac index measured by right heart catheterization	March 2023

Table 7. Continued

Class of drug	Trial name (NCT#)	Drug name	Phase	Patient number	Comparison	Primary endpoint	Estimated completion date
Others	A Study to Assess the Safety, Tolerability and Efficacy of IONIS-AGT-LRx in Participants With Chronic Heart Failure With Reduced Ejection Fraction (ASTRAAS-HF).	IONIS-AGT-LRx (ASO directed to hepatocyte-derived angiotensinogen)	2	72	vs. placebo	Percent change in plasma AGT concentration from baseline to study day 85	January 2023
	OPtimizing Aldosterone Receptor Antagonist Therapy by Sodium Zirconium Cyclosilicate in Heart Failure (OPRA-HF) (NCT04789239).	Sodium zirconium cyclosilicate	2	230	vs. placebo	Optimization of MRA usage by Sodium Zirconium Cyclosilicate in HFrEF	June 30, 2024
	Modulation of SERCA2a of Intra-myocytic Calcium Trafficking in Heart Failure With Reduced Ejection Fraction (MUSIC-HFrEF1) (NCT04703842).	SRD-001	2	56	vs. placebo	Change of NYHA, KCCQ, 6MWT, LV function, HF-related events at month 6 and month 12	December 2028
	A Phase IIa Clinical Trial on TSG-01 in the Treatment of Chronic Heart Failure in Patients With Coronary Heart Disease.	TSG-01	2	90	vs. placebo	NYHA and 6MWT at week 12	May 7, 2022
	Evaluate the Effect of Injectable Neucardin on the Cardiac Function of Subjects With Chronic Systolic Heart Failure (NCT04468529).	Neucardin	3	140	vs. placebo	Left Ventricular End-Systolic Volume Index (LVESVI) change from baseline on day 30	May 20, 2022
	Safety and Efficacy of AT-001 in Patients With Diabetic Cardiomyopathy (NCT04083339).	AT-001 (Aldose Reductase Inhibitor)	3	675	vs. placebo	Peak VO_2 during cardiopulmonary exercise test at month 15	December 2025
	Study to Evaluate Effects of INL1 in Patients With Heart Failure and Reduced Ejection Fraction (TRACER-HF) (NCT03875183).	INL1	2	200	vs. placebo	Change in NT-proBNP at week 12	January 2023
	Survival Study of the Recombinant Human Neuregulin-1β in Subjects With Chronic Heart Failure (NCT03388593).	RhNRG-1 (recombinant human neuregulin-1)	3	1600	vs. placebo	All-cause death	February 2023
	Randomized Placebo-controlled Trial of FCM as Treatment for Heart Failure With Iron Deficiency (HEART-FID) (NCT03037931).	Ferric carboxymaltose	3	3068	vs. placebo	1. All-cause death 2. Heart failure hospitalization 3. Change in 6MWT distance	June 2023

AGT, angiotensinogen; ARNI, angiotensin receptor neprilysin inhibitor; Cmax, maximum serum concentration; cTnT, cardiac troponin T; CV, cardiovascular; GIP, gastric inhibitory polypeptide; GLP1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HHF, heart failure hospitalization; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricle; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B type natriuretic peptide; NYHA, New York Heart Association; sGC, soluble guanylate cyclase; SGLT2, sodium-glucose co-transporter 2 inhibitor; UACR, urine albumin-creatinine ratio; VO_2, oxygen consumption; 6MWD, 6-minute working distance.

Hsieh has received honorarium from AstraZeneca, Boehringer Ingelheim, Novartis, Bayer, MSD, Sanofi, Daiichi Sankyo, Pfizer, and Eli Lilly. Dr. C.-C. Wang has received honorarium from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Novartis, and Pfizer. Dr. C.-H. Chen reports honoraria from Novartis and Daiichi Sankyo. Dr. P.-H. Chu has received honorarium from AstraZeneca. Dr. S.-J. Yeh has received honorarium from Tanabe. Dr. W.-J. Chen has received honorarium from Astrazeneca, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Novartis, Pfizer, and Sanofi. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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SUPPLEMENTARY MATERIALS

Supplemental Table 1. Timing of in-hospital initiation and definitions of hemodynamically stable conditions

	Timing	Hemodynamic stability				
		SBP	O_2 supply	IV diuretic	IV vasodilator	IV inotrope
PIONEER[S1]	≥ 24 hours to 10 days after hospitalization	≥ 100 mmHg	No mention	No increase in dose ≥ 6 hours	No use ≥ 6 hours	No use ≥ 24 hours
SOLOIST-WHF[S2]	Before discharge to ≤ 3 days after discharge	≥ 100 mmHg	No O2 supply or mechanical ventilation ≥ 24 hours	No iv diuretic	No iv vasodilator (except nitrates) ≥ 24 hours	No use ≥ 24 hours
EMPULSE[S3]	≥ 24 hours to < 5 days after hospitalization	≥ 100 mmHg	No mention	No increase in dose ≥ 6 hours	No use ≥ 6 hours	No use ≥ 24 hours
STRONG-HF[S4]	Hospital admission within the 72 hours prior to screening	≥ 100 mmHg	No mention	No mention	No mention	No mention

IV, intravenous; SBP, systolic blood pressure.

Supplemental Table 2. Primary endpoint in recent heart failure trials

Trials	Primary endpoint
PARADIGM-HF[S5]	Cardiovascular death + hospitalization for heart failure
PARAGON-HF[S6]	Cardiovascular death + total hospitalizations for heart failure
DAPA-HF[S7]	Cardiovascular death + worsening heart failure
DELIVER[S8]	Cardiovascular death + worsening heart failure
EMPEROR-Reduced[S9]	Cardiovascular death + hospitalization for heart failure
EMPEROR-Preserved[S10]	Cardiovascular death + hospitalization for heart failure
SOLOIST-WHF[S2]	Cardiovascular death + total hospitalizations for heart failure + worsening heart failure
VICTORIA[S11]	Cardiovascular death + hospitalization for heart failure
GALACTIC-HF[S12]	Cardiovascular death + worsening heart failure

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