Paradigm Shifts of Heart Failure Therapy: Do We Need Another Paradigm?

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ABSTRACT

Heart failure (HF) is a progressive condition with intermittent acute decompensation leading to poor prognosis despite established guideline-directed therapy. A paradigm of HF therapy has been shifted over last four decades. Until the early 1970s, HF was empirically managed, then was managed with the hemodynamic concept until the early 1980s. According to the results of large randomized clinical trials, HF therapy has been shifted to the neurohormonal paradigm since the late 1980s until recently. Korean Acute Heart Failure (KorAHF) registry is a multi-center registry that recruited a total of 5625 admitted patients with acute HF from 2011 to 2014 and followed until 2019. Through KorAHF registry, we could obtain invaluable information or messages in various fields such as epidemiology, clinical characteristics, and treatment of acute HF in Korea and also had opportunities to fill the gap between guideline-directed care and real-world practice. Considering significant unmet needs in HF therapy even at this moment, we do need another paradigm shift for HF therapy, such as molecular and regenerative paradigm using gene, stem cells, mechanical support as well as novel pharmacological agents.

Keywords: Heart failure; Guideline-directed medical therapy; KorAHF registry

PARADIGM SHIFTS OF PHARMACOLOGICAL THERAPIES OF HEART FAILURE

Heart failure (HF) is a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection. Also, HF is a progressive condition with intermittent acute decompensation leading to poor prognosis despite established guideline-directed therapy.¹ A paradigm of HF therapy has been shifted over the decades. Until the 1970s, when ventricular hemodynamic physiology was not fully understood, HF management was mostly focused on the relief of symptoms and signs such as dyspnea and edema with limiting physical activity, digitalis, and thiazide or furosemide diuretic with potassium supplementation in patients with moderately severe HF.²

In the early 1980s, with a better understanding of hemodynamic changes consequent to decreased ventricular contractility, HF management shifted to correct abnormally increased...
preload with diuretics, increased afterload with vasodilators, and decreased ventricular contractility with an inotropic agents. Among deranged hemodynamic factors that cause symptoms and signs of HF, peripheral vasoconstriction, which increases afterload, a compensatory mechanism in order to maintain blood flow to vital organs, was proposed as an essential pathophysiologic mechanism of HF progression. The mechanism is that increased afterload can further suppress myocardial contractility or ventricular function and therefore induce a vicious cycle of HF progression.

Vasodilator in Heart Failure Trial (V-HeFT)\textsuperscript{3} was the first clinical trial to test the hemodynamic hypothesis of HF progression, in which effect of vasodilator therapy on outcomes in patients with chronic congestive HF was evaluated. The addition of hydralazine and isosorbide dinitrate in New York Heart Association (NYHA) class II–III chronic HF patients was associated with a 23% reduction in mortality at 3 years, but another vasodilator, prazosin, failed to show a beneficial effect on mortality despite comparable hemodynamic improvement to hydralazine and isosorbide dinitrate group. The result of this study, different outcomes with similar hemodynamic improvement, suggested that another factor in addition to hemodynamic derangement might be involved in HF progression.

Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) study,\textsuperscript{4} which showed mortality reduction by 31% at 12 months with prolonged administration of angiotensin-converting enzyme inhibitor (ACEI), enalapril, in NYHA class IV severe HF patients was the first clinical trial that revealed the role of the renin-angiotensin system in HF progression. The ACEI was also tested to be useful in the Studies of Left Ventricular Dysfunction (SOLVD) study, where enalapril reduced mortality and hospitalization in mild to moderate HF.\textsuperscript{4} SOLVD biomarker study also supported the role of neurohormones in HF progression by showing that neurohormones such as plasma norepinephrine, renin activity, atrial natriuretic peptide, and arginine vasopressin were increased even in patients with asymptomatic left ventricular dysfunction as well as symptomatic HF. Moreover, the degree of neurohormonal activation was correlated to the severity of HF or left ventricular dysfunction.\textsuperscript{5} All the study results using ACEIs shifted the paradigm of HF therapy from hemodynamic to neurohormonal paradigm.

PROspective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) study, which evaluated inotropic agent, oral milrinone, was the trial whether hemodynamic improvement contractility might improve outcomes of HF patients. Despite its beneficial hemodynamic effects, long-term therapy with oral milrinone increased the morbidity and mortality of patients with severe chronic HF. Such a result further supported that underlying neurohormonal activation rather than hemodynamic derangement is a crucial pathophysiologic mechanism of HF progression.

Once myocardial contractility or ventricular function decreases, neurohormones are activated as adaptive mechanisms in order to keep hemodynamic stability in the acute phase. However, prolonged activation of the neurohormonal system can not only induce further myocardial injury but decrease ventricular function through maladaptive mechanisms such as hypertrophy, remodeling, and apoptosis.

The neurohormonal hypothesis of HF progression and known activation of the sympathetic nervous system in HF prompted the clinical trials which evaluate the effects of beta-blocker on outcomes in patients with chronic HF. Beta-blockers were not indicated in HF therapy...
due to negative inotropic effect until the early 1980s, however, all clinical trials using beta-blockers, such as carvedilol,\(^6\) bisoprolol,\(^7\) and metoprolol,\(^8\) showed remarkable reductions in morbidity and mortality by 34% to 65% and supported the neurohormonal theory of HF progression further. Moreover, the RALES trial demonstrated the effect of mineral corticoid receptor, spironolactone, in reducing mortality in NYHA class III or IV HF patients in the presence of renin-angiotensin system inhibitors.\(^9\)\(^10\)

Under the concept of a blockade of neurohormonal activation in HF therapy, several clinical trials evaluating another neurohormonal blocker such as tumor necrosis factor (TNF)-alpha blocker,\(^11\) natriuretic peptide,\(^12\) and vasopressin inhibitor,\(^13\) were tried with negative results. ATMOSPHERE trial, which evaluated aliskiren, a direct renin inhibitor, in addition to enalapril in chronic HF patients, also failed to show beneficial effects on outcomes as well as more adverse events in chronic HF patients taking both enalapril and aliskiren compared to those with enalapril only.\(^14\)

Failed clinical trials that tried complete neurohormonal inhibition in chronic HF suggested another way or paradigm in addition to neurohormonal blockade for HF therapy. Following myocardial or vascular stress or injury, 2 types of neurohormonal change contribute to the evolution and progression of HF. One is increased activity or response to maladaptive mechanisms or bad neurohormones, and the other is decreased activity or response to adaptive mechanisms or good neurohormones. Prospective Comparison of Angiotensin Receptor Neprylisn Inhibitor (ARNI) With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial\(^15\) was conducted in order to test the hypothesis that improving neurohormonal imbalance, not only by suppressing bad neurohormones like the renin-angiotensin-aldosterone system but also enhancing good neurohormones such as natriuretic peptides can induce additional benefit over neurohormonal suppression only in patients heart failure with reduced ejection fraction (HFrEF). Compared to enalapril, LCZ696 (sacubitril/valsartan), ARNI significantly reduced primary endpoint(cardiovascular death or heart failure hospitalization) by suppressing maladaptive mechanism of the renin-angiotensin system with angiotensin type 1 receptor blocker, valsartan, and by blocking natriuretic peptide degradation with neprylisn inhibitor, sacubitril. The PARADIGM-HF study proved the synergism of multiple neuroendocrine pathway modulation and shifted the paradigm of HF management from neurohormonal inhibition to neurohormonal modulation.

Heart rate modulation is another area of managing HF. As baseline heart rate at rest is related to cardiovascular risk, the SHIFT study, evaluating the effect of heart rate slowing agent, ivabradine, reduced primary composite endpoint of cardiovascular death or hospital admission for worsening HF by 18% especially in chronic HF patients with heart rate equal or greater than 77/min despite full beta-blocker use.\(^16\) And very recently, vericiguat, a novel oral soluble guanylate cyclase stimulator showed survival benefit in NYHA II–IV HFrEF patients.\(^17\)

Last but not least, diabetes mellitus (DM) is another target of HF management. DM is present in nearly 35% of patients admitted to the hospital with acute HF.\(^18\) Multiple factors such as ischemia, hypertention, and extracellular fluid volume expansion are involved in the pathogenesis of HF in DM.\(^19\) DM is associated with increased cardiovascular morbidity and mortality in patients with chronic HF.\(^20\) The sodium-glucose co-transporter-2 (SGLT-2) inhibitors, a novel class of oral hypoglycemic agents that increase urinary excretion of glucose and sodium in the renal tubules,\(^21\) have shown remarkable results as a potential HF
therapeutic agents. Empagliflozin showed unexpected colossal success in the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) study.\textsuperscript{22} Empagliflozin reduced HF hospitalization and cardiovascular death in patients with type 2 DM, with a consistent benefit in patients with HF. The DAPA-HF trial also confirmed the favorable effects of SGLT2 inhibitors in HFrEF patients, regardless of the presence or absence of type 2 DM.\textsuperscript{23} Glucagon-like peptide-1 (GLP-1) receptor agonists are another class of antidiabetic drugs which showed favorable cardiovascular outcomes, although there has been no data in HF therapeutics.\textsuperscript{24}

The survival improvement of HF patients from the landmark pharmacological studies was summarized in Figure 1. Also, the full scope of landmark pharmacological and non-pharmacological studies of HF was excellently summarized in the recent review article by Choi et al.\textsuperscript{25}

THE KOREAN ACUTE HEART FAILURE REGISTRY: FILLING GAPS OF THE REAL-WORLD PRACTICE

The prevalence of HF is rapidly growing in many countries due to the aging population, increasing prevalence of risk factors, and better survival from acute cardiovascular diseases. Korea is also moving toward an aged society at the fastest pace in the world. According to the reports from the Korean Health Insurance Service, the prevalence of HF increased by 4.5\% per year, and the medical cost per year increased by about 50\% from 2009 to 2013.\textsuperscript{26} The prevalence of HF in Korea is significantly increased during the last ten years, reaching 1.53\% in 2015. Furthermore, if the scope were narrowed into the elderly population, HF prevalence in the population >60 years of age is over 5\%, which is more than 6-fold higher than the prevalence of the younger generation in Korea. Such rapid social change, along with ethnic differences, revealed an unmet need for a robust investigation to fill the gap between the evidence from the clinical trials and real-world practice. For this purpose, the registry of Korea Acute Heart Failure (KorAHF) was established from 2011 to 2019.\textsuperscript{27} Ten regionally-representative, university hospitals participated in the KorAHF registry, enrolled 5,625 patients from 2011 to 2013 then followed up until 2019.

Despite rapid population aging in Korea, Korean HF patients were still younger than those of Japan, the US, and Europe but older than those of Africa and Asia-Pacific countries. One of the most remarkable characteristics of the KorAHF registry was a low incidence of hypertensive HF. Although hypertension was found in 60\% of HF patients, the prevalence of hypertensive HF adjudicated by the principal investigator of each institution was only 4\%. One of the most likely explanations might be improved awareness, treatment, and control of hypertension in Korea since 2000. Four major causes or etiologies of acute HF were ischemic heart disease, dilated cardiomyopathy, valvular heart disease, and tachycardia-induced HF, which took charge of 83\% of overall HF cases. Ischemia and cardiomyopathy are main etiologies of HFrEF, whereas valvular heart disease, tachyarrhythmia, and hypertension play a more prominent role in heart failure with preserved ejection fraction (HFpEF). The most frequent causes of HF aggravation were ischemia (26\%), tachyarrhythmia (21\%), and infection (18\%) and noncompliance, including a high salt diet, while a definitive cause of aggravation was not found in 10\% of patients. Interestingly, non-ischemic aggravating factors were predominant (97.5\%) among HF due to non-ischemic etiology, whereas both ischemic (66\%) and non-ischemic (33\%) factors were involved in HF with ischemic etiology.
European HF guidelines proposed a new term for patients with HF and a left ventricular ejection fraction (LVEF) that ranges from 40% to 49% as ‘heart failure with midrange ejection fraction (HFmrEF).’

In the KorAHF registry, 57% belong to the traditional HFrEF, and 24% belong to HFpEF. Furthermore, 14% belong to the HFmrEF group. Compared with patients with HFrEF, patients with HFpEF tend to be older and female predominant. The prevalence of DM and ischemic heart disease is higher in HFrEF, while the prevalence of hypertension and atrial fibrillation is higher in HFpEF patients. Grossly, HFmrEF showed the mixed feature of HFrEF and HFpEF and tended to be more likelihood of de novo cases with ischemic origin.

Figure 1. Survival improvement from the landmark clinical studies of heart failure. (A) Mortality comparison in the landmark studies of heart failure. (B) The cumulative impact of the remarkable clinical studies of heart failure.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; CIBIS = Cardiac Insufficiency Bisoprolol Study; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; DAPA-HF = Dapagliflozin And Prevention of Adverse outcomes in Heart Failure; MERIT-HF = Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; PARADIGM-HF = Prospective Comparison of ARNI With ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure; RALES = Randomized ALdactone Evaluation Study; RRR = relative risk reduction; SHIFT = Systolic Heart failure treatment with the If inhibitor ivabradine Trial; SGLT-2 = sodium-glucose co-transporter-2; SOLVD = Studies of Left Ventricular Dysfunction; V-HeFT = Vasodilator in Heart Failure Trial.
ischemic heart disease or borderline valvular heart disease, which was decompensated by ischemia or tachyarrhythmia.

One of the main contributions of the KorAHF registry was calling attention to guideline-directed medical therapy (GDMT). During admission for acute HF, afterload reduction treatment with vasodilators or diuretics was less frequently performed. In contrast, parenteral inotropes were frequently used, which seemed to be associated with increased mortality. Although the proportion of patients who received GDMT increased from admission to discharge, even at discharge, only 50%, 65%, and 45% of patients were on beta-blockers, renin-angiotensin system inhibitors, and aldosterone antagonists, respectively. Unmet needs in GDMT in real-world practice was reported as well as the importance of GDMT.

Lastly, KorAHF registry found several prognostic factors of HF, which might be frequently overlooked, such as increased neutrophil-lymphocyte ratio (>7.0 with infection/ischemia, >5.0 without), low blood pressure below 130/70 mmHg, hyperglycemia (>200 mg/dL) on admission, and intraventricular conduction disturbance. Notably, several clinical presentations were found to have significant clinical implications. Hyponatremia was a well-known bad sign of mortality. Previously, hyponatremia was thought to be caused by renal dysfunction and volume overload. However, KorAHF data suggested that hyponatremia was linked with right ventricular dysfunction, which might be more significantly related to prognosis. Surprisingly, in HF patients with atrial fibrillation, the incidence of stroke reached 4.5% in the first year after HF hospitalization. Therefore, early stroke prevention after HF is essential.

Other key messages and publications from KorAHF registry were summarized in Table 1.

| Table 1. Key messages from KorAHF registry papers |
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| **Title** | **Category** | **Key message** | **Authors** | **Year** |
| A multicentre cohort study of acute heart failure syndromes in Korea: rationale, design, and interim observations of the Korean Acute Heart Failure (KorAHF) registry | Characteristics | In AHF patients, in-hospital mortality was 5.2%, and 0.9% of patients received urgent heart transplantation. The post-discharge 30-day and 180-day all-cause mortality were 1.2% and 9.2%, respectively. | Lee SE/Oh BH | 2014 |
| Clinical characteristics and outcome of acute heart failure in Korea: results from the Korean Acute Heart Failure Registry (KorAHF) | Characteristics | Ischemia was the most frequent etiology (27.6%) and aggravating factor (26.3%). RAS inhibitors/BBs/AAs are prescribed in 68.8%, 52.2%, and 46.6% of the patients at discharge, respectively. | Lee SE/Lee HY | 2017 |
| Prognostic significance of left axis deviation in acute heart failure patients with left bundle branch block: an analysis from the Korean Acute Heart Failure (KorAHF) registry | Characteristics | Among AHF with LBBB patients, LAD did not predict mortality, but it could be used as a significant predictor of worse LVEF and RV dilatation. | Choi KH/Jeon ES | 2018 |
| Fate of acute heart failure patients with mid-range ejection fraction | Characteristics | 1/3 HFrEF patients showed improved LVEF. RAS inhibitors/AAs could improve the survival of HFmrEF patients. | Gwag HB/Jeon ES | 2018 |
| Hyponatremia and its prognosis in acute heart failure is related to right ventricular dysfunction | Characteristics | In patients with AHF, hyponatremia was more common with RV dysfunction. RV dysfunction, rather than hyponatremia, was more significantly related to prognosis. | Lee H/Lee SE | 2018 |
| Characteristics, outcomes, and treatment of heart failure with improved ejection fraction | Characteristics | 1/3 of HFpEF patients showed improved ejection fraction within one year of hospitalization. The use of β-blockers may be beneficial. | Park CS/Choi DJ | 2019 |
| Comparison of characteristics and 3-year outcomes in patients with acute heart failure with preserved, mid-range, and reduced ejection fraction | Characteristics | 58%, 16%, 25% of HF patients belonged to HFrEF, HFmrEF, and HFpEF category. HFmrEF patients showed intermediate epidemiological profiles between HFrEF and HFpEF and had a propensity to present as de-novo HF with ischemic etiology. | Cho JH/Cho HJ | 2019 |
| Management and prognosis of heart failure in octogenarians: final report from the KorAHF registry | Characteristics | Octogenarian patients showed higher mortality. GDMT were less applied; however, adequate use of GDMT was still associated with improved survival. | Oh GC/Lee HY | 2020 |

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| Title                                                                 | Category | Key message                                                                 | Authors           | Year |
|----------------------------------------------------------------------|----------|------------------------------------------------------------------------------|-------------------|------|
| Characteristics and outcomes of HFrEF with declining ejection fraction | Characteristics | Of HFrEF patients, 9.6% declined LVEF below 50%, showing increased risk for mortality (HR, 1.82) despite medication. | Park JJ/Choi DJ   | 2020(4) |
| Effects of widespread inotrope use in acute heart failure patients   | GDMT     | Inotrope use was an independent predictor for mortality in patients with normal initial SBP (>90 mmHg). Clinicians should be cautious with the usage of inotropes in AHF. | Kang JH/Cho HJ    | 2018(4) |
| Outcomes after predischarge initiation of β-blocker in patients hospitalized for severe decompensated heart failure requiring inotropic therapy | GDMT     | Pre-discharge BB initiation is associated with better clinical outcomes after severe acute decompensated HF requiring inotropic therapy (HR, 0.70). | Cho MS/Kim JJ     | 2018(5) |
| The effect of door-to-diuretic time on clinical outcomes in patients with acute heart failure | GDMT     | Door-to-diuretic time was not associated with clinical outcomes in a large prospective cohort of patients with AHF who were presenting to an emergency room. | Park JJ/Choi DJ   | 2018(7) |
| Effects of angiotensin receptor blocker at discharge in patients with heart failure with reduced ejection fraction: Korean Acute Heart Failure (KorAHF) registry | GDMT     | In HFrEF, ARB shows a comparable mortality benefit to ACEI, with better tolerability. | Choi KH/Jeon ES   | 2018(10) |
| Guideline-directed medical therapy for patients with heart failure with midrange ejection fraction: a patient-pooled analysis from the KorHF and KorAHF registries | GDMT     | In HFrEF after hospitalization, BBs, and RAS inhibitors on discharge were associated with reduced risk of all-cause mortality (HR, 0.758 and 0.760). | Choi KH/Choi JO    | 2018(4) |
| Effect of renin-angiotensin system blockade in patients with severe renal insufficiency and heart failure | GDMT     | Early RAS inhibitor treatment in AHF patients with severe renal insufficiency (GFR <30 mL/min/1.73 m²) was related to a better prognosis, especially in patients receiving renal replacement therapy. | Jang SY/Chae SC   | 2018(5) |
| β-blockers and 1-year postdischarge mortality for heart failure and reduced ejection fraction and slow discharge heart rate | GDMT     | In 30% of HFrEF patients having heart rate <70 BPM, β-blockers may have a limited effect on survival. | Park JJ/Choi DJ   | 2018(9) |
| Beta-blockers in patients with heart failure with preserved ejection fraction: results from The Korea Acute Heart Failure (KorAHF) registry | GDMT     | In HFrEF patients, the use of beta-blockers is associated with reduced all-cause death (HR, 0.80; 95% CI, 0.69–0.94) but not with reduced rehospitalization. | Kim SH/Baek SH   | 2018(9) |
| The mortality benefit of carvedilol versus bisoprolol in patients with heart failure with reduced ejection fraction | GDMT     | In HFrEF, carvedilol and bisoprolol showed comparable mortality benefits (BB vs. no BB; HR, 0.59). | Choi KH/Jeon ES   | 2019(4) |
| Guideline-directed medical therapy in elderly patients with heart failure with reduced ejection fraction: a cohort study | GDMT     | GDMT was associated with reduced 3-year all-cause mortality in elderly HFrEF patients. | Seo WW/Choi DJ   | 2020(5) |
| Coronary artery bypass graft versus percutaneous coronary intervention in acute heart failure | GDMT     | Compared with PCI, CAGB is associated with significantly lower all-cause mortality in patients with AHF (HR, 0.57). | Lee SE/Lee HY    | 2020(4) |
| Guideline-directed therapy at discharge in patients with heart failure and atrial fibrillation | GDMT     | Better adherence to GDMT, including anticoagulation, was associated with better survival in patients with HF with AF. | Ahn MS/Yoo BS    | 2020(5) |
| Neutrophil-lymphocyte ratio in patients with acute heart failure predicts in-hospital and long-term mortality | Patients outcomes | Elevated NLR (>/7.0 with infection/ischemia, >5.0 without) in AHF patients at the index hospitalization is an independent predictor for in-hospital and post-discharge 3-year mortality. | Cho JH/Cho HJ   | 2020(9) |
| Reverse J-curve relationship between on-treatment blood pressure and mortality in patients with heart failure | Patients outcomes | BP <130/70 mm Hg at discharge and during follow-up was associated with worse survival in HF patients. | Lee SE/Lee HY   | 2017(9) |
| Short and long-term prognostic value of hyponatremia in heart failure with preserved ejection fraction versus reduced ejection fraction: an analysis of the Korean Acute Heart Failure registry | Patients outcomes | Hyponatremia is a significant risk factor for adverse in-hospital outcomes; however, its long-term prognostic value is only limited to HFrEF, but not for HFrEF. | Park JJ/Choi DJ   | 2017(6) |
| Nutritional risk index as a predictor of mortality in acutely decompensated heart failure | Patients outcomes | Poor nutritional status was associated with mortality in HF patients. The nutritional risk index is valuable in risk stratification. | Cho JY/Kim KH   | 2018(10) |
| Validation of the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) heart failure risk score and the effect of adding natriuretic peptide for predicting mortality after discharge in hospitalized patients with heart failure | Patients outcomes | MAGGIC risk score + BNP/NT-proBNP effectively predict survival in HF patient (C index of 0.736). | Khanam SS/Yoo BS | 2018(7) |
| Predictors and prognostic value of worsening renal function during admission in HFrEF versus HFrEF: data from the KorAHF (Korean Acute Heart Failure) registry | Patients outcomes | In AHF patients, worsening renal function is an independent predictor of adverse in-hospital and follow-up outcomes in both HFrEF and HFrEF. | Kang JH/Choi DJ | 2018(10) |
| Outcomes of de novo and acute decompensated heart failure patients according to ejection fraction | Patients outcomes | HFrEF may indicate a better prognosis compared with HFrEF in acute decompensated HF, but not in de novo AHF. | Choi KH/Jeon ES | 2018(9) |

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CONCLUSIONS

In conclusion, despite significant advances in HF therapies over the last four decades, the prognosis of HF is worse than those of most cancers, and 5-year mortality reaches up to 40–50%. Although there are still substantial unmet needs in the management of HFrEF, huge and urgent unmet needs are in the management of HFpEF and acute HF. All the clinical trials so far have failed to show beneficial evidence of current neurohormonal agents or investigational drugs in HFpEF and acute HF. Therefore, we have to find a new target or paradigm based upon pathophysioligic mechanisms of HF progression. For example, new drugs targeting neurohormonal aberration such as guanylate cyclase activator, or drug for recovering loss of contractile capacity with myosin activator, omecamtiv mecarbil, are under trials. Other novel therapeutic modalities using genes, stem cells, or mechanical circulatory support are also eagerly anticipated. Furthermore, simultaneously, clinical studies with real-world data, including the HF registry, should be continued to fill the gaps of clinical practice.

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