Int J Heart Fail. 2020 Jul;2(3):145-156
https://doi.org/10.36628/ijhf.2020.0010
pISSN 2636-154X·eISSN 2636-1558

International Journal of Heart Failure
IJHF

Review Article

Check for updates

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

Hae-Young Lee, MD[1] and Byung-Hee Oh, MD, PhD[2]

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea
[2]Division of Cardiology, Cardiovascular Center, Mediplex Sejong Hospital, Incheon, Korea

OPEN ACCESS

Received: Mar 16, 2020
Revised: Apr 1, 2020
Accepted: Apr 1, 2020

Correspondence to
Byung-Hee Oh, MD, PhD
Division of Cardiology, Cardiovascular Center, Mediplex Sejong Hospital, 20, Gyeyangmunhwa-ro, Gyeyang-gu, Incheon 21080, Korea.
E-mail: ohbhmed@snu.ac.kr

ORCID iDs
Hae-Young Lee
https://orcid.org/0000-0002-9521-4102
Byung-Hee Oh
https://orcid.org/0000-0002-9945-4306

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Oh BH; Writing - original draft: Lee HY; Writing - review & editing: Oh BH.

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 registy

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)[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,[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.[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.[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 Neprilysin 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 neprilysin 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, hypertension, 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.[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.[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.[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.[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.[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.[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.

https://doi.org/10.36628/ijhf.2020.0010

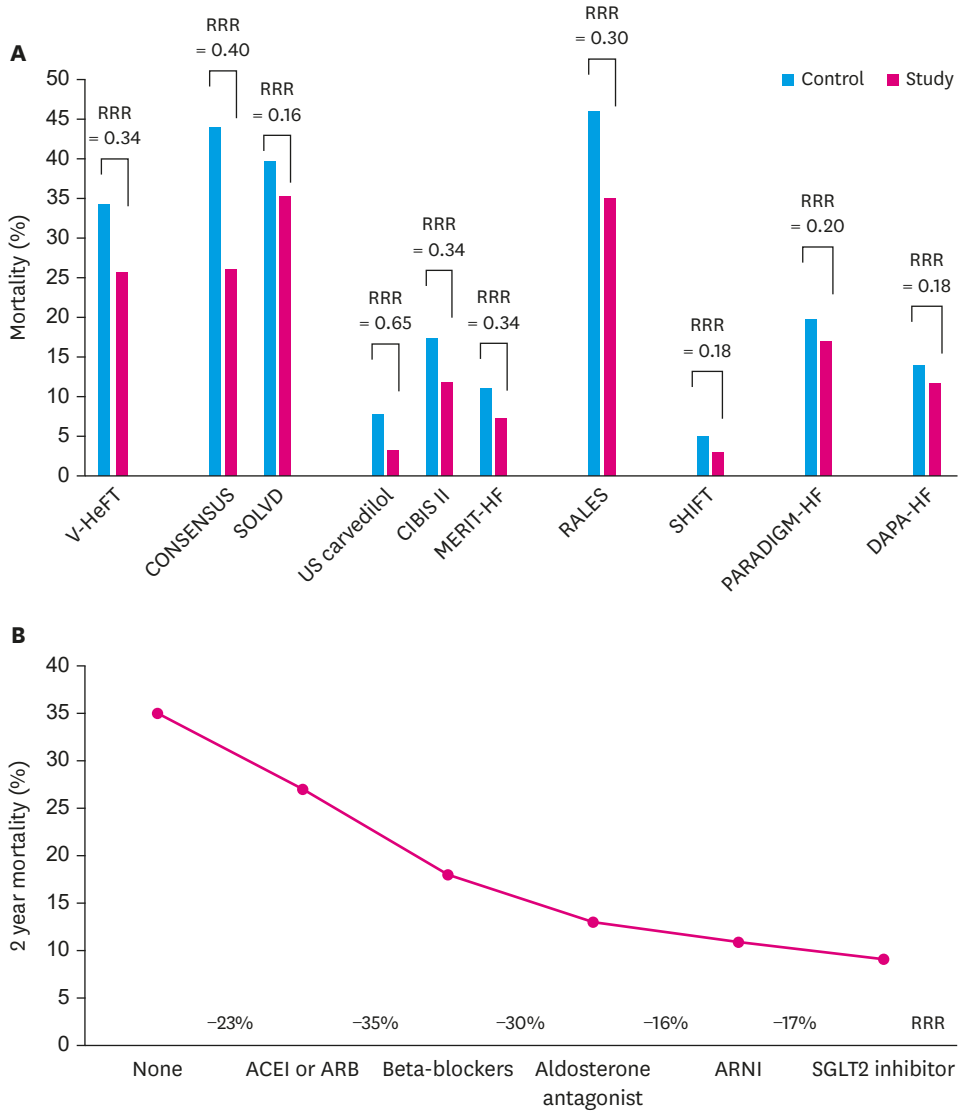

Figure 1. Survival improvement from the landmark clinical studies of heart failure. (A) Mortality comparison in the landmark studies of heart failure. (B) The cumulative impact of the remarkable clinical studies of heart failure.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor 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.

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).'[28] 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.[29] The typical feature of HFmrEF might be long-standing compensated

https://doi.org/10.36628/ijhf.2020.0010

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).[27] 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.[30] 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[30] as well as the importance of GDMT.[31-33]

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),[34] low blood pressure below 130/70 mmHg,[35] hyperglycemia (>200 mg/dL) on admission,[36] and intraventricular conduction disturbance.[37] 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.[38] 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.[39] Other key messages and publications from KorAHF registry were summarized in **Table 1.**[27][29-39][40-60]

Table 1. Key messages from KorAHF registry papers

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[27]
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 (37.6%) 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[41]
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[42]
Fate of acute heart failure patients with mid-range ejection fraction	Characteristics	1/3 HFmrEF patients showed improved LVEF. RAS inhibitors/AAs could improve the survival of HFmrEF patients.	Gwag HB/Jeon ES	2018[43]
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[38]
Characteristics, outcomes, and treatment of heart failure with improved ejection fraction	Characteristics	1/3 of HFrEF patients showed improved ejection fraction within one year of hospitalization. The use of β-blockers may be beneficial.	Park CS/Choi DJ	2019[44]
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[29]
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[45]

(continued to the next page)

Table 1. (Continued) Key messages from KorAHF registry papers

Title	Category	Key message	Authors	Year
Characteristics and outcomes of HFpEF with declining ejection fraction	Characteristics	Of HFpEF patients, 9.6% declined LVEF below 50%, showing increased risk for mortality (HR, 1.82) despite medication.	Park JJ/Choi DJ	2020[46]
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[30]
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[31]
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[47]
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[48]
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 HFmrEF 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[49]
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 m^2) was related to a better prognosis, especially in patients receiving renal replacement therapy.	Jang SY/Chae SC	2018[32]
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	2019[50]
Beta-blockers in patients with heart failure with preserved ejection fraction: results from The Korea Acute Heart Failure (KorAHF) registry	GDMT	In HFpEF 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	2019[51]
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[52]
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[53]
Coronary artery bypass graft versus percutaneous coronary intervention in acute heart failure	GDMT	Compared with PCI, CABG is associated with significantly lower all-cause mortality in patients with AHF (HR, 0.57).	Lee SE/Lee HY	2020[54]
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[33]
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[34]
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[35]
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 HFpEF.	Park JJ/Choi DJ	2017[55]
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[56]
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[57]
Predictors and prognostic value of worsening renal function during admission in HFpEF 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 HFpEF.	Kang JH/Choi DJ	2018[58]
Outcomes of de novo and acute decompensated heart failure patients according to ejection fraction	Patients outcomes	HFpEF may indicate a better prognosis compared with HFrEF in acute decompensated HF, but not in de novo AHF.	Choi KH/Jeon ES	2018[59]

(continued to the next page)

Table 1. (Continued) Key messages from KorAHF registry papers

Title	Category	Key message	Authors	Year
Predicting stroke and death in patients with heart failure using CHA_2DS_2-VASc score in Asia	Patients outcomes	The majority of strokes occurred relatively shortly after HF hospitalization associated with high mortality. Thus, early stroke prevention after HF is essential.	Son MK/Park HY	2019[39]
Risk prediction for 30-day heart failure-specific readmission or death after discharge: data from the Korean Acute Heart Failure (KorAHF) registry	Patients outcomes	Risk score using 12 independent variables (age, NYHA class, hypertension, HF admission, COPD, HF etiology, SBP, LVEF, serum sodium, BNP/NT-BNP at discharge, BB/ACEI/ARB) effectively predicts 30-day HF-specific readmission or death (C index of 0.710).	Lim NK/Park HY	2019[60]
Artificial intelligence algorithm for predicting mortality of patients with acute heart failure	Patients outcomes	A deep-learning-based artificial intelligence algorithm can predict the in-hospital and long-term mortality of AHF more accurately than the conventional risk scores.	Kim KH/Oh BH	2019[61]
Prognostic implication of ventricular conduction disturbance pattern in hospitalized patients with acute heart failure syndrome	Patients outcomes	LBBB and NICD were independently associated with an increased risk of a 1-year adverse event in hospitalized patients with HF (HR, 1.392, and 1.278), whereas the prognostic impacts of RBBB were limited.	Lee JH/Choi DJ	2019[37]
Admission hyperglycemia as a predictor of mortality in acute heart failure: comparison between the diabetics and non-diabetics	Patients outcomes	Admission hyperglycemia (>200 mg/dL) was a significant predictor of in-hospital and 1-year death in AHF.	Cho JY/Kim KH	2020[36]

AA = aldosterone antagonist; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; AHF = acute heart failure; ARB = angiotensin II receptor blocker; BB = β-blocker; BNP = brain natriuretic peptide; BP = blood pressure; CABG = coronary artery bypass grafting; CI = confidence interval; COPD = chronic obstructive pulmonary disease; GDMT = guideline-directed medical therapy; GFR = glomerular filtration rate; HF = heart failure; HFmrEF = heart failure with midrange ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; KorAHF = Korean Acute Heart Failure; LAD = left-axis deviation; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure; NICD = nonspecific intraventricular conduction delay; NLR = neutrophil-lymphocyte ratio; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RBBB = right bundle branch block; RV = right ventricular; SBP = systolic blood pressure.

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 pathophysiologic 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,[61] 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.

ACKNOWLEDGEMENTS

The authors express sincere gratitude to all members of KorAHF registry; Hyun-Jai Cho (Seoul National University Hospital), Sang-Eun Lee, Jae-Joong Kim (Asan Medical Center), Jin-Oh Choi, Eun-Seok Jeon (Samsung Medical Center), Jae Yeong Cho, Kye Hun Kim (Chonnam National University Hospital), Ju-Hee Lee, Kyung-Kuk Hwang, Myeong-Chan Cho (Chungbuk National University Hospital), Se Yong Jang, Shung Chull Chae (Kyungpook National University Hospital), Jin Joo Park, Dong-Ju Choi (Seoul National University Bundang Hospital), Jong-Chan Yoon, Sang Hong Baek (Seoul St. Mary's Hospital), Byung-Su Yoo (Yonsei University Wonju Severance Christian Hospital), Jaewon Oh, Seok-Min Kang (Yonsei University Severance Hospital).

REFERENCES

1. Gheorghiade M, De Luca L, Fonarow GC, Filippatos G, Metra M, Francis GS. Pathophysiologic targets in the early phase of acute heart failure syndromes. Am J Cardiol 2005;96:11G-17G.
PUBMED | CROSSREF
2. Klamerus KJ. Current concepts in clinical therapeutics: congestive heart failure. Clin Pharm 1986;5:481-98.
PUBMED
3. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. results of a Veterans Administration Cooperative Study. N Engl J Med 1986;314:1547-52.
PUBMED | CROSSREF
4. SOLVD InvestigatorsYusuf S, Pitt B, Davis CE, Hood WB, Cohn JN, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.
PUBMED | CROSSREF
5. Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). Circulation 1990;82:1724-9.
PUBMED | CROSSREF
6. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996;334:1349-55.
PUBMED | CROSSREF
7. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9-13.
PUBMED | CROSSREF
8. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-7.
PUBMED | CROSSREF
9. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709-17.
PUBMED | CROSSREF
10. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309-21.
PUBMED | CROSSREF
11. Mann DL, McMurray JJ, Packer M, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation 2004;109:1594-602.
PUBMED | CROSSREF
12. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2011;365:32-43.
PUBMED | CROSSREF
13. Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA 2007;297:1319-31.
PUBMED | CROSSREF
14. McMurray JJ, Krum H, Abraham WT, et al. Aliskiren, enalapril, or aliskiren and enalapril in heart failure. N Engl J Med 2016;374:1521-32.
PUBMED | CROSSREF
15. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
PUBMED | CROSSREF
16. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010;376:875-85.
PUBMED | CROSSREF
17. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. N Engl J Med. 2020 [Epub ahead of print].
PUBMED | CROSSREF
18. Nieminen MS, Brutsaert D, Dickstein K, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006;27:2725-36.
PUBMED | CROSSREF
19. Dei Cas A, Khan SS, Butler J, et al. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. JACC Heart Fail 2015;3:136-45.
PUBMED | CROSSREF

20. De Groote P, Lamblin N, Mouquet F, et al. Impact of diabetes mellitus on long-term survival in patients with congestive heart failure. Eur Heart J 2004;25:656-62.
PUBMED | CROSSREF
21. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZ. Sodium glucose cotransporter-2 inhibition in heart failure: potential mechanisms, clinical applications, and summary of clinical trials. Circulation 2017;136:1643-58.
PUBMED | CROSSREF
22. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.
PUBMED | CROSSREF
23. McMurray JJ, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995-2008.
PUBMED | CROSSREF
24. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311-22.
PUBMED | CROSSREF
25. Choi HM, Park MS, Youn JC. Update on heart failure management and future directions. Korean J Intern Med 2019;34:11-43.
PUBMED | CROSSREF
26. Lee JH, Lim NK, Cho MC, Park HY. Epidemiology of heart failure in Korea: present and future. Korean Circ J 2016;46:658-64.
PUBMED | CROSSREF
27. Lee SE, Cho HJ, Lee HY, et al. A multicentre cohort study of acute heart failure syndromes in Korea: rationale, design, and interim observations of the Korean Acute Heart Failure (KorAHF) registry. Eur J Heart Fail 2014;16:700-8.
PUBMED | CROSSREF
28. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.
PUBMED | CROSSREF
29. Cho JH, Choe WS, Cho HJ, et al. Comparison of characteristics and 3-year outcomes in patients with acute heart failure with preserved, mid-range, and reduced ejection fraction. Circ J 2019;83:347-56.
PUBMED | CROSSREF
30. Kang J, Cho HJ, Lee HY, et al. Effects of widespread inotrope use in acute heart failure patients. J Clin Med 2018;7:E368.
PUBMED | CROSSREF
31. Cho MS, Kim MS, Lee SE, et al. Outcomes after predischarge initiation of β-blocker in patients hospitalized for severe decompensated heart failure requiring inotropic therapy. Can J Cardiol 2018;34:1145-52.
PUBMED | CROSSREF
32. Jang SY, Chae SC, Bae MH, et al. Effect of renin-angiotensin system blockade in patients with severe renal insufficiency and heart failure. Int J Cardiol 2018;266:180-6.
PUBMED | CROSSREF
33. Ahn MS, Yoo BS, Yoon J, et al. Guideline-directed therapy at discharge in patients with heart failure and atrial fibrillation. Heart 2020;106:292-8.
PUBMED | CROSSREF
34. Cho JH, Cho HJ, Lee HY, et al. Neutrophil-lymphocyte ratio in patients with acute heart failure predicts in-hospital and long-term mortality. J Clin Med 2020;9:E557.
PUBMED | CROSSREF
35. Lee SE, Lee HY, Cho HJ, et al. Reverse J-curve relationship between on-treatment blood pressure and mortality in patients with heart failure. JACC Heart Fail 2017;5:810-9.
PUBMED | CROSSREF
36. Cho JY, Kim KH, Lee SE, et al. Admission hyperglycemia as a predictor of mortality in acute heart failure: comparison between the diabetics and non-diabetics. J Clin Med 2020;9:E149.
PUBMED | CROSSREF
37. Lee JH, Park JJ, Cho Y, et al. Prognostic implication of ventricular conduction disturbance pattern in hospitalized patients with acute heart failure syndrome. Korean Circ J 2019;49:602-11.
PUBMED | CROSSREF

38. Lee H, Lee SE, Park CS, et al. Hyponatraemia and its prognosis in acute heart failure is related to right ventricular dysfunction. Heart 2018;104:1670-7.
PUBMED | CROSSREF
39. Son MK, Lim NK, Park HY. Predicting stroke and death in patients with heart failure using CHA_2DS_2-VASc score in Asia. BMC Cardiovasc Disord 2019;19:193.
PUBMED | CROSSREF
40. Lee SE, Lee HY, Cho HJ, et al. Clinical characteristics and outcome of acute heart failure in Korea: results from the Korean Acute Heart Failure Registry (KorAHF). Korean Circ J 2017;47:341-53.
PUBMED | CROSSREF
41. Choi KH, Han S, Lee GY, et al. 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. Korean Circ J 2018;48:1002-11.
PUBMED | CROSSREF
42. Gwag HB, Lee GY, Choi JO, et al. Fate of acute heart failure patients with mid-range ejection fraction. Circ J 2018;82:2071-8.
PUBMED | CROSSREF
43. Park CS, Park JJ, Mebazaa A, et al. Characteristics, outcomes, and treatment of heart failure with improved ejection fraction. J Am Heart Assoc 2019;8:e011077.
PUBMED | CROSSREF
44. Oh GC, Cho HJ, Lee SE, et al. Management and prognosis of heart failure in octogenarians: final report from the KorAHF registry. J Clin Med 2020;9:E501.
PUBMED | CROSSREF
45. Park JJ, Park CS, Mebazaa A, et al. Characteristics and outcomes of HFpEF with declining ejection fraction. Clin Res Cardiol 2020;109:225-34.
PUBMED | CROSSREF
46. Park JJ, Kim SH, Oh IY, et al. The effect of door-to-diuretic time on clinical outcomes in patients with acute heart failure. JACC Heart Fail 2018;6:286-94.
PUBMED | CROSSREF
47. Choi KH, Lee GY, Choi JO, et al. Effects of angiotensin receptor blocker at discharge in patients with heart failure with reduced ejection fraction: Korean Acute Heart Failure (KorAHF) registry. Int J Cardiol 2018;257:168-76.
PUBMED | CROSSREF
48. Choi KH, Choi JO, Jeon ES, et al. Guideline-directed medical therapy for patients with heart failure with midrange ejection fraction: a patient-pooled analysis from the KorHF and KorAHF registries. J Am Heart Assoc 2018;7:e009806.
PUBMED | CROSSREF
49. Park JJ, Park HA, Cho HJ, et al. β-blockers and 1-year postdischarge mortality for heart failure and reduced ejection fraction and slow discharge heart rate. J Am Heart Assoc 2019;8:e011121.
PUBMED | CROSSREF
50. Kim SH, Yun SC, Park JJ, et al.KorAHF investigator. Beta-blockers in patients with heart failure with preserved ejection fraction: results from The Korea Acute Heart Failure (KorAHF) registry. Korean Circ J 2019;49:238-48.
PUBMED | CROSSREF
51. Choi KH, Lee GY, Choi JO, et al. The mortality benefit of carvedilol versus bisoprolol in patients with heart failure with reduced ejection fraction. Korean J Intern Med 2019;34:1030-9.
PUBMED | CROSSREF
52. Seo WW, Park JJ, Park HA, et al. Guideline-directed medical therapy in elderly patients with heart failure with reduced ejection fraction: a cohort study. BMJ Open 2020;10:e030514.
PUBMED | CROSSREF
53. Lee SE, Lee HY, Cho HJ, et al. Coronary artery bypass graft versus percutaneous coronary intervention in acute heart failure. Heart 2020;106:50-7.
PUBMED | CROSSREF
54. Park JJ, Cho YJ, Oh IY, et al. 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. Int J Cardiol 2017;248:239-45.
PUBMED | CROSSREF
55. Cho JY, Kim KH, Cho HJ, et al. Nutritional risk index as a predictor of mortality in acutely decompensated heart failure. PLoS One 2018;13:e0209088.
PUBMED | CROSSREF

56. Khanam SS, Choi E, Son JW, et al. 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. PLoS One 2018;13:e0206380.
PUBMED | CROSSREF
57. Kang J, Park JJ, Cho YJ, et al. Predictors and prognostic value of worsening renal function during admission in HFpEF versus HFrEF: data from the KorAHF (Korean Acute Heart Failure) registry. J Am Heart Assoc 2018;7:e007910.
PUBMED | CROSSREF
58. Choi KH, Lee GY, Choi JO, et al. Outcomes of de novo and acute decompensated heart failure patients according to ejection fraction. Heart 2018;104:525-32.
PUBMED | CROSSREF
59. Lim NK, Lee SE, Lee HY, et al. Risk prediction for 30-day heart failure-specific readmission or death after discharge: data from the Korean Acute Heart Failure (KorAHF) registry. J Cardiol 2019;73:108-13.
PUBMED | CROSSREF
60. Kwon JM, Kim KH, Jeon KH, et al. Artificial intelligence algorithm for predicting mortality of patients with acute heart failure. PLoS One 2019;14:e0219302.
PUBMED | CROSSREF
61. Teerlink JR, Diaz R, Felker GM, et al. Omecamtiv mecarbil in chronic heart failure with reduced ejection fraction: rationale and design of GALACTIC-HF. JACC Heart Fail. 2020 [Epub ahead of print].
PUBMED | CROSSREF