Heart failure (HF) is a clinical syndrome caused by a cardiac abnormality and characterized by typical signs and symptoms.¹² Left ventricular ejection fraction (LVEF) has traditionally been used to classify HF. In general, patients with a LVEF less than 40% are classified as having HF with reduced ejection fraction (HFrEF), patients with LVEF within the range of 40–49% are classified as having HF with mid-range ejection fraction (HFmrEF), and patients with LVEF exceeding 50% are classified as having HF with preserved ejection fraction (HFpEF).¹³ The prevalence of HF in the United States was 5.7 million in 2009, and increased to 6.2 million in 2013.⁹ Between 2005 and 2010, 50% of patients hospitalized with HF showed a reduced ejection fraction.⁴ Similarly, in Korea, the prevalence of HF increased from 0.37 million in 2002 to 0.75 million in 2013, which was 0.75% and 1.53% of total Korean population, respectively.⁵ As the population ages, there may be a substantial increase in the epidemiologic burden of HF with diverse comorbidities such as diabetes, hypertension, and functional mitral regurgitation.⁶⁻⁸

Keywords: Clinical trial; Drug therapy; Heart failure; Ventricular dysfunction

INTRODUCTION

Heart failure (HF) is an important cardiovascular disease because of the increasing prevalence, high morbidity and mortality, and rapid expansion of health care costs. Over the past decades, efforts have been made to modify the prognosis of patients with HF. Regarding HF with reduced ejection fraction (HFrEF), several drugs have shown to improve mortality and morbidity, based on large-scale randomized controlled trials, leading to a critical paradigm shift in its pharmacological treatment. The paradigm of HFrEF pathophysiology has shifted from cardiorenal disease to hemodynamic changes, and neurohormonal activation is currently considered the prime pathophysiological mechanism of HFrEF. This review summarizes evidence on the pharmacological management of HFrEF derived from major randomized controlled trials, which have accomplished improvements in survival benefits.
Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Kim ES; Supervision: Youn JC; Validation: Baek SH; Writing - review & editing: Kim ES.

Since the 1980s, clinical studies have made aimed to improve the survival of patients with HFrEF. A timeline of patient enrollment in clinical trials related to the pharmacological treatment of HFrEF is shown in Figure 1. In this review, we discuss drugs that have shown to improve the mortality of patients with HFrEF, and identify other attempts that have been made to improve the survival of these patients.

CHANGES IN HEART FAILURE TREATMENT TARGETS

With the progress in the understanding of the pathophysiology of HF, there have been many advances in treatment and diagnosis of HF, including advances in cardiac imaging, biomarkers, and genetic testing. The conceptual models of HF have evolved over a few decades, with several leaps in the pharmacological treatment of HF, mainly HFrEF. Figure 2 shows changes in the concept of HF pathophysiology.

Figure 1. Timeline of patient enrollment (from the first year of enrollment) in clinical trials related to heart failure with reduced ejection fraction. ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; BB = beta-blocker; CCB = calcium channel blocker; DRI = direct renin inhibitor; ERA = endothelin receptor antagonist; H-ISDN = hydralazine-isosorbide dinitrate; MRA = mineralocorticoid receptor antagonist; PDE = phosphodiesterase; sGC = soluble guanylate cyclase; SGLT2 = sodium-glucose co-transporter-2.
In the 1940s, HF was mainly explained by cardiac dysfunction resulting in renal hypoperfusion. Early treatments for HF aimed to control symptoms, such as dyspnea and edema, and included diuretics, water and salt restriction, bed rest, and mechanical removal of edema fluid. In the 1960s, the hemodynamic model emerged and reducing left ventricular loading became a treatment target. Soon, vasodilators received attention for reducing peripheral resistance. Additionally, positive inotropes were used to increase cardiac contractility. Although these treatments alleviated patients' symptoms, they had no significant effect on the survival rate. In the 1980s, the neurohormonal model became the most prominent explanation of HFrEF pathophysiology. This model consists of three axes: the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), and natriuretic peptide (NP) system. By targeting these systems, improvements in survival have been demonstrated in randomized controlled trials (RCTs) with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers (BBs), and mineralocorticoid receptor antagonists (MRAs). Currently, pharmacological treatments targeting neurohormonal activation are the mainstay of various chronic heart failure (CHF) guidelines.

Various additional treatment strategies for HF were identified, which attempted to reinforce the neurohormonal model or to improve outcomes for patients with HF. Some of these succeeded and were incorporated into new guidelines. However, despite efforts, there remains a gap between real-life practice and guideline-directed medical treatment.

**Current pharmacological treatment for HFrEF with survival benefits**

Several clinical trials have demonstrated significant survival benefits for patients with HFrEF. Table 1 summarizes clinical trials on drugs that reduce mortality in patients with HFrEF. Here, we review the current pharmacological treatment of HFrEF.
Table 1. Summary of clinical trials that reported reduced mortality in patients with HF

| Study          | Year  | Participants | Number | Intervention | Comparator | Follow-up | Primary endpoint | Mortality outcome |
|----------------|-------|--------------|--------|--------------|------------|-----------|-----------------|------------------|
| ACEIs          |       |              |        |              |            |           |                 |                  |
| CONSENSUS[1]   | 1987  | NYHA class IV | 253    | Enalapril    | Placebo    | Mean 6 months | All-cause mortality | • Mortality reduced by 40% (p=0.002) at the end of the study |
| SOLVD[6]       | 1991  | EF ≤35%      | 2,569  | Enalapril    | Placebo    | Mean 41 months | All-cause mortality | • Mortality reduced by 16% (95% CI, 5% to 26%; p=0.0036) |
| SAVE[2]        | 1992  | Post-MI EF ≤40% without overt HF | 2,231  | Captopril    | Placebo    | Mean 42 months | All-cause mortality | • Mortality reduced by 19% (95% CI, 3% to 32%; p=0.0019) |
| TRACE[5]       | 1995  | Post-MI EF ≤35% | 1,749  | Trandolapril | Placebo    | Mean 36 months | All-cause mortality | • Mortality risk 0.78 (95% CI, 0.67 to 0.91; p=0.001) |

| ARBs           |       |              |        |              |            |           |                 |                  |
| ELITE II[17]   | 2000  | EF ≤40%, NYHA class II–IV | 3,152  | Losartan     | Captopril  | Median 555 days | All-cause mortality | • No significant differences in all-cause mortality (HR, 1.13; 95.7% CI, 0.95 to 1.35; p=0.16) |
| Val-HeFT[10]   | 2001  | NYHA class II–IV ACEIs (93%), BBs (35%) | 5,010  | Valsartan    | Placebo    | Mean 23 months | Mortality and a combined end point of mortality and morbidity | • Death from any cause (during entire trial) (RR, 1.02; 95% CI, 0.88 to 1.18; p=0.80) |
| OPTIMAAL[14]   | 2002  | Post-MI EF ≤35%, NYHA class I–IV | 5,477  | Losartan     | Captopril  | Mean 2.7 years | All-cause mortality | • All-cause mortality (HR, 1.13; 95% CI, 0.99 to 1.28; p=0.07) |
| CHARM-Alternative, Added[21,22] | 2003  | EF ≤40%, NYHA class II–IV | 4,576  | Candesartan  | Placebo    | Median 40 months | CV death or admission to hospital for management of worsening CHF | • CV death or hospitalization for CHF (HR, 1.02; 95% CI, 0.94 to 1.18; p=0.98) |
| VALIANT[29]    | 2003  | Post-MI EF ≤35% | 14,703 | Valsartan    | Captopril  | Median 24.7 months | All-cause mortality | • All-cause-mortality valsartan vs. captopril (HR, 1.00; 97.5% CI, 0.90 to 1.11; p=0.98) |
| ONTARGET[23]   | 2008  | High-risk patients with CVD or DM, but no HF | 25,620 | Telmisartan  | Ramipril   | Mean 56 months | Death from CV cause, myocardial infarction, stroke, or hospitalization for heart failure | • Telmisartan vs. ramipril primary outcome (RR, 1.01; 95% CI, 0.94 to 1.09) |

| BB             |       |              |        |              |            |           |                 |                  |
| MDC[40]        | 1993  | HF from idiopathic DCM, EF ≤40% | 383    | Metoprolol   | Placebo    | Mean 14 months | All-cause mortality or listing for cardiac transplantation | • Primary endpoint reduced by 34% (95% CI, 6 to 62%; p=0.058) |
| CIBIS-I[29]    | 1994  | EF ≤40%, NYHA class III–IV | 641    | Bisoprolol   | Placebo    | Mean 1.9 years | All-cause mortality | • Mortality (RR, 0.8; 95% CI, 0.56 to 1.15; p=0.32) |
| U.S. Carvedilol Heart Failure[3] | 1996  | CHF EF ≤35% | 1,094  | Carvedilol   | Placebo    | Mean 6.5 months | All-cause mortality | • Mortality reduced by 65% (95% CI, 39 to 80%; p=0.001) |
| CIBIS-HF[20]   | 1999  | EF ≤35%, NYHA class III–IV | 2,647  | Bisoprolol   | Placebo    | Mean 1.3 years | All-cause mortality | • All-cause mortality (HR, 1.92; 95% CI, 0.54 to 6.81; p<0.001) |
| MERIT-HF[30]   | 1999  | EF ≤40%, NYHA class III–IV | 3,991  | Metoprolol   | CR/XL      | Mean 1 years | All-cause mortality | • All-cause mortality (HR, 1.66; 95% CI, 0.53 to 5.03; p<0.001) |
| COPERNICUS[21] | 2001  | EF ≤25%, NYHA class III–IV | 2,289  | Carvedilol   | Placebo    | Mean 10.4 months | All-cause mortality or hospital admission for CV cause | • Mortality reduced by 35% (95% CI, 19 to 48%; p=0.0014) |
| CAPRICORN[28]  | 2001  | Post-MI EF ≤40% | 1,959  | Carvedilol   | Placebo    | Mean 1.3 years | All-cause mortality or hospital admission for CV cause | • All-cause mortality (HR, 0.77; 95% CI, 0.60 to 0.98; p=0.03) |

(continued to the next page)
## Pharmacotherapy of with Reduced Ejection Fraction

### Table 1. (Continued) Summary of clinical trials that reported reduced mortality in patients with HF

| Study                        | Year | Participants | Number | Intervention          | Comparator | Follow-up | Primary endpoint                                                                 | Mortality outcome                                                                 |
|------------------------------|------|--------------|--------|------------------------|------------|-----------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| **MRA**                      |      |              |        |                        |            |           |                                                                                  |                                                                                  |
| RALES(30)                    | 1999 | EF ≤35%      | 1,663  | Spironolactone         | Placebo    | Mean 24 months | All-cause mortality                                                                  | All-cause mortality (HR, 0.70; 95% CI, 0.60 to 0.82; p<0.001)                     |
|                              |      |              |        |                        |            |           |                                                                                  | • Death from any cause (RR, 0.85; 95% CI, 0.75 to 0.96; p=0.008)                  |
|                              |      |              |        |                        |            |           |                                                                                  | • Death from CV causes or hospitalization for CV events (RR, 0.87; 95% CI, 0.79 to 0.95; p=0.002) |
| EPHESUS(31)                  | 2003 | EF ≤40%      | 6,632  | Eplerenone             | Placebo    | Mean 16 months | All-cause mortality                                                                  | All-cause mortality (HR, 0.70; 95% CI, 0.60 to 0.82; p<0.001)                     |
|                              |      |              |        |                        |            |           |                                                                                  | • Death from any cause (RR, 0.85; 95% CI, 0.75 to 0.96; p=0.008)                  |
| EPMPHASIS-HF(32)             | 2011 | EF ≤35% NYHA class II | 2,737 | Eplerenone             | Placebo    | Median 21 months | Death from CV causes or a first hospitalization for CV events | Death from CV causes or a first hospitalization for CV events (RR, 0.87; 95% CI, 0.79 to 0.95; p=0.002) |
| **ISDN**                     |      |              |        |                        |            |           |                                                                                  |                                                                                  |
| V-HeFT-I(33)                 | 1986 | EF ≤45%      | 642    | H-ISDN                 | Prazosin    | Mean 2.3 years | All-cause mortality                                                                  | Primary outcome (HR, 0.63; 95% CI, 0.54 to 0.74; p<0.001)                       |
|                              |      |              |        |                        | Placebo    |           |                                                                                  | • Mortality reduced by 34% (p=0.028)                                             |
| V-HeFT-II(34)                | 1991 | EF ≤45%      | 804    | H-ISDN                 | Enalapril   | Mean 2.3 years | All-cause mortality                                                                  | Primary outcome (HR, 0.63; 95% CI, 0.54 to 0.74; p<0.001)                       |
|                              |      |              |        |                        | Placebo    |           |                                                                                  | • Mortality reduced by 28% in enalapril (p=0.0016)                               |
| A-HeFT(35)                   | 2004 | EF ≤45%, NYHA class III–IV | 1,050 | H-ISDN                 | Placebo    | Mean 10 months | Death from any cause, a first hospitalization for HF                              | Primary outcome (HR, 0.63; 95% CI, 0.54 to 0.74; p<0.001)                       |
|                              |      |              |        |                        |            |           |                                                                                  | • Death from any cause (HR, 0.57; p<0.01)                                      |
| **ACEI**                     |      |              |        |                        |            |           |                                                                                  |                                                                                  |
| **β channel inhibitor**      |      |              |        |                        |            |           |                                                                                  |                                                                                  |
| SHIFT(36)                    | 2010 | EF ≤35% Sinus rhythm with heart rate >90 bpm | 6,558 | Ivabradine             | Placebo    | Mean 2.5 years | CV death or hospital admission for worsening HF                                   | CV death (HR, 0.95; 95% CI, 0.87 to 1.04; p=0.007)                              |
|                              |      |              |        |                        |            |           |                                                                                  | • CV death (HR, 0.92; 95% CI, 0.80 to 1.03; p=0.038)                             |
|                              |      |              |        |                        |            |           |                                                                                  | • All-cause death (HR, 0.92; 95% CI, 0.80 to 1.02; p=0.038)                       |
| **ARNI**                     |      |              |        |                        |            |           |                                                                                  |                                                                                  |
| OVERTURE(37)                 | 2002 | EF ≤30%, NYHA class II–IV | 5,770 | Omapatrilat            | Enalapril   | Mean 14.5 months | All-cause mortality or hospitalization for HF                                   | • Primary outcome (HR, 0.94; 95% CI, 0.86 to 1.03; p=0.187)                    |
|                              |      |              |        |                        |            |           |                                                                                  |                                                                                  |
| PARADIGM-HF(38)              | 2014 | EF ≤40%, NYHA class II–IV | 8,442 | Sacubitril–Valsartan   | Enalapril   | Median 27 months | Death from CV causes or hospitalization for HF                               | • Primary outcome (HR, 0.80; 95% CI, 0.73 to 0.87; p=0.001)                    |
|                              |      |              |        |                        |            |           |                                                                                  | • All-cause death (HR, 0.84; 95% CI, 0.76 to 0.93; p=0.001)                     |
| **SGLT inhibitor**           |      |              |        |                        |            |           |                                                                                  |                                                                                  |
| DAPA-HF(39)                  | 2019 | EF ≤40%, NYHA class II–IV | 4,744 | Dapagliflozin          | Placebo    | Median 18.2 months | Worsening HF or CV death                                           | • Primary outcome (HR, 0.74; 95% CI, 0.65 to 0.85; p<0.001)                    |
|                              |      |              |        |                        |            |           |                                                                                  | • CV death or HF hospitalization (HR, 0.75; 95% CI, 0.65 to 0.85; p<0.001)     |
|                              |      |              |        |                        |            |           |                                                                                  | • All-cause death (HR, 0.83; 95% CI, 0.71 to 0.97; p=NA)                       |
| **Oral sGC stimulator**      |      |              |        |                        |            |           |                                                                                  |                                                                                  |
| VICTORIA(40)                 | 2020 | EF ≤45%, NYHA class II–IV | 5,050 | Vericiguat             | Placebo    | Median 10.8 months | Death from CV causes or first hospitalization for HF | • Primary outcome (HR, 0.90; 95% CI, 0.82 to 0.98; p=0.02)                    |
|                              |      |              |        |                        |            |           |                                                                                  | • All-cause death or first hospitalization for HF (HR, 0.90; 95% CI, 0.83 to 0.98; p=0.02) |
|                              |      |              |        |                        |            |           |                                                                                  | • All-cause death (HR, 0.95; 95% CI, 0.84 to 1.07; p=0.38)                     |

ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta-blocker; CHF = chronic heart failure; CI = confidence interval; CR/XL = controlled-release/extended-release preparation; CV = cardiovascular; CVD = cardiovascular disease; DCM = dilated cardiomyopathy; DM = diabetes mellitus; EF = ejection fraction; HF = heart failure; HR = hazard ratio; H-ISDN = hydralazine-isosorbide dinitrate; MI = myocardial infarction; NYHA = New York Heart Association; RR = relative risk; QOL = quality of life; sGC = soluble guanylate cyclase; SGLT = sodium-glucose co-transporter 2.
ACEIs
Currently, ACEIs are the main drugs used to treat HF. The effectiveness of ACEIs in patients with HFrEF has been validated in several clinical studies. Data from the CONSENSUS trial were published in 1988, and showed that enalapril reduced mortality by 40% over 6 months and by 27% at the end of the study compared to placebo in 253 patients with chronic heart failure (CHF).13

Based on the CONSENSUS trial, the SOLVD trial enrolled a larger population of patients with HFrEF (n=2,569), and showed that enalapril reduced the mortality risk by 16% and hospitalization for CHF by 26% compared with placebo.40 The SAVE and TRACE trials compared the effects of captopril and trandolapril with placebo in patients with asymptomatic left ventricular (LV) dysfunction after myocardial infarction (MI). Both trials showed reduced morbidity and mortality in the ACEI group compared with the placebo group.15,16

ARBs
ARBs were expected to provide an effective alternative treatment for patients with intolerance to ACEIs, by inhibiting RAAS through a different mechanism than ACEIs.44 In the ELITE II trial published in 2000, the effects of losartan and captopril were compared in 3,152 patients with HFrEF. There were no significant differences in total deaths, sudden deaths, or resuscitated arrests and hospital admissions. In addition, fewer patients in the losartan group discontinued medications from any adverse effect or cough.17 Losartan demonstrated non-inferiority to captopril with regards to survival in the OPTIMAAL trial.19 In the VALIANT trial, valsartan demonstrated non-inferiority compared to captopril. However, the combination of valsartan and captopril presented no survival benefit, but was associated with more frequent drug-related adverse events.22

Combined treatment with an ACEI and an ARB has been evaluated in RCTs in patients with HF. The CHARM program,20,21 Val-HeFT,18 and later the ONTARGET trial, confirmed that the combination of ACEI and ARB resulted in a higher frequency of hypotensive symptoms, syncope, and renal dysfunction than ARB monotherapy.23 On the basis of these results, combined treatment with an ACEI and an ARB is not recommended in the current guidelines due to an increased risk of adverse events.

BBs
Early studies using metoprolol, bisoprolol, and carvedilol were conducted to determine whether beta-blockade affects the overall survival of patients with HF. The MDC trial compared metoprolol24; the CIBIS trial compared bisoprolol24; and the U.S. Carvedilol Heart Failure Study compared carvedilol with placebo in patients with HFrEF. Carvedilol therapy, as compared with placebo, resulted in a 65% reduction in overall mortality and a 27% reduction in the risk of hospitalization for cardiovascular causes.26 Later, CIBIS-II27 and MERIT-HF28 trials were performed in a larger population with bisoprolol and metoprolol CR/ XL, and significant reductions were reported in all-cause mortality compared with placebo when treated with ACEI. The survival benefits of BBs in patients with acute myocardial infarction (AMI) and LV dysfunction, and in patients with severe HF were also reported in the COPERNICUS29 and CAPRICORN30 trials.

MRAs
As the importance of the RAAS in HF pathophysiology becomes evident, the role of aldosterone is highlighted. The RALES trial showed that spironolactone, an aldosterone-receptor

https://doi.org/10.36011/cpp.2020.2.e17
antagonist, can improve survival in patients with CHF. In patients with AMI complicated by LV dysfunction, eplerenone demonstrated survival benefits in the EPHESUS trial. A reduction in mortality was observed with eplerenone in EMPHASIS-HF, which enrolled patients with mild symptoms of New York Heart Association (NYHA) functional class II.

Hydralazine-isosorbide dinitrate (H-ISDN)

Hydralazine and nitrates act on venous capacitance and arteriolar resistance vessels, respectively, reducing preload and afterload in patients with HF. The V-HeFT I trial, published in 1986, compared the effects of a combination of H-ISDN, prazosin, with placebo on mortality in patients with CHF. The use of H-ISDN was found to reduce all-cause mortality. However, the trial was limited to a relatively small population of 642 patients, and only included males. In V-HeFT II, the effects of enalapril and H-ISDN were compared in 804 male patients with CHF. The overall mortality was higher in the H-ISDN group. As neurohormonal blockers became standard treatment for HF, the A-HeFT trial compared the effects of H-ISDN with placebo in patients receiving standard HF therapy. The trial included 1,050 black patients, and tested the hypothesis that vasodilator therapy might be more effective in black patients based on the results of previous trials. The use of H-ISDN resulted in a significant reduction in mortality compared with placebo.

I, channel inhibitors

In patients with coronary artery disease and LV dysfunction, elevated heart rate (70 bpm or higher) is associated with an increased risk of cardiovascular (CV) outcomes. Ivabradine is a specific inhibitor of the I_{pr} current in the sinoatrial node, which slows the heart rate in patients with sinus rhythm. In the SHIFT trial, ivabradine was compared with placebo in patients with HF receiving conventional therapy. The trial enrolled 6,558 patients with an ejection fraction of less than 35% and a resting heart rate greater than 70 bpm, and followed them for an average of 22.9 months. At the end of the study, the heart rate of patients in the ivabradine group was 8.1 bpm lower than that of patients in the placebo group. Furthermore, the primary endpoint, a composite of CV death or hospital admission for worsening HF, was also significantly lower in the ivabradine group. All-cause mortality was lower in the ivabradine group, although the difference was not statistically significant. However, there were fewer deaths from HF, all-cause hospital admissions, and serious adverse events.

ARNIs

Clinical studies have also investigated the natriuretic peptide (NP) system, which represents one of the neurohormonal mechanisms of HF. Omapatrilat is a combination drug comprising an ACEI and a neprilysin inhibitor. In patients with HFrEF, omapatrilat and enalapril were compared in the OVERTURE trial, which was published in 2002. Omapatrilat was shown to reduce the risk of death and hospitalization in patients with CHF, but was not more effective than ACEI alone in reducing the risk of a primary clinical event. In terms of adverse events, angioedema was reported more frequently in the omapatrilat group compared with the enalapril group. Additionally, frequent angioedema was observed in another clinical trial using omapatrilat.

The effect of ARNI, a drug combining sacubitril and valsartan, was investigated on angioedema in the PARADIGM-HF trial, which included 8,442 patients with CHF and an ejection fraction less than 40%, and followed-up for a median duration of 27 months. ARNI and enalapril were compared for death from CV causes or hospitalization for HF as a primary outcome. This trial was terminated early due to significant primary outcome improvement in the ARNI group with a hazard ratio (HR) of 0.80. This beneficial effect was observed in death.
from any cause, with no major adverse events compared to enalapril. More recent clinical trials with ARNI will broaden the eligibility of this drug in HFrEF patients.

**Sodium-glucose co-transporter 2 (SGLT) inhibitor**

SGLT2 inhibitors represent a novel class of anti-hyperglycemic agents, which increase urinary excretion of glucose in the renal tubules. Trials investigating cardiovascular outcomes with empagliflozin, canagliflozin, and dapagliflozin demonstrated improved clinical outcomes, especially in terms of HF hospitalization. The previous clinical trials targeted diabetic patients, while the DAPA-HF trial enrolled patients with HF irrespective of diabetic status. In total, 4,744 patients with HF and an ejection fraction of ≤40% were randomly assigned to receive dapagliflozin or placebo, in addition to standard medical therapy. The primary outcome was a composite of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or cardiovascular CV death. Among patients with HFrEF, dapagliflozin reduced the primary endpoint by 26% compared with the control. In addition, the dapagliflozin group had a lower risk of all-cause mortality without an excess risk of significant adverse events, such as severe hypoglycemia.

**Oral soluble guanylate cyclase (sGC) stimulators**

As our understanding of the mechanisms underlying HF has increased, several novel signaling pathways have been identified, including the nitric oxide (NO)-sGC-cyclic guanylyl monophosphate (cGMP) pathway. Agonists of sGC can increase cGMP production, which has a protective effect on cells and tissues, including the prevention of ventricular hypertrophy and fibrosis. Recently, vericiguat, an oral sGC stimulator, demonstrated good clinical outcomes in patients with an ejection fraction less than 45%. During a median period of 10.8 months, there were significantly fewer primary endpoint events (death from CV causes or first hospitalization for HF) with an HR of 0.90, among patients in the vericiguat group compared with control group. Moreover, a composite of all-cause mortality or first hospitalization for HF was also lower in the vericiguat group.

**Other drugs investigated in clinical trials of HF**

With the advent of drugs targeting the RAAS, the mortality rate of patients with HFrEF has improved significantly. However, other efforts have been made to improve the outcomes of these patients. Such efforts aimed to augment cardiac systolic function, induce vasodilation, and target other molecules associated with the RAAS. Additionally, attempts have been made to treat patients with HFrEF based on novel molecular mechanisms; not all have been successful in lowering the mortality rate. Here, we discuss studies that despite failing to reach their primary endpoint, provided meaningful insights. These studies are summarized in Table 2.

**STRENGTHENING MYOCARDIAL CONTRACTILITY**

**Dobutamine**

Dobutamine is a sympathetic adrenergic receptor agonist that has an inotropic effect, and is useful in patients with acute refractory HF. However, it was not clear whether dobutamine would be effective in patients with severe CHF when used continuously. In the DICE trial, patients with advanced HFrEF were subjected to intermittent low-dose dobutamine infusion in addition to standard therapy for 6 months, and the outcomes were compared with placebo. Patients tolerated treatment well, but there was no improvement in mortality or functional capacity compared with placebo.
### Table 2. Summary of clinical trials in patients with HF reporting equivalent or negative results

| Target Study | Year | Participants | Number | Follow-up | Results |
|--------------|------|--------------|--------|-----------|---------|
| **Cardiostimulatory drugs** | | | | | |
| **Cardiostimulatory drugs** | | | | | |
| Dopamine | DICE55) | 1999 | NYHA class III–IV, EF ≤30% | 38 | 6 months | Intermittent low-dose dobutamine did not improve the functional status or mortality rate compared with placebo |
| Amrinone | Massie et al.56) | 1985 | NYHA class III–IV | 99 | 12 weeks | Adverse reactions were significantly more frequent and more severe with amrinone, occurring in 83% of patients |
| Milrinone | PROMISE57) | 1991 | NYHA class III–IV, EF ≤30% | 1,088 | Median 6.1 months | There was a 28% increase in all-cause mortality with milrinone therapy compared with placebo |
| Enoximone | ESSENTIAL58) | 2009 | NYHA class III–IV, EF ≤30% | 1,854 | Median 16.6 months | Composite of time to all-cause mortality or CV hospitalization did not differ compared with placebo |
| Vesnarinone | Jay et al.59) | 1998 | NYHA class III–IV, EF ≤30% | 3,833 | Mean 9.5 months | Dose-dependent increase in mortality with vesnarinone compared with placebo |
| Pimobendan | PICO60) | 1996 | NYHA class II–III, EF ≤45% | 317 | 24 weeks | In both pimobendan groups (2.5 and 5 mg) combined the hazard of death was 1.8 times higher compared with placebo |
| **Drugs with a vasodilatory effect** | | | | | |
| **Drugs with a vasodilatory effect** | | | | | |
| Levothymidine | LevoRep61) | 2014 | NYHA class III–IV, EF ≤35% | 120 | 24 weeks | Pulsed infusions of levosimendan did not significantly improve functional capacity or quality of life compared with placebo |
| Levothymidine | LION-HEART62) | 2018 | NYHA class III–IV, EF ≤35% | 69 | 12 weeks | Pulsed infusions of levosimendan significantly reduced NT-proBNP levels and risk of hospitalization Reduction of all-cause death was not statistically significant compared with placebo |
| Digoxin | DIG63) | 1997 | EF ≤45% | 3,397 | Mean 37 months | Reduced rate of hospitalization both overall and for worsening HF (RR, 0.72) compared with placebo |

**Provisional**
Phosphodiesterase inhibitors

Increased cyclic adenosine monophosphate (cAMP) in the heart induces a positive chronotropic and inotropic effect, and phosphodiesterases (PDEs) are involved in cAMP breakdown. Several subtypes of PDE exist, including PDE3, which is found in cardiac tissues.

Table 2. (Continued) Summary of clinical trials in patients with HF reporting equivalent or negative results

| Target Study | Year | Participants | Number | Follow-up | Results |
|--------------|------|--------------|--------|----------|---------|
| RAAS modulators |
| Aliskiren ALOFT[74] 2008 NYHA class II–IV 302 3 months | Reduced plasma BNP and urinary aldosterone with aliskiren |
| Aliskiren ASTRONAUT[75] 2013 NYHA class II–IV, EF ≤30% BNP >400 pg/mL or NT-proBNP >1,600 pg/mL 1,615 Median 11.3 months | No reduction in CV death or HF rehospitalization compared with placebo |
| Aliskiren ATMOSPHERE[76] 2016 NYHA class II–IV, EF ≤35% BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL 2,336 Median 36.6 months | No benefit of aliskiren added to enalapril but increased adverse events |
| Antithrombotic drugs |
| Aspirin WASH[77] 2004 EF ≤35% 279 Mean 27 month | No benefit in clinical outcome compared with placebo |
| Warfarin | More patients in the aspirin group were hospitalized for worsening HF |
| Aspirin HELAS[78] 2006 EF <35% 197 Mean 21.9 months | No clinical benefit of aspirin or warfarin compared with placebo |
| Statins |
| Rosuvastatin CORONA[82] 2007 NYHA class II–IV Age ≥60 years 5,011 Median 32.8 months | No reduction in mortality in the rosuvastatin group, but fewer hospitalization compared with placebo (p<0.001) |
| Rosuvastatin GISSI-HF[83] 2008 NYHA class II–IV (EF ≤40%: 4,113) Median 3.9 years | Rosuvastatin had no benefit on clinical outcomes including the subgroup with EF ≤40% compared with placebo |
| Anti-cytokine drugs |
| Infliximab ATTACH[84] 2003 NYHA class III–IV, EF ≤35% 150 28 weeks | No clinical benefit, and higher dose of infliximab (10 mg/kg) increased the combined risk of death from any cause or hospitalization compared with placebo due to CHF |
| Etanercept RENEWAL[85] 2004 NYHA class II–IV, EF ≤30% (RECOVER) 1,123 Median 24 weeks | Etanercept had no effect on death or hospitalization due to CHF |
| Canakinumab CANTOS[86] 2019 Prior MI hsCRP ≥2 mg/L 10,061 (HF: 2,173) Median 3.7 years | Dose-dependent reduction in hospitalization for HF and the composite of hospitalization for HF or HR-related mortality compared with placebo |

BNP = B-type natriuretic peptide; CHF = chronic heart failure; CV = cardiovascular; EF = ejection fraction; HF = heart failure; HR = hazard ratio; hsCRP = high-sensitivity C-reactive protein; LV = left ventricular; MI = myocardial infarction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; RAAS = renin-angiotensin-aldosterone system; RR = relative risk.
myocytes and has been studied widely. Amrinone is an early class drug that inhibits PDE3. However, in a trial recruiting patients with advanced HF, the use of amrinone increased the incidence of adverse effects without any significant improvement in clinical outcomes when compared with placebo. Another PDE3 inhibitor, milrinone, and enoximone have been investigated for the treatment of advanced HFrEF. However, the use of milrinone increased all-cause mortality by 28% and CV mortality by 34% when compared with placebo. In addition, the risks of hospitalization and adverse events were higher in the milrinone group. The use of enoximone did not improve clinical outcomes in patients with NYHA class II–III HFrEF compared with placebo. Similar results were reported in the ESSENTIAL trial, which included more patients with NYHA class III–IV than previous trials. A study with vesnarinone, a PDE3 inhibitor and a ion-channel modifier, resulted in a dose-dependent increase in mortality among patients with advanced HF. Consequently, PDE inhibitors are currently only used in patients with acute decompensated HF.

Calcium sensitizers
Calcium sensitizers increase myocardial contractility by retaining the calcium-binding site of troponin C in an active form, even under low calcium conditions. Pimobendan is a calcium sensitizer and PDE3 inhibitor. These agents were expected to exert a positive effect on HF by strengthening the heart muscle and relaxing the peripheral blood vessels. In the PICO trial, the effects of placebo and pimobendan were compared in patients with HFrEF. However, in the pimobendan group, both all-cause death and death or first hospitalization were higher, compared with the placebo group. Studies have also been performed using levosimendan, another calcium sensitizer. In the LevoRep trial, the effects of levosimendan and placebo were compared in patients with advanced HF and shown to improve functional capacity and quality of life. However, levosimendan did not significantly reduce event-free survival compared with placebo. In the LION-HEART trial, levosimendan was compared with placebo in a relatively small number of patients. Sixty-nine patients with HFrEF were treated with levosimendan via a 6-hour intravenous infusion every 2 weeks for 12 weeks. Levosimendan significantly reduced N-terminal pro-B-type natriuretic peptide (NT-proBNP) and hospitalization in patients with HF compared with placebo, but did not improve mortality. A larger trial may be required in future.

Cardiac glycosides
Digoxin is a cardiac glycoside that has an inotropic effect and has been widely used in patients with CHF. In the DIG trial, the effects of digoxin and placebo were compared in 3,397 patients (ejection fraction ≤45%) receiving standard treatment, including ACEI and diuretics. During the follow-up period of an average 37 months, there was no significant difference in all-cause mortality between groups. However, digoxin therapy reduced the incidence of death attributed to worsening HF (relative risk [RR], 0.88) and hospitalization due to worsening HF (RR, 0.72). Currently, digoxin is prescribed for patients with advanced HF to improve symptoms.

DRUGS WITH A VASODILATORY EFFECT

Calcium channel blockers (CCBs)
CCBs exacerbate chronic HF due to negative inotropic effects and neuroendocrine activation. Despite this, CCBs have been investigated for their potential use as vasodilators in patients with CHF. When vasodilators such as H-ISDN were a focus of HF treatment, the survival benefits of some first-generation CCBs were assessed in patients with HFrEF when added
to conventional therapy. A study evaluating the effectiveness of a first-generation CCB, nifedipine, divided patients into four groups: placebo, nifedipine, isosorbide dinitrate (ISDN), and combined nifedipine and ISDN. When either nifedipine or combination therapy was used, patients experienced more hospitalization and worse episodes of HF than patients in the ISDN group. In the DAVIT-II trial, verapamil failed to show clinical benefits in patients with HF. Similarly, a study comparing diltiazem and placebo in post-infarction patients with LV dysfunction did not show any beneficial effects, but rather increased the risk of CHF.

The second-generation CCBs, amlodipine, and felodipine have little or no negative inotropic activity at the usual therapeutic doses. Based on this, the PRAISE-I and PRAISE-II trials compared the effects of amlodipine addition in patients with HFrEF. Amlodipine did not increase CV morbidity or mortality, or demonstrated any favorable effects compared with placebo. Felodipine was also compared with placebo in patients with CHF. The drug was considered safe, and increased exercise tolerance and quality of life; however, no improvement in survival was reported. Most CCBs are not recommended for clinical use in the guidelines. Only amlodipine and felodipine are recommended for use in limited indications.

Dopamine
Ibopamine is an orally active dopamine agonist that activates DA-1 and DA-2 receptors. Dopamine agonists induce renal and peripheral vasodilation, and has a minimal inotropic effect at low doses. Based on this, dopamine was used in the early days of HF treatment, based on the belief that it caused decongestion and preserved renal function. In the PRIME-II trial, ibopamine was compared with placebo in patients with advanced HFrEF. However, the trial was stopped early because of higher mortality in the ibopamine group (RR, 1.26).

Currently, dopamine is used in some patients with acute HF who have low blood pressure; however, the evidence for long-term treatment remains insufficient.

Endothelin (ET) receptor antagonists
ET receptors contribute to blood vessel constriction by binding to ET-1 and causing the proliferation of vascular smooth muscle and cardiac hypertrophy. ET receptors are divided into ETα and ETβ, and the former subtype is mainly responsible for vasoconstriction in response to ET-1. In addition, reports have indicated that ET-1 is elevated in patients with chronic HF. Thus, the endothelin receptor antagonist (ERA) has been used as a treatment for HF via vasodilation and reversal of myocardial hypertrophy. The effectiveness of a non-selective ETA/ETβ ERA, darusentan, in patients with HFrEF was compared with placebo in the EARTH trial. Mortality was not investigated in this study, and no improvements in LV end-systolic volume or symptoms were reported. The effect on morbidity and mortality was confirmed in the ENABLE trial, which was conducted with bosentan, an ETα receptor-selective ERA. However, in patients with advanced HFrEF, there was no difference in the primary outcome (death from any cause or hospitalization for HF) between bosentan and control groups. In addition, patients in the bosentan group experienced more peripheral edema or weight gain at baseline.

Quinolone vasodilators
Flosequinan is categorized as a quinolone vasodilator with peripheral arteriolar and venous vasodilatory effects. In addition, it increases intracellular calcium levels, resulting in positive inotropic and chronotropic effects, which differ from the effects of other vasodilators or inotropes. The effects of flosequinan were demonstrated in the PROFILE trial, which enrolled patients with advanced HFrEF. However, the trial was stopped due to safety concerns after a higher number of deaths were reported in the flosequinan group (HR, 1.39).
TARGETING OTHER MOLECULES IN THE RAAS

Renin inhibitors
Direct renin inhibitors (DRIs) are novel upstream RAAS inhibitors. Aliskiren is a first-in-class, orally active DRI that is approved for the treatment of hypertension. Several clinical trials have investigated aliskiren in patients with HF. For example, the ALOFT trial compared the effects of aliskiren with placebo in patients with HF receiving standard treatment, such as ACEI and BB. Aliskiren was well tolerated by patients and succeeded in lowering plasma NT-proBNP, plasma renin activity, and urinary aldosterone excretion. However, it did not improve symptoms or other important clinical indicators. In the ASTRONAUT trial, clinical outcomes in patients with HFrEF were compared following treatment with aliskiren or placebo. The results showed that aliskiren increased the rate of hyperkalemia, hypotension, and renal dysfunction, and did not reduce CV death or HF rehospitalization when compared with placebo. In the ATMOSPHERE trial, patients were divided into 3 groups: aliskiren and enalapril, or a combination of aliskiren and enalapril. In patients with HFrEF and high BNP levels, there was no difference in the primary outcome (a composite of death from CV causes or hospitalization for HF); however, the pre-specified criterion for non-inferiority was not met. Combination therapy was reported to increase the occurrence of adverse events, such as hypotension, hyperkalemia, and serum creatinine elevation when compared with enalapril.

DRUGS WITH OTHER MECHANISMS

Antithrombotic drugs
Patients with HF have a high probability of sudden death from thromboembolic events such as MI or stroke. Arrhythmias, such as atrial fibrillation, lead to a higher risk of such events. However, it was unclear whether all patients with HF should receive antithrombotic therapy. Considering this, several RCTs have been conducted with antithrombotic drugs.

The WASH trial compared placebo, aspirin, and warfarin in patients with HFrEF who had no other indication for aspirin or warfarin. Patients with atrial fibrillation did not account for a large proportion of the study population (4% in the placebo group, 7% in the aspirin group, and 7% in the warfarin group). Although all-cause hospitalization was higher in the aspirin group compared with the placebo and warfarin groups, there were no differences in other clinical outcome. In the HELAS trial, placebo and aspirin were administered to patients with HFrEF and ischemic heart disease, and placebo and warfarin were administered to patients with HFrEF and dilated cardiomyopathy. In addition, there was no significant correlation between treatment and clinical outcome. The WATCH trial was conducted in patients with HFrEF patients and sinus rhythm. Aspirin, clopidogrel, and warfarin were compared, with no difference in mortality reported between the 3 groups. Similarly, there were no differences in clinical outcomes when comparing aspirin and warfarin in the WARCEF trial in patients with sinus rhythm and HFrEF.

Antithrombotic drugs have not been found to reduce mortality in patients with LV dysfunction and sinus rhythm; however, the development of factor-Xa inhibitors has raised expectations. In the COMMANDER HF trial, rivaroxaban, a factor Xa inhibitor, was compared with placebo in patients with HF and coronary artery disease, ejection fraction less than 40%, and no atrial fibrillation. No statistically significant benefit was reported in the composite of death from any cause, myocardial infarction, or stroke, which was the primary outcome (HR, 0.94; 95% confidence interval, 0.84–1.05; p=0.27).
Statins

Statins are prescribed widely for patients with CV disease, especially in those with coronary artery disease, for the prevention of MI. However, the effectiveness of statins in patients with HF has not been well proven. Statins may help HF by improving endothelial function owing to their anti-inflammatory properties. However, they may also induce cardiac myopathy by inhibiting the synthesis of coenzyme Q10 and selenoproteins. The CORONA trial compared rosuvastatin and placebo in elderly patients with HFrEF. Compared with placebo, the levels of high-sensitivity C-reactive protein (hsCRP) and low-density lipoprotein cholesterol were lower in the rosuvastatin group. No safety concerns were observed, and the rosuvastatin group had fewer hospitalization for CV disease. However, there was no difference in mortality between the 2 groups when compared with placebo.82) The GISSI-HF trial, which was conducted in a large population of patients with HFrEF aged 18 years or older, also compared rosuvastatin and placebo. Similarly, there was no significant difference in clinical outcomes compared with placebo.83)

Anti-cytokine drugs

Owing to a more detailed understanding of HF pathophysiology, the importance of inflammation on ventricular remodeling in HF has become evident, through mechanisms such as immunosenescence and age-related changes in the immune system.95) Several attempts have been made to reduce the mortality of patients with HF using anti-inflammatory agents. The first attempt to modulate the immune system involved the use of prednisone.96) Drugs used for the treatment of gout, such as colchicine97) and allopurinol,98) were subsequently evaluated; however, these treatments did not have a significant effect on clinical outcomes. Eventually, drugs targeting pro-inflammatory cytokines were assessed in patients with HFrEF.

Previous studies have investigated tumor necrosis factor (TNF)-α inhibitors. The ATTACH trial focused on infliximab,99) a chimeric monoclonal antibody against TNF-α, and the RENEWAL trial targeted etanercept, a recombinant human TNF receptor that binds to circulating TNF. These anti-inflammatory drugs were compared with placebo in patients with advanced HFrEF. However, the results showed no risk reduction on mortality or hospitalization. Recently, a large RCT was conducted with an interleukin-1β inhibitor, canakinumab. In the CANTOS trial, patients were randomly assigned to treatment with canakinumab 50, 150, 300 mg, or placebo. The study enrolled 10,061 patients with prior history of MI and hsCRP >2 mg/L. In the canakinumab group, there was a trend for a dose-dependent reduction in hospitalization for HF and a composite of hospitalization for HF or HF-related mortality. However, these results were not statistically significant in patients who initially had a history of CHF.86) Despite these findings, the CANTOS trial provided possibilities for the identification of novel treatments for HFrEF.

CONCLUSION

In patients with HFrEF, pharmacological treatments involving neurohormonal blockade have demonstrated substantial success. However, in phase III clinical trials, many drugs demonstrated no significant improvement in primary endpoints, despite the potential benefits found in pilot studies and based on the underlying mechanisms of action. These efforts have led to a better understanding of HFrEF pathophysiology and have provided insights into the identification of new drug targets. Several novel drugs and interventions are under evaluation in patients with HFrEF. The novel pharmacotherapy for HFrEF may open a new paradigm for improving the outcome of these patients.
REFERENCES

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowski EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 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.

2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, Michelson EL, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128:1810-52.

3. Kim MS, Lee IH, Kim EL, Park DG, Park SJ, Park JJ, Shin MS, Yoo BS, Youn JC, Lee SE, Ihm SH, Jang SY, Jo SH, Cho JY, Cho HJ, Choi S, Choi JO, Han SW, Hwang KK, Jeon ES, Cho MC, Chae SC, Choi DJ. Korean guidelines for diagnosis and management of chronic heart failure. Korean Circ J 2017;47:555-64.

4. Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Dasi SR, Delling FN, Dzau VJ, Fung PC, Fung W, Geraci SA, Glidden DV, Gersh BJ, Granger CB, Gualdi-Russo E, Handler J, Hage ME, Haga S, Hagiwara M, Hiatt WR, Hlatky MA, Hong YK, Hostetter TH, Hotamisligil GS, Iribarren C, Izzat SB, Jacewicz SR, Jorgensen J, Josephson KE, Jordan LC, Khan SS, Kissela BM, Knudsen KL, Kwon D, Lang RM, Lee KR, Lee RT, Lewis T, Lichtman JH, Lopez-Jimenez F, Lurbe E, MacFarlane PW, McKenney JM, Mehta JS, Mehilli J, Mehta RH, Melgar V, Meschia JF, Mende DR, Mentz RJ, Mirowski P, Mok A, Moulton PL, Napolitano LM, O’Rourke RA, Olson LS, Palinski W, Park MC, Paty PS, Peberdy MA, Peiris A, Perak AM, Philpot M, Plowman P, Powers WJ, Probstfield JL, Quinn PE, Rand GM, Ratcliffe J, Rgi M, Rosing J, Rotem A, Ruilope LM, Savonuzzi M, Schmieder RE, Schulte-Monting J, Schuster RM, Selker HP, SKassebaum NJ, Slavens ME, Sperling MR, Spyropoulos AC, Stein J, Stern M, Stewart JA, Stroes ES, Sullivan LM, Tighiouart M, Towfighi A, Trivedi RH, Tyroler HA, Uribarri J, Uy-Esquivel CR, Valente AR, Violante F, Virani SS; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation 2019;139:e56-528.

5. Lee JH, Lim NK, Cho MC, Park HY. Epidemiology of heart failure in Korea: present and future. Korean Circ J 2016;46:658-64.

6. Youn JC, Han S, Ryu KH. Temporal trends of hospitalized patients with heart failure in Korea. Korean Circ J 2017;47:16-24.

7. Lee SE, Lee HY, Cho HJ, Cheo WS, Kim H, Choi JO, Jeon ES, Kim MS, Kim JJ, Hwang KK, Chae SC, Baek SH, Kang SM, Choi DI, Yoo BS, Kim KH, Park HY, Cho MC, Oh BH. 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.

8. Stewart Coats AI. Common co-morbidities in heart failure – diabetes, functional mitral regurgitation and sleep apnoea. Int J Heart Fail 2019;1:25-41.

9. Choi HM, Park MS, Youn JC. Update on heart failure management and future directions. Korean J Intern Med 2019;34:944.

10. Packer M. How should physicians view heart failure? The philosophical and physiological evolution of three conceptual models of the disease. Am J Cardiol 1993;71:3C-4C.

11. Pepper GS, Lee RW. Sympathetic activation in heart failure and its treatment with beta-blockade. Arch Intern Med 1999;159:225-34.

12. Lee HY, Oh BH. Paradigm shifts of heart failure therapy: do we need another paradigm? Int J Heart Fail 2020;2:145-56.

13. Swedberg K, Kjekshus J. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). Am J Cardiol 1988;62:60A-6A.
14. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, 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.

15. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EL Jr, Cuddy TE, Davis RR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Hawkins CM. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. N Engl J Med 1992;327:669-77.

16. Køber L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, Videbaek J, Cole DS, Auclert L, Pauly NC. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 1995;333:1670-6.

17. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, Konstam MA, Riegger G, Klinger GH, Neaton J, Sharma D, Thiyagarajan B. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. Lancet 2000;355:1582-7.

18. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2000;345:1667-75.

19. Dickstein K, Kjekshus J; OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet 2002;360:752-60.

20. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S; CHARM Investigators and Committees. Effects of losartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362:759-66.

21. Young JB, Dunlap ME, Pfeffer MA, Probstfield JL, Cohen-Solal A, Dietz R, Granger CB, Hradec J, Kuch J, McKelvie RS, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Solomon SD, Yusuf S, Swedberg K; Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) Investigators and Committees. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. Circulation 2004;110:2618-26.

22. Pfeffer MA, McMurray JJ, Velazquez EI, Rouleau JL, Kober L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkovsk S, Sellers MA, Caillf RM; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349:1893-906.

23. ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547-59.

24. Waagstein F, Bristow MR, Swedberg K, Camerini F, Fowler MB, Silver MA, Gilbert EM, Johnson MR, Goss FG, Hjalmarson A. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDCG) Trial Study Group. Lancet 1993;342:1441-6.

25. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. Circulation 1994;90:1765-73.

26. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. 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.

27. Drummond GA, Squire IB. The Cardiac Insufficiency Bisoprolol Study II. Lancet 1999;353:1361.
28. MERIT-HF Study Group. 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.

29. Packer M, Coats AJ, Fowler MB, Katus HA, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roeger EB, Schulz MK, DeMets DL; Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651-8.

30. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001;357:1385-90.

31. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709-17.

32. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleinman J, Gatlin M; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:309-21.

33. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11-21.

34. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH, Goldman S, Cobb FR, Shah PM, Saunders R, Fletcher RD, Loeb HS, Hughes VC, Baker B. 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.

35. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB, Loeb H, Wong M, Bhat G, Goldman S, Fletcher RD, Doherty J, Hughes CV, Carson P, Cintron G, Shabetai R, Haakenson C. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303-10.

36. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr, Ferdinand K, Taylor M, Adams K, Sabolinski M, Worcel M, Cohn JN; African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351:2049-57.

37. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010;376:875-85.

38. Packer M, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau JL, Swedberg K. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation 2002;106:920-6.

39. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizzkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.

40. McMurray JJV, Solomon SD, Inzucchi SE, Kaber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bellohlavěk J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukat A, Ge J, Howlett LG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O’Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Doherty KF, Hjund PS, Bengtsson O, Sjøstrand M, Langkilde AM; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995-2008.

41. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CSP, Ponikowski P, Voors AA, Jia G, McNulty SE, Patel MJ, Roessig L, Koglin J, O’Connor CM; VICTORIA Study Group. Vericiguat in patients with heart failure and reduced ejection fraction. N Engl J Med 2020;382:1883-93.
42. Kim KJ, Cho HJ, Kim MS, Kang J, Kim KH, Kim D, Seo SM, Yang JH, Cha MJ, Choi JJ, Choi DJ. Focused update of 2016 Korean Society of Heart Failure guidelines for the management of chronic heart failure. Int J Heart Fail 2019;1:4-24.

43. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;136:e137-61.

44. Goodfriend TL, Elliott ME, Cartt KJ. Angiotensin receptors and their antagonists. N Engl J Med 1996;334:1649-54.

45. Massie B, Chatterjee K, Werner J, Greenberg B, Hart R, Parmley WW. Hemodynamic advantage of combined administration of hydralazine orally and nitrates nonparenterally in the vasodilator therapy of chronic heart failure. Am J Cardiol 1977;40:794-801.

46. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R; BEAUTIFUL investigators. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. Lancet 2008;372:817-21.

47. DiFrancesco D. Funny channels in the control of cardiac rhythm and mode of action of selective blockers. Pharmacol Res 2006;53:399-406.

48. Kostis JB, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. Am J Hypertens 2004;17:103-41.

49. Kim JJ, Youn JC. Eligibility and usage of sacubitril/valsartan in Korea. Int J Heart Fail 2019;1:69-71.

50. Vasilakou D, Karagiannis T, Athanasiadou E, Mainoudou M, Liakos A, Bekiaris E, Sarigianni M, Matthews DR, Tsapas A. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013;159:262-74.

51. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedel U, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.

52. Neel B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Ernoud N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.

53. Wickstrom SD, Rat I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JP, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruif CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:543-57.

54. Stach JP, Packer P, Evgenov OV. Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease. Circulation 2011;123:2263-73.

55. Oliva F, Latini R, Politi A, Staszeswsky L, Maggioni AP, Nicolii E, Mau E. Intermittent 6-month low-dose dobutamine infusion in severe heart failure: DICE multicenter trial. Am Heart J 1999;138:247-53.

56. Massie B, Bourassa M, DiBianco R, Hess M, Konstam M, Likoff M, Packer M. Long-term oral administration of amrinone for congestive heart failure: lack of efficacy in a multicenter controlled trial. Circulation 1985;71:963-71.

57. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendris GH, Bonner WJ, Elkayam U, Kukin ML, Mallis GI, Sollano JA, Shannon J, Tandon PK, DeMets DL; The PROMISE Study Research Group. Effect of oral milrinone on mortality in severe chronic heart failure. N Engl J Med 1991;325:1468-75.
58. Metra M, Eichhorn E, Abraham WT, Linseman J, Böhm M, Corbalan R, DeMets D, De Marco T, Elkayam U, Gerber M, Komajda M, Liu P, Mareev V, Perrone SV, Poole-Wilson P, Roecker E, Stewart J, Swedberg K, Tendera M, Wiens B, Bristow MR; ESSENTIAL Investigators. Effects of low-dose oral enoximone administration on mortality, morbidity, and exercise capacity in patients with advanced heart failure: the randomized, double-blind, placebo-controlled, parallel group ESSENTIAL trials. Eur Heart J 2009;30:3015-26. PUBMED | CROSSREF

59. Cohn JN, Goldstein SO, Greenberg BH, Lorette BH, Bourge RC, Jaski BE, Gottlieb SO, McGrew F 3rd, DeMets DL, White BG. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. Vesnarinone Trial Investigators. N Engl J Med 1998;339:1810-6. PUBMED | CROSSREF

60. Lubsen J, Just H, Hjalmarsson AC, La Framboise D, Remme WJ, Heinrich-Nols J, Dumont JM, Seed P. Effect of pimobendan on exercise capacity in patients with heart failure: main results from the Pimobendan in Congestive Heart Failure (PICO) trial. Heart 1996;76:223-31. PUBMED | CROSSREF

61. Altenberger J, Parissis JT, Costard-Jaekle A, Winter A, Ebner C, Karavidas A, Sihorsch K, Avgeropoulou E, Weber T, Dimopoulos L, Ulmer H, Poezl G. Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study: a multicentre randomized trial. Eur J Heart Fail 2014;16:898-906. PUBMED | CROSSREF

62. Comín-Colet J, Manito N, Segovia-Cubero J, Delgado J, Garcia Pinilla JM, Almenar L, Crespo-Leiro MG, Sionis A, Blasco T, Pascual-Figal D, Gonzalez-Vilchez F, Lambert-Rodriguez JL, Grau M, Bruguera J; LION-HEART Study Investigators. Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: the LION-HEART multicentre randomised trial. Eur J Heart Fail 2018;20:1128-36. PUBMED | CROSSREF

63. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525-33. PUBMED | CROSSREF

64. Elkayam U, Amin J, Mehr A, Vasquez J, Weber L, Rahimtoola SH. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. Circulation 1990;82:1954-61. PUBMED | CROSSREF

65. Danish Study Group on Verapamil in Myocardial Infarction. Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II--DAVIT II). Am J Cardiol 1990;66:779-85. PUBMED | CROSSREF

66. Goldstein RE, Boccuzzi SJ, Cruess D, Nettel S. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. Circulation 1991;83:52-60. PUBMED | CROSSREF

67. Packer M, O’Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, Miller AB, Neuberg GW, Frid D, Wertheimer IH, Cropp AB, DeMets DL. Effect of amiodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amiodipine Survival Evaluation Study Group. N Engl J Med 1996;335:1107-14. PUBMED | CROSSREF

68. Packer M, Carson P, Elkayam U, Konstam MA, Moe G, O’Connor C, Rouleau JL, Schocken D, Anderson SA, DeMets DL; PRAISE-2 Study Group. Effect of amiodipine on the survival of patients with severe chronic heart failure due to a nonischemic cardiomyopathy: results of the PRAISE-2 study (prospective randomized amiodipine survival evaluation 2). JACC Heart Fail 2013;1:308-14. PUBMED | CROSSREF

69. Cohn JN, Ziesche S, Smith R, Anand I, Dunkman WB, Loeb H, Cintron G, Boden W, Baruch L, Rochin P, Loss L. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. Vasodilator-Heart Failure Trial (V-HeFT) Study Group. Circulation 1997;96:856-63. PUBMED | CROSSREF

70. Hampton JR, van Veldhuisen DJ, Kleber FX, Cowley AJ, Ardia A, Block P, Cortina A, Cserhalmi L, Folliath F, Jensen G, Kayanakis J, Lie KL, Mancia G, Skene AM. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. Lancet 1997;349:571-7. PUBMED | CROSSREF
71. Anand I, McMurray J, Cohn JN, Konstam MA, Notter T, Quitzau K, Ruschitzka F, Lüscher TF; EARTH investigators. Long-term effects of darusentan on left-ventricular remodelling and clinical outcomes in the EndothelinA Receptor Antagonist Trial in Heart Failure (EARTH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364:347-54.

72. Packer M, McMurray JJV, Krum H, Kiowski W, Massie BM, Caspi A, Pratt CM, Petrie MC, DeMets D, Kobrin I, Roux S, Wedberg K; ENABLE Investigators and Committees. Long-term effect of endothelin receptor antagonism with bosentan on the morbidity and mortality of patients with severe chronic heart failure: primary results of the ENABLE trials. JACC Heart Fail 2017;5:317-26.

73. Packer M, Pitt B, Rouleau JL, Wedberg K, DeMets DL, Fisher L. Long-term effects of flosequinan on the morbidity and mortality of patients with severe chronic heart failure: primary results of the PROFILE trial after 24 years. JACC Heart Fail 2017;5:399-407.

74. McMurray JJ, Pitt B, Latini R, Maggioni AP, Solomon SD, Keefe DL, Ford J, Verma A, Lewsey J; Aliskiren Observation of Heart Failure Treatment (ALOFT) Investigators. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. Circ Heart Fail 2008;1:17-24.

75. Gheorghiade M, Böhm M, Greene SJ, Fonarow GC, Lewis EF, Zannad F, Solomon SD, Baschiera F, Botha J, Hua TA, Gimpelwiecz CR, Jaumont X, Lesogor A, Maggioni AP, ASTRONAUT Investigators and Coordinators. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial. JAMA 2013;309:1125-35.

76. McMurray JJ, Krum H, Abraham WT, Dickstein K, Køber LV, Desai AS, Solomon SD, Greenlaw N, Ali MA, Chiang Y, Shao Q, Tarnsby G, Massie BM; ATMOSPHERE Committees Investigators. Aliskiren, enalapril, or aliskiren and enalapril in heart failure. N Engl J Med 2016;374:1521-32.

77. Cleland JG, Findlay I, Jafri S, Sutton G, Falk R, Bullpitt C, Prentice C, Ford I, Trainer A, Poole-Wilson PA. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. Am Heart J 2004;148:157-64.

78. Cokkinos DV, Haralabopoulos GC, Kostis JB, Toutouzas PK; HELAS investigators. Efficacy of antithrombotic therapy in chronic heart failure: the HELAS study. Eur J Heart Fail 2006;8:428-32.

79. Massie BM, Collins JF, Ammon SE, Armstrong PW, Cleland JG, Ezekowitz M, Jafri SM, Krol WF, O’Connor CM, Schulman KA, Too K, Warren SR; WATCH Trial Investigators. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. Circulation 2009;119:1616-24.

80. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, Ammon SE, Graham S, Sacco RL, Mann DL, Mohr JP, Massie BM, Labovitz AJ, Anker SD, Lok DJ, Ponikowski P, Estol CJ, Lip GY, Di Tullio MR, Sanford AR, Meija V, Gabriel AP, de Valles ML, Buchsbaum R; WARCEF Investigators. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med 2012;366:1859-69.

81. Zannad F, Anker SD, Byra WM, Cleland JGF, Fu M, Gheorghiade M, Lam CSP, Mehra MR, Neaton JD, Nessel CC, Sprio TE, van Veldhuisen DJ, Greenberg B; COMMANDER HF Investigators. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. N Engl J Med 2018;379:1332-42.

82. Kjeskhus I, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel HJ, Dunselman P, Fonseca C, Guoide A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Janso A, Kamensky G, Komajda M, Kowricki J, Kuius T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schafelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J; CORONA Group. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357:2248-61.

83. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G; GISSI-HF Investigators. Effect of rosvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1231-9.

84. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT; Anti-TNF Therapy Against Congestive Heart Failure Investigators. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure.

https://e-jcpp.org
failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation 2003;107:3133-40.

85. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, Dijan I, Drexler H, Feldman A, Kober L, Krum H, Liu P, Nieminen M, Tavazzi L, van Veldhuisen DJ, Waldenstrom A, Warren M, Westheim A, Zannad F, Fleming T. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation 2004;109:1594-602.

86. Everett BM, Cornel JH, Lainscak M, Anker SD, Abbate A, Thuren T, Libby P, Glynn RJ, Ridker PM. Anti-inflammatory therapy with canakinumab for the prevention of hospitalization for heart failure. Circulation 2019;139:1289-99.

87. Leroy J, Fischmeister R. Inhibit a phosphodiesterase to treat heart failure? Circulation 2018;138:2003-6.

88. Uretsky BF, Jessup M, Konstam MA, Dec GW, Leier CV, Benotti J, Murali S, Herrmann HC, Sandberg JA. Multicenter trial of oral enoximone in patients with moderate to moderately severe congestive heart failure. Lack of benefit compared with placebo. Enoximone Multicenter Trial Group. Circulation 1990;82:774-80.

89. Lee JH, Kim MS, Yoo BS, Park SJ, Park JJ, Shin MS, Youn JC, Lee SE, Jang SY, Choi S, Cho HJ, Kang SM, Choi DJ. KSHF guidelines for the management of acute heart failure: Part II. Treatment of acute heart failure. Korean Circ J 2019;49:22-45.

90. Kas DA, Solaro RJ. Mechanisms and use of calcium-sensitizing agents in the failing heart. Circulation 2006;113:305-15.

91. Francis GS. Calcium channel blockers and congestive heart failure. Circulation 1991;83:336-8.

92. Lüscher TF, Barton M. Endothelins and endothelin receptor antagonists: therapeutic considerations for a novel class of cardiovascular drugs. Circulation 2000;102:2434-40.

93. Gradman AH, Kad R. Renin inhibition in hypertension. J Am Coll Cardiol 2008;51:519-28.

94. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993;22:6A-13A.

95. Park MS, Youn JC. A new era of targeting pathogenic immune mechanisms in cardiovascular disease. Korean Circ J 2018;48:489-44.5.

96. Parrillo JE, Cunnon RE, Epstein SE, Parker MM, Suroedini AF, Brenner M, Schaer GL, Palmeri ST, Cannon RO 3rd, Alling D, Wittes JT, Ferrans VI, Rodriguez ER, Fauci AS. A prospective, randomized, controlled trial of prednisone for dilated cardiomyopathy. N Engl J Med 1989;321:1061-8.

97. Deftereos S, Giannopoulou G, Panagopoulou V, Bouras G, Raisakos K, Kossyvakis C, Karageorgiou S, Papadimitriou C, Vastaki M, Kaoukis A, Angelidis C, Pagoni S, Pyrgakis V, Alexopoulos D, Manolis AS, Stefanadis C, Cleman MW. Anti-inflammatory treatment with colchicine in stable chronic heart failure: a prospective, randomized study. JACC Heart Fail 2014;2:131-7.

98. Givertz MM, Anstrom KJ, Redfield MM, Deswal A, Haddad H, Butler J, Tang WH, Dunlap ME, LeWinter MM, Mann DL, Felker GM, O'Connor CM, Goldsmith SR, Offili EO, Saltzberg MT, Margulies KB, Cappola TP, Konstam MA, Semigran MJ, McNulty SE, Lee KL, Shah MR, Hernandez AF; NHLBI Heart Failure Clinical Research Network. Effects of xanthine oxidase inhibition in hyperuricemic heart failure patients: the Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) study. Circulation 2015;131:1763-71.