Journal of Cardiology 81 (2023) 26–32

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Review

New paradigm shift in the pharmacotherapy for heart failure-where are we now and where are we heading?

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ARTICLE INFO

Article history:
Received 4 November 2021
Revised 24 January 2022
Accepted 8 February 2022
Available online 25 February 2022

Keywords:
Pharmacotherapy
Heart failure
Angiotensin receptor-neprilysin inhibitor
Sodium glucose co-transporter inhibitor
Ivabradine

ABSTRACT

Over the past 30 years, accumulating evidence has shown that three main therapies including angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, ß-blockers, and mineralocorticoid receptor antagonists are the standard treatment for patients with heart failure (HF) who exhibit reduced ejection fraction (EF). However, lessons learned from recent large-scale clinical trials have added a paradigm shift including angiotensin receptor-neprilysin inhibitor, sodium glucose co-transporter 2 inhibitor, and ivabradine. In addition, soluble guanyl cyclase stimulator and omecamtiv mecarbil are also suggested as next generation therapeutic measures for these patients. From these clinical trials, we learned some patients with preserved EF will benefit from certain agents, which has been one of the largest unmet needs over these decades. This article will review these paradigm shifts over the past 10 years and address a new therapeutic algorithm for patients with HF.

Introduction

The three major drugs of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEI/ARB), β-blocker, and mineralocorticoid receptor antagonists (MRAs) have long been used as the standard treatment agents for patients with heart failure (HF). Since the aging society has progressed, HF with preserved ejection fraction (EF) has been drawing attention, and numerous clinical studies have been conducted over time, yet the effective treatment for such HF cases has not been established. A new category of HF with mildly-reduced EF was introduced in the 2017 revision of the Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure in Japan, against which no treatment method has been established to date [1]. Under these circumstances, various studies have reported the efficacy of new treatment agents for HF, which consequently increased the need to review the new standard treatment agent for HF. The present article discusses the efficacy and application of the recently approved agents in Japan and the prospects of several unapproved agents under review.

Angiotensin receptor-neprilysin inhibitor

Atrial natriuretic peptide (ANP) was isolated for the first time from human atrial muscle in 1984 [2], and since then the research of natriuretic hormone has rapidly progressed, and the natriuretic peptide was isolated at ventricular muscle as well [3]. ANP is stored as granules and secreted in response to various stimuli, whereas brain natriuretic peptide (BNP) induces its gene expression in response to stretching [4]. Both hormones increase in patients with HF exponentially according to the level of severity, and it is a well-known fact that they are used as the biomarker of patients with HF. In addition, natriuretic peptides act protectively *in vivo* against cardiac hypertrophy or fibrosis induced by various stress, as evidenced by the fact that cardiac hypertrophy and fibrosis are induced in natriuretic peptide receptor-A (NPR-A) knockout mice without ANP/BNP receptors [5]. Cardiac hypertrophy and fibrosis are also exacerbated in BNP knockout mice with pressure overload [6]. Guanyl cyclase (GC) is an intracellular second messenger, and GC-A knockout mice exhibit cardiac hypertrophy, which can be reversed by simultaneous deletion of angiotensin type 1 receptor [7] (Fig. 1).

As above, the protective effects of ANP and BNP are evident, yet somehow, these effects in humans remained elusive, as exemplified in the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF), in which a total of 7141 patients with acute HF were randomized into two groups of nesiritide-administered group and placebo-administered group. The number of deaths in the 30 days duration did not show any significant difference [8]. A similar study using ANP formulated carperitide was conducted in Japan, in which the total number of deaths or rehospitalization in the observation period of 18 months was significantly lower in the carperitide administered

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https://doi.org/10.1016/j.jjcc.2022.02.008
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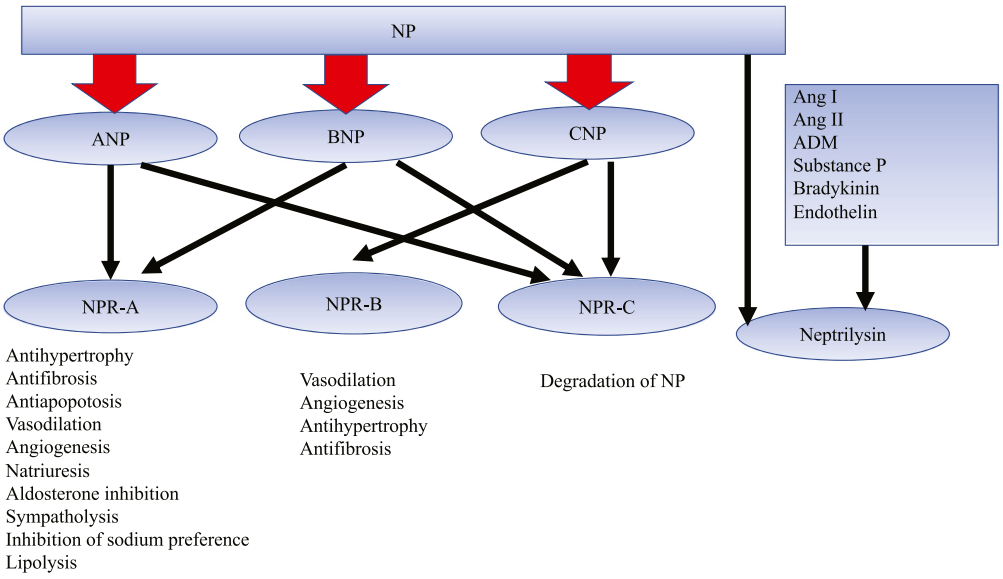

Fig. 1. Metabolic pathway of natriuretic peptides
NP, natriuretic peptide; ANP/BNP/CNP, atrial/brain/C type NP; NPR-A/NPR-B/NPR-C, NP receptor-A/B/C; Ang, angiotensin; ADM, adrenomedullin.

group. However, the study population included only 49 cases and the study was an open-label design [9].

Neprilysin inhibitors inhibit degradation of the natriuretic peptide to increase endogenous natriuretic peptide concentration. Omapatrilat that inhibits both angiotensin-converting enzyme and neprilysin was developed. A study targeting patients with HF was conducted as the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial, but the development was terminated due to the occurrence of angioedema [10]. One of the reasons for the occurrence was probably associated with the fact that various vasoactive substances are also the substrates of neprilysin, such as bradykinin [11]. The effect of ACEI that increases endogenous bradykinin concentration by inhibiting kininase II probably contributed to the occurrence of angioedema [12,13]. Angiotensin II is also included as the substrates of neprilysin; therefore, it is desirable to administer the ARB to antagonize the increase of angiotensin II. Thus, sacubitril/valsartan has come to be used in clinical applications.

In the Prospective Comparison of ARNI with ACE inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF), a series of double-blind randomized trials of sacubitril/valsartan were performed on a total of 8442 cases of patients with chronic HF with less than 35% of left ventricular EF, those with BNP concentration $\geq$ 150 pg/ml or N-terminal proBNP (NT-proBNP) concentration $\geq$ 600 pg/ml (if the patient had a history of hospitalization with HF in the past 12 months, thresholds were $\geq$ 100 pg/ml and $\geq$ 400 pg/ml, respectively), and those receiving appropriate HF medication of ACEI, ARB, or β-blocker. The tolerance against ACEI and sacubitril/valsartan was checked in advance of the randomization. The 200 mg dosage of sacubitril/valsartan was administered twice per day for the sacubitril/valsartan administered group, and 10 mg of enalapril was administered twice per day for the ACEI administered group. During the observation period, the primary endpoint with a median of 27 months was hospitalization due to cardiovascular death or HF, 20% of which decreased in the sacubitril/valsartan administered group. The number of total deaths also decreased by 16% in the sacubitril/valsartan administered group [14]. Similar studies on smaller scales were conducted in Japan as well. Participants were randomly assigned to the relevant groups after administering 50 mg per dose of sacubitril/valsartan twice to confirm their tolerance. Although no significant difference was observed in both groups regarding the same primary endpoint as the PARADIGM-HF trial, the sacubitril/valsartan administered group showed a lower value in the secondary endpoint of the NT-proBNP concentration [15]. The drug has been approved for insurance coverage based on the results of these studies.

A study targeting cases of acute HF, PIONEER-HF (Comparison of Sacbitril-Valsartan versus Enalapril on Effect of NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode), was performed as well. Hospitalized participants with stable hemodynamics were assigned randomly to the sacubitril/valsartan administered group or the enalapril administered group. Patients were enrolled in this trial a median of 68 h (interquartile range, 48–98 h) after initial presentation to the hospital. The primary endpoint of NT-proBNP concentration showed a lower value in the sacubitril/valsartan administered group. It should be noted that the number of those who were administered either ACEI or ARB prior to the randomization in this study was less than half of the participants [16].

In addition, studies were also conducted on HF cases with preserved EF. A total of 4822 patients with chronic HF showing left ventricular EF of $\geq$ 45% and a high concentration level of BNP or NT-proBNP participated in the study, using valsartan as the control drug. The primary endpoint of the number of cardiovascular deaths or hospitalizations due to HF decreased by 13% in the sacubitril/valsartan administered group without reaching the level of significance. The predominance of sacubitril/valsartan was confirmed at left ventricular EF $\leq$ 57% in the preset stratified analysis [17].

According to the results above, medical guidelines in Europe, the USA, and Japan recommend switching from ACEI/ARB to ARNI for HF cases with reduced EF and persistent HF symptoms [18–20]. Switching to ARNI should be possible during the recovery from acute HF. Setting 36 h interval is recommended in switching from ACEI, while ARB can be replaced with ANRI immediately. More than 30 ml/min/m^2 of estimated glomerular filtration rate (eGFR) is recommended; in the presence of eGFR $<$ 30 ml/min/m^2, careful administration is required. The administration of a MRA is not necessarily mandatory prior to ARNI; it can be administered

in HF cases without ACEI/ARB administration. The ARNI administration to the patients with HF without ACEI/ARB administration showed improvement in left ventricular EF by 12% in the PROVE-HF trial [21]. The primary endpoint of decrease in NT-proBNP also showed a similar decrease level in the patient group without ACEI/ARB administration in the PIONEER-HF trial [16]. As shown in the above results, ANRI administration is recommended even for the patients without ACEI/ARB administration in the ACC/AHA Expert Consensus Document [19]. Its application to patients with HF with preserved EF is not currently recommended. However, the stratified analysis results in the PARAGON-HF trial indicated that the ANRI application to the patients with HF with mildly-reduced EF could show promising effects. The JCS/JHFS 2021 guideline focused update described switching from ACEI/ARB to ARNI as class I and evidence level A. However, for ACEI/ARB naïve patients, indication of ARNI for HF with reduced EF was class IIa, although not approved for insurance coverage. For patients with HF with mildly-reduced EF and those with preserved EF, indication was class IIa and class IIb, respectively [20].

There are some concerns regarding some aspects using ARNI in clinical practice in patients with HF, such as renal function, serum potassium level, and control of diabetes. In this regard, post-hoc analyses of PARADIGM-HF have shown that HbA1c level was decreased to a greater extent in patients who received ARNI than those who received enalapril, and HbA1c level was persistently lower in patients who received ARNI over the 3-year follow-up period. New use of insulin was 29% lower in patients receiving sacubitril/valsartan compared with those receiving enalapril [22]. In addition, sacubitril/valsartan attenuated the effect of diabetes to accelerate the deterioration of renal function that occurred in patients with HF [23]. Severe hyperkalemia was more common in patients assigned to enalapril than to sacubitril/valsartan among patients taking an MRA at baseline [24]. Since ß-amyloid peptide is also a substrate for neprilysin, some investigators wonder if this agent might accelerate the accumulation of ß-amyloid peptide in the brain, causing Alzheimer's disease [25]. Although there is no evidence supporting this issue for other neprilysin inhibitors, we should address the safety of sacubiril/valsartan over the long-term period.

SGLT2i

A number of studies have addressed the effects of SGLT2i in various patient groups (Table 1) [26–37]. Among them, a series of outcomes trials subjecting patients with type II diabetes on SGLT2i using empagliflozin, dapagliflozin, and canagliflozin in the period from 2015 to 2019 indicated that the number of cardiovascular deaths or HF hospitalizations were significantly decreased [26–28]. The effects manifested very early at the initiation stage of dosage and did not show relevance to any vascular events related to the arteriosclerosis, including myocardial infarction and stroke; therefore, it was considered irrelevant to the secondary prevention effect against diabetes. Although it has not been proven yet, various mechanisms as shown in Fig. 2 have been proposed thus far, suggesting a possibility of the direct effect different from the antidiabetic drug [38,39]. Thus, the clinical trials of SGLT2i as an HF treatment agent have been conducted regardless of the presence/absence of diabetes.

The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial was conducted in patients with chronic HF showing New York Heart Association class II/III, left ventricular EF $\leq$ 40%, and a high concentration of NT-proBNP. A total of 4744 patients were assigned either to the dapagliflozin administered group or the placebo administered group, regardless of the presence/absence of diabetes. The primary endpoint of the number of cardiovascular deaths or HF hospitalizations decreased by 26% in the dapagliflozin administered group in the 18.2 months' observation period. The same degree of effect was confirmed among patients regardless of the presence/absence of diabetes [34]. Of note, dapaglifozin reduced the risk of death and worsening HF and improved symptoms across the broad spectrum of age in this study [40]. The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trial is a similar test targeting patients with chronic HF. The number of cardiovascular deaths or hospitalizations due to HF exacerbation decreased by 25% [35]. Another trial subjecting HF cases with preserved EF, EMPEROR-Preserved trial, was conducted. In this trial, 5988 patients with class II-IV HF and left ventricular EF $>$ 40% and increased NT-proBNP level were randomized to receive 10 mg empaglifozin or placebo. Over a median follow-up period of 26.2 months, the primary endpoint defined as a composite of cardiovascular death or hospitalization due to HF exacerbation was decreased by 21% [36]. As for sotagliflozin, which affects intestinal glucose absorption through the SGLT1 inhibiting effect as well, cardiovascular death or HF hospitalization was decreased in acute HF cases complicating diabetes [37]. Dapaglifozin reduced the risk of kidney failure and cardiovascular death/HF hospitalization and prolonged survival in chronic kidney disease with or without type 2 diabetes, which was independent of history of HF [41]. From these findings, JCS/JHFS guideline focused update described that dapaglifozin and empaglifozin are recommended as class I and evidence level A drugs for HF with reduced EF, in patients who are already taking ACEI/ARB [20].

Ivabradine

The heart rate (HR) has been regarded as a crucial prognosticator in cases such as coronary artery disease since the 1980s [42]. The Framingham Heart Study results indicate that the HR increase would lead to a poor vital prognosis in the general public, showing data of the increase in sudden death or HF cases [43,44]. Generally speaking, mammals with a high level of HR have a shorter lifespan, suggesting a concept that the amount of energy or oxygen consumed in the entire life was fixed [45]. Humans are exceptions among mammals, showing a relatively long lifespan despite the HR; contributing factors, such as lifestyle, medical advancement, achievements in preventive medicine, and improvement in nutrition intake, play a crucial role, yet at the same time, the HR increase in humans would also lead to a poor prognosis.

Various clinical studies in HF cases have also demonstrated that the HR increase would lead to a poor prognosis. For instance, numerous studies investigating the effect of β-blockers in HF cases have suggested the correlation between HR and the prognostic significance [46–48]. The HR shows the influence on prognosis, not only in HF cases with reduced EF but also in those with preserved EF [49-52].

The HR increase has long been considered as one of the compensatory mechanisms in HF cases. However, the HR increase in the healthy heart is accompanied by an increase in the index of cardiac contractility, such as dp/dt or cardiac output, whereas in the HF cases, it shows the opposite results [53]. Gwathmey et al. measured calcium transient by aequorin using ventricular muscle from diseased and healthy subjects. The calcium transient and the muscle tension in the healthy heart showed increases in response to the increased pacing frequency, whereas muscle tension in the HF cases did not show an increase despite the calcium transient increase, suggesting calcium desensitization of the myocardial fiber [54].

Those accumulated findings had led to a treatment strategy in HF cases to reduce the HR. Ivabradine is a blocker of the hyperpolarization-activated cyclic nucleotide-gated channel (HCN) at the sinus node. It blocks the HCN4 channel to regulate

Table 1
Clinical trials on SGLT2i.

Trial	Drug	Subjects	Results
Type II DM+CV disease and/or CV risk factors			
EMPA-REG OUTCOME [26]	Empaglifozin	Type II DM and high CV risk	CV death↓ HF hospitalization↓ All cause death↓
CANVAS Program [27]	Canaglifozin	Uncontrolled DM+history or high CV risk	CV death/nonfatal MI or stroke↓ HF hospitalization↓ Renal outcome↓
DECLARE-TMI 58 [28]	Dapaglifozin	Type II DM+history or high CV risk	CV death or HF hospitalization↓
SCORED [29]	Sotaglifozin	Type II DM+CV risk factors+moderately impaired renal function	CV death or HF hospitalization↓
VERTIS CV [30]	Ertugliflozin	Type II DM+ established CV disease	CV death or HF hospitalization not significant
CKD±type II DM			
CREDENCE [31]	Canagliflozin	Type II DM+moderately impaired renal function	Renal outcome 30%↓ CV death/MI/stroke/HF hospitalization↓
DAPA-CKD [32]	Dapaglifozin	CKD	Renal outcome 39%↓ All cause death↓ HF hospitalization↓
EMPA-Kidney [33]	Empagliflozin	CKD	Incident or worsening nephropathy 39%↓ Doubling of the serum creatinine level 44%↓ Renal replacement therapy 44%↓
HF±type II DM			
DAPA-HF [34]	Dapaglifozin	Chronic HF+LVEF ≤ 40% + NT-proBNP↑	CV death pr HF hospitalization 26%↓
EMPEROR-Reduced [35]	Empagliflozin	Chronic HF+LVEF ≤ 40% + NT-proBNP↑	CV death or HF hospitalization 25%↓
EMPEROR-Preserved [36]	Empagliflozin	Chronic HF+LVEF > 40% + NT-proBNP↑	CV death or HF hospitalization 21%↓
SOLOIST-WHF [37]	Sotagliflozin	Type II DM+visit or hospitalization of worsening HF	CV death or HF hospitalization 33%↓

DM, diabetes mellitus; CV, cardiovascular; CKD, chronic kidney disease; HF, heart failure; LVEF, left ventricular ejection fraction; MI myocardial infarction.

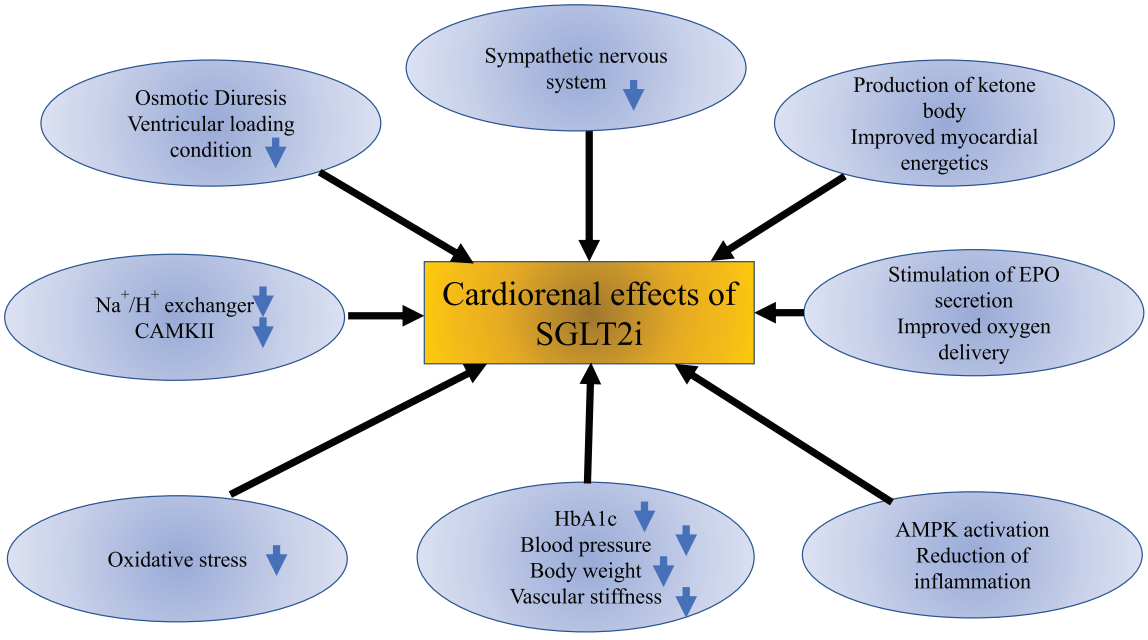

Fig. 2. Cardiorenal effects of SGLT2i
CAMKII, calcium-calmodulin dependent kinase II; EPO, erythropoietin; AMPK, adenosine monophosphate-activated protein kinase; HbA1c, hemoglobin A1c.

hyperpolarization-activated cation current (If), and it does not affect the cardiac function, which is different from β-blockers. Patients with relatively stable chronic HF showing left ventricular EF ≤ 35%, resting HR ≥ 70 bpm were enrolled in the Systolic Heart Failure Treatment with the I_f inhibitor Ivabradine Trial (SHIFT). A total of 6505 cases were randomly assigned either to the ivabradine administered group or placebo administered group. The dosage amount was set as twice with 5 mg per dose in the initial stage, and those who showed more than 60 bpm of resting HR after administration were uptitrated to the twice with 7.5 mg per dose, while those with less than 50 bpm resting HR were administered twice with a decreased dose of 2.5 mg per dose.

The resting HR in the ivabradine administered group dropped by 15.4 bpm on post administration day 28. The primary endpoint of cardiovascular deaths or HF hospitalization decreased by 25% in the ivabradine administered group. The total number of deaths also decreased by 17% in the ivabradine administered group. These effects were evidently observed in patients with more than 75 bpm of resting HR. Age, sex, the presence/absence of β-blocker administration, or the cause of HF did not affect the results [55]. The analysis results of HR on day 28 from administration initiation indicated the lowest event occurrence rate in the patients with less than 60 bpm of resting HR [56]. Similar studies in patients with chronic HF showing more than 75 bpm of resting HR were conducted in Japan. The initial dosage amount of ivabradine was set as twice with 2.5 mg per dose. The primary endpoint of cardiovascular deaths or hospitalization due to HF exacerbation showed a 0.67 hazard ratio, indicating a decreasing trend in the ivabradine administered group, yet the number of cases was not large enough to show any statistical significance. Improvements in left ventricular

EF, end-diastolic volume, and end-systolic volume were observed in the ivabradine administered group. No significant difference was confirmed in the concentrations of BNP and NT-proBNP [57].

These results indicate the necessity to consider ivabradine administration in patients with chronic HF with reduced EF with: (1) stable sinus rhythm, (2) resting HR $\geq$ 75 bpm, and (3) a history of β-blocker administration or a condition that makes uptitration difficult or a condition that β-blocker is contraindicated. JCS/JHFS 2021 guideline focused update described an indication of ivabradine for above patients as class IIa [20]. The ivabradine administration should start at two doses with 2.5 mg per dose, and the dosage amount can be uptitrated to two doses with 7.5 mg per dose, targeting the resting HR of 60 bpm. It should not be administered to patients with symptomatic sick sinus syndrome without pacemaker treatment or those with hypotension. A specific side effect is a photopsia, which was observed in 6.3% of the clinical studies in Japan.

Soluble GC stimulator

GC is an enzyme that produces cyclic guanosine monophosphate (cGMP), which becomes an intracellular second messenger, such as nitric monoxide. cGMP decreases intracellular calcium concentration by suppressing the production of inositol trisphosphate, inhibiting calcium channels, and activating outward calcium pump, all of which lead to preload/afterload reduction from vasodilation. Moreover, cGMP increase in the myocardial cell leads to suppressing fibrosis, improving relaxation, and suppressing remodeling. In HF, vascular endothelial function is disorganized, and nitric monoxide is decreased [58]. Expectations for a treatment agent that would directly activate GC have increased in these circumstances.

Riociguat is used as a treatment agent for pulmonary hypertension. A study using riociguat was conducted in patients with HF accompanying increased pulmonary vascular resistance. Although any significant decrease was not observed in the primary endpoint of mean pulmonary artery pressure, the cardiac index and pulmonary/systemic vascular resistance showed a sufficient improvement [59]. Vericiguat is a newly developed drug that can be administered once a day. In the dose-finding phase II study of the SOCRATES-REDUCED trial subjecting HF with reduced EF, the NT-proBNP concentration was reduced with a high dose, improving the subjective symptoms [60]. Followed by the results, the phase III placebo-controlled randomized trial, the VICTORIA trial, was conducted, in which 5050 patients with chronic HF with left ventricular EF $<$ 45% and high concentration levels of NT-proBNP were assigned. The primary endpoint of cardiovascular deaths or HF hospitalization decreased by 10% in the vericiguat administered group in the median 10.8 months observation period [61]. In this trial, patients with relatively severe cases of HF with eGFR $\geq$ 15 ml/min/1.73 m^2 were enrolled; effects of vericiguat were evident in those with NT-proBNP $<$ 5314 pg/ml. ANRI also has an effect of activating GC activity and was concomitantly used in 14.7% of cases in this trial, but the presence/absence of ANRI did not affect the effect. The trials subjecting patients with HF with preserved EF was also conducted without showing any improvement in NT-proBNP level, left atrial volume, or subjective symptoms [62,63].

Omecamtiv mecarbil

Omecamtiv mecarbil is a drug that affects the catalytic portion of myosin to enhance its binding with actin. The investigation using isolated myocardial cells indicated the effect of contraction enforcement and prolonged contraction duration without affecting the intracellular calcium concentration, which were different from conventional cardiotonic agents [64]. The dose-finding study of the COSMIC-HF trial showed effects of prolonged contraction duration, decreased left ventricular end-diastolic dimension, and reduced HR in the high-dose group [65]. The phase III trial of the GALACTIC-HF trial was also conducted, with the subjects of 8256 cases of chronic HF of left ventricular EF $\leq$ 35%. The initial HF-related event or cardiovascular death was reduced by 8% in the omecamtiv mecarbil administered group. The stratified analysis results showed an evident effect in patients with left ventricular EF $\leq$ 28% [66].

A new algorithm and unmet needs

The treatment guidelines for HF have been modified drastically according to the emergence of newly developed treatment agents, as shown in the discussion above. Switching from ACEI/ARB to ARNI is recommended for cases of reduced EF with subjective symptoms. Although ACEI currently remain the first choice for the treatment of HF with reduced EF, the possibility of ARNI replacing ACEI can be predicted in the near future. ACEI is currently the choice in patients with asymptomatic left ventricular dysfunction as well, but a change is also possible in the future. Vaduganathan et al. estimated lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with HF with reduced EF using database obtained from three pivotal trials, EMPHASIS-HF, PARADIGM-HF, and DAPA-HF. They found that the hazard ratio for the imputed treatment effects of comprehensive disease-modifying therapy versus conventional therapy on the primary endpoint of cardiovascular death or hospital admission for HF was as low as 0.38 [67].

Effective treatment for cases of HF with mildly-reduced EF has not been established yet. According to the recent clinical study results, introduction of ARNI is probably the correct choice. SGLT2i can be another choice. As for β-blocker, its improving effects on cardiac function and prognosis in patients with HF with mildly-reduced EF have been shown in a meta-analysis [68]. Empagliflozin has been found effective in cases with HF with preserved EF, probably determining the application sequence of SGLT2i in the future. It is also possible that ARNI is effective in some cases with HF with preserved EF. Regarding β-blockers and ivabradine that decrease HR, their effectiveness in cases with atrial fibrillation remains questionable, which requires further investigation in the future. Although agents like vericiguat or omecamtiv mecarbil should be applicable to cases with advanced HF, their positions in the treatment algorithm have not been established yet.

Declaration of Competing Interest

There is no conflict of interest concerning this manuscript.

Funding source

Author received Grand-in-Aid for Scientific Research (#23591062, #26461088, #16K09469, #18K08056, #21K08142), and Sakakibara Clinical Research Grant for the Promotion of Sciences from 2012–2021.

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