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ORIGINAL ARTICLE
Heart Failure

Effect of Vericiguat on Left Ventricular Reverse Remodeling in Patients Who Have Heart Failure With Reduced Ejection Fraction

— Special Focus on Patients Without Quadruple Medical Therapy —

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Background: A novel cardioprotective drug, vericiguat, reduces the risk of cardiovascular mortality for patients already on guideline-directed medical therapy. However, the effect of vericiguat on left ventricular (LV) reverse remodeling in patients with reduced LV ejection fraction (LVEF) with or without guideline-directed medical therapy, known as quadruple medical therapy, remains undetermined.

Methods and Results: This study comprised 73 heart failure (HF) patients with reduced LVEF (<45%) from 5 institutions in Japan. Echocardiography was performed before and 6.1±3.9 months after administration of vericiguat. LV reverse remodeling was observed in all patients (LV end-diastolic volume 156.1±52.6 vs. 139.3±60.0 mL; P<0.001; LV end-systolic volume 108.1±41.2 vs. 91.8±51.2 mL; P<0.001; LVEF 31.8±7.4 vs. 37.6±12.3 %; P<0.001). LV reverse remodeling was also observed in 54 patients who could not undergo quadruple medical therapy for several reasons. Moreover, the incidence of cardiovascular events was also similar for patients who received or did not receive quadruple medical therapy (log-rank P=0.555).

Conclusions: Significant LV reverse remodeling was observed in HF patients with reduced LVEF following administration of vericiguat. LV reverse remodeling was also observed in patients who could not receive quadruple medical therapy, thus making administration of vericiguat a potential new approach for treatment of these patients.

Key Words: Echocardiography; Heart failure; Left ventricular reverse remodeling; Vericiguat

The number of heart failure (HF) patients continues to increase worldwide and has become a social issue. As HF patients are known to have a high mortality rate due to repeated worsening HF despite appropriate treatment, novel therapeutic drugs that improve prognosis need to be developed. Despite recent therapeutic advancements for treatment of patients who have HF with reduced left ventricular (LV) ejection fraction (LVEF), many of these patients continue to experience worsening HF events and face an exceptionally high risk of death following worsening of their health status.[1,2] The standard treatment for HF with reduced ejection fraction (HFrEF) is quadruple medical therapy consisting of β-blockers, angiotensin receptor neprilysin inhibitor (ARNI), mineralocorticoid receptor antagonist (MRA) and sodium-glucose cotransporter-2 (SGLT2) inhibitors, and this therapy is recommended for patients with HFrEF, featuring recommendation class I and evidence level A according to the current guidelines of the American College of Cardiology and European Society of Cardiology.[3,4] Quadruple medical therapy is recommended in patients with HFrEF according to the current guidelines;[5,6] however, not all patients with HFrEF can be treated with quadruple medical therapy mainly because of low blood

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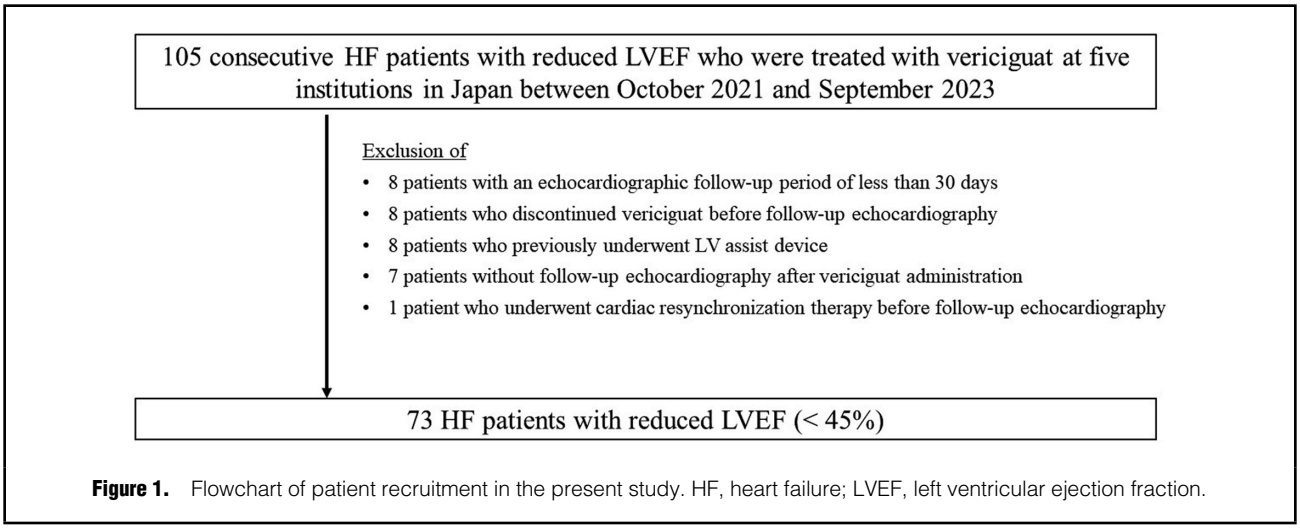

Figure 1. Flowchart of patient recruitment in the present study. HF, heart failure; LVEF, left ventricular ejection fraction.

pressure or diminished renal function.

The VICTORIA (VerICiguaT Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial demonstrated that vericiguat, a soluble guanylate cyclase stimulator, reduced the risk of mortality and HF hospitalizations for HF patients with reduced LVEF (<45%) who had recently been hospitalized or had received intravenous diuretic agents within 3 months of randomization for a trial of guideline-directed medical therapy (GDMT).[7] Current guidelines of the American Heart Association/American College of Cardiology and European Society of Cardiology now give vericiguat a Class IIb recommendation for selected high-risk patients already on GDMT who have recently experienced worsening of HF events.[5,6]

LV reverse remodeling after initiation of vericiguat was observed in a VICTORIA echocardiography substudy,[8] even though the ARNI prescription rate was low at 15% and none of the subjects received SGLT2 inhibitors due to a lack of reimbursement at the time the trial was conducted, with a standard of care different from what it is currently. The effect of vericiguat on LV reverse remodeling in HF patients with reduced LVEF who received quadruple medical therapy therefore remains uncertain. In addition, the effect of vericiguat on LV reverse remodeling in HF patients with reduced LVEF who could not receive quadruple medical therapy for several reasons also remains uncertain. Therefore, the aim of the present study was to investigate the effect of vericiguat on LV reverse remodeling in HF patients with reduced LVEF who received or did not receive quadruple medical therapy.

Methods

Study Population

For this study, 105 consecutive HF patients with reduced LVEF (<45%) who were treated with vericiguat between October 2021 and September 2023 at 5 institutions in Japan, namely, Kobe University Hospital, Akashi Medical Center, Hyogo Prefectural Harima-Himeji General Medical Center, Hyogo Prefectural Awaji Medical Center and Okamoto Cardiovascular Clinic, were retrospectively enrolled. The timing of administration and uptitration of vericiguat were left to the judgment of the physician. A total of 32 patients was excluded, 8 with an echocardiography follow-up period of <30 days, 8 who discontinued vericiguat before follow-up echocardiography, 8 who previously had an LV assist device implanted, 7 without follow-up echocardiography after vericiguat administration, and 1 who underwent cardiac resynchronization therapy before follow-up echocardiography (**Figure 1**). The remaining 73 HF patients with reduced LVEF (<45%) were enrolled in the present study. This study was approved by the local Ethics Committee of our institution in conformity with the Declaration of Helsinki (No. B230065).

Echocardiography Examination

Echocardiography studies were performed before and 6.1±3.9 months after administration of vericiguat by cardiologists or sonographers, and all echocardiography analysis was performed by cardiologists in a blind manner. All echocardiography data were obtained using a commercially available echocardiography system. Standard echocardiography measurements were made in accordance with the current guidelines of the American Society of Echocardiography.[9]

Definition of Study Endpoint

The primary endpoint for all patients was defined as a comparison of LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LVEF at baseline and after initiation of vericiguat. One secondary endpoint was defined as a comparison of LVEDV, LVESV and LVEF of patients who could not receive quadruple medical therapy. Another secondary endpoint was defined as a composite of cardiovascular events including cardiovascular death or HF hospitalization of patients with and without quadruple medical therapy for a median follow-up period of 1.0±0.5 years.

Statistical Analysis

Continuous variables were expressed as mean values and standard deviation for normally distributed data, and as median and interquartile range for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The parameters of the two subgroups were compared using Student's t-test or the Mann-Whitney

Table 1. Baseline Characteristics of All Patients

	All patients (n=73)	Patients with quadruple medical therapy (n=19)	Patients without quadruple medical therapy (n=54)	P value
Clinical characteristics				
Age (years)	71.9±11.4	68.9±12.0	73.0±11.1	0.178
Male gender	55 (76)	16 (85)	39 (73)	0.304
Body mass index (kg/m^2)	21.4±3.8	22.1±4.3	21.1±3.7	0.328
SBP (mmHg)	108.9±18.5	109.1±17.9	108.8±18.9	0.954
Heart rate (beats/min)	75±13	71±11	76±13	0.113
Previous history of hospitalization for HF	59 (81)	14 (74)	45 (84)	0.498
Ischemic etiology	37 (51)	5 (27)	32 (60)	0.017
Blood examination				
Hemoglobin (mg/dL)	13.0±2.0	13.8±2.1	12.7±2.0	0.039
Serum creatinine (mg/dL)	1.5±1.1	1.3±0.8	1.6±1.2	0.429
eGFR (mL/min/1.73 m^2)	42.8±17.9	49.2±19.7	40.7±16.9	0.081
BNP (pg/dL)	427 [224–1,040]	486 [187–1,293]	400 [224–918]	0.779
NT-proBNP (pg/dL)	4,773 [1,584–12,330]	2,473 [354–5,043]	5,940 [2,948–12,877]	0.033
NYHA functional class				
I	5 (7)	2 (11)	3 (6)	0.587
II	33 (46)	8 (43)	25 (47)	1.000
III	30 (42)	6 (32)	24 (45)	0.581
IV	3 (5)	1 (6)	2 (4)	0.566
Comorbidities				
Hypertension	38 (53)	9 (48)	29 (54)	0.790
Diabetes	25 (35)	5 (27)	20 (38)	0.575
Dyslipidemia	36 (50)	6 (32)	30 (56)	0.109
Paroxysmal AF	17 (24)	10 (53)	7 (13)	0.001
Persistent AF	17 (24)	1 (6)	16 (30)	0.032
Medication				
ACE inhibitor/ARB	20 (27)	0 (0)	20 (37)	<0.001
ARNI	25 (35)	19 (100)	6 (12)	<0.001
β-blockers	59 (81)	19 (100)	40 (75)	0.015
MRA	55 (76)	19 (100)	36 (67)	0.004
SGLT2 inhibitor	51 (70)	19 (100)	32 (60)	<0.001
Loop diuretic	53 (73)	13 (69)	40 (75)	0.766
Tolvaptan	23 (32)	6 (32)	17 (32)	1.000
Ivabradine	3 (5)	2 (11)	1 (2)	0.164
SOC device				
ICD	11 (16)	2 (11)	9 (17)	0.717
Biventricular pacemaker	11 (16)	3 (16)	8 (15)	1.000
Echocardiography data				
LVEDV (mL)	156.1±52.6	177.4±54.9	148.6±50.1	0.039
LVESV (mL)	108.1±41.2	122.3±43.4	103.1±39.6	0.080
LVEF (%)	31.8±7.4	31.8±7.0	31.8±7.6	0.986

Data are presented as mean±SD for normally distributed data, median [IQR] for non-normally distributed data, or n (%). ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BNP, B-type natriuretic peptide; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LV, left ventricular; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; MRAs, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of BNP; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT2, sodium glucose cotransporter 2; SOC, standard of care.

U test, depending on data distribution. Proportional differences were evaluated with the Fisher's exact test. Survival curves for freedom from cardiovascular death or HF hospitalization were determined with the Kaplan-Meier method, and cumulative event rates were compared by using the log-rank test. For all steps, a P value of <0.05 was considered statistically significant. All analyses were performed with commercially available software (MedCalc software, version 22.021; MedCalc Software, Mariakerke, Belgium).

Results

Baseline Characteristics

The baseline characteristics of all 73 patients are summarized in **Table 1**. Mean age was 71.9±11.4 years, baseline systolic

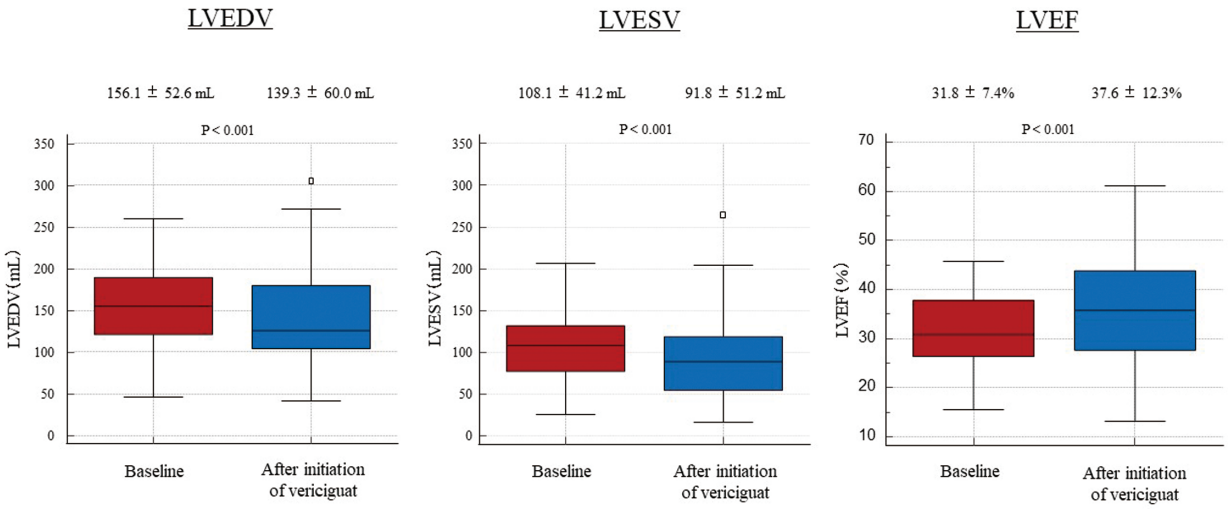

Figure 2. Bar graphs showing changes in left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left ventricular ejection fraction (LVEF) after initiation of vericiguat for all patients, indicating significant left ventricular reverse remodeling.

Table 2. Comparison Parameters Before and After Initiation of Vericiguat in All Patients

	Baseline	After administration of vericiguat	P value
SBP (mmHg)	108.9±18.5	110.5±17.0	0.380
Heart rate (beats/min)	75±13	74±13	0.814
eGFR (mL/min/1.73 m^2)	42.8±17.9	40.8±19.3	0.051
BNP (pg/dL)	427 [224–1,040]	221 [92–466]	0.012
NT-proBNP (pg/dL)	4,773 [1,584–12,330]	4,035 [780–7,503]	0.221
Dose of vericiguat (mg)	–	6.9±3.2	–
10	–	36 (49)	–
7.5		2 (3)	–
5	–	18 (25)	–
2.5	–	16 (22)	–
1.25		1 (1)	–
Echocardiography parameters			
LVEDV (mL)	156.1±52.6	139.3±60.0	<0.001
LVESV (mL)	108.1±41.2	91.8±51.2	<0.001
LVEF (%)	31.8±7.4	37.6±12.3	<0.001
LAVI (mL/m^2)	57.8±23.5	57.5±25.9	0.695
LVMI (g/m^2)	135.0±32.4	125.7±38.1	0.010
Aortic stenosis	1 (1)	1 (1)	1.000
Aortic regurgitation	10 (14)	9 (12)	0.567
Mitral regurgitation	27 (37)	24 (33)	0.442
Tricuspid regurgitation	22 (30)	17 (23)	0.132

Data are presented as mean ± SD for normally distributed data, median [IQR] for non-normally distributed data, or n (%). Abbreviations as described in Table 1.

blood pressure was 108.9±18.5 mmHg, and 55 (76%) were male. Thirty-three (46%) patients were classified as New York Heart Association (NYHA) Class II, 30 (42%) as class III, and 3 (5%) as class IV. The mean LVEDV was 156.1±52.6 mL, mean LVESV was 108.1±41.2 mL and mean LVEF was 31.8±7.4%.

Comparison of Baseline Characteristics of Patients With and Without Quadruple Medical Therapy

Baseline clinical findings and the characteristics of patients with and without quadruple medical therapy are summarized and compared in **Table 1**. Nineteen (26%) patients were able to receive quadruple medical therapy, while 54 (74%) could not for several reasons. Patients without qua-

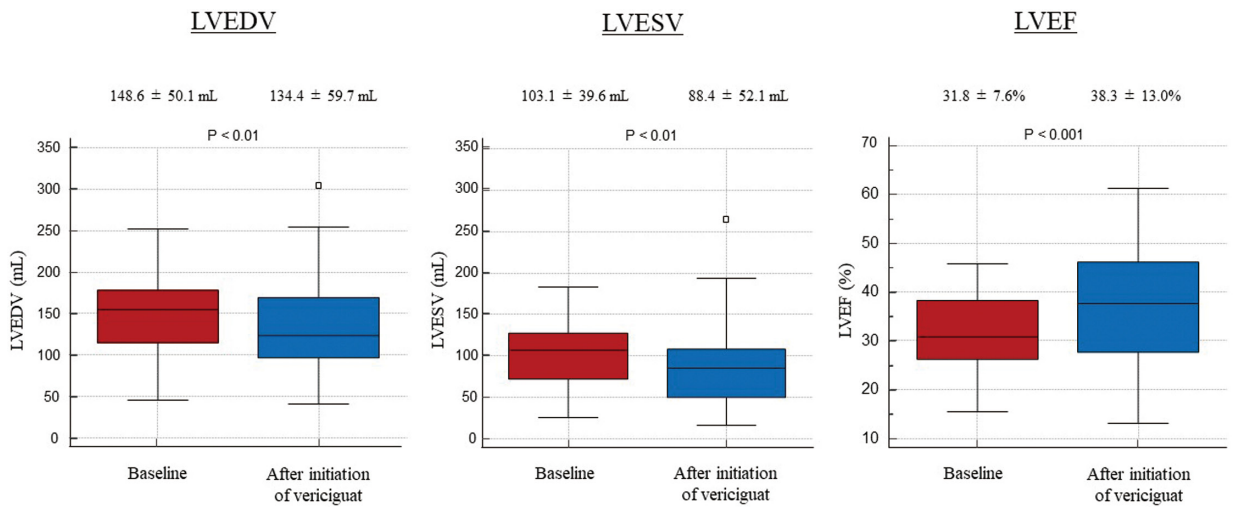

Figure 3. Bar graphs showing changes in left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left ventricular ejection fraction (LVEF) after initiation of vericiguat for patients without quadruple medical therapy, indicating significant left ventricular reverse remodeling.

druple medical therapy were more likely to have persistent atrial fibrillation (30 vs. 6%; P=0.032), higher N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) levels (5,940 [2,948–12,877] vs. 2,473 [354–5,043] pg/dL; P=0.033), and lower hemoglobin levels (12.7±2.0 vs. 13.8±2.1 mg/dL; P=0.039). In addition, patients without quadruple medical therapy tended to have higher serum creatinine levels (1.6±1.2 vs. 1.3±0.8 mg/dL; P=0.429) and lower estimated glomerular filtration rate (eGFR) levels (40.7±16.9 vs. 49.2±19.7 mL/min/1.73 m^2; P=0.081).

LV Reverse Remodeling Following Initiation of Vericiguat

Results of the primary endpoint of LV reverse remodeling after initiation of vericiguat for all patients are shown in **Figure 2**. Significant LV reverse remodeling was observed in all patients (LVEDV 156.1±52.6 vs.139.3±60.0 mL; P<0.001; LVESV 108.1±41.2 vs.91.8±51.2 mL; P<0.001; LVEF 31.8±7.4 vs. 37.6±12.3%; P<0.001).

Other parameters before and after initiation of vericiguat are summarized in **Table 2**. The mean dose of vericiguat was 6.9±3.2 mg, and 35 (48%) patients attained the target dose of 10 mg. Systolic blood pressure and eGFR for all patients were similar before and after initiation of vericiguat (systolic blood pressure 108.9±18.5 vs. 110.5±17.0 mmHg; P=0.38; eGFR 42.8±17.9 vs. 40.8±19.3 mL/min/1.73 m^2; P=0.051). BNP levels were significantly lower after initiation of vericiguat (427 [224–1,040] vs. 221 [92–466] pg/dL; P=0.012), while NT-proBNP levels tended to be lower (4,773 [1,584–12,330] vs. 4,035 pg/dL [780–7,503]; P=0.221).

LV Reverse Remodeling Following Initiation of Vericiguat in Patients Without Quadruple Medical Therapy

Results for patients without quadruple medical therapy of the secondary endpoint of LV reverse remodeling after initiation of vericiguat are shown in **Figure 3**. These results demonstrate that significant LV reverse remodeling also occurred in patients without quadruple medical therapy (LVEDV 148.6±50.1 vs. 134.4±59.7 mL; P<0.01; LVESV 103.1±39.6 vs. 88.4±52.1 mL; P<0.01; LVEF 31.8±7.6 vs. 38.3±13.0%; P<0.001). For the 19 patients with quadruple medical therapy, LVESV was significantly reduced from 122.3±43.4 mL to 101.3±48.0 mL (P=0.035) after initiation of vericiguat, while LVEDV tended to decrease from 177.4±54.9 mL to 153.1±59.6 mL (P=0.065) and LVEF tended to improve from 31.8±7.0% to 35.6±9.8% (P=0.13), but these changes were not statistically significant due to the small number of patients.

Comparison of the Incidence of Cardiovascular Events

Results for another secondary endpoint of a composite of cardiovascular events including cardiovascular death or HF hospitalization for patients with and without quadruple medical therapy are shown in **Figure 4**. During the follow-up period, 18 (25%) patients experienced cardiovascular events. The Kaplan-Meier curve shows that outcomes for patients with and without quadruple medical therapy were similar (log-rank P=0.555).

Discussion

The findings of the present study demonstrate that significant LV reverse remodeling was observed after initiation of vericiguat for HF patients with reduced LVEF (<45%). Furthermore, patients without quadruple medical therapy for several reasons also showed significant LV reverse remodeling after initiation of vericiguat, as well as outcomes similar to those of patients with quadruple medical therapy.

Vericiguat for HF Patients With Reduced LVEF

HF is a progressive disease characterized by periods of clinical stability interrupted by episodes of worsening signs and symptoms, which are recognized as a distinct phase in the natural history of the disease. This deterioration of HF in HF patients is strongly associated with outcome,[10,11] so that the prevention of worsening HF is essential. Quadru-

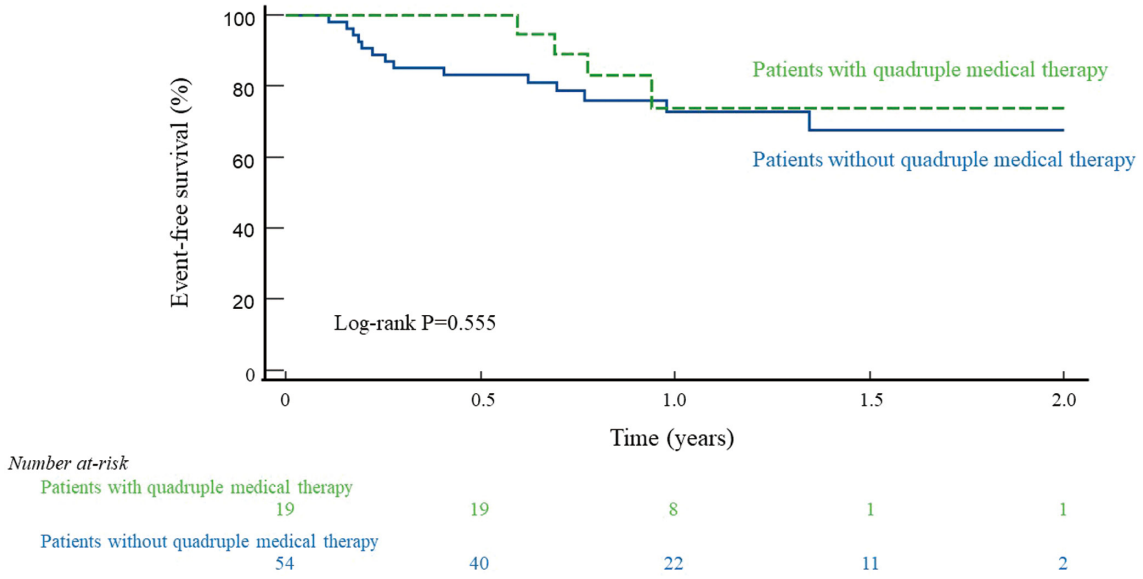

Figure 4. Kaplan-Meier curve representing the secondary endpoint of a composite of cardiovascular events, including cardiovascular death or heart failure hospitalization as the primary endpoint, which shows similar outcomes for patients with and without quadruple medical therapy.

ple medical therapy is highly recommended for reducing cardiovascular mortality and HF hospitalizations for patients with HFrEF,[5,6] while uptitration of guideline-directed medication dosing to attain target doses is also recommended for reducing cardiovascular mortality and HF hospitalizations for such patients.[3,5] Current guidelines give vericiguat a Class IIb recommendation for selected high-risk patients already on GDMT who have experienced recent worsening of HF events.[5,6] Although quadruple medical therapy is fundamental for all eligible patients with worsening HF and with reduced LVEF if tolerated, additional therapy involving the initiation of vericiguat should be seriously considered for reducing residual clinical risks (quintuple therapy with vericiguat) according to the American College of Cardiology and European Society of Cardiology.[3,4] Thus, the usefulness of vericiguat is likely to increase even more during the current era of HF pandemic.

LV Reverse Remodeling After Initiation of Vericiguat

The VICTORIA echocardiography substudy using 419 HF patients with LVEF ≤45% showed that the LVESV index significantly declined from 60.7±26.8 mL/m^2 to 56.8±30.4 mL/m^2 (P<0.01) and LVEF significantly increased from 33.0±9.4% to 36.1±10.2% (P<0.01) 8 months after initiation of vericiguat.[8] The ARNI prescription rate for the VICTORIA trial was low at 15% and none of the subjects received SGLT2 inhibitors because of the lack of reimbursement during the trial, at a time when circumstances were different from the current standard of care. The present study showed significant LV reverse remodeling in patients with reduced LVEF who had already received quadruple medical therapy, and was also observed in patients with reduced LVEF without quadruple medical therapy.

Previous studies have shown that LV reverse remodeling was observed after administration of cardioprotective drugs for patients with HFrEF.[12] Specifically, an absolute improvement in LVEF was 4% with renin-angiotensin-aldosterone system inhibitors,[13] 5.5% with β-blockers,[14] and 9.6% with ARNI[15] at 12 months after drug administration. This study showed an absolute LVEF improvement of 5.8% at 6.1 months after administration of vericiguat, and the effect of LV reverse remodeling by vericiguat was not inferior to other HF medications.

Mechanism of LV Reverse Remodeling by Vericiguat

Soluble guanylate cyclase (sGC) has emerged as a therapeutic target in patients with HF sGC activity in patients with HF is low, leading to reduced intracellular cyclic guanosine monophosphate (cGMP) generation and disturbed cGMP-dependent signaling with unfavorable effects on the cardiac and vascular system because of increased oxidative stress and reduced nitric oxide bioavailability.[16] Vericiguat is a novel molecule that directly stimulates the activity of intracellular sGC, thereby restoring reduced cGMP levels and cGMP-dependent signaling pathways. The reduced sGC activity is associated with LV remodeling increased cardiomyocyte stiffness, and myocardial dysfunction,[17,18] so that sGC stimulator (vericiguat) may be beneficial in patients with HFrEF.

Clinical Implications

The current guidelines recommend quadruple medical therapy for patients with HFrEF as a Class I recommendation and evidence level A.[5,6] However, not all patients with HFrEF can be treated with quadruple medical therapy.[19] For example, administration of β-blockers and ARNI for HF patients with low blood pressure is problematic, as it is for the use of ARNI, MRAs and SGLT2 inhibitors for those with diminished renal function, and of β-blockers for those with a low heart rate. Furthermore, SGLT2 inhibi-

tors are less likely to be used for patients who are at risk of them causing genital fungal skin infections and for those with diabetic ketoacidosis.

The VICTORIA trial[7] was different from many other HFrEF trials in that it included higher-risk patients with severe kidney disease with eGFR as low as 15mL/min/1.73m^2, who had experienced a recent worsening of HF events. Analysis of a subgroup of the VICTORIA trial showed that the trajectories for eGFR and creatinine with vericiguat were similar to those for a placebo during a 48-week follow up.[20] This analysis also showed that the beneficial effects of vericiguat on the primary outcome were not affected by baseline eGFR or by the occurrence of adverse events. Systolic blood pressure of both the vericiguat and the placebo group in the VICTORIA trial declined slightly over the first 16 weeks and then returned to baseline. There was no significant difference in the frequency of symptomatic hypotension or syncope between the vericiguat and placebo groups. Our study showed vericiguat can be used for HF patients with diminished renal function and low blood pressure and resulted in significant LV reverse remodeling, thus making it an effective treatment for these patients.

Recent guidelines have recommended uptitration of guideline-directed medication dosing to attain target doses for reducing cardiovascular mortality and HF hospitalizations of patients with HFrEF,[3,5] implying that vericiguat may be effective for patients with HFrEF who have already received quadruple medical therapy, but not attained the target dose.

Study Limitations

This study was retrospective and comprised a small number of patients with a short follow-up period, so future prospective studies with larger patient populations and longer follow-up periods will be needed to validate our findings. Also, the treatment for HF depended on the attending physicians in this study so that the timing of initiation of vericiguat or the decision on timing of the assessment of echocardiography or blood examination such as BNP/NT-proBNP was not standardized.

Conclusions

Significant LV reverse remodeling following initiation of vericiguat was observed in HF patients with reduced LVEF (<45%), which was also observed in patients without quadruple medical therapy. Furthermore, short-term outcomes for patients who had not received quadruple medical therapy were similar for those who had. Vericiguat may be effective for not only symptomatic HF patients who have received quadruple medical therapy, but also for those who have not or could not.

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Disclosures

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IRB Information

Kobe University Hospital Clinical and Translational Research Center (Reference No. B230065).

Data Availability

The de-identified participant data will not be shared.

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