Comparative effects of nebivolol and carvedilol on left ventricular diastolic function in older patients with heart failure and preserved ejection fraction

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ABSTRACT

Background: Although many studies have compared carvedilol and nebivolol in heart failure (HF) patients with reduced left ventricular ejection fraction (LVEF), such comparative studies for the elderly have not been reported yet. Nebivolol is known to be effective for improving diastolic function of elderly patients with HF. Thus, this study aimed to determine whether nebivolol could improve LV diastolic function to a greater extent than carvedilol in older patients aged over 70 years.

Methods: This trial was a prospective, randomized, open-label, single-center, active-controlled study that enrolled 62 patients with class II or III HF over 70 years of age with an LVEF $\geq$40%. Patients were randomized into a carvedilol group or a nebivolol group. Transthoracic echocardiography was performed at baseline and 12 months by the same investigator who was blinded to clinical data. The primary endpoint was E/e' measured by echocardiographic evaluation 12 months after treatment.

Results: The median duration of follow-up was 24 months. Baseline clinical characteristics and echocardiographic parameters, such as LV diastolic function indices, did not differ significantly between carvedilol and nebivolol groups. Twelve-month follow-up echocardiography data showed no significant difference in E/e' or other LV diastolic function indices between the two groups. There were no significant changes in echocardiographic parameters over 12 months in either group.

Conclusions: There was no difference between carvedilol and nebivolol for improving diastolic function of elderly HF patients with LVEF $\geq$40%. This study showed no superiority of nebivolol over carvedilol in elderly patients with HF.

1. Introduction

Heart failure (HF) is a disease of elderly people; up to 50% of HF diagnoses and 90% of HF deaths occur in the population of age over 70 [1,2]. In addition, a large portion of elderly HF patients has preserved systolic function [3], which has poor prognosis, comparable to that of HF with reduced EF [4]. Thus, it is important to diagnose and treat HF with preserved EF. Diastolic dysfunction increases left ventricle filling pressure at rest or on exertion, which aggravates dyspnea, impairs exercise capacity, and decreases survival in HF patients with preserved EF [5]. Beta-blockers are thought to potentially improve diastolic dysfunction by its negative chronotropic effect [6]. A previous retrospective observational study has indicated that a seven-year long-term exposure to beta-blocker can improve LV diastolic function in HF patients with preserved EF [7]. Recently, carvedilol and nebivolol as third generation beta-blockers with vasodilatory action have been introduced into practice. Carvedilol is a non-selective beta-blocker with additional alpha1-blocking and antioxidant activities [8]. Nebivolol is a selective beta-1 adrenergic receptor blocker with nitric oxide dependent vasodilator and antioxidant effects [9,10]. The SENIORS trial investigated the effect of nebivolol in HF patients aged over 70 years and demonstrated a significant reduction in the risk of death and cardiovascular-related hospitalization [11]. Nebivolol has also favorable effects on diastolic and systolic functions [12]. To date, many studies have compared carvedilol and nebivolol in patients with reduced LVEF. However, such comparative studies enrolling the elderly have not been reported yet. Thus, this study aimed to compare effects of carvedilol and nebivolol on diastolic function in elderly HF patients with

LVEF ≥40%.

2. Methods

This was a prospective, randomized, open-label, single-center study with two groups. Patients over 70 years of age were eligible for enrollment if they had preserved LVEF, NYHA functional class II or III status, and clinical stability without hospital admission for HF in the preceding three months. In the present study, preserved LVEF was defined as an LVEF of ≥40% using a modified Simpson's rule. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was used as a biomarker for the diagnosis of HF. The protocol required patients to have an NT-proBNP level of more than 300 pg/mL for inclusion in the study. The selection of the age of patients enrolled in our study as 70 years or older was based on the SENIORS study [11].

Exclusion criteria were: history or clinical documentation of pulmonary embolism, primary valvular heart disease, pericardial disease, severe obstructive lung disease, primary pulmonary hypertension, occupational lung disease, asthma, severe renal failure (serum creatinine >2.0 mg/dL), significant peripheral vascular disease, severe bradycardia (heart rate <50 beats/minutes), second or third-degree atrio-ventricular block, atrial fibrillation, life expectancy <1 year, concern for inability of the patient to comply with study procedures and/or follow-up, any condition which in the opinion of the Investigator would make it unsafe or unsuitable for the patient to participate in this study, participation in another clinical study with an investigational product during the preceding 30 days, or unable to give informed consent.

Details of the study design were described previously [13]. Briefly, all new patients admitted to Dong-A University Cardiology Department were screened for eligibility for participation in this study by the principal investigator. Pretest assessments including a detailed clinical evaluation, electrocardiogram, laboratory tests, and echocardiography were performed for patients who presented with symptoms and/or signs compatible with HF. Eligible patients were randomly assigned at a 1:1 ratio to receive nebivolol or carvedilol. Random treatment assignments were generated using Excel (Microsoft Corporation, Redmond, WA, USA). Randomization was performed by an individual not involved in the study. In the drug dose regimen for the nebivolol group, a starting dose of 1.25 mg/day was given. If tolerated, it was increased to 2.5 mg once daily by the end of week 1, 5 mg once daily by week 2. Then the dose was up-titrated to a target dose of 10 mg/day by week 4. For the carvedilol arm, a starting dose of 3.125 mg twice daily was given. If tolerated, it was increased to 6.25 mg twice daily by the end of week 1, 12.5 mg twice daily by week 2. The dose was then up-titrated to a target dose of 25 mg twice daily by week 4. If side effects attributable to the study medications occurred, up-titration was delayed, the dose was decreased. If up-titration was not clinically feasible, either because of hypotension or bradycardia, the previous dose was administered subsequently as the maximal tolerable dose. Any patient who was found to take less than 80% or more than 120% of the assigned study drug as assessed by tablet counts was considered non-compliant. After 12 months of follow-up visit, clinical and laboratory data were obtained from outpatient department visits. This study was approved by the Institutional Review Board of Dong-A University Hospital.

2.1. Study endpoints

The primary endpoint was E/e′ ratio as assessed by echocardiographic evaluation after 12 months of treatment. Among various echocardiographic indices for evaluating diastolic function, E/e′ was selected as the primary endpoint in our study because it could be easily measured reliably with low intra- and inter-observer variability [14]. The secondary endpoints were symptom severity (NYHA classification) and hospitalization due to HF.

2.2. Echocardiography

Transthoracic echocardiography was performed by the same investigator who was blinded to patient's information at baseline and 12 months. Echocardiography was performed using an iE33 ultrasound system and 2.5 MHz transducers (Philips Ultrasound, Bothell, WA, USA). Standard 2D and Doppler echocardiography were performed according to recommendations of the American Society of Echocardiography [15]. LV end-diastolic (LVEDD) and LV end-systolic (LVESD) dimensions were measured at the chordae level. LVEF was measured with the modified Simpson's method. Left atrial volume (LAV) was measured using the biplane area-length method from the apical four- and two-chamber views. LAVI was calculated as LAV divided by body surface area. LV diastolic function was determined with a conventional Doppler (mitral E, mitral A, E/A ratio, DT, IVRT), and tissue Doppler imaging (TDI). TDI sample volume was placed at the mitral annulus from the apical four-chamber view. Peak systolic (s′), early diastolic (e′), and late diastolic (a′) annular velocities were obtained at septal and lateral sides of the mitral annulus. The average of septal and lateral annular velocities was considered the mitral annular velocity. Global LV strain was also measured for 16 segments from the three apical views. LV global longitudinal strain (GLS) was measured by averaging regional values in apical views [16]. Intra- and inter-observer variability were calculated by the mean percentage error, defined as the absolute difference between the two sets of measurements divided by mean of the measurements. The first observer re-analyzed the E, e′, and GLS analyses one week after initial measurements. A second observer who was blinded to the first observer's data then measured the above parameters one week after that. Mean intra- and inter-observer variabilities of were 5.1% and 5.6% for E, 3.6% and 4.8% for e′, and 7.2% and 7.4% for GLS respectively.

2.3. Statistical analyses

The primary question to be tested was whether nebivolol improved diastolic function in elderly patients with EF of 40% or greater during a follow-up period of 1 year compared with the usual dose of carvedilol in the control group. The sample size was calculated using the primary objective of this study to detect a difference in E/e′ ratio of 5.0 between carvedilol and nebivolol group with a power of 90%. We assumed that the standard deviation of E/e′ was approximately 5.0 for both treatment groups. The sample size was adjusted for an estimated follow-up loss rate of 30% with a two-sided level of significance level of α = 5%, and a power of 1-β = 90%. Therefore, 31 patients were required for each group. Baseline clinical and laboratory characteristics and echocardiographic parameters of study patients were collected and analyzed. The intent-to-treat analysis set was used for efficacy analyses. Data are presented as mean value with standard deviation for normally distributed continuous variables or median (interquartile range [IQR]), and as numbers with percentages for categorical variables. Continuous variables were assessed using the Student's t-test and categorical variables were compared using χ2 test or Fisher exact test. The study endpoint was assessed using Student's t-test if samples were normally distributed or if their variances were homogeneous. Otherwise, Mann-Whitney *U* test was used. Assessments for other echocardiographic indices were compared between treatment groups after 12 months of follow-up using Student's t-test. A paired *t*-test was used to detect changes in LV diastolic function indices from randomization until the end of treatment in the two study groups. Correlation between E/e′ ratio and NT-proBNP was determined based on Pearson's correlation coefficient. This analysis was performed with the full analysis set consisting of patients who received at least one dose of the study drug. Statistical significance was set at p < 0.05. All statistical analyses were conducted using SPSS 12.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

Participant recruitment began in September 2015. It was completed in December 2019. A total of 62 patients were enrolled (Fig. 1). All patients were followed up for a median of 24 months. No one was lost to follow-up. The mean patient age was 78.4 ± 4.9 years and 59.5% were female. Baseline characteristics of patients in the carvedilol and nebivolol groups were similar (Table 1). All levels of liver function tests were within their normal ranges. The NYHA class was not significantly different between the two groups at baseline. The median NT-proBNP level was 1102 (IQR: 564–2194) pg/mL in the carvedilol group and 1414 (IQR: 732–2826) pg/mL in the nebivolol group. The target dose of the study drug was achieved in 35.5% of patients in the carvedilol group and 38.7% in the nebivolol group (p = 0.87) (Table 2). Four (12.9%) patients in the carvedilol group and five (16.1%) in the nebivolol group withdrew consent. Thus, they had no echocardiography data at the end of the trial.

3.2. Study outcomes

At baseline, echocardiographic findings were not different between the two groups (Table 1). Twelve-month follow-up echocardiography data were available for 42 patients (67.7%). Twelve-month follow-up echocardiography data showed no difference in E/e′ or other LV diastolic function indices between the two groups (Table 3). Changes in the indices of LV diastolic function in the echocardiographic parameters of each study drug group over 12 months were also insignificant. LV GLS was improved in both groups at the follow-up echocardiography (from −14.8 ± 3.3% to −16.4 ± 3.9%, p = 0.20 in the carvedilol group, from −15.5 ± 3.5% to −18.5 ± 5.1%, p = 0.06 in the nebivolol group). These improvements were slightly higher in the nebivolol group than in the carvedilol group. We evaluated changes in diastolic function according to different NYHA functional class status after administration of the drug. In the evaluation of the difference, no statistical difference was found between the two groups.

The NYHA class was not significantly different between the two groups at the 12-month follow-up. There were no significant changes in the NYHA class of each study drug group over 12 months either, (p = 0.76 in the carvedilol group and p = 0.19 in the nebivolol group, Fig. 2). Table 3 shows serial changes in echocardiographic parameters in both

groups at the 12-month follow-up. Hospitalization for HF occurred in five patients in the carvedilol group and four patients in the nebivolol group (12-month cumulative event rates of 16.1% and 12.9%, respectively), showing no significant difference between the two groups. Over 12 months, NT-proBNP levels were decreased in both carvedilol and nebivolol groups. However, such decreases were statistically insignificant (p = 0.25 and p = 0.06, respectively). The decreased amount of NT-proBNP levels was also comparable in carvedilol and nebivolol groups at 12 months (954.9 ± 830.8 pg/mL, 979.5 ± 752.8 pg/mL, respectively, p = 0.92). There was still no difference in NYHA class and rates of hospitalization due to HF between the two groups up to 24-month follow-up.

Table 1

Baseline characteristics of patients in carvedilol and nebivolol-treated groups.

	Carvedilol (n=31)	Nebivolol (n=31)	p value
Age – years	78.7 ± 4.8	78.0 ± 5.0	0.61
Female sex – no. (%)	12 (38.7%)	13 (41.9%)	0.78
Body surface area – m²	1.59 ± 0.19	1.60 ± 0.15	0.85
Body mass index – kg/m²	23.9 ± 4.9	24.0 ± 3.3	0.95
NYHA functional class – no. (%)			0.44
Class II	12 (38.7%)	13 (41.9%)	
Class III	19 (61.3%)	18 (58.1%)	
Smoking – no. (%)	2 (6.5%)	2 (6.5%)	0.92
Hypertension – no. (%)	18 (58.0%)	15 (48.4%)	0.60
Diabetes – no. (%)	9 (29.0%)	8 (25.8%)	0.95
Dyslipidemia – no. (%)	13 (41.9%)	9 (29.0%)	0.37
Systolic blood pressure – mmHg	125.3 ± 15.6	126.4 ± 17.1	0.84
Diastolic blood pressure – mmHg	65.5 ± 9.7	69.8 ± 11.9	0.20
Heart rate – beats/min	67.3 ± 9.9	71.5 ± 16.3	0.32
Creatinine – mg/dL	1.0 ± 0.3	1.2 ± 0.7	0.16
Sodium – mmol/L	138.5 ± 3.8	136.2 ± 4.7	0.10
Potassium – mmol/L	3.9 ± 0.5	4.3 ± 0.5	0.05
Hemoglobin – g/dL	11.9 ± 2.1	11.9 ± 1.5	0.94
NT-proBNP – pg/mL	1102 (564–2194)	1414 (732–2826)	0.34
ACEI/ARB – no. (%)	13 (41.9%)	7 (22.6%)	0.12
Calcium channel blocker– no. (%)	8 (25.8%)	10 (32.3%)	0.39
Statin – no. (%)	14 (45.2%)	11 (35.5%)	0.58
Diuretics – no. (%)	22 (71.0%)	20 (64.5%)	0.96

NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
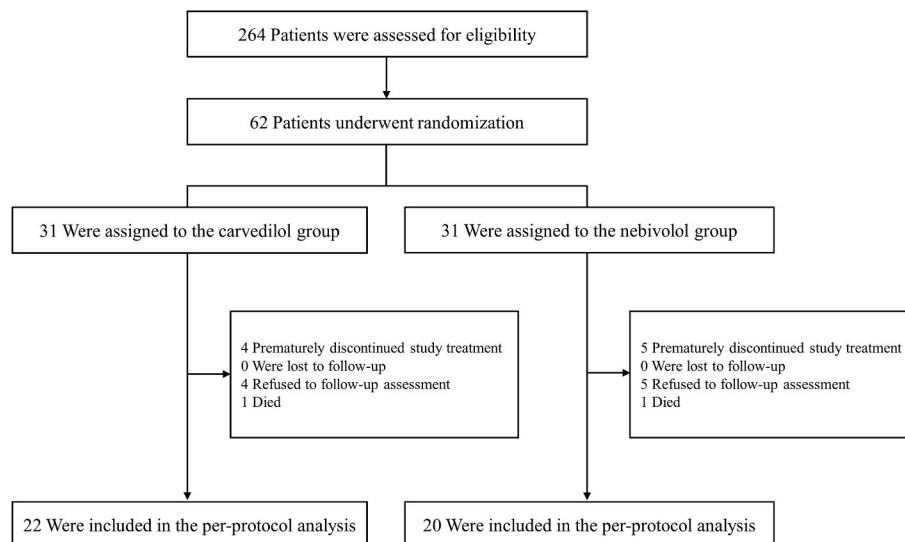

Fig. 1. Randomization and follow-up. The intention-to-treat population included all patients who had undergone randomization with valid informed consent and received at least one dose of study medication.

Table 2

Clinical and laboratory data of carvedilol and nebivolol groups at the 12-month follow-up.

Study outcomes	Carvedilol (n=31)	Nebivolol (n=31)	p value
Study drug dose – mg	26.8 ± 12.4	6.3 ± 3.5	<0.01
Proportion of patients reaching study drug target	11 (35.4%)	12 (38.7%)	0.87
Non-compliance of study drugs	5 (16.1%)	6 (19.4%)	0.46
Systolic blood pressure – mmHg	124.2 ± 14.2	123.7 ± 16.9	0.78
Diastolic blood pressure – mmHg	64.3 ± 7.9	65.9 ± 10.3	0.82
Heart rate – beats/min	59.2 ± 8.4	62.7 ± 9.5	0.35
NYHA class III	12 (40.0%)	9 (30.0%)	0.58
NT-proBNP – pg/mL	524 (248–1246)	678 (332–1402)	0.88

NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

We conducted an analysis of the association between primary and the secondary endpoints. There was a correlation between the E/e′ ratio and NT-proBNP (correlation coefficient: 0.47, p < 0.03), whereas there was no correlation between the E/e′ ratio and NYHA classification (correlation coefficient: 0.23, p = 0.62) or between E/e' ratio and hospitalization due to HF (correlation coefficient: 0.44, p = 0.55) (Table 4).

3.3. Safety

Overall, serious adverse events, including non-cardiac death, were reported in one (3.2%) patient in the carvedilol group and one (3.2%) patient in the nebivolol group. During the study period, adverse events that led to discontinuation of carvedilol or nebivolol were reported in 4 (12.9%) patients in the carvedilol group and 5 (16.1%) patients in the nebivolol group. Incidence of drug-related adverse events during randomized treatment are summarized in Table 5. No correlation was found between liver and kidney function depending on the dose of the drug. Nebivolol or carvedilol treatment resulted in a significant decrease in heart rate (p = 0.04), but not in systolic blood pressure (p = 0.83).

4. Discussion

The incidence of HF with preserved EF increases with age [1,2]. Aging is associated with declining cardioprotective effects and the development of HF due to progression of the disease [17]. The aged myocardium has decreased tolerance to stress, decreased mitochondrial function, decreased contractile function, and increased susceptibility to

apoptosis and necrosis [18]. Aging also deteriorates the vascular system [19,20]. Arterial stiffening and early wave reflections are representative vascular features in HF with preserved EF [21,22].

The utility of beta-blockers in HF with preserved EF lacks sufficient evidence. Some studies support the use of beta-blockers in HF patients with preserved EF [23,24]. However, a recent patient-based meta--analysis of 11 randomized HF trials did not demonstrate any benefit of beta-blocker for HF patients with preserved EF [25]. There are few data on comparative effectiveness of carvedilol and nebivolol for HF [26,27]. However, the current trial was the first head-to-head comparison of diastolic effects of nebivolol and carvedilol in HF patients with preserved EF in the elderly. In the present study, we demonstrated that
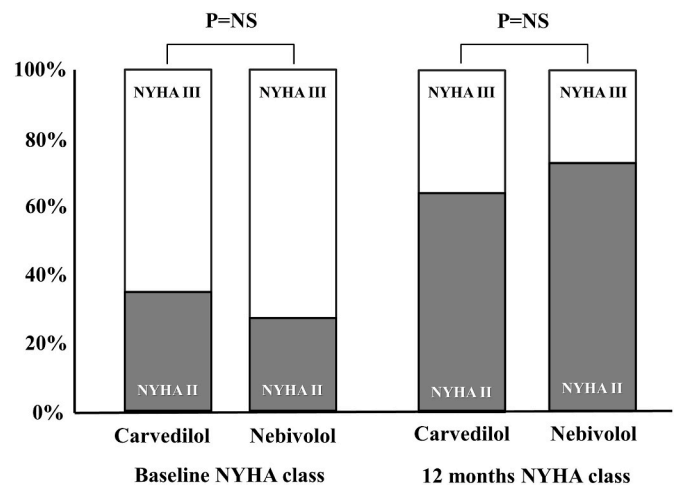

Fig. 2. Functional capacity in carvedilol and nebivolol groups. There was no significant difference in NYHA function class at baseline or 12 months between the two groups. Although the NYHA class was improved at 12 months in both groups, the improvement was insignificant (p = 0.764 in the carvedilol group and p = 0.194 in the nebivolol group).

Table 4

Correlation between primary and secondary endpoints.

		E/e′	p-value
NYHA classification	r	0.23	0.62
Hospitalization due to heat failure	r	0.44	0.55

Table 3

Echocardiographic variables at baseline and last observation.

	Carvedilol (n=31)			Nebivolol (n=31)				
	Baseline	12 months	P1	Baseline	12 months	P2	P3	P4
LVEDD (mm)	46.4 ± 4.9	45.8 ± 5.5	0.73	46.8 ± 4.0	46.4 ± 4.6	0.66	0.78	0.33
LVESD (mm)	30.4 ± 6.6	29.5 ± 6.4	0.66	30.5 ± 5.1	31.8 ± 8.4	0.53	0.98	0.32
LVMI (g/m²)	97.0 ± 32.8	101.0 ± 32.6	0.89	98.2 ± 16.9	99.7 ± 20.4	0.87	0.84	0.92
LVEF (%)	59.6 ± 8.7	59.1 ± 8.1	0.83	57.5 ± 9.0	58.5 ± 8.3	0.73	0.44	0.80
LAVI (ml/m²)	40.7 ± 18.4	44.4 ± 22.2	0.55	41.9 ± 16.7	47.0 ± 19.3	0.38	0.83	0.70
Mitral E (cm/s)	70.5 ± 28.3	73.8 ± 27.5	0.70	81.1 ± 37.1	77.0 ± 26.5	0.71	0.31	0.69
Mitral A (cm/s)	88.5 ± 24.5	82.7 ± 25.6	0.46	84.2 ± 27.5	86.1 ± 26.9	0.83	0.61	0.689
E/A	1.8 ± 0.4	1.1 ± 1.1	0.29	1.0 ± 0.7	0.9 ± 0.6	0.80	0.31	0.70
Mitral DT (ms)	227.1 ± 61.9	230.6 ± 45.8	0.83	190.8 ± 69.1	203.6 ± 76.3	0.58	0.08	0.17
IVRT (ms)	91.0 ± 18.8	95.4 ± 22.1	0.45	80.1 ± 24.5	87.5 ± 25.3	0.35	0.11	0.28
Mitral e′ (cm/s)	5.3 ± 1.5	5.7 ± 1.9	0.46	6.2 ± 1.5	6.1 ± 2.2	0.81	0.05	0.57
Mitral a′ (cm/s)	8.8 ± 2.7	8.5 ± 2.1	0.68	9.1 ± 2.5	8.9 ± 2.5	0.59	0.68	0.59
LV GLS (%)	−14.8 ± 3.3	−16.4 ± 3.9	0.20	−15.5 ± 3.5	−18.5 ± 5.1	0.16	0.56	0.11
E/e′	13.7 ± 5.8	14.6 ± 9.1	0.68	13.0 ± 4.1	13.5 ± 5.0	0.69	0.63	0.62

Left ventricular diastolic dimension; LVESD, left ventricular systolic dimension; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; DT, deceleration time; IVRT, isovolumetric relaxation time; LV GLS, left ventricular global longitudinal strain. P1 and P2, comparisons of baseline and 12-month follow-up. P3, comparisons of two groups at baseline; P4, comparisons of two groups at 12-month follow-up.
NYHA, New York Heart Association.

Table 5

Incidence of drug-related adverse events during randomized treatment.

System Organ Class/Preferred Term	Carvedilol (n=31)		Nebivolol (n=31)	
	n	(%)	n	(%)
Nervous system disorders	2	(6.5)	2	(6.5)
Dizziness	1	(3.2)	0	(0.0)
Dizziness postural	1	(3.2)	2	(6.5)
Vascular disorders	3	(9.7)	4	(12.9)
Hypotension	0	(0.0)	1	(3.2)
Orthostatic hypotension	3	(9.7)	3	(9.7)
Gastrointestinal disorders	1	(3.2)	0	(0.0)
Abdominal pain	0	(0.0)	0	(0.0)
Diarrhea	1	(3.2)	0	(0.0)
General disorders and administration site conditions	0	(0.0)	1	(3.2)
Asthenia	0	(0.0)	0	(0.0)
Chest discomfort	0	(0.0)	1	(3.2)
Investigations	1	(3.2)	1	(3.2)
Blood creatinine increased	1	(3.2)	1	(3.2)
Hemoglobin decreased	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	1	(3.2)	1	(3.2)
Cough	1	(3.2)	0	(0.0)
Oropharyngeal pain	0	(0.0)	1	(3.2)
Metabolism and nutrition disorders	1	(3.2)	0	(0.0)
Hyperkalemia	1	(3.2)	0	(0.0)
Renal and urinary disorders	0	(0.0)	1	(3.2)
Nephropathy	0	(0.0)	1	(3.2)

diastolic parameters including E/e′ were not improved in elderly HF patients with preserved LVEF at 12 months of follow-up after treatment with beta-blockers. Although LV GLS was slightly improved in each group, it was not statistically significant and not comparable between the carvedilol and nebivolol groups. GLS is known to be a parameter used for objective and reliable assessment of systolic function [28]. Recently, GLS has also been proposed a surrogate index to evaluate LV diastolic function [29]. Some studies have shown that impaired GLS is highly prevalent in patients with HF with preserved EF and that the degree of decreased GLS is related to their prognosis [30,31]. Cho et al. [32] have demonstrated that GLS could be a marker to identify HF in patients with preserved EF. Although the improvement of GLS during the 12-month follow-up in this study was not statistically significant, this study showed the potential of GLS as a candidate marker for detecting subtle changes in myocardial dysfunction in elderly HF patients with preserved EF.

Carvedilol is a nonselective beta-blocker without intrinsic sympathomimetic activity and nebivolol is a selective beta-blocker. They both have a vasodilator action, that might improve diastolic relaxation of LV through reduction of afterload [9,10]. However, unlike in HF with reduced EF, beta-blocker could not improve cardiovascular outcome in HF patients with preserved EF [33]. In fact, beta-blocker may worsen symptoms by further reducing heart rate and delaying left ventricular relaxation [34].

Sarma et al. have reported that some HF patients with preserved EF had reduced beta receptor responsiveness compared to controls, which may contribute to chronotropic incompetence in these patients [35]. Thus, the lack of improvement of diastolic function after beta-blocker treatment in this study may be due to impairment of beta receptor responsiveness. The underdose in the prescription of beta-blockers in the present study might be another cause of the lack of treatment effect. It has been known that the dose and duration of beta-blockers are key determinants of therapeutic effects of beta-blockers in HF patients with preserved EF [36,37]. In this study, approximately two thirds of patients did not reach the dose planned at the beginning of the study, which may have led to imprecise and irrational results. Underdose of beta-blockers are particularly common in elderly patients due to their intolerability in older patients [38]. Besides, comorbidities or concomitant medications in elderly patients are common reasons for underuse of beta-blockers. Additionally, heterogenic phenotype of HF with preserved EF may

have led to lack of improvement of diastolic function after beta-blocker treatment in this study. Because of phenotypic heterogeneity, personalized therapeutic strategies are under investigation for better outcome in HF patients with preserved EF [39,40].

Several limitations of our study should be noted. First, this study was underpowered for the primary end point because the number of subjects enrolled was small and echocardiographic measurements were not conducted in all subjects enrolled. Owing to the COVID-19 pandemic, echocardiographic assessment was limited to patients for whom a 12-month assessment was planned. Due to the small sample size of the current study, the conclusion may lack statistical power. Additional studies should be conducted to confirm our findings in the current study. Second, since this study was conducted between 2015 and 2019, HF classification criteria according to recent recommendation could not be applied to our study. Although patients with an EF of 40% or more were eligible for enrollment in this study, there were no patients with an EF of 40–49% among actually enrolled patients. Thus, even if the 2022 AHA/ACC/HFSA Guideline was applied, patients with LVEF ≥50% as HFpEF would be enrolled in the present study. Third, among various echocardiographic indices that could evaluate diastolic function, E/e′ was selected as the primary endpoint in our study because it could be easily measured reliably with low intra- and inter-observer variability [14]. Although it was a very limited approach to evaluate diastolic function with one index, we evaluated other diastolic function indicators together to reduce its limitations. Fourth, coronary angiography was not performed for enrolled patients. Thus, the possibility of heart failure due to atherosclerosis could not be excluded.

5. Conclusion

At 12 months of follow-up after treating elderly HF patients with preserved LVEF with carvedilol and nebivolol, overall effects of both drugs on LV function were similar, showing no significant difference.

Ethics

This study follows the principles set forth in the Helsinki Declaration, meaning that all patients signed a written informed consent stating that their participation was voluntary and that their participation could be withdrawn at any time. The current study was approved by the Ethical Review Board in Dong-A University Hospital (approval number: 2015–174, version #1, 7 October 2015).

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Author contributions

THP contributed to general project coordination, study design, work data interpretation, and critical manuscript revision. KP contributed to study concept, study sample size calculation, critical manuscript revision, and all other aspects of the study. Both authors have read and approved the final manuscript.

Declaration of competing interest

The authors have no conflicts of interests relevant to this study to disclose.

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