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ORIGINAL ARTICLE

Myocardial strain to identify benefit from beta-blockers in patients with heart failure with reduced ejection fraction

Chan Soon Park[1], Jin Joo Park[2]*, In-Chang Hwang[2], Jun-Bean Park[1], Jae-Hyeong Park[3] and Goo-Yeong Cho[2]

[1]*Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Korea;* [2]*Division of Cardiology, Cardiovascular Center & Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, Korea; and* [3]*Department of Internal Medicine, Chungnam National University College of Medicine, Chungnam National University Hospital, Daejeon, Korea*

Abstract

Aims Not all patients with heart failure with reduced ejection fraction (HFrEF) benefit equally from beta-blockers. Previous studies suggest that myocardial strain that reflects myocardial deformation may have a better prognostic value than the left ventricular ejection fraction. We aimed to evaluate the differential effect of beta-blockers according to the global longitudinal strain (GLS) in patients with HFrEF.

Methods and results Of the 4312 patients in the Strain for Risk Assessment and Therapeutic Strategies in Patients with Acute Heart Failure registry, we included 2126 HFrEF patients whose data on beta-blocker use and GLS were available. Patients were categorized into two groups: one group of patients had GLS $\geq$ 10%, and the other group had GLS $<$ 10%. The primary outcome was 5 year all-cause mortality according to beta-blocker use. Of the 2126 patients with HFrEF, 526 (24.7%) and 1600 (75.3%) patients had GLS $\geq$ 10% and $<$10%, respectively. Overall, 1399 patients (65.8%) received beta-blockers, and 864 (40.6%) patients died during the 5 year follow-up. Beta-blocker use was associated with improved survival in patients with GLS $<$ 10% in both the inverse probability treatment-weighted (hazard ratio 0.70, 95% confidence interval 0.59–0.83, $P < 0.001$) and Cox regression analyses (hazard ratio 0.69, 95% confidence interval 0.59–0.81; $P < 0.001$). However, beta-blocker use was not associated with better survival in patients with GLS $\geq$ 10% in the inverse probability treatment-weighted and Cox regression analyses (both $P > 0.05$).

Conclusions Beta-blocker use appears to be associated with improved survival in patients with HFrEF and GLS $<$ 10%, but this is not the case in patients with GLS $\geq$ 10%. Therefore, GLS may be used to identify patients who have attenuated benefits from beta-blockers in HFrEF.

Clinical Trial Registration: ClinicalTrials.gov: NCT03513653 (https://clinicaltrials.gov/ct2/show/NCT03513653).

Keywords Beta-blocker; Heart failure with reduced ejection fraction; Mortality; Myocardial strain; Prognosis

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**Correspondence to: Jin Joo Park, Division of Cardiology, Cardiovascular Center & Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Gumiro 166, Bundang, Seongnam, Gyeonggi-do, Korea. Tel: +82-31-787-7074. Email: jinjooparkmd@gmail.com*

Introduction

Heart failure (HF) has high morbidity and mortality, and its incidence and prevalence rates are increasing worldwide.[1,2] Currently, according to the left ventricular ejection fraction (LVEF), HF is classified into HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).[3] Although the prognosis of the two HF phenotypes is similar,[4] responses to various pharmacological treatments differ.[3,5] In patients with HFrEF, beta-blockers improve patients' survival. However, it is controversial whether the effects of beta-blockers are attenuated in patients with lower heart rates[6,7] or in those with atrial fibrillation,[8–10] suggesting that not all patients may respond equally and receive survival benefits from beta-blockers.

Myocardial strain is an index of myocardial deformation measured with the speckle-tracking method, and it can be used objectively and reliably to assess left ventricular systolic

function.[11] Recently, we reported that the global longitudinal strain (GLS) provided better prognostic information than LVEF, which has been traditionally used as an index for left ventricular systolic function.[12] We also reported that stratification of patients with HFpEF according to the GLS could distinguish who among these patients may benefit from beta-blockers; the use of beta-blockers was associated with reduced mortality in patients with HFpEF and reduced GLS.[13]

Myocardial strain reflects left ventricular systolic function and is an individual prognostic marker of HF. Because patients with similar GLS have a similar prognosis independent of LVEF, we hypothesized that they may have a similar response to medical therapy. Therefore, we hypothesized that GLS could be used to identify patients with HFrEF who may and may not benefit from beta-blockers. To explore this hypothesis, we investigated the differential effect of beta-blockers according to GLS in patients with HFrEF.

Methods

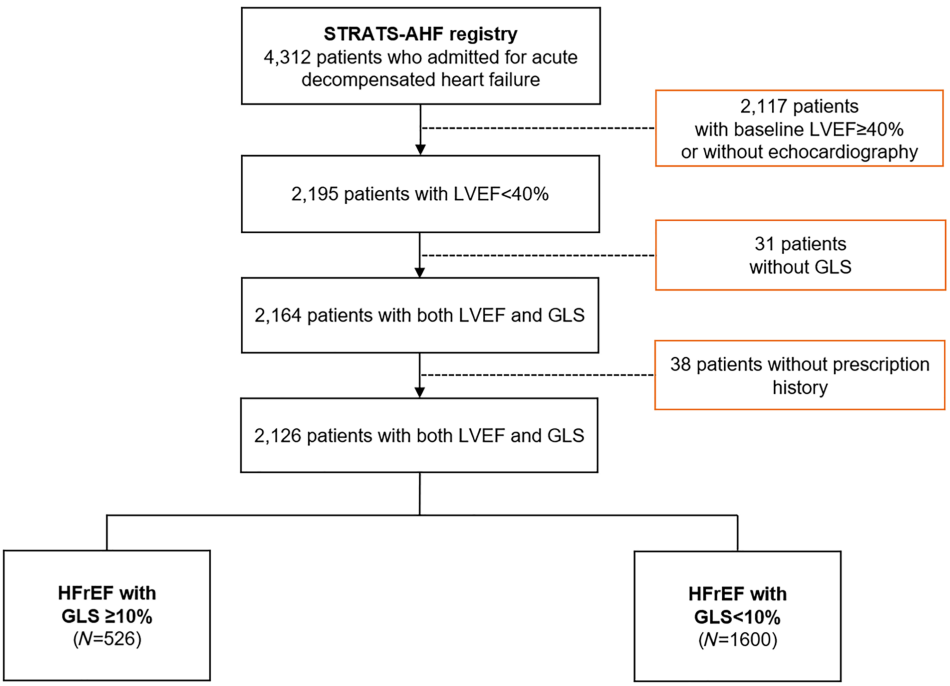
Participants

The design and primary outcomes of the Strain for Risk Assessment and Therapeutic Strategies in Patients with Acute Heart Failure (STRATS-AHF) registry are described elsewhere.[12] In summary, we recruited 4312 consecutive patients hospitalized for acute HF in three tertiary university hospitals in Korea between January 2009 and December 2016. The study included patients who had compatible symptoms and signs of HF and at least one of the following inclusion criteria: (i) pulmonary oedema defined as rales on physical examination or congestion on chest radiography or (ii) objective findings of left ventricular systolic dysfunction or structural heart disease. The STATS-AHF registry included only hospitalized patients. Of these, we included 2126 patients with an LVEF of $<$40% and data on GLS and beta-blocker use (*Figure 1*). The study protocol was approved by the ethics committee of each institution, and it complied with the principles set forth in the Declaration of Helsinki. The need for written informed consent was waived.

Echocardiography and strain analysis

All echocardiographic images were obtained using a standard ultrasound machine with a 2.5 MHz probe manufactured by GE, Philips, and Siemens, and echocardiographic examinations were performed according to the established guidelines.[14] Images were uploaded to the strain core laboratory for strain analysis, strain analysis was performed as previously described, and digitally acquired baseline echocardiographic images in digital imaging and communications in medicine format with acceptable image quality were uploaded to TomTec software (Image Arena 4.6, Munich,

Figure 1 Study population. Flow chart of this study is presented. GLS, global longitudinal strain; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; STRATS-AHF, Strain for Risk Assessment and Therapeutic Strategies in Patients with Acute Heart Failure.



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Germany) for deformation analyses (two-dimensional cardiac performance analysis). Echocardiography was performed during the index hospitalization (median time interval between admission and echocardiography, 1 day [inter-quartile range, 0–2 days]). All strain measurements were performed by one strain specialist in the core laboratory who was blinded to the patients' other data. To validate reproducibility, GLS measurement was repeated by the same strain specialist on 20 randomly selected patients after ≥3 months. An additional strain specialist measured GLS in the same patients. The intraclass coefficients of interobserver and intraobserver variability were 97.0% ($P < 0.001$) and 99.3% ($P < 0.001$), respectively. For myocardial strain, endocardial borders were traced on the end-systolic frame in three apical views (four-chamber, two-chamber, and three-chamber), with end-systole defined by the QRS complex or as the smallest left ventricular volume during the cardiac cycle. LVEF was measured using the Simpson biplane method, unless Simpson's method was not possible.

Study variables and definitions

Based on echocardiography findings at index hospitalization, HFrEF was defined as an LVEF < 40%. As GLS is a negative value, we used the absolute value of GLS for easier interpretation. Participants were categorized as having either a GLS < 10% or GLS ≥ 10%. GLS 10% was the median value in the STRATS-AHF registry, and it was also a cut-off value for risk stratification in previous reports.[12] In addition, GLS value of 10% showed prognostic implications in various cardiovascular fields. For sensitivity analyses, we used a GLS of 7% and 13% as additional cut-off values. The GLS cut-off value of 7% was able to best predict 5 year all-cause mortality in a receiver operating characteristic curve analysis, and that of 13% was derived from our previous study in which patients with HFpEF and GLS < 13% appeared to benefit from beta-blocker use.[13] In terms of medication, the use of beta-blockers was defined when they were prescribed during discharge of a patient. Unless contraindicated, beta-blockers were initiated after haemodynamic stabilization in the patient.

The primary outcome was 5 year all-cause mortality according to beta-blocker use. Mortality data were obtained and verified using a centralized database of national death records. The secondary outcome was the composite of 5 year all-cause mortality and hospitalization for HF according to beta-blocker use.

Statistical analyses

Data are presented as numbers and frequencies for categorical variables and as mean ± standard deviation for continuous variables. The χ^2 test or Fisher's exact test was used for categorical variables, and the unpaired Student's *t*-test for continuous variables was used for comparison between groups. The chronological trend of the clinical outcomes was expressed as Kaplan–Meier estimates, and these were compared according to beta-blocker use. The log-rank test was performed for the comparison of the differences in the clinical outcomes. The multivariable Cox proportional hazards regression model was used to determine the independent predictors of all-cause 5 year mortality. We included variables associated with mortality with a *P*-value <0.05 in the univariate analysis, and they were age, sex, body mass index, previous history of hypertension, diabetes mellitus, ischaemic heart disease, atrial fibrillation, heart rate, systolic blood pressure, glomerular filtration rate, renin–angiotensin system inhibitors at discharge, and mineralocorticoid receptor antagonists at discharge. We performed inverse probability treatment-weighted (IPTW) analyses and propensity score matching (PSM) analysis to account for the confounders in each HFrEF patient with a GLS of <10% and ≥10%. The following variables were included for matching: age, sex, body mass index, previous history of hypertension, diabetes mellitus, ischaemic heart disease, atrial fibrillation, systolic blood pressure, diastolic blood pressure, heart rate, New York Heart Association functional class, glomerular filtration rates, left atrial diameter, left ventricular end-diastolic diameter, renin–angiotensin system inhibitor at discharge, and mineralocorticoid receptor antagonist at discharge. The magnitude of mortality risk reduction with beta-blocker use according to GLS was estimated using Cox regression analysis.

Two-sided *P* values of <0.05 were considered statistically significant. Statistical tests were performed using IBM SPSS Version 23 (SPSS Inc., Chicago, IL, USA) and R programming Version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographic and clinical characteristics

Of the 4312 patients in the STRATS-AHF registry, 2195 patients were diagnosed with LVEF < 40% at baseline echocardiography. Among them, we excluded 31 patients whose GLS data were not available on account of inappropriate image quality, and 38 patients were excluded because their beta-blocker prescription data were incomplete. Therefore, a total of 2126 patients were finally included in the study. In accordance with this definition, 526 (24.7%) and 1600 (75.3%) patients were classified as having GLS ≥ 10% and GLS < 10%, respectively.

Table 1 demonstrates the clinical characteristics of the crude population, and Supporting Information, *Tables S1*

Table 1 Baseline characteristics of the original and matched population

	Original population (n = 526)		
Patients with GLS ≥ 10%	With beta-blocker (n = 396)	Without beta-blocker (n = 130)	P-value
Demographics			
Age (years)	68.0 ± 13.9	68.8 ± 14.1	0.570
Male (%)	231 (58.3)	79 (60.8)	0.624
Body mass index (kg/m^2)	23.2 ± 4.0	22.6 ± 3.6	0.129
Medical history			
Hypertension	207 (52.3)	63 (48.5)	0.451
Diabetes mellitus	130 (32.8)	33 (25.4)	0.111
Ischaemic heart disease	144 (36.4)	37 (28.5)	0.100
Atrial fibrillation	67 (17.1)	17 (13.8)	0.386
Physical examination at the admission			
Systolic blood pressure (mmHg)	127.4 ± 25.2	127.2 ± 27.5	0.959
Diastolic blood pressure (mmHg)	73.7 ± 14.6	73.2 ± 17.2	0.762
Heart rate (b.p.m.)	81.7 ± 21.3	86.3 ± 22.6	0.037
NYHA class			<0.001
I, II	36 (10.4)	10 (10.5)	
III	214 (61.8)	37 (38.9)	
IV	96 (27.7)	48 (50.5)	
Laboratory and echocardiographic findings			
GFR (mL/min/1.73 m^2)	65.2 ± 30.1	63.7 ± 31.8	0.636
Left atrial diameter (mm)	43.8 ± 8.6	44.0 ± 8.5	0.761
Left ventricular end-diastolic diameter (mm)	56.2 ± 8.2	56.7 ± 9.3	0.547
Left ventricular ejection fraction (%)	31.5 ± 6.0	32.6 ± 6.2	0.070
Global longitudinal strain	12.5 ± 2.1	12.7 ± 2.2	0.401
Medication			
Renin–angiotensin system inhibitor	343 (86.6)	88 (67.7)	<0.001
Mineralocorticoid receptor antagonist	230 (58.1)	43 (33.1)	<0.001
Diuretics	325 (82.1)	83 (63.8)	<0.001
	Original population (n = 1600)		
Patients with GLS < 10%	With beta-blocker (n = 1003)	Without beta-blocker (n = 597)	P-value
Demographics			
Age (years)	67.1 ± 14.1	70.8 ± 13.9	<0.001
Male (%)	611 (60.9)	399 (66.8)	0.018
Body mass index (kg/m^2)	23.5 ± 4.6	22.5 ± 3.8	<0.001
Medical history			
Hypertension	556 (55.4)	342 (57.3)	0.470
Diabetes mellitus	398 (39.7)	223 (37.4)	0.356
Ischaemic heart disease	356 (35.5)	208 (34.8)	0.792
Atrial fibrillation	291 (29.4)	156 (26.7)	0.251
Physical examination at the admission			
Systolic blood pressure (mmHg)	126.8 ± 26.0	125.2 ± 25.9	0.263
Diastolic blood pressure (mmHg)	76.9 ± 17.4	73.5 ± 16.7	<0.001
Heart rate (b.p.m.)	95.9 ± 23.9	97.0 ± 26.1	0.428
NYHA class			<0.001
I, II	55 (6.0)	29 (5.5)	
III	498 (54.7)	169 (32.0)	
IV	357 (39.2)	330 (62.5)	
Laboratory and echocardiographic findings			
GFR (mL/min/1.73 m^2)	61.2 ± 28.9	55.8 ± 28.4	<0.001
Left atrial diameter (mm)	45.2 ± 8.2	46.2 ± 9.9	0.043
Left ventricular end-diastolic diameter (mm)	57.9 ± 8.9	59.7 ± 9.4	<0.001
Left ventricular ejection fraction (%)	26.2 ± 7.0	26.7 ± 7.4	0.202
Global longitudinal strain	6.8 ± 2.0	6.3 ± 2.	<0.001
Medication			
Renin–angiotensin system inhibitor	841 (83.8)	350 (58.6)	<0.001
Mineralocorticoid receptor antagonist	585 (58.3)	230 (38.5)	<0.001
Diuretics	833 (83.1)	380 (63.7)	<0.001

GFR, glomerular filtration rate; GLS, global longitudinal strain; NYHA, New York Heart Association.

and *S2* present those of IPTW populations and PSM populations according to the myocardial strain and beta-blocker use. In the crude population, the mean age was 68.4 years, 62.1% were male, 54.9% had hypertension, 36.9% had diabetes mellitus, 35.0% had ischaemic heart disease, and 25.0% had atrial fibrillation. Among the included patients, 1399 (65.8%) received beta-blockers. Patients who did not receive beta-blockers showed higher New York Heart Association functional classes in both the GLS $\geq$ 10% and <10% groups than in those who received beta-blockers. Among the patients with GLS $<$ 10%, those without beta-blockers were older; had lower body mass index, diastolic blood pressure, and glomerular filtration rate; and had larger left atrial and left ventricular end-diastolic diameters. Patients receiving beta-blockers received more renin–angiotensin system inhibitors and mineralocorticoid receptor antagonists than those not taking beta-blockers in both groups of patients with GLS $\geq$ 10% and GLS $<$ 10%. There was no significant difference in LVEF between patients with and without beta-blockers in the group with GLS $<$ 10% (26.2 ± 7.0% vs. 26.7 ± 7.4%, P = 0.202) or in those with GLS $\geq$ 10% (31.5 ± 6.0% vs. 32.6 ± 6.2%, P = 0.070). Regarding the IPTW and PSM populations, the absolute standardized difference showed that the matched populations were generally well balanced in both groups of patients with GLS $\geq$ 10% and GLS $<$ 10%, except for the use of mineralocorticoid receptor antagonists and renin–angiotensin system inhibitors; the clinical characteristics according to GLS are presented in *Table 2*. Briefly, there was no significant difference in age, sex, and previous history of hypertension or ischaemic heart disease between patients with GLS $<$ 10% and those with GLS $\geq$ 10%. However, patients with GLS $<$ 10% had more previous history of diabetes mellitus and atrial fibrillation.

There was a significant positive correlation between LVEF and GLS (r = 0.419, P $<$ 0.001), and patients with GLS $<$ 10% showed lower LVEF levels than those with GLS $\geq$ 10% (26.4 ± 7.2% vs. 31.8 ± 6.0%, P $<$ 0.001).

Clinical outcomes

The median follow-up duration was 31.2 months (inter-quartile range, 10.9–53.6 months). Overall, 864 patients (40.6%) died during the 5 year follow-up: 43.9% (703/1600) patients died in the GLS $<$ 10% group, whereas 30.6% (161/526) patients died in the GLS $\geq$ 10% group. The deceased had more unfavourable characteristics such as older age, higher incidence of previous hypertension, diabetes mellitus, ischaemic heart disease, and higher New York Heart Association functional class. They received less beta-blockers, renin–angiotensin system inhibitors, and mineralocorticoid receptor antagonists (Supporting Information, *Table S3*).

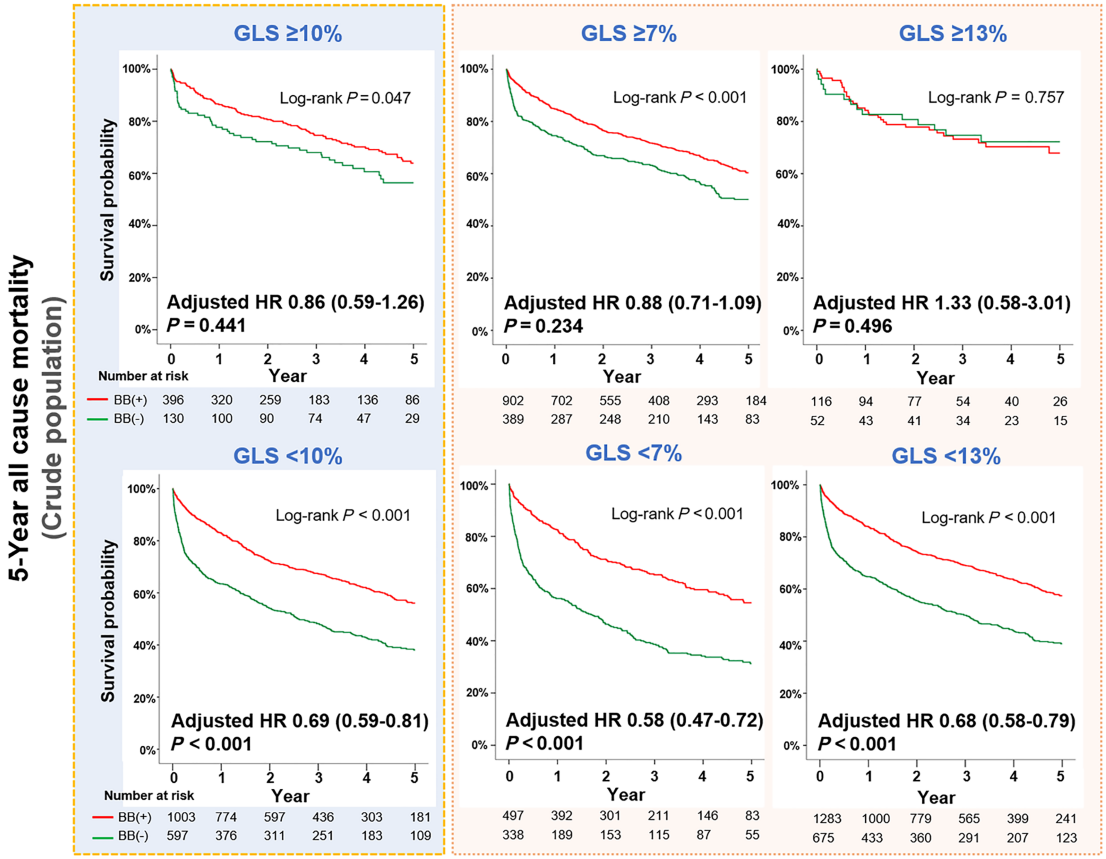
In the crude population, patients who received beta-blockers had lower mortality than those who did not receive beta-blockers in the GLS $\geq$ 10% group (log-rank P = 0.047) and GLS $<$ 10% groups (log-rank P $<$ 0.001; *Figure 2*). However, when the covariates were adjusted, use of beta-blockers was found to be associated with a reduced

Table 2 Baseline characteristics according to left ventricular GLS

	All (n = 2126)	GLS $<$ 10% (n = 1600)	GLS $\geq$ 10% (n = 526)	P-value
Demographics				
Age (years)	68.4 ± 14.1	68.5 ± 14.1	68.2 ± 13.9	0.694
Male (%)	1320 (62.1)	1010 (63.1)	310 (58.9)	0.086
Body mass index (kg/m^2)	23.1 ± 4.2	23.1 ± 4.3	23.1 ± 3.9	0.853
Medical history				
Hypertension	1168 (54.9)	898 (56.1)	270 (51.3)	0.055
Diabetes mellitus	784 (36.9)	621 (38.8)	163 (31.0)	0.001
Ischaemic heart disease	745 (35.0)	564 (35.3)	181 (34.4)	0.726
Atrial fibrillation	531 (25.4)	447 (28.4)	84 (16.3)	<0.001
Physical examination at the admission				
Systolic blood pressure (mmHg)	126.5 ± 25.9	126.2 ± 26.0	127.3 ± 25.8	0.386
Diastolic blood pressure (mmHg)	75.1 ± 16.8	75.6 ± 17.2	73.6 ± 15.3	0.011
Heart rate (b.p.m.)	93.0 ± 24.7	96.3 ± 24.7	82.8 ± 21.7	<0.001
NYHA class				<0.001
I, II	130 (6.9)	84 (5.8)	46 (10.4)	
III	918 (48.9)	667 (46.4)	251 (56.9)	
IV	831 (44.2)	687 (47.8)	144 (32.7)	
Laboratory and echocardiographic findings				
GFR (mL/min/1.73 m^2)	60.6 ± 29.3	59.2 ± 28.8	64.8 ± 30.5	<0.001
Left atrial diameter (mm)	45.1 ± 8.8	45.6 ± 8.9	43.8 ± 8.6	<0.001
Left ventricular end-diastolic diameter (mm)	58.0 ± 9.0	58.5 ± 9.1	56.3 ± 8.5	<0.001
Medication				
Beta-blocker	1399 (65.8)	1003 (62.7)	396 (75.3)	<0.001
Renin–angiotensin system inhibitor	1622 (76.3)	1191 (74.4)	431 (81.9)	<0.001
Mineralocorticoid receptor antagonist	1088 (51.2)	815 (50.9)	273 (51.9)	0.701

GFR, glomerular filtration rate; GLS, global longitudinal strain; NYHA, New York Heart Association.

Figure 2 Clinical outcomes according to beta-blockers (BB) stratified by global longitudinal strain (GLS) in the crude population. Left panel: Kaplan–Meier survival curves for 5 year mortality according to BB use are presented in both the crude population of patients with GLS values of <10% and ≥10%. Right panel: KaplanMeier survival curves using different GLS cut-off values (7% and 13%) in the sensitivity analyses. HR, hazard ratio.



mortality in the GLS < 10% group (HR 0.69, 95% CI 0.59–0.81, $P < 0.001$), but not in the GLS ≥ 10% group (HR 0.86, 95% CI 0.59–1.26, $P = 0.441$). Both univariate and multivariate analyses of all adjusted variables were presented in Supporting Information, *Table S4*. Similar results were observed when we used 7% and 13% as alternative GLS cut-off values. In addition, the use of beta-blockers was not associated with a reduced risk of composite of all-cause mortality and hospitalization for HF in patients with GLS ≥ 10% (Supporting Information, *Figure S1*). In contrast to the differential effects of beta-blockers according to GLS level in patients with HFrEF, beta-blockers showed therapeutic benefits in patients with LVEF < 30% and in those with LVEF 30–39% (Supporting Information, *Figure S2*).

In the IPTW population, the use of beta-blockers was associated with improved survival in the GLS < 10% group [hazard ratio (HR) 0.70, 95% confidence interval (CI) 0.59–0.83, $P < 0.001$], but not in the GLS ≥ 10% group (HR 0.87, 95% CI 0.55–1.37, $P = 0.543$; Supporting Information, *Figure S3*). In the sensitivity analyses using 7% and 13% as GLS cut-off values, the results were similar; patients taking beta-blockers showed better survival in patients with GLS < 7% or with GLS < 13% (HR 0.62, 95% CI 0.50–0.77, $P < 0.001$, and HR 0.69, 95% CI 0.59–0.81, $P < 0.001$, for GLS cut-off values of 7% and 13%, respectively), but not in their counterparts. In the PSM cohort, the use of beta-blockers was also associated with better survival in the GLS < 10% group (HR 0.63, 95% CI 0.52–0.75, $P < 0.001$), but not in those with GLS ≥ 10% (HR 0.82, 95% CI 0.53–1.29, $P < 0.390$) (Supporting Information, *Figure S4*).

Subgroup analysis

We performed exploratory subgroup analyses that included age, sex, history of hypertension, diabetes mellitus, ischaemic heart disease, and atrial fibrillation, heart rate, and GLS (*Figure 3A*). There was no significant interaction of beta-blocker effect with any subgroup except for an interaction between GLS and use of beta-blockers (P for interaction = 0.001). Consistent with these results, similar findings were observed when we performed further stratification.

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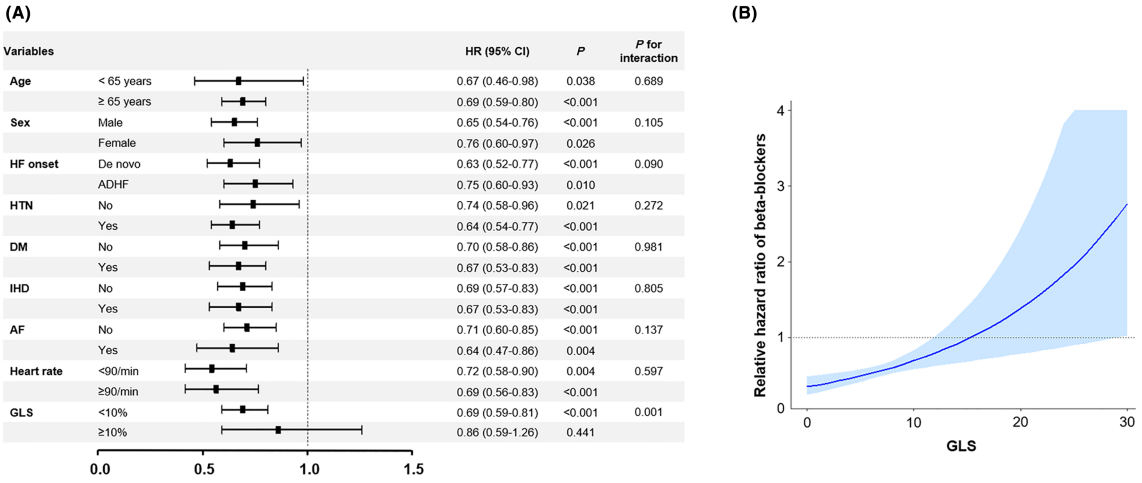
Figure 3 Association between 5 year all-cause mortality and beta-blocker use in subgroups. (A) The effect of beta-blockers in subgroups stratified by age, sex, heart failure (HF) onset, previous history of hypertension (HTN), diabetes mellitus (DM), ischaemic heart disease (IHD), and atrial fibrillation (AF), heart rate, and global longitudinal strain (GLS) is presented. The squares with horizontal lines indicate the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). (B) Cox regression analysis demonstrates the relative HRs (solid line) and 95% CIs (shaded area) for patients taking beta-blockers in comparison with those not taking beta-blockers. ADHF, acute decompensated heart failure.



Beta-blocker use was associated with improved outcomes, regardless of rhythm (HR 0.71, 95% CI 0.59–0.86, $P < 0.001$, for patients with sinus rhythm, and HR 0.66, 95% CI 0.48–0.90, $P = 0.010$, for patients with atrial fibrillation) and heart rate (HR 0.74, 95% CI 0.57–0.96, $P = 0.022$, for patients with heart rate <90 b.p.m., and HR 0.67, 95% CI 0.54–0.83, $P < 0.001$, for patients with heart rate ≥90 b.p.m.) in HFrEF patients with GLS < 10%. In contrast, the effect of beta-blockers was attenuated regardless of rhythm (HR 1.01, 95% CI 0.67–1.53, $P = 0.973$, for patients with sinus rhythm, and HR 0.97, 95% CI 0.30–3.15, $P = 0.958$, for patients with atrial fibrillation) and heart rate (HR 0.78, 95% CI 0.48–1.24, $P = 0.288$, for patients with heart rate <90 b.p.m., and HR 1.07, 95% CI 0.56–2.04, $P = 0.836$) in HFrEF patients with GLS ≥ 10%. Cox regression analysis also showed that the relative magnitude of survival benefit with beta-blockers was prominent in patients with GLS < 10% (*Figure 3B*).

Discussion

The use of beta-blockers was robustly associated with a 30% reduced risk of all-cause mortality in patients with reduced ejection fraction and GLS < 10% in this study. Intriguingly, the survival benefit of beta-blocker use seemed to be attenuated in patients with GLS ≥ 10%. These results were consistently observed in the multivariate Cox regression and IPTW analyses. Furthermore, there was a significant interaction between beta-blocker effects and GLS levels. To the best of our knowledge, this study is the first of its kind to identify patients who have attenuated benefit from beta-blockers among patients with HFrEF using myocardial strain. Based on these results, we suggest that not all patients with HFrEF benefit equally from beta-blockers.

Because neurohormonal activation plays a crucial role in the development and progression of HF,[15,16] various treatments targeting neurohormonal pathways have been developed for patients with HF.[17–20] Among these advances, beta-blockers have significantly improved the prognosis of patients with HFrEF in several randomized controlled trials.[21–25] Nonetheless, not all patients benefit equally from beta-blockers, and patients who do not benefit from beta-blockers have poorer prognosis than their counterparts.[26,27] Therefore, there is a need to predict the response to beta-blockers for better stratification.

Left ventricular ejection fraction, a volume-based parameter, is a classic parameter to assess left ventricular systolic function and to predict the prognosis, and current guidelines use LVEF to classify HF phenotypes and to guide therapy.[3,5,28,29] However, LVEF has some intrinsic limitations due to various geometric assumptions and confounding factors.[30] In contrast, GLS measures myocardial deformation directly and evaluates systolic function better than LVEF, especially in the presence of geometric confounders.[30] In addition, GLS shows better prognostic value than LVEF.[10,31]

Because patients with similar GLS have similar prognosis regardless of LVEF,[12] they may have similar properties, including the response to medical therapy. The key finding of this study was that patients with HFrEF and GLS < 10% benefitted more pronouncedly from beta-blockers. In addition, we previously reported that patients with HFpEF and reduced GLS (GLS < 14%) had better survival when they received beta-blockers.[8] Taken together, beta-blockers may

be beneficial in HF patients with GLS $<$ 10%, but not in those with GLS $\geq$ 10%, regardless of LVEF.

Regarding the 'classic' differential effect of beta-blockers in HFrEF and HFpEF, we have the following explanation. Because there is a substantial positive correlation between LVEF and GLS,[10,32] there are many patients with reduced GLS in HFrEF and few patients with reduced GLS in HFpEF. This may explain the 'overall' positive and neural effects of beta-blockers in HFrEF and HFpEF, respectively.

In this study, we found that the well-validated benefits of beta-blockers in patients with HFrEF are more pronounced in those with concomitant GLS $<$ 10%, and those with GLS $\geq$ 10% may have limited benefit from beta-blockers. As a clinical implication, we do not suggest that patients with HFrEF and GLS $\geq$ 10% do not receive beta-blockers. Nonetheless, we raise the possibility that there may exist patients whose responsiveness to beta-blockers would be attenuated and who consequently need particular medical attention. Furthermore, we believe that these controversial findings may provoke and stimulate research into the underlying characteristics, pathophysiology, and treatment of patients with HFrEF.

Limitations

This study has several limitations. Because we enrolled only Asian patients with acute HF in the STRATS-AHF study, it is unknown whether these findings could be extrapolated to other ethnicities or to patients with chronic HF. Second, considering the highly complex cardiac mechanics, we did not measure global radial and circumferential strain, which may have strengthened the study findings. The recent universal definition of HF defines HFrEF as patients with LVEF $\leq$ 40%. By applying this new definition,[33] 84 patients would have been included in the study. In addition, we did not explore the differential effect of beta-blockers according to the GLS in patients with mildly reduced ejection fraction, because patients with an LVEF $>$ 40% had been excluded. In addition, we did not collect data on the vital signs or echocardiographic examination at the time of discharge; therefore, the prognostic values of heart rate, LVEF, and GLS at discharge remain unknown. Furthermore, the use of beta-blockers may have changed during the follow-up. Owing to the observational nature of the study design, we performed multivariate and IPTW analyses and additional sensitivity analyses using alternative cut-off values to overcome bias. For example, relatively small sample size or event number might raise the possibility of type II error. We performed IPTW and PSM as sensitivity analyses; however, the use of renin–angiotensin system inhibitors and mineralocorticoid receptor antagonists was inadequately balanced because of significant interactions among the medications. Although we adjusted for these medications in the Cox regression analysis, careful interpretation is still required. The consistency of the results implies the robustness of the findings. Nonetheless, our study findings should be confirmed in large-scale, randomized clinical trials to rigorously assess the effect of beta-blockers in patients with HFrEF.

Conclusions

We found that the use of beta-blockers was associated with improved survival in patients with HFrEF and GLS $<$ 10%, but not in those with GLS $>$ 10%. Therefore, GLS may be used to identify patients with HFrEF whose responsiveness to beta-blockers may be attenuated and who may demand particular medical attention. Further studies are necessary to validate the differential effect of beta-blockers according to myocardial strain in patients with HFrEF.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Clinical outcomes of composite outcomes of all-cause mortality and HHF according to BB stratified by GLS.
Figure S2. Clinical outcomes according to beta-blockers stratified by LVEF.
Figure S3. Clinical outcomes according to beta-blockers stratified by GLS in the IPTW cohort.
Figure S4. Clinical outcomes according to beta-blockers stratified by GLS in the propensity score matching cohort.
Table S1. Baseline characteristics of the IPTW population.
Table S2. Baseline characteristics of the propensity score matched population.
Table S3. Baseline characteristics according to 5-year mortality.
Table S4. Univariate and multivariate Cox regression analysis to predict 5-year all-cause mortality.

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