BEEAF$_2$ Score: A New Risk Stratification Score for Patients With Stage B Heart Failure From the KUNIUMI Registry Chronic Cohort

Odajima, Susumu ; Fujimoto, Wataru ; Takegami, Misa ; Nishimura, Kunihiro ; Iwasaki, Masamichi ; Okuda, Masanori ; Konishi, Akihide ;…

(Citation)
Journal of the American Heart Association,13(19):e034793

(Issue Date)
2024-10-01

(Resource Type)
journal article

(Version)
Version of Record

(URL)
https://hdl.handle.net/20.500.14094/0100491722

Journal of the American Heart Association

ORIGINAL RESEARCH

BEEAF$_2$ Score: A New Risk Stratification Score for Patients With Stage B Heart Failure From the KUNIUMI Registry Chronic Cohort

Susumu Odajima, MD, PhD; Wataru Fujimoto, MD; Misa Takegami, PhD; Kunihiro Nishimura, PhD; Masamichi Iwasaki, MD, PhD; Masanori Okuda, MD, PhD; Akihide Konishi, MD, PhD; Masakazu Shinohara, MD, PhD; Manabu Nagao, MD, PhD; Ryuji Toh, MD, PhD; Ken-ichi Hirata, MD, PhD; Hidekazu Tanaka, MD, PhD

BACKGROUND: Stage B heart failure (HF) refers to structural heart disease without signs or symptoms of HF, so that early intervention may delay or prevent the onset of overt HF. However, stage B HF is a very broad concept, and risk stratification of such patients can be challenging.

METHODS AND RESULTS: We conducted a prospective study of data for 1646 consecutive patients with HF from the KUNIUMI (Kobe University Heart Failure Registry in Awaji Medical Center) registry chronic cohort. The definition of HF stages was based on current guidelines for classification of 29 patients as stage A HF, 761 as stage B HF, 827 as stage C HF, and 29 patients as stage D HF. The primary end point was the time-to-first-event defined as cardiovascular death or HF hospitalization within 2.0 years of follow-up. A maximum of 6 adjustment factor points was assigned based on Cox proportional hazards analysis findings for the hazard ratio (HR) of independent risk factors for the primary end point: 1 point for anemia, estimated glomerular filtration rate <45 mL/min per 1.73 m^2, brain natriuretic peptide ≥150 pg/mL, and average ratio of early transmitral flow velocity to early diastolic mitral annular velocity >14, and 2 points for clinical frailty scale >3. Patients with stage B HF were stratified into 3 groups, low risk (0–1 points), moderate risk (2–3 points), and high risk (4–6 points). Based on this scoring system (BEEAF$_2$ [brain natriuretic peptide, estimated glomerular filtration rate, ratio of early transmitral flow velocity to early diastolic mitral annular velocity, anemia, and frailty]), the outcome was found to become worse in accordance with risk level. High-risk patients with stage B HF and patients with stage C HF showed similar outcomes.

CONCLUSIONS: Our scoring system offers an easy-to-use evaluation of risk stratification for patients with stage B HF.

Key Words: echocardiography ■ preclinical heart failure ■ risk stratification ■ stage B heart failure

Heart failure (HF) is classified into stages A to D based on structural changes and symptoms.[1] This classification emphasizes the development and progression of the disease and can be used to describe both individuals and populations and advancement of severity of HF in corresponding order.[2] Because HF is considered a progressive disorder that can be represented as a clinical continuum, individuals at a particular HF stage require specific management with the long-term goal of avoiding HF progression. Stage B HF refers to structural heart disease without signs or symptoms of HF. Transition from stage B to C

Correspondence to: Hidekazu Tanaka, MD, PhD, FACC, FASE, FAHA, FESC, Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-2, Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. Email: tanakah@med.kobe-u.ac.jp

This article was sent to Sula Mazimba, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.034793

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- We created an easy-to-use scoring system for predicting cardiovascular death or heart failure (HF) hospitalization for patients with stage B HF.
- Stratification of the patients with stage B HF into 3 groups (low risk, moderate risk, and high risk) based on our scoring system showed that the outcome became worse in order of risk level.
- High-risk patients with stage B HF and patients with stage C HF showed similar outcomes; the assessment of frailty was necessary for patients with stage B HF.

What Are the Clinical Implications?

- High-risk patients with stage B HF require closer follow-up and strict lifestyle control.
- It is necessary to treat high-risk patients with stage B HF in a manner similar to that for patients with stage C HF.
- Cardiac rehabilitation is desirable for high-risk patients with stage B HF.

Nonstandard Abbreviations and Acronyms

E	early transmitral flow velocity
e′	early diastolic mitral annular velocity
KUNIUMI	Kobe University Heart Failure Registry in Awaji Medical Center
SGLT	sodium glucose cotransporter

HF portends a 5-fold increase in mortality risk for both men and women,[2] but early intervention may delay or prevent the onset of overt HF for patients with stage B HF. This has led to closer attention to screening results for high-risk patients with stage B HF because of growing interest in addressing stage B HF as the best way to prevent eventual progression to clinical HF. However, stage B HF is a very broad concept,[3] so that risk stratification of patients with stage B HF can be challenging. We therefore designed and conducted a single-center prospective cohort study to create a scoring system for predicting cardiovascular death or HF hospitalization of patients with stage B HF.

METHODS

Study Design and Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. The KUNIUMI (Kobe University Heart Failure Registry in Awaji Medical Center) registry chronic cohort is a community-based, single-center, prospective, observational study of chronic HF on Awaji Island, Japan. The island is a semienclosed area with a low migration rate, so that incidence and follow-up data can be compared with previous registry data for superior quality results. A total of 1646 consecutive patients with HF, accounting for 1.3% of the population of Awaji Island, were prospectively enrolled in this study between March 2019 and March 2021. Written informed consent was obtained. This study was approved by the local ethics committee of our institution in conformity with the Declaration of Helsinki (Approval No. 21-20, 5 October 2018) and registered with the Japan Registry of Clinical Trials (jRCT1050200024).

Definition of Stages of HF

The definition of HF stages was based on the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America guideline for the management of HF.[3] Stage A HF was defined as at risk for HF and includes hypertension, atherosclerotic cardiovascular disease, diabetes, metabolic syndrome and obesity, exposure to cardiotoxic agents, genetic variant for cardiomyopathy, or positive family history of cardiomyopathy but without symptoms, structural heart disease, or cardiac biomarkers of stretch or injury. Stage B HF was defined as no symptoms or signs of HF and evidence of 1 of the following criteria: left ventricular (LV) wall thickness ≥12 mm, relative wall thickness >0.42, LV mass index >116 g/m^2 (men)/95 (women) g/m^2, LV wall motion abnormalities, left atrial volume index ≥29 mL/m^2, E (early transmitral flow velocity)/e′ (early diastolic mitral annular velocity) >15 (average), e′ <7 cm/s (septal), e′ <10 cm/s (lateral), tricuspid regurgitation velocity >2.8 m/s, estimated pulmonary artery systolic pressure >35 mm Hg, brain natriuretic peptide (BNP) ≥35 pg/mL, and more than moderate valvular heart disease. Stage C HF was defined as structural heart disease with current or previous symptoms of HF.[4] Stage D HF was defined as marked HF symptoms that interfere with daily life and with recurrent hospitalizations despite attempts to optimize guideline-directed medical therapy. Of the 1646 consecutive patients with HF enrolled in our study, 29 were ascertained as stage A HF, 761 as stage B HF, 827 as stage C HF, and 29 as stage D HF.

Echocardiographic Examination

All echocardiographic examinations were performed with commercially available ultrasound systems, and standard echocardiographic measurements were obtained in accordance with the current guidelines of the America Society of Echocardiography.[5] All

echocardiographic examinations were performed by senior echocardiologists or sonographers.

A Risk Stratification Model for Patients With Stage B HF

For this study, we created a risk stratification model, comprising medical history, laboratory data, and echocardiographic parameters, for predicting the primary end point for patients with stage B HF. Specifically, this model consisted of 30 items that were selected in consultation with several cardiologists specializing in HF, focusing on items that are common and frequently used in a real-world clinical practice divided into 3 groups: (1) medical history consisting of age, sex, body mass index, clinical frailty scale, heart rate, history of hypertension, diabetes, dyslipidemia, atrial fibrillation, percutaneous coronary intervention, peripheral arterial disease, stroke and cardiac surgery, and use of β-blockers, renin-angiotensin-aldosterone system-inhibitors, statin, sodium glucose cotransporter (SGLT2) inhibitors and insulin; (2) laboratory data consisting of hemoglobin, albumin, estimated glomerular filtration rate (eGFR), BNP, and troponin-I; and (3) echocardiographic parameters consisting of relative wall thickness, LV mass index, LV ejection fraction, left atrial volume index, E/e′ (average), tricuspid regurgitation velocity, and valvular disease. The validity of this model was determined by using a receiver operating characteristic curve analysis.

Definition of Primary End Ppoint

The primary end point was the time-to-first-event defined as a composite of cardiovascular death or HF hospitalization within 2.0 years of follow-up.

Statistical Analysis

Continuous variables were expressed as mean values with corresponding SDs for normally distributed data and as medians with corresponding interquartile range for nonnormally distributed data. Categorical variables were expressed as frequencies and percentages. The parameters of the 3 subgroups were compared using Student's *t* test for continuous variables and a χ^2 test for categorical variables. Proportional differences were evaluated with Fisher's exact test. The associations of clinical parameters with primary end point for patients with stage B HF were analyzed by means of linear logistic regression models for univariable and multivariable analysis. For the selection of independent variables for entry into the multivariable model, Pearson's correlation analyses between independent variables were performed in advance to avoid multicollinearity. Variables with a univariable value of $P<0.05$ were incorporated into the multivariable analysis. Time-to-event data for the composite of cardiovascular death or HF hospitalization were evaluated using Cox proportional hazard analysis to calculate HRs, 95% CI, and 2-sided *P* values. To create a risk stratification score for patients with stage B HF, univariable and multivariable Cox proportional hazards analysis was performed to predict the primary end point for patients with stage B HF by using the aforementioned risk stratification model with the categorical variables based on the cutoff value for predicting the primary end point obtained by means of receiver operating characteristic curve analysis. Adjustment factor points were assigned by taking the HR of the independent risk factors for the primary end point into consideration. For all steps, a *P* value of <0.05 was considered statistically significant. All analyses were performed with a commercially available software (MedCalc software version 19.0.7; MedCalc Software, Mariakerke, Belgium).

RESULTS

Baseline Characteristics and Prognosis of Patients With Stage A–D HF

The baseline characteristics of all 1646 patients are summarized in Table 1. Their mean age was 76.0±11.1 years and 1084 patients (65.9%) were men. The primary end point for 2.0 years was reached for 231 patients (14.1%). As expected, the Kaplan–Meier curve representing the primary end point showed that patients with a more advanced stage of HF showed a worse prognosis (Figure 1). The cumulative incidence of the primary end point at 2.0 years for patients with stage A, B, C, and D HF was 0%, 5.0%, 21.3%, and 58.6%, respectively.

Baseline Characteristics of Patients With Stage B HF

The baseline characteristics of 761 patients with stage B HF are summarized in Table 2. Their mean age was 73.2±10.4 years, and 558 patients (73.3%) were men. The primary end point of for 2.0 years was reached for 38 patients (5.0%). Patients who reached the primary end point were more likely to be older (79.0±10.2 versus 72.8±10.3 years, $P<0.01$), have a lower body mass index (22.1±3.7 versus 23.4±3.5 kg/m^2, $P=0.02$), be rated higher on the clinical frailty scale (4.1±1.3 versus 3.2±0.6, $P<0.01$), and have a higher heart rate (76.6±12.4 versus 71.4±12.6, $P=0.01$), lower prevalence of dyslipidemia (44.7% versus 71.4%, $P<0.01$) and percutaneous coronary intervention (50.0% versus 70.8%, $P<0.01$), higher prevalence of peripheral arterial disease (21.1% versus 10.2%, $P=0.04$), stroke (26.3% versus 5.9%, $P<0.01$), and cardiac surgery (36.8% versus 11.6%, $P<0.01$), use fewer renin-angiotensin-aldosterone system inhibitors (52.6% versus 72.2%, $P<0.01$) and less statin (39.5% versus 71.4%, $P<0.01$), and show lower levels of hemoglobin (11.9±1.8 versus

Table 1. Baseline Characteristics of Overall Patients

	Overall patients (N=1646)	Stage A HF (N=29)	Stage B HF (N=761)	Stage C HF (N=827)	Stage D HF (N=29)
Clinical characteristics					
Age, y	76.0±11.1	69.0±8.5	73.2±10.4	78.5±11.1	85.3±8.3
Sex, men, n (%)	1084 (65.9)	27 (93.1)	558 (73.3)	486 (58.8)	13 (44.8)
Body mass index, kg/m^2	22.7±4.0	24.4±2.7	23.4±3.5	22.2±4.4	20.4±3.9
Clinical frailty scale	3.6±1.2	3.0±0.0	3.2±0.7	3.9±1.3	5.7±1.6
Heart rate, beats/min	72.0±12.9	74.1±12.8	71.7±12.6	72.0±13.0	75.5±15.5
Comorbidities, n (%)					
Hypertension	1218 (74.0)	22 (75.9)	570 (74.9)	608 (73.5)	18 (62.1)
Diabetes	609 (37.0)	15 (51.7)	302 (39.7)	282 (34.1)	10 (34.5)
Dyslipidemia	885 (53.8)	27 (93.1)	533 (70.0)	317 (38.3)	8 (27.6)
Atrial fibrillation	510 (31.0)	0 (0)	115 (15.1)	376 (45.5)	19 (65.5)
Peripheral arterial disease	99 (6.0)	3 (10.3)	53 (7.0)	41 (5.0)	2 (6.9)
Stroke	232 (14.1)	1 (3.4)	98 (12.9)	130 (15.7)	3 (10.3)
History of percutaneous coronary intervention	857 (52.1)	0 (0)	565 (74.2)	253 (30.6)	10 (34.5)
History of cardiac surgery	227 (13.8)	0 (0)	82 (10.8)	142 (17.2)	3 (10.3)
Medications, n (%)					
β-blockers	1094 (66.5)	8 (27.6)	465 (61.1)	599 (72.4)	22 (75.9)
Renin-angiotensin-aldosterone system inhibitors	1231 (74.8)	17 (58.6)	542 (71.2)	648 (78.4)	24 (82.8)
Statin	863 (52.4)	22 (75.9)	531 (69.8)	301 (36.4)	9 (31.0)
Sodium glucose cotransporter 2 inhibitor	175 (10.6)	4 (13.8)	88 (11.6)	80 (9.7)	3 (10.3)
Insulin	115 (7.0)	2 (6.9)	43 (5.7)	69 (8.3)	1 (3.4)
Laboratory data					
Hemoglobin, mg/dL	12.7±2.1	14.4±1.7	13.2±1.8	12.2±2.2	10.6±1.8
Albumin, mg/dL	3.7±0.5	4.2±0.9	3.9±0.4	3.6±0.6	3.0±0.6
Estimated glomerular filtration rate, mL/min per 1.73 m^2	51.5±23.6	68.4±14.4	57.7±22.6	45.7±22.9	35.1±22.3
Brain natriuretic peptide, pg/mL	131 (124–141)	12.8 (8.2–19.0)	64.4 (61.3–79.6)	226 (214–252)	618 (446–820)
Troponin I, ng/mL	0.018 (0.017–0.019)	0.007 (0.006–0.010)	0.014 (0.013–0.015)	0.024 (0.022–0.027)	0.048 (0.033–0.105)
Echocardiographic data					
Relative wall thickness	0.41±0.11	0.38±0.03	0.41±0.10	0.41±0.12	0.42±0.20
LV mass index, g/m^2	100.2±32.2	71.4±11.2	92.3±27.1	107.5±33.4	132.6±45.8
LV ejection fraction, %	53.3±12.6	65.5±5.2	56.3±9.8	50.6±13.9	41.1±15.4
Left atrial volume index, mL/m^2	45.6±28.0	22.7±4.0	35.9±18.1	54.7±32.0	66.3±29.4
Early transmitral flow velocity/e′, early diastolic mitral annular velocity, average	13.6±6.9	8.8±1.9	11.8±5.3	15.1±7.6	20.6±9.7
Tricuspid regurgitation velocity, m/s	2.4±0.5	2.1±0.3	2.2±0.4	2.5±0.5	2.7±0.5
Valvular heart disease, n (%)	671 (40.8)	0 (0)	180 (23.7)	467 (56.5)	24 (82.8)

Data are mean±SD for normally distributed data and median and interquartile range for nonnormally distributed data, or n (%). HF indicates heart failure; and LV, left ventricular.

13.3±1.7 mg/dL, P<0.01), albumin (3.5±0.4 versus 3.9±0.4 mg/dL, P<0.01), and eGFR (34.6±24.8 versus 58.9±21.8 mL/min per 1.73 m^2, P<0.01), and higher levels of BNP (218 [134–321] versus 64.3 [58.2–75.9]) pg/mL, P<0.01) and troponin I (0.028 [0.019–0.051] versus 0.013 [0.012–0.014]) ng/mL, P<0.01). In terms of echocardiographic parameters, patients who reached the primary end point were more likely to show a higher LV mass index (106.6±38.0 versus 91.6±26.2 g/m^2, P<0.01), left atrial volume index (42.2±25.0 versus 35.6±17.6 mL/m^2, P=0.03), E/e′ (average; 16.0±6.8 versus 11.6±5.2, P<0.01), tricuspid regurgitation velocity (2.4±0.4 versus 2.2±0.4 m/s, P=0.02), and prevalence of valvular heart disease (50.0% versus 22.3%, P<0.01).

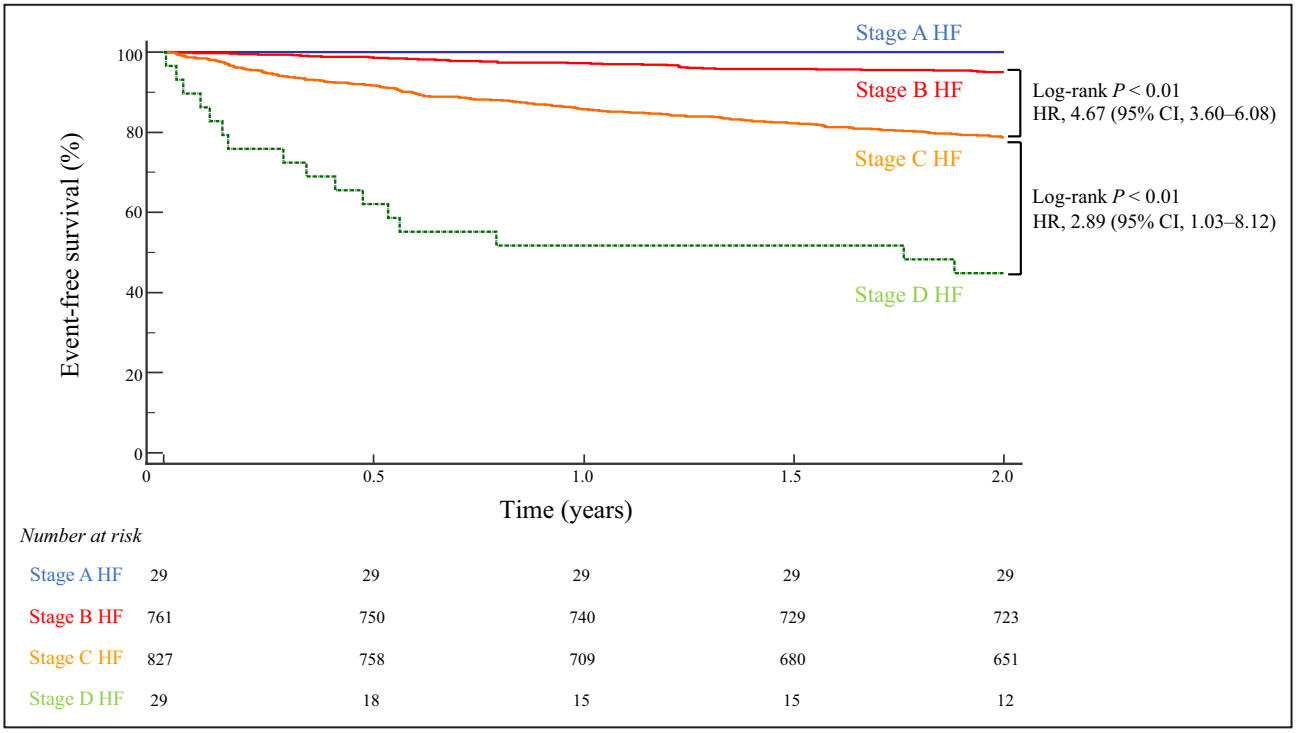

Figure 1. Kaplan–Meier curve representing the primary end point for patients with stage A–D HF, showing that the more advanced the stage of HF is, the worse the prognosis for patients with HF becomes.
HF indicates heart failure; and HR, hazard ratio.

Validity of the Risk Stratification Model for Patients With Stage B HF

The risk stratification model for predicting the primary end point for patients with stage B HF developed in this study consists of 30 items, comprising medical history, laboratory data, and echocardiographic parameters. The validity of this model was determined by means of receiver operating characteristic curve analysis (Figure 2). Area under the curve of this model was 0.86 (95% CI, 0.83–0.88).

Associations of Clinical Parameters With Primary End Point for Patients With Stage B HF

Table 3 shows univariable and multivariable Cox proportional hazards analysis for predicting the primary end point for patients with stage B HF using the stratification model described in the preceding paragraph with the addition of the following categorical variables: clinical frailty >3, anemia (hemoglobin <13 mg/dL for men/12 mg/dL for women), eGFR <45 mL/min per 1.73 m^2, BNP ≥150 pg/mL, and E/e′ (average) >14. These variables were determined to be the independent risk factors for patients with stage B HF to reach the primary end point.

To devise a scoring system for predicting the primary end point for patients with stage B HF, a total of 6 adjustment factor points were assigned by taking the HR of the independent risk factors for reaching the primary end point into consideration: 1 point was scored for anemia, eGFR <45 mL/min per 1.73 m^2, BNP ≥150 pg/mL, and E/e′ (average) >14, and 2 points for clinical frailty scale >3 (Table 3). These findings were then used to categorize patients with stage B HF into 3 groups: low risk (0–1 points), moderate risk (2–3 points) and high risk (4–6 points). The cumulative incidence of reaching the primary end point at 2.0 years was 0.6% for low-risk, 6.4% for moderate-risk and 26.7% for high-risk patients. Figure 3 shows the Kaplan–Meier curves representing the primary end point for low-risk, moderate-risk and high-risk patients with stage B HF, showing that outcomes for moderate-risk patients with stage B HF were better than for high-risk patients with stage B HF but worse than for low-risk patients, whereas the HRs for reaching the primary end point for moderate-risk and high-risk patients were as high as 10.6 and 49.5, respectively. It was noteworthy that the Kaplan–Meier curves revealed that high-risk patients with stage B HF and all patients with stage C HF showed similar outcomes (Figure 4). Kaplan–Meier survival curves for individual cardiovascular events such as cardiovascular death and HF hospitalization are shown in Figures S1 and S2. Figure 5 summarizes the results of this scoring system for risk stratification of patients with stage B HF ($BEEAF_2$ score: BNP, eGFR,

Table 2. Baseline Characteristics of Patients With Stage B HF

	Overall patients with stage B HF (N=761)	Patients without primary end point (N=723)	Patients with primary end point (N=38)	*P* value
Clinical characteristics				
Age, y	73.2±10.4	72.8±10.3	79.0±10.2	<0.01
Sex, men, n (%)	558 (73.3)	535 (74.0)	23 (60.5)	0.07
Body mass index, kg/m^2	23.4±3.5	23.4±3.5	22.1±3.7	0.02
Clinical frailty scale	3.2±0.7	3.2±0.6	4.1±1.3	<0.01
Heart rate, beats/min	71.7±12.6	71.4±12.6	76.6±12.4	0.01
Comorbidities, n (%)				
Hypertension	570 (74.9)	543 (75.1)	27 (71.1)	0.57
Diabetes	302 (39.7)	286 (39.6)	16 (42.1)	0.75
Dyslipidemia	533 (70.0)	516 (71.4)	17 (44.7)	<0.01
Atrial fibrillation	115 (15.1)	107 (14.8)	8 (21.1)	0.29
Peripheral arterial disease	82 (10.8)	74 (10.2)	8 (21.1)	0.04
Stroke	53 (7.0)	43 (5.9)	10 (26.3)	<0.01
History of percutaneous coronary intervention	565 (74.2)	512 (70.8)	19 (50.0)	<0.01
History of cardiac surgery	98 (12.9)	84 (11.6)	14 (36.8)	<0.01
Medications, n (%)				
β-blockers	465 (61.1)	446 (61.7)	19 (50.0)	0.15
Renin-angiotensin-aldosterone system inhibitors	542 (71.2)	522 (72.2)	20 (52.6)	<0.01
Statin	531 (69.8)	516 (71.4)	15 (39.5)	<0.01
Sodium glucose cotransporter 2 inhibitor	88 (11.6)	87 (12.0)	1 (2.6)	0.08
Insulin	43 (5.7)	39 (5.4)	4 (10.5)	0.18
Laboratory data				
Hemoglobin, mg/dL	13.2±1.8	13.3±1.7	11.9±1.8	<0.01
Albumin, mg/dL	3.9±0.4	3.9±0.4	3.5±0.4	<0.01
Estimated glomerular filtration rate, mL/min per 1.73 m^2	57.7±22.6	58.9±21.8	34.6±24.8	<0.01
Brain natriuretic peptide, pg/mL	64.4 (61.3–79.6)	64.3 (58.2–75.9)	218 (134–321)	<0.01
Troponin I, ng/mL	0.014 (0.013–0.015)	0.013 (0.012–0.014)	0.028 (0.019–0.051)	<0.01
Echocardiographic data				
Relative wall thickness	0.41±0.10	0.41±0.10	0.44±0.09	0.08
LV mass index, g/m^2	92.3±27.1	91.6±26.2	106.6±38.0	<0.01
LV ejection fraction, %	56.3±9.8	56.4±9.6	55.7±12.3	0.69
Left atrial volume index, mL/m^2	35.9±18.1	35.6±17.6	42.2±25.0	0.03
Early transmitral flow velocity/early diastolic mitral annular velocity (average)	11.8±5.3	11.6±5.2	16.0±6.8	<0.01
Tricuspid regurgitation velocity, m/s	2.2±0.4	2.2±0.4	2.4±0.4	0.02
Valvular heart disease, n (%)	180 (23.7)	161 (22.3)	19 (50.0)	<0.01

Data are mean±SD for normally distributed data and median and interquartile range for nonnormally distributed data, or n (%). HF indicates heart failure; and LV, left ventricular.

E/e′ and anemia assigned for 1 point, and frailty assigned for 2 points).

DISCUSSION

Our study based on the KUNIUMI registry chronic cohort findings provides an easy-to-use scoring system (BEEAF$_2$ score) for predicting cardiovascular death or HF hospitalization for patients with stage B HF.

Importance of Risk Stratification for Stage B HF

A previous population cohort study published in 2007 reported that the 5-year survival rates for patients with stages A, B, C, and D HF were 97%, 96%, 75%, and 20%, respectively.[2] For our prospective cohort study of consecutive patients with HF, we examined the occurrence of cardiovascular death or HF hospitalization over a 2-year period. We focused mainly on patients

with stage B HF, using data from the KUNIUMI registry chronic cohort enrolled between March 2019 and March 2021. Our findings show that the cumulative incidence of cardiovascular death or HF hospitalization at 2.0 years for patients with stage B HF was 5.0%. Some patients with stage B HF reached cardiovascular death or HF hospitalization, although the percentage was not high. An accurate identification of high-risk patients from among those with stage B HF is therefore important, but such a risk stratification of patients with stage B HF can be challenging. Previous reports have dealt with independent prognostic factors for patients with stage B HF using biomarkers such as BNP and cardiac troponin I[6] and echocardiographic parameters such as LV mass index,[7] LV ejection fraction[8] and global longitudinal strain.[9] However, most of the studies focused on an individual parameter so that specific algorithms of risk stratification for patients with stage B HF may be needed because stage B HF represents a very broad concept. Our scoring system (the $BEEAF_2$ score) was established as a result of this study and is composed of parameters frequently used in real-world clinical practice for predicting cardiovascular death or HF hospitalization for patients with stage B HF, and proved to be successful for stratifying risk.

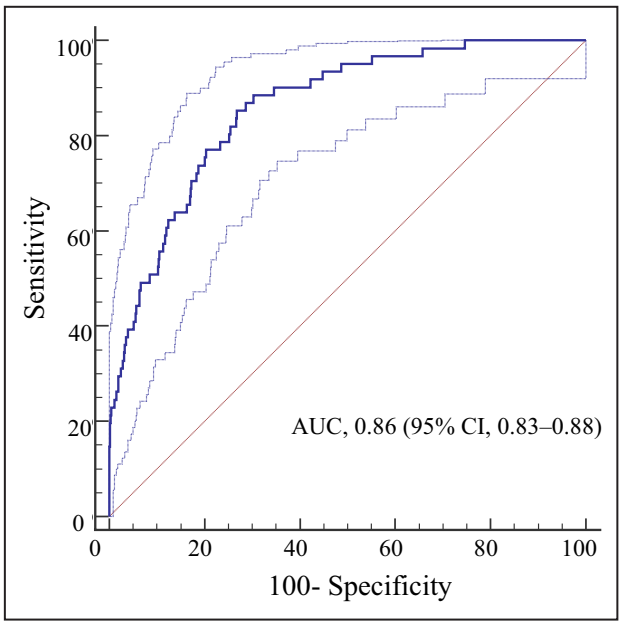

Figure 2. Receiver operating characteristic curve analysis of the risk stratification model for predicting primary end point for stage B heart failure.
AUC indicates area under the curve; and ROC, receiver operating characteristic. The dark blue line shows the ROC curve, and the light blue lines show the 95% confidence bounds.

How to Use Our Risk Stratification Score for Stage B HF and Perspectives for Future Applications

Stratification of patients with stage B HF into 3 groups (low risk, moderate risk, and high risk) based on our scoring system ($BEEAF_2$ score) showed that the outcome became worse in order of risk level. That is to say, high-risk patients with stage B HF require closer follow-up and strict lifestyle control. As to the frequency of follow-up, high intensity follow-up might be needed in high-risk stage B HF. In STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-ProBNP [N-Terminal Pro-Brain Natriuretic Peptide] Testing, of Heart Failure Therapies) trial, an intensive treatment strategy of rapid uptitration of guideline-directed medication and close follow-up after an acute HF admission reduced the risk of 180-day all-cause death or HF readmission compared with usual care.[10] In addition, sufficient time should be spent to help the patient understand his or her own current level of risk and to improve the patient's willingness and compliance to treatment. As to lifestyle control, for example, blood pressure of patients with high-risk stage B HF should be more strictly controlled in accordance with published clinical practice guidelines. Similarly, SGLT2 inhibitors may be effective for high-risk patients with diabetes complicated by stage B HF because of their proven effectiveness for prevention of HF hospitalization of patients with diabetes and either an established cardiovascular disease or at high cardiovascular risk.[11,12]

Outcomes were similar for high-risk patients with stage B HF and patients with stage C HF enrolled in this study. It may thus be necessary to treat high-risk patients with stage B HF, and especially those with risk factors incorporated in the $BEEAF_2$ score, in a manner similar to that for patients with stage C HF. For example, because SGLT2 inhibitors and finerenone have proved to be useful for reducing the risk of HF hospitalization for patients with diabetes and chronic kidney disease,[13,14] the aggressive use of these medications should be considered for high-risk patients with stage B HF with diabetes and chronic kidney disease. In addition, high-risk patients with stage B HF with LV diastolic dysfunction may be treated with SGLT2 inhibitors, and iron deficiency anemia may be aggressively corrected in such patients.

It is well known that frailty is associated with a poor prognosis for patients with HF,[15] and it has also been reported that frailty increases the incidence of HF in the general population.[16,17] Furthermore, frailty and HF reportedly share some underlying mechanisms, symptoms, and manifestations, among them chronic inflammation and oxidative stress, sarcopenia and skeletal muscle weakness, as well as impaired cardiorespiratory and physical performance.[18] Meng et al reported that frail patients with stage B HF have a

Table 3. Univariable and Multivariable Cox Proportional Hazards Analysis for Predicting Primary End Point in Patients With Stage B HF Using Stratification Model With Categorical Variable

Covariate	Univariate			Multivariate			Adjustment factor points
	HR	95% CI	*P* value	HR	95% CI	*P* value	
Age ≥80 y	2.36	1.25–4.45	<0.01				
Sex, men, n (%)	0.55	0.29–1.06	0.07				
Body mass index <18.5 kg/m^2	3.09	1.36–7.05	<0.01				
Clinical frailty scale >3	9.09	4.74–17.4	<0.01	4.17	1.98–8.76	<0.01	2
Heart rate ≥80 beats/min	2.14	1.12–4.10	0.02				
Hypertension	0.81	0.40–1.64	0.56				
Diabetes	1.11	0.58–2.12	0.75				
Dyslipidemia	0.33	0.18–0.63	<0.01				
Atrial fibrillation	1.53	0.70–3.33	0.29				
Peripheral arterial disease	2.31	1.06–5.05	0.04				
Stroke	5.17	2.51–10.6	<0.01				
History of percutaneous coronary intervention	0.42	0.22–0.79	<0.01				
History of cardiac surgery	4.23	2.19–8.18	<0.01				
Use of β-blockers	0.27	0.14–0.52	<0.01				
Use of renin-angiotensin-aldosterone system inhibitors	0.63	0.33–1.18	0.15				
Use of statin	0.44	0.23–0.83	0.01				
Use of sodium glucose cotransporter 2 inhibitors	0.20	0.03–1.48	0.12				
Use of insulin	2.02	0.72–5.68	0.18				
Hemoglobin <13 mg/dL (men)/12 mg/dL (women)	5.35	2.60–11.0	<0.01	2.57	1.12–5.91	0.03	1
Albumin ≤3.5 mg/dL	4.34	2.30–8.20	<0.01				
Estimated glomerular filtration rate <45 mL/min per 1.73 m^2	5.19	2.72–9.88	<0.01	2.63	1.29–5.36	<0.01	1
Brain natriuretic peptide ≥150 pg/mL	5.43	2.81–10.5	<0.01	2.23	1.08–4.59	0.03	1
Troponin I ≥0.03 ng/mL	3.85	2.02–7.34	<0.01				
Relative wall thickness >0.42	1.83	0.97–3.47	0.06				
LV mass index >116 g/m^2 (men)/95 g/m^2 (women)	2.43	1.26–4.69	<0.01				
LV ejection fraction <50%	1.50	0.75–3.03	0.25				
Left atrial volume index >40 mL/m^2	1.63	0.85–3.12	0.14				
Early transmitral flow velocity/early diastolic mitral annular velocity >14 (average)	4.35	2.27–8.34	<0.01	2.30	1.09–4.81	0.03	1
Tricuspid regurgitation velocity >2.8 m/s	3.16	1.23–8.14	0.02				
Valvular heart disease, n (%)	3.35	1.77–6.33	<0.01				
Total score							6 points

HF indicates heart failure; HR; hazard ratio; and LV, left ventricular.

higher incidence of all-cause mortality or HF rehospitalization.[19] Although most instruments for the assessment of frailty are time consuming and require physical measurements, the clinical frailty scale is a very simple frailty assessment tool that is practical in busy clinical settings.[20] Clinical frailty scale has been also shown to correlate with mortality in patients with cardiovascular diseas.[21,22] In our study, we were able to show that a clinical frailty scale of 3 points was an independent predictor of the primary end point for patients with stage B HF. Baseline characteristics of patients with stage B HF according to clinical frailty scale (3 points or >3 points) are shown in Table S1. This table indicates that assessment of frailty may be necessary for patients with stage B HF, especially high-risk patients, and cardiac rehabilitation may also be desirable for such patients. These various measures for high-risk patients with stage B HF discussed here are only suggestions, and future clinical studies are needed to determine whether these interventions for high-risk patients with stage B HF can reduce the risk of conversion to stage C HF.

Study Limitations

This study is a single-center study and the number of patients who reached the primary end point was small; therefore, future studies of larger number of

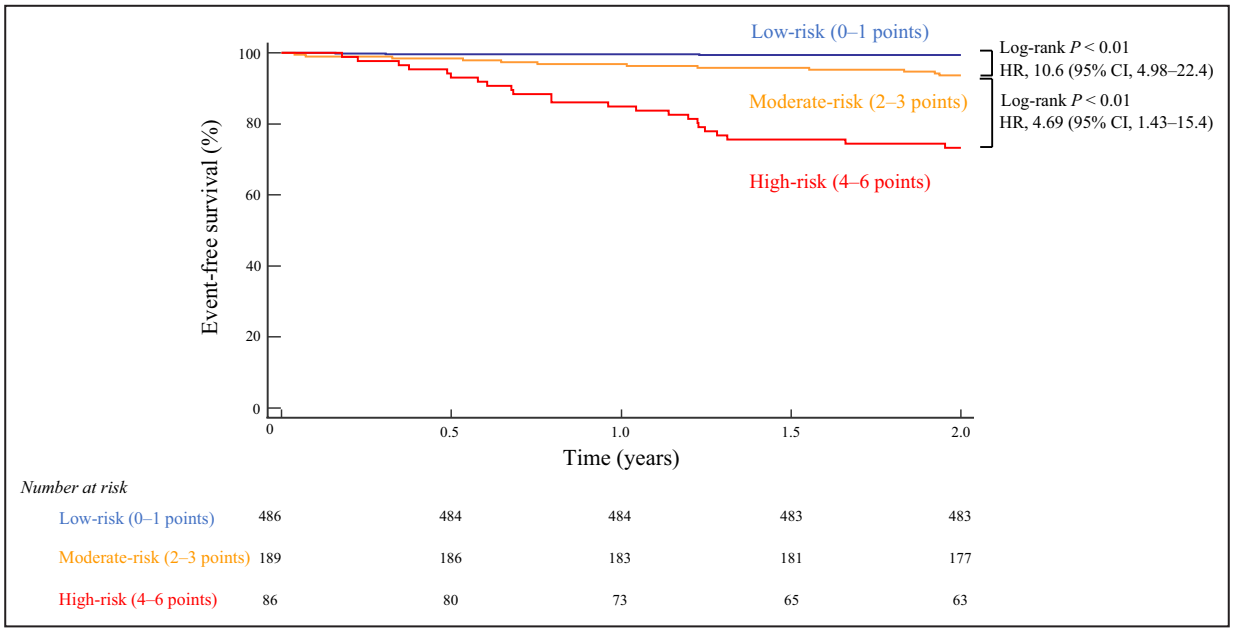

Figure 3. Kaplan–Meier curve representing the primary end point for low-risk, moderate-risk, and high-risk patients with stage B HF, showing that outcomes for moderate-risk patients with stage B HF were better than for high-risk patients but worse than for low-risk patients.
HF indicates heart failure; and HR, hazard ratio.

patients from several centers will be needed to validate our findings. Moreover, the prescription rates of sacubitril/valsartan, SGLT2 inhibitors, and finerenone used in this study are low because this study was conducted before these drugs had been fully approved in Japan.

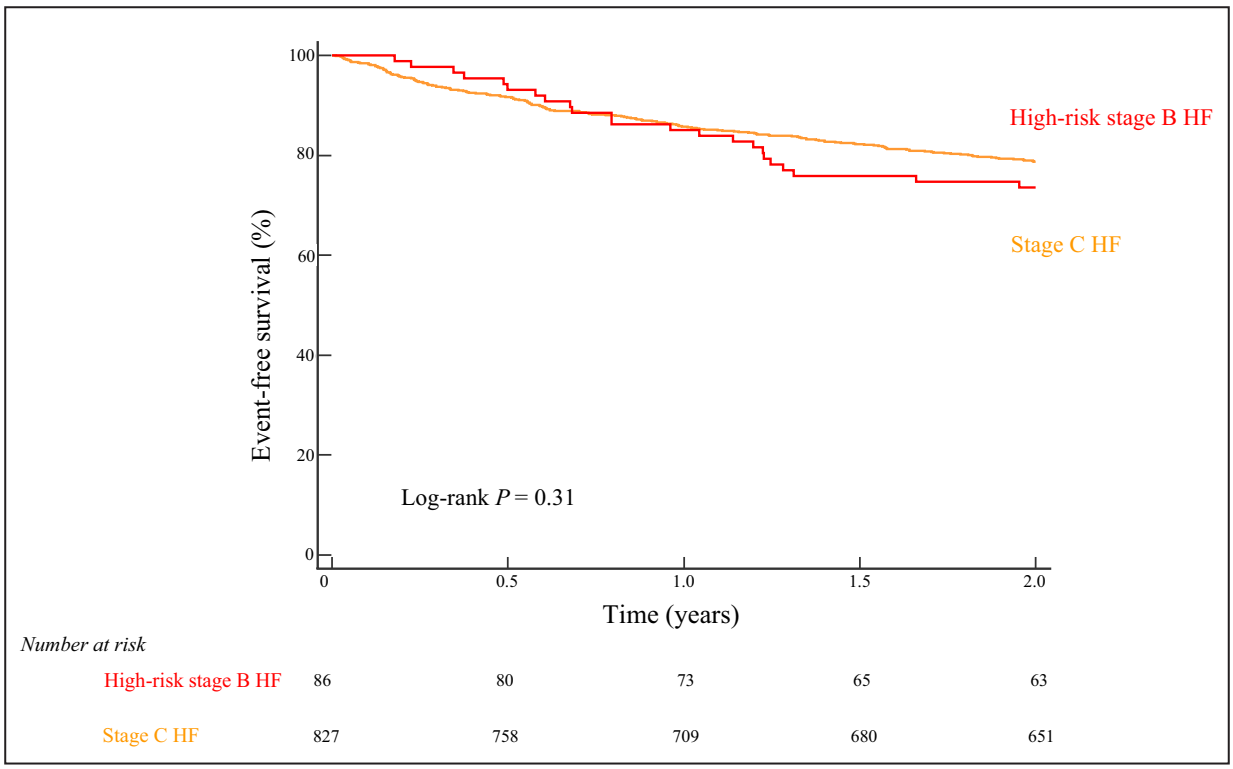

Figure 4. Kaplan–Meier curve representing the primary end point for high-risk patients with stage B HF and patients with stage C HF, showing similar outcomes.
HF indicates heart failure; and HR, hazard ratio.

Risk factors of stage B HF for cardiovascular death and HF hospitalization	Risk score (**BEEAF$_2$ score**)	Risk stratification	Hazard ratio (vs Low risk)
BNP ≥ 150 pg/mL	1	Low-risk (0–1 points)	Reference
eGFR < 45 ml/min/1.73m^2	1	Moderate-risk (2–3 points)	HR:10.6 (95% CI, 4.98–22.4)
E/e' (average) > 14	1		
Anemia; hemoglobin < 13 mg/dL (male) / 12 mg/dL (female)	1	High-risk (4–6 points)	HR: 49.5 (95% CI, 16.9–145)
Frail; Clinical Frailty Scale > 3	2		

Figure 5. Summary of our scoring system (BEEAF$_2$ score) for evaluation of risk stratification of patients with stage B HF.
BEEAF$_2$ indicates BNP, eGFR, E/e′, anemia, and frailty; BNP, brain natriuretic peptide; E/e′, ratio of early transmitral flow velocity to early diastolic mitral annular velocity; eGFR, estimated glomerular filtration rate; HF, heart failure; and HR, hazard ratio.

CONCLUSIONS

Our scoring system (BEEAF$_2$ score) provides an easy-to-use evaluation of risk stratification for patients with stage B HF.

ARTICLE INFORMATION

Received January 31, 2024; accepted May 16, 2024.

Affiliations

Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan (S.O., W.F., K.-i.H., H.T.); Department of Cardiology, Hyogo Prefectural Awaji Medical Center, Sumoto, Japan (W.F., M.I., M.O.); Department of Preventive Medicine and Epidemiology, National Cerebral and Cardiovascular Center, Suita, Japan (M.T., K.N.); Department of Public Health and Health Policy, Graduate School of Medicine, The University of Tokyo, Japan (M.T.); Clinical and Translational Research Center, Kobe University Hospital, Kobe, Japan (A.K.); Division of Epidemiology (M.S.), and Division of Evidence-Based Laboratory Medicine (M.N., R.T., K.-i.H.), Kobe University Graduate School of Medicine, Kobe, Japan.

Acknowledgments

The authors would like to thank Shiho Fukushima, Haruna Okada, Michiko Iwasaki, Yukimi Kato, Hitomi Kotani, Mami Motomura, and Yoko Fujimoto for collecting and managing the data for this study.

Sources of Funding

This work was financially supported by the Osaka Gas Group Welfare Foundation, Japan.

Disclosures

Dr Tanaka received remuneration from AstraZeneca plc, Ono Pharmaceutical Company, Limited, Pfizer Inc, Otsuka Pharmaceutical Co., Ltd., Daiichi Sankyo Company, Limited, Eli Lilly and Company, Boehringer Ingelheim GmbH, Abbott Japan LLC, and Novartis International AG. Dr Hirata has received research funding from Daiichi Sankyo Company, Limited, Actelion Pharmaceuticals Japan, Terumo Corporation, Abbott Vascular Japan, Otsuka Pharmaceutical Company, Limited, Kowa Company, Limited, Takeda Pharmaceutical Company Limited, Nihon Medi-Physics Company Limited, Novartis Pharma Company Limited, Bayer Company Limited, Biotronic Japan Company Limited, FUJIFILM Toyama Chemical Company Limited, Medtronic Japan Company Limited, and Sysmex Company Limited. The remaining authors have no disclosures to report.

Supplemental Material

Table S1
Figures S1–S2

REFERENCES

1. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *Circulation*. 2022;145:e895–e1032. doi: 10.1161/cir.0000000000001063
2. Ammar KA, Jacobsen SJ, Mahoney DW, Kors JA, Redfield MM, Burnett JC Jr, Rodeheffer RJ. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association Heart Failure Staging Criteria in the community. *Circulation*. 2007;115:1563–1570. doi: 10.1161/circulationaha.106.666818
3. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *Circulation*. 2022;145:e876–e894. doi: 10.1161/cir.0000000000001062
4. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the framingham study. *N Engl J Med*. 1971;285:1441–1446. doi: 10.1056/nejm197112232852601
5. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular

Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.e14. doi: 10.1016/j.echo.2014.10.003
6. Okuyama R, Ishii J, Takahashi H, Kawai H, Muramatsu T, Harada M, Yamada A, Motoyama S, Matsui S, Naruse H, et al. Combination of high-sensitivity troponin I and N-terminal pro-B-type natriuretic peptide predicts future hospital admission for heart failure in high-risk hypertensive patients with preserved left ventricular ejection fraction. *Heart Vessel*. 2017;32:880–892. doi: 10.1007/s00380-017-0948-9
7. Pugliese NR, Fabiani I, La Carrubba S, Conte L, Antonini-Canterin F, Colonna P, Caso P, Benedetto F, Santini V, Carerj S, et al. Classification and prognostic evaluation of left ventricular remodeling in patients with asymptomatic heart failure. *Am J Cardiol*. 2017;119:71–77. doi: 10.1016/j.amjcard.2016.09.018
8. Dini FL, Whalley G, Poppe K, Fontanive P, Rosa GM, Doughty RN, Di Bello V. Plasma N-terminal protype-B natriuretic peptide and restrictive mitral flow to risk-stratify patients with stage B heart failure. *Clin Cardiol*. 2009;32:711–717. doi: 10.1002/clc.20617
9. Haji K, Huynh Q, Wong C, Stewart S, Carrington M, Marwick TH. Improving the characterization of stage A and B heart failure by adding global longitudinal strain. *JACC Cardiovasc Imaging*. 2022;15:1380–1387. doi: 10.1016/j.jcmg.2022.03.007
10. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, Metra M, Ponikowski P, Sliwa K, Voors AA, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. *Lancet*. 2022;400:1938–1952. doi: 10.1016/S0140-6736(22)02076-1
11. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128. doi: 10.1056/NEJMoa1504720
12. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380:347–357. doi: 10.1056/NEJMoa1812389
13. Nuffield Department of Population Health Renal Studies G, Consortium SiM-AC-RT. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet*. 2022;400:1788–1801. doi: 10.1016/S0140-6736(22)02074-8
14. Agarwal R, Filippatos G, Pitt B, Anker SD, Rossing P, Joseph A, Kolkhof P, Nowack C, Gebel M, Ruilope LM, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the fidelity pooled analysis. *Eur Heart J*. 2022;43:474–484. doi: 10.1093/eurheartj/ehab777
15. Kamiya K, Sato Y, Takahashi T, Tsuchihashi-Makaya M, Kotooka N, Ikegame T, Takura T, Yamamoto T, Nagayama M, Goto Y, et al. Multidisciplinary cardiac rehabilitation and long-term prognosis in patients with heart failure. *Circ Heart Fail*. 2020;13:e006798. doi: 10.1161/circheartfailure.119.006798
16. Khan H, Kalogeropoulos AP, Georgiopoulou VV, Newman AB, Harris TB, Rodondi N, Bauer DC, Kritchevsky SB, Butler J. Frailty and risk for heart failure in older adults: the health, aging, and body composition study. *Am Heart J*. 2013;166:887–894. doi: 10.1016/j.ahj.2013.07.032
17. Bielecka-Dabrowa A, Ebner N, Dos Santos MR, Ishida J, Hasenfuss G, von Haehling S. Cachexia, muscle wasting, and frailty in cardiovascular disease. *Eur J Heart Fail*. 2020;22:2314–2326. doi: 10.1002/ejhf.2011
18. Uchmanowicz I, Lee CS, Vitale C, Manulik S, Denfeld QE, Uchmanowicz B, Rosińczuk J, Drozd M, Jaroch J, Jankowska EA. Frailty and the risk of all-cause mortality and hospitalization in chronic heart failure: a meta-analysis. *ESC Heart Fail*. 2020;7:3427–3437. doi: 10.1002/ehf2.12827
19. Meng C, Chai K, Li YY, Luo Y, Wang H, Yang JF. Prevalence and prognosis of frailty in older patients with stage B heart failure with preserved ejection fraction. *ESC Heart Fail*. 2023;10:1133–1143. doi: 10.1002/ehf2.14274
20. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173:489–495. doi: 10.1503/cmaj.050051
21. Shimura T, Yamamoto M, Kano S, Kagase A, Kodama A, Koyama Y, Tsuchikane E, Suzuki T, Otsuka T, Kohsaka S, et al. Impact of the clinical frailty scale on outcomes after transcatheter aortic valve replacement. *Circulation*. 2017;135:2013–2024. doi: 10.1161/circulationaha.116.025630
22. Takeji Y, Yamaji K, Tomoi Y, Okazaki J, Tanaka K, Nagae A, Jinnouchi H, Hiramori S, Soga Y, Ando K. Impact of frailty on clinical outcomes in patients with critical limb ischemia. *Circ Cardiovasc Interv*. 2018;11:e006778. doi: 10.1161/CIRCINTERVENTIONS.118.006778