







Heart failure with improved versus persistently reduced left ventricular ejection fraction: A comparison of the BIOSTAT-CHF (European) study with the ASIAN-HF registry

Thong Huy Cao^{1,2,3*}, Wan Ting Tay⁴, Donald J.L. Jones^{1,3,5}, John G.F. Cleland⁶, Jasper Tromp^{4,7}, Johanna Elisabeth Emmens⁸, Tiew-Hwa Katherine Teng⁴, Chanchal Chandramouli⁴, Oliver Charles Slingsby^{1,2,3}, Stefan D. Anker⁹, Kenneth Dickstein¹⁰, Gerasimos Filippatos¹¹, Chim C. Lang¹², Marco Metra¹³, Piotr Ponikowski¹⁴, Nilesh J. Samani^{1,2}, Dirk J. Van Veldhuisen⁸, Faiez Zannad¹⁵, Inder S. Anand¹⁶, Carolyn S.P. Lam^{4†}, Adriaan A. Voors⁸, and Leong L. Ng^{1,2,3*}

¹Department of Cardiovascular Sciences, College of Life Sciences, University of Leicester, Leicester, UK; ²National Institute for Health and Care Research Leicester Biomedical Research Centre, University Hospitals of Leicester NHS Trust, Glenfield Hospital, Leicester, UK; ³Leicester van Geest Multi-OMICS facility, University of Leicester, Leicester, UK; ⁴National Heart Centre Singapore and Duke–National University of Singapore, Singapore, Singapore; ⁵Leicester Cancer Research Centre, University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, University of Leicester, Leicester, UK; ⁶British Heart Foundation Centre of Research Excellence, School of Cardiovascular and Metabolic Health, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK; ⁷Saw Swee Hock School of Public Health, National University of Singapore and the National University Health System, Singapore, Singapore; ⁸Department of Cardiology, University of Groningen, Groningen, The Netherlands; ⁹Division of Cardiology and Metabolism, Department of Cardiology (CVK), and Berlin-Brandenburg Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) Partner Site Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany; ¹⁰University of Bergen, Stavanger University Hospital, Stavanger, Norway; ¹¹Department of Cardiology, Heart Failure Unit, Athens University Hospital Attikon, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; ¹²Division of Molecular and Clinical Medicine, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK; ¹³Institute of Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; ¹⁴Department of Heart Diseases, Wrocław Medical University and Cardiology Department, Military Hospital, Wrocław, Poland; ¹⁵Inserm CIC 1433, Université de Lorraine, Nancy, France; and ¹⁶Department of Medicine, University of Minnesota Medical School and VA Medical Center, Minneapolis, MN, USA

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Aims

We investigated the prevalence, clinical characteristics, and prognosis of patients with heart failure (HF) with improved ejection fraction (HFimpEF).

Methods and results

We used data from BIOSTAT-CHF including patients with a left ventricular ejection fraction (LVEF) $\leq 40\%$ at baseline who had LVEF re-assessed at 9 months. HFimpEF was defined as a LVEF $>40\%$ and a LVEF $\geq 10\%$ increase from baseline at 9 months. We validated findings in the ASIAN-HF registry. The primary outcome was a composite of time to HF rehospitalization or all-cause mortality. In BIOSTAT-CHF, about 20% of patients developed HFimpEF, that was associated with a lower primary event rate of all-cause mortality (hazard ratio [HR] 0.52, 95% confidence interval [CI] 0.28–0.97, $p = 0.040$) and the composite endpoint (HR 0.46, 95% CI 0.30–0.70, $p < 0.001$) compared with patients who remained in persistent HF with reduced ejection fraction (HFrefEF). The findings were similar in the ASIAN-HF (HR 0.40, 95% CI 0.18–0.89, $p = 0.024$, and HR 0.29, 95% CI 0.17–0.48, $p < 0.001$). Five independently common predictors for HFimpEF in both BIOSTAT-CHF and ASIAN-HF were female sex, absence of ischaemic heart disease, higher LVEF, smaller left ventricular end-diastolic and end-systolic diameter at baseline. A predictive

*Corresponding author. Department of Cardiovascular Sciences, College of Life Sciences, University of Leicester, Leicester, LE1 7RH, and National Institute for Health and Care Research Leicester Biomedical Research Centre, University Hospitals of Leicester NHS Trust, Glenfield Hospital, Leicester LE3 9QP, UK. Email: tch10@le.ac.uk and lln1@le.ac.uk

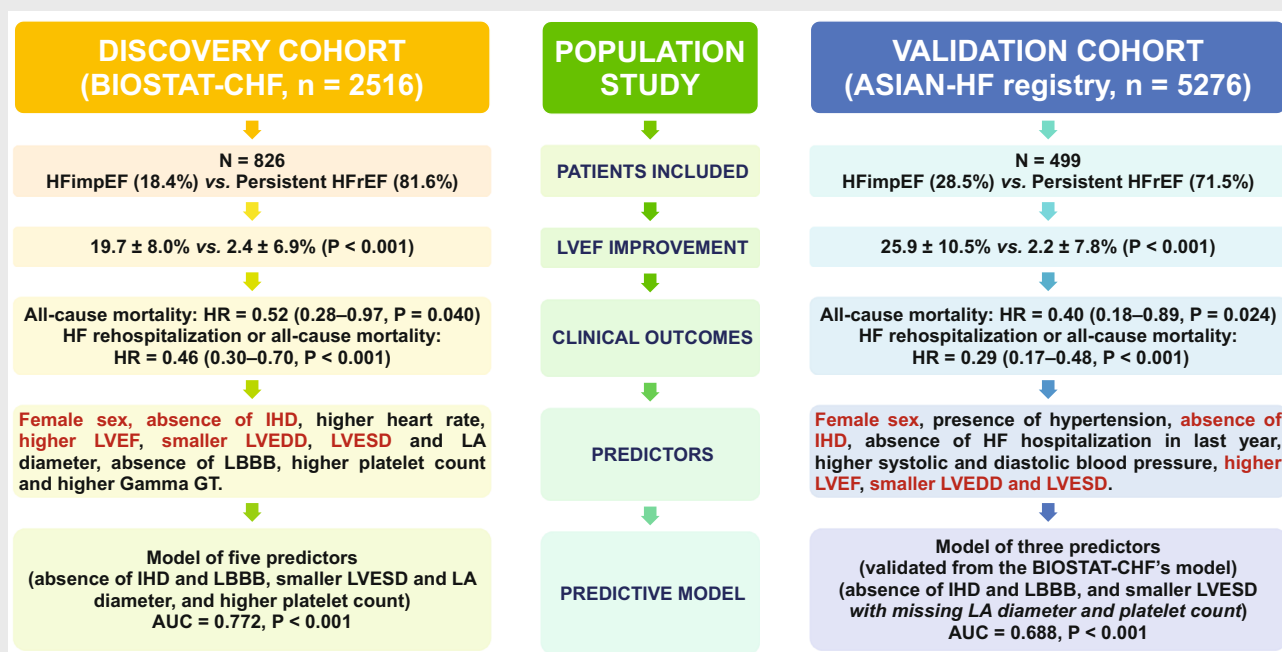
†On behalf of the ASIAN-HF Investigators

model combining only five predictors (absence of ischaemic heart disease and left bundle branch block, smaller left ventricular end-systolic and left atrial diameter, and higher platelet count) for HFimpEF in the BIOSTAT-CHF achieved an area under the curve of 0.772 and 0.688 in the ASIAN-HF (due to missing left atrial diameter and platelet count).

Conclusions

Approximately 20–30% of patients with HFrEF improved to HFimpEF within 1 year with better clinical outcomes. In addition, the predictive model with clinical predictors could more accurately predict HFimpEF in patients with HFrEF.

Graphical Abstract



Findings of LVEF improvement, clinical outcomes, predictors and a predictive model comparing HFimpEF and persistent HFrEF in BIOSTAT-CHF and validated in the ASIAN-HF registry. Approximately 20–30% of patients with HFrEF improved within 1 year (HFimpEF) with better clinical outcomes. In addition, the predictive model with clinical predictors (absence of IHD and LBBB, smaller LVESD and LA diameter, and higher platelet count) could more accurately predict HFimpEF in patients with HFrEF and be easily applied in clinical practice. Common predictors in red. AUC, area under the curve; GT, glutamyl transferase; HF, heart failure; HFimpEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; IHD: ischemic heart disease; LA, left atrium; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter.

Keywords

Clinical outcome • Heart failure • Heart failure with improved ejection fraction • Left ventricular ejection fraction • Heart failure with reduced ejection fraction • Predictive model • Predictor

Introduction

Heart failure (HF) therapy can improve left ventricular ejection fraction (LVEF) in patients with HF with reduced ejection fraction (HFrEF) that is associated with better outcomes.^{1–6} According to a recent consensus report of the International Societies of HF, the experts recommended defining patients with improved LVEF as a separate subcategory because the improvement of LVEF has led to an interest in the long-term outcomes and management of these patients as compared to those whose LVEF did not improve with

treatment.⁷ Here, HF with improved ejection fraction (HFimpEF) was defined as HF with a baseline LVEF of $\leq 40\%$, a ≥ 10 -point increase from baseline in LVEF and a second measurement of LVEF of $> 40\%$.⁷ Patients with HFimpEF may be distinct in terms of clinical demographics, biochemical laboratory, and outcomes from those with HFrEF or HF with preserved LVEF.^{2,3,8} However, data on HFimpEF have been sparse. Early identification of patients with HFimpEF and persistent HFrEF during diagnosis would be useful in clinical decision-making and therapeutic management. Therefore, our aims in this study were to investigate

the clinical characteristics, predictors and the prognostic impact of improved LVEF on outcomes. Additionally, as secondary aims, we determined predictive models and recommended a LVEF threshold for improvement of LVEF in patients with HFimpEF as compared to those with persistent HFrefEF. To do this, we analysed clinical data from a multinational European, prospective clinical study (BIOSTAT-CHF)⁹ and validated our findings in an independent multinational cohort (ASIAN-HF registry).^{10,11} The findings could inform the optimization of pharmacotherapy and improve outcomes in patients with HF.

Methods

Study design and participants

The EU FP7 funded BIOSTAT-CHF (A systems BIOlogy Study to Tailored Treatment in Chronic Heart Failure) project was a multinational, prospective clinical study in Europe.⁹ The main aim of this project was to employ a systems biology approach (including demographics, biomarkers, proteomics and genetics) in order to identify poor outcomes in HF patients with standard therapy described elsewhere.^{12–18} This study was conducted according to the Declaration of Helsinki and was approved by local and national ethics committees. All patients ($n = 2516$) in this study provided written informed consent. Patients from 69 centres in 11 European countries who met inclusion and exclusion criteria according to the European Society of Cardiology (ESC) guidelines were recruited into this study.¹⁹ In brief, patients more than 18 years old with presentations of HF symptoms and a LVEF $\leq 40\%$ and/or B-type natriuretic peptide (BNP) > 400 pg/ml or N-terminal pro-B-type natriuretic peptide (NT-proBNP) > 2000 pg/ml who were receiving suboptimal HF treatment (untreated or treated with $\leq 50\%$ of the target dose of both angiotensin-converting enzyme inhibitors [ACEi] or angiotensin receptor blockers [ARB] and beta-blockers) were invited into the study (online supplementary Figure S1). The patients were optimized with standard treatment for HF by initiating or up-titrating ACEi or ARB and beta-blockers during the first 3 months. Clinical endpoints such as HF rehospitalization and mortality were assessed.⁹ The assessment for LVEF was performed at the beginning and at 9 months of the study. Patients with HFimpEF were those with a baseline LVEF $\leq 40\%$, a ≥ 10 -point increase from baseline in LVEF at a second measurement of LVEF $> 40\%$ at 9 months.⁷ A flow diagram of selected patients in this study is displayed in online supplementary Figure S2, and online supplementary Table S1 presents the baseline characteristics of HF patients included or excluded in BIOSTAT-CHF.

Outcomes

Clinical endpoints were assessed for patients with HF in BIOSTAT-CHF.⁹ The primary endpoint included a composite of time to HF rehospitalization or all-cause mortality. After the 9-month visit, a standard clinic follow-up or contact via telephone was performed every 6 months. The median follow-up time for the primary endpoint was 21 (interquartile range [IQR] 15–27) months.

Validation analysis

The findings of this study were validated in the ASIAN-HF registry that was a prospective multinational study of 5276 patients of ≥ 18 years old with symptomatic HF (stage C) from 11 Asian regions (44 centres).^{10,11}

This analysis included 499 patients with LVEF $\leq 40\%$ at the baseline visit and available LVEF measurement at 1-year follow-up. ASIAN-HF also complied with the Declaration of Helsinki and was approved by medical ethics committees of participating centres. All patients provided written informed consent. Online supplementary Table S2 presents the baseline characteristics of HF patients included and excluded in ASIAN-HF.

Statistical analysis

The statistical software SPSS 26.0 for Windows was used for statistical analyses in this study. Continuous variables were displayed using mean \pm standard deviation (SD) for normally distributed continuous variables, median (IQR) for non-normally distributed variables, and categorical variables were expressed as numbers with percentages. Values were compared using Student's *t*-tests, Mann–Whitney U tests or Chi-square tests for group comparisons as appropriate. Cox proportional hazard models were employed to calculate hazard ratios (HR), adjusted for the effect of potential confounders. The predictive models for HFimpEF were built using logistic regression with backward and forward stepwise selection of the clinical variables. All statistical tests were performed two-tailed, and a *p*-value < 0.05 was considered statistically significant.

Role of the funding source

The study's funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Changes in left ventricular ejection fraction

Of 2516 patients enrolled in BIOSTAT-CHF, 2243 (89.2%) had an echocardiographic assessment of LVEF at baseline; 2008 of those met the inclusion criteria of a LVEF $\leq 40\%$. A total of 329 patients died before the visit at 9 months for a reassessment of LVEF, and 871 patients had a LVEF assessment at 9 months, of whom 152 (18.4%) patients were classified as HFimpEF according to the universal definition and classification of HF⁷ and 674 patients (81.6%) had persistent HFrefEF (online supplementary Figure S2). By definition, there was a highly significant LVEF improvement of $19.7 \pm 8.0\%$ in patients with HFimpEF ($29.8 \pm 6.8\%$ at baseline vs. $49.5 \pm 5.7\%$ at 9 months) as compared to patients with persistent HFrefEF ($\Delta 2.4 \pm 6.9\%$, $27.8 \pm 7.2\%$ at baseline vs. $30.2 \pm 7.2\%$ at 9 months) ($p < 0.001$) (Table 1 and Figure 1).

Demographic and clinical characteristics

The baseline demographic and clinical characteristics of patients with HFimpEF and persistent HFrefEF are described in Table 1. As compared to patients with persistent HFrefEF, patients with HFimpEF were more likely to be younger ($p = 0.017$), female ($p = 0.002$), but less likely to have ischaemic heart disease (IHD)

Table 1 Patient characteristics at baseline and 9 months in comparison between heart failure with improved ejection fraction and persistent heart failure with reduced ejection fraction groups in BIOSTAT-CHF

Characteristics	Baseline		p-value	9 months		p-value
	HFimpEF (n = 152)	Persistent HFrEF (n = 674)		HFimpEF (n = 152)	Persistent HFrEF (n = 674)	
Age, years	63.7 ± 12.8	66.3 ± 11.6	0.017			
Male sex, n (%)	105 (69.1)	542 (80.4)	0.002			
Medical history, n (%)						
Hypertension	80 (52.6)	421 (62.5)	0.025			
Ischaemic heart disease	38 (25.0)	312 (46.3)	<0.001			
Valvular surgery	11 (7.2)	46 (6.8)	0.856			
Atrial fibrillation	65 (42.8)	238 (35.3)	0.085			
Diabetes mellitus	31 (20.4)	201 (29.8)	0.019			
Stroke	9 (5.9)	55 (8.2)	0.351			
Peripheral arterial disease	5 (3.3)	61 (9.1)	0.018			
COPD	22 (14.5)	103 (15.3)	0.802			
HF hospitalization in last year	41 (27.0)	210 (31.2)	0.311			
Clinical profile						
Heart rate, bpm	85.9 ± 23.8	77.5 ± 17.2	<0.001	70.5 ± 14.4	72.0 ± 15.7	0.291
Systolic blood pressure, mmHg	125.8 ± 21.6	124.3 ± 20.2	0.411	130.8 ± 21.8	122.2 ± 19.8	<0.001
Diastolic blood pressure, mmHg	78.0 ± 14.2	76.5 ± 11.9	0.208	77.2 ± 12.1	74.9 ± 11.6	0.027
BMI, kg/m ²	27.3 ± 5.4	27.8 ± 4.9	0.310	27.8 ± 5.4	28.1 ± 5.6	0.569
NYHA class III/IV, n (%)	68 (45.0)	349 (52.5)	0.098	14 (9.7)	174 (26.3)	<0.001
Orthopnoea, n (%)	41 (27.0)	150 (22.3)	0.216	3 (2.3)	50 (8.0)	0.018
Pulmonary rales, n (%)	64 (43.8)	293 (44.3)	0.926	6 (5.2)	73 (12.1)	0.028
Peripheral oedema, n (%)	60 (49.6)	269 (49.9)	0.949	10 (9.4)	128 (25.1)	<0.001
Jugular venous pressure, n (%)	26 (25.0)	115 (24.8)	0.972	0 (0.0)	46 (9.9)	0.002
Third heart sound, n (%)	11 (7.3)	69 (10.3)	0.261	1 (0.8)	31 (5.0)	0.030
Hepatomegaly, n (%)	18 (11.8)	106 (15.8)	0.223	1 (0.8)	50 (8.1)	0.003
Echocardiography						
LVEF, %	29.8 ± 6.8	27.8 ± 7.2	0.003	49.5 ± 5.7	30.2 ± 7.2	<0.001
LVEDD, mm	59.3 ± 8.0	64.3 ± 8.2	<0.001	54.3 ± 6.8	64.0 ± 8.7	<0.001
LVESD, mm	48.3 ± 8.2	52.7 ± 9.7	<0.001	39.3 ± 7.1	51.8 ± 10.1	<0.001
LA diameter, mm	43.8 ± 8.6	47.7 ± 7.6	<0.001	41.6 ± 6.0	47.9 ± 7.7	<0.001
ECG, n (%)						
LBBB	18 (12.0)	163 (24.4)	<0.001	14 (9.4)	135 (21.2)	<0.001
RBBB	14 (9.3)	42 (6.3)	0.184	9 (6.0)	45 (7.1)	0.656
LVH	22 (14.7)	81 (12.1)	0.400	13 (8.7)	60 (9.4)	0.793
Laboratory						
Serum creatinine, µmol/L	89.2 (79.0–107.0)	100.0 (82.0–126.0)	<0.001	88.6 (76.7–114.8)	106.0 (86.6–132.6)	<0.001
Blood urea, mmol/L	8.9 (6.6–14.5)	11.3 (7.5–18.0)	<0.001	8.1 (6.0–12.1)	11.1 (7.3–17.9)	<0.001
eGFR, ml/min ⁻¹	72.6 ± 23.5	68.7 ± 26.5	0.092	71.8 ± 26.1	63.7 ± 24.6	0.001
Sodium, mEq/L	139.5 ± 3.3	139.7 ± 3.9	0.528	139.8 ± 3.0	139.5 ± 3.7	0.441
Potassium, mEq/L	4.2 ± 0.5	4.3 ± 0.6	0.044	4.4 ± 0.4	4.5 ± 0.6	0.008
Glucose, mg/dl	6.7 ± 2.7	6.8 ± 2.7	0.870	6.7 ± 2.7	6.6 ± 2.4	0.784
HbA1c, %	6.6 ± 1.4	6.5 ± 1.5	0.737	6.5 ± 1.3	6.3 ± 1.5	0.488
Total cholesterol, mmol/L	4.6 ± 1.3	4.4 ± 1.3	0.191	4.8 ± 1.2	4.6 ± 1.4	0.291
HDL cholesterol, mmol/L	1.1 ± 0.4	1.1 ± 0.4	0.898	1.2 ± 0.3	1.1 ± 0.4	0.096
LDL cholesterol, mmol/L	2.8 ± 1.0	2.7 ± 1.0	0.433	2.8 ± 1.0	2.8 ± 1.3	0.900
Triglycerides, mmol/L	1.5 ± 1.0	1.5 ± 0.9	0.873	1.8 ± 1.2	1.9 ± 1.5	0.684
Haemoglobin, g/dl	13.7 ± 1.9	13.5 ± 1.7	0.296	13.4 ± 1.6	13.3 ± 1.7	0.507
Red blood cell count, million/mm ³	4.5 ± 0.6	4.5 ± 0.7	0.965	4.4 ± 0.5	4.5 ± 0.6	0.405
White blood cell count, 1000/mm ³	8.2 ± 3.0	8.1 ± 2.7	0.849	7.2 ± 2.3	7.7 ± 2.5	0.069
Platelet count, 1000/mm ³	249.8 ± 87.8	221.6 ± 81.1	0.001	242.9 ± 77.9	220.6 ± 66.5	0.010
Total bilirubin, µmol/L	12.3 (8.3–18.2)	13.0 (9.5–18.8)	0.265	10.2 (7.2–13.0)	12.0 (8.7–17.0)	0.005
AST, U/L	28.0 (21.0–37.0)	23.0 (18.0–32.0)	<0.001	24.0 (20.0–29.5)	22.0 (18.0–28.0)	0.107
ALT, U/L	33.0 (21.0–51.0)	24.5 (16.3–35)	<0.001	24.0 (18.7–29.5)	21.0 (16.0–30.0)	0.045
Gamma GT, U/L	61.5 (30.3–128.8)	41.0 (24.8–81.3)	0.002	38.0 (22.0–72.3)	35.0 (23.5–66.0)	0.494
Alkaline phosphatase, µg/L	77.5 (63.4–109.3)	81.0 (61.0–117.0)	0.900	79.5 (68.0–114.5)	99.0 (68.0–141.6)	0.041
TSH, mU/L	1.7 (1.1–2.6)	1.9 (1.0–3.0)	0.581	1.7 (1.1–2.3)	1.7 (1.0–3.0)	0.358
FT4, pmol/L	15.5 ± 4.8	15.7 ± 7.5	0.909	15.5 ± 2.7	14.7 ± 4.0	0.353
Troponin I, µg/L	0.03 (0.01–0.08)	0.03 (0.01–0.10)	0.613	0.01 (0.002–0.014)	0.02 (0.01–0.03)	0.013
Troponin T, µg/L	0.03 (0.02–0.04)	0.03 (0.01–0.06)	0.884	0.014 (0.012–0.025)	0.026 (0.013–0.066)	0.140
NT-proBNP, pg/ml	3874.0 (2147.5–6646.0)	3412.5 (1622.3–7811.8)	0.587	791.0 (173.3–1985.5)	1810.0 (668.4–5251.0)	<0.001

Table 1 (Continued)

Characteristics	Baseline			9 months		
	HFimpEF (n = 152)	Persistent HFrefEF (n = 674)	p-value	HFimpEF (n = 152)	Persistent HFrefEF (n = 674)	p-value
Medication, n (%)						
ACEi/ARB	120 (78.9)	536 (79.5)	0.874	142 (93.4)	627 (93.0)	0.862
Beta-blocker	127 (83.6)	578 (85.8)	0.488	142 (93.4)	644 (95.5)	0.270
MRA	73 (48.0)	391 (58.0)	0.025	67 (44.1)	437 (65.1)	<0.001
Loop diuretics	152 (100)	671 (99.6)	0.410	120 (78.9)	635 (94.6)	<0.001
Digoxin	30 (19.7)	111 (16.5)	0.333	23 (15.1)	116 (17.3)	0.522

Values are mean \pm standard deviation, or median (interquartile range), unless otherwise specified.

ACEi, angiotensin-converting enzyme inhibitor; ALT, alanine transaminase; ARB, angiotensin receptor blocker; AST, aspartate transaminase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; FT4, free thyroxine; GT, glutamyl transferase; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HF, heart failure; HFimpEF, heart failure with improved ejection fraction; HFrefEF, heart failure with reduced ejection fraction; LA, left atrial; LBBB, left bundle branch block; LDL, low-density lipoprotein; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVH, left ventricular hypertrophy; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RBBB, right bundle branch block; TSH, thyroid-stimulating hormone.

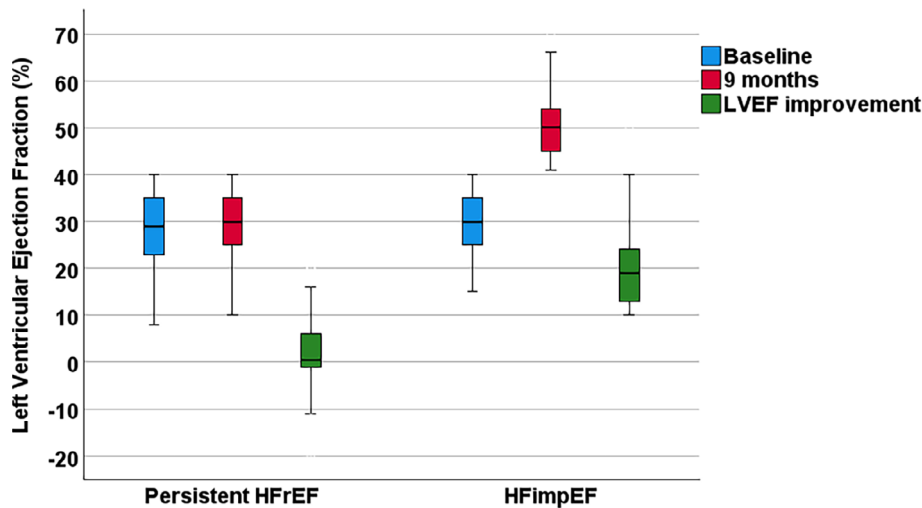


Figure 1 Left ventricular ejection fraction (LVEF) at baseline and at 9 months and improvement in comparisons between heart failure with improved ejection fraction (HFimpEF) and persistent heart failure with reduced ejection fraction (HFrefEF) in BIOSTAT-CHF.

($p < 0.001$), hypertension ($p = 0.025$), diabetes mellitus ($p = 0.019$) and peripheral arterial disease ($p = 0.018$). Heart rate was higher in patients with HFimpEF ($p < 0.001$). Patients with HFimpEF had a higher LVEF ($29.8 \pm 6.8\%$ vs. $27.8 \pm 7.2\%$, $p = 0.003$) and a smaller left ventricular end-diastolic diameter (LVEDD) ($p < 0.001$), left ventricular end-systolic diameter (LVESD) ($p < 0.001$) and left atrial (LA) diameter ($p < 0.001$) as compared to patients with persistent HFrefEF (Figure 2). The HFimpEF group (vs. persistent HFrefEF group) had a lower prevalence of left bundle branch block (LBBB) on electrocardiography ($p < 0.001$). In clinical laboratory variables, there were significant differences for blood urea ($p < 0.001$), serum creatinine ($p < 0.001$), serum potassium ($p = 0.044$) and higher platelet count ($p = 0.001$), aspartate transaminase ($p < 0.001$), alanine transaminase ($p < 0.001$) and gamma glutamyl transferase (GT) ($p = 0.002$) in patients with HFimpEF as compared to those with persistent HFrefEF. Fewer patients with HFimpEF were treated

with mineralocorticoid receptor antagonist (MRAs) as compared to the persistent HFrefEF group at baseline ($p = 0.025$).

Clinical characteristics of patients with HFimpEF and persistent HFrefEF at 9 months are described and compared with baseline clinical characteristics in Table 1. All clinical and chemical laboratory variables that had significant differences between both HF groups at baseline remained significant at 9 months, except for differences in heart rate ($p = 0.291$), aspartate transaminase ($p = 0.107$) and gamma GT ($p = 0.494$). At 9 months, the HFimpEF group had a better symptomatic profile for orthopnoea ($p = 0.018$), pulmonary rales ($p = 0.028$), peripheral oedema ($p < 0.001$), jugular venous pressure ($p = 0.002$), third heart sound ($p = 0.030$), hepatomegaly ($p = 0.003$) and a lower prevalence of New York Heart Association (NYHA) class III or IV ($p < 0.001$). In addition, the HFimpEF group had better clinical chemistry profiles of estimated glomerular filtration rate ($p = 0.001$), total bilirubin ($p = 0.005$), alkaline

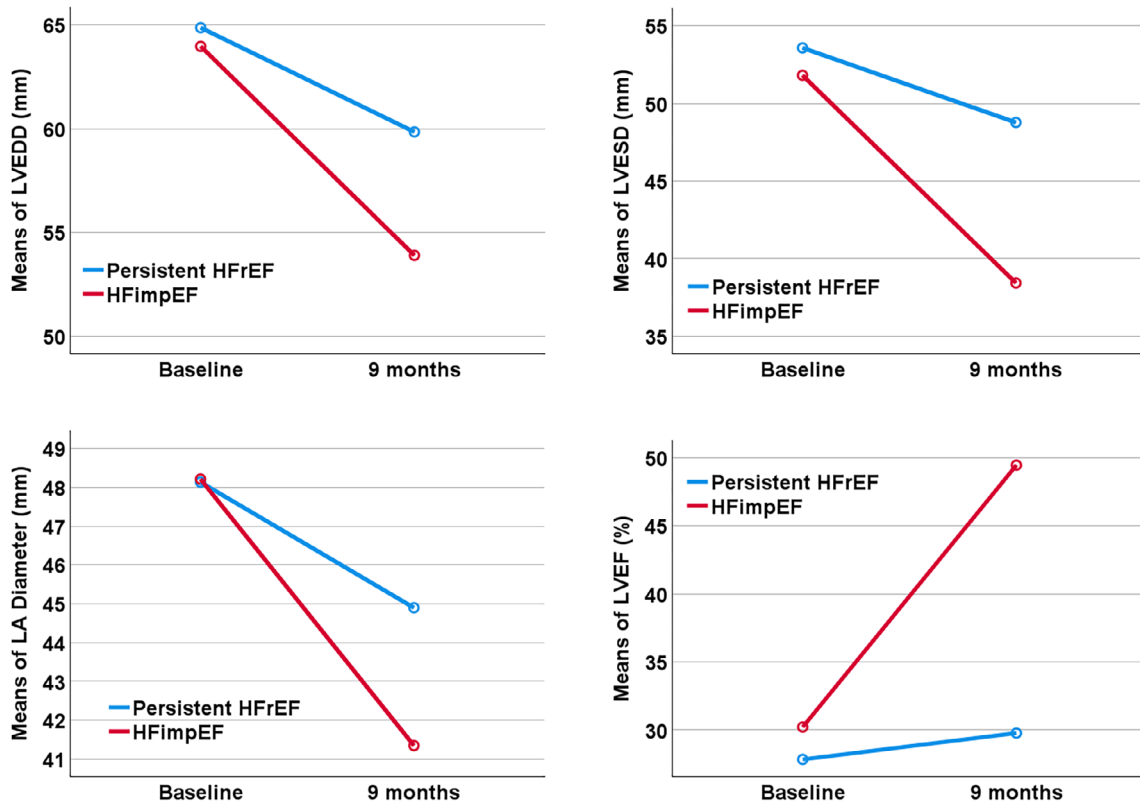


Figure 2 Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left atrial (LA) diameter and left ventricular ejection fraction (LVEF) in comparisons between baseline and 9 months according to heart failure with improved ejection fraction (HFimpEF) and persistent heart failure with reduced ejection fraction (HFrEF) in BIostat-CHF.

phosphatase ($p=0.041$), troponin I ($p=0.013$) and NT-proBNP (pg/ml) (791.0 [173.3 – 1985.5] vs. 1810.0 [668.4 – 5251.0], $p<0.001$). Furthermore, there was a significant decrease of LVEDD, LVESD, and LA diameter (mm) of 5.5 ± 7.0 , 9.5 ± 8.4 and 2.5 ± 8.3 in patients with HFimpEF as compared to those with persistent HFrEF (Δ 0.8 ± 5.2 , 1.5 ± 7.1 and -0.4 ± 6.7 at $p<0.001$, $p<0.001$ and $p=0.003$, respectively) (Table 1 and Figure 2).

Predictors and predictive models for improvement of left ventricular ejection fraction in BIostat-CHF

Independent predictors for development to HFimpEF are shown in Table 2. The predictors were female sex, absence of IHD, higher heart rate, higher LVEF, smaller LVEDD, LVESD and LA diameter, absence of LBBB, higher platelet count, higher gamma GT and lower rate of MRA use. We developed a model with these 10 predictors (except for lower rate of MRA use that might be a confounding variable) using logistic regression in which all these predictors were entered simultaneously. The predictive capability of this model for HFimpEF had an area under the curve (AUC) value of 0.810 (95% confidence interval [CI] 0.739 – 0.881 , $p<0.001$) (online supplementary Figure S3A). Furthermore, from

a logistic regression (backward and forward selection) analysis, we identified a predictive model for HFimpEF that included only five predictors: absence of IHD and LBBB, smaller LVESD and LA diameter, and higher platelet count. The performance of this model for the predictive probability of HFimpEF in HFrEF patients achieved an AUC of 0.772 (95% CI 0.715 – 0.829 , $p<0.001$) (online supplementary Figure S3B). The Hosmer and Lemeshow test was performed using binary logistic regression that showed predictions made by the model fit well with observed group memberships (Chi-square p -value = 0.246). The predictive model classified 82.0% of cases overall in accuracy.

Clinical outcomes

Over a median follow-up of 21 (IQR 15–27) months, patients with HFimpEF had better prognosis during the follow-up time for the primary endpoints. Crude deaths occurred in 11 (7.2%) patients with HFimpEF compared to 97 (14.4%) in the persistent HFrEF group ($p=0.018$). Figure 3 shows Cox regression analysis for all-cause mortality (HR 0.52, 95% CI 0.28–0.97, $p=0.040$) and the composite of HF rehospitalization or all-cause mortality (HR 0.46, 95% CI 0.30–0.70, $p<0.001$) for HFimpEF versus persistent HFrEF. Furthermore, the cardiovascular and non-cardiovascular mortality rates were lower in patients with HFimpEF as compared to those

Table 2 Predictors of heart failure with improved ejection fraction in patients with heart failure with reduced ejection fraction at baseline in BIOSTAT-CHF

Predictors	OR	95% CI	p-value*
Female sex	1.842	1.220–2.782	0.004
Ischaemic heart disease	0.461	0.306–0.695	<0.001
Heart rate	1.017	1.008–1.026	<0.001
LVEF	1.049	1.021–1.078	<0.001
LVEDD	0.916	0.891–0.943	<0.001
LVESD	0.939	0.912–0.966	<0.001
LA diameter	0.941	0.915–0.967	<0.001
LBBB	0.431	0.251–0.739	0.002
Platelet count	1.003	1.000–1.005	0.018
Gamma GT	1.003	1.000–1.005	0.032
MRA	0.664	0.458–0.962	0.030

CI, confidence interval; GT, glutamyl transferase; LA, left atrial; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MRA, mineralocorticoid receptor antagonist; OR, odds ratio.

*Multivariable model: adjusted for age, sex, ischaemic heart disease, systolic blood pressure, diabetes mellitus and estimated glomerular filtration rate.

with persistent HF_rEF (4.6% vs. 10.4% and 2.6% vs. 4.0%, $p < 0.001$) (online supplementary Table S3).

Validation of findings in the ASIAN-HF registry

To confirm the findings in BIOSTAT-CHF, we employed the ASIAN-HF registry. Of 499 patients in the ASIAN-HF registry, 28.5% of patients developed HF_{imp}EF and 71.5% had persistent

HF_rEF. There was also a highly significant LVEF improvement of $25.9 \pm 10.5\%$ in patients with HF_{imp}EF at 1 year as compared to those with persistent HF_rEF ($\Delta 2.2 \pm 7.8\%$, $p < 0.001$). Baseline demographic and clinical characteristics of patients with HF_{imp}EF and persistent HF_rEF in the ASIAN-HF cohort (online supplementary Table S4) were similar to BIOSTAT-CHF. Independent predictors of the development of HF_{imp}EF in ASIAN-HF are reported in online supplementary Table S5. Patients with HF_{imp}EF in ASIAN-HF also had better prognosis for all-cause mortality (4.9% vs. 13.5%; HR 0.40, 95% CI 0.18–0.89, $p = 0.024$) and the composite endpoint of HF rehospitalization or all-cause mortality (12.0% vs. 38.4%; HR 0.29, 95% CI 0.17–0.48, $p < 0.001$) as compared to those with persistent HF_rEF (460 patients [92.2%] were eligible for the Cox regression model). Furthermore, the cardiovascular and non-cardiovascular mortality rates in ASIAN-HF were lower in the HF_{imp}EF group as compared to the persistent HF_rEF group (4.9% vs. 10.9% and 0% vs. 2.5%, $p = 0.037$ and $p = 0.056$, respectively) (online supplementary Table S3). These confirmed the results in BIOSTAT-CHF (Figure 3). In addition, we tested the predictive model for HF_{imp}EF in the ASIAN-HF cohort that was developed in the BIOSTAT-CHF cohort including five predictors: absence of IHD and LBBB, smaller LVESD and LA diameter, and higher platelet count. Unfortunately, LA diameter and platelet count were not available in the ASIAN-HF cohort. Therefore, this predictive model with missing LA diameter and platelet count only yielded an AUC of 0.688 (95% CI 0.634–0.742, $p < 0.001$) (online supplementary Figure S3C). Moreover, the predictive model using absence of IHD and LBBB, and smaller LVESD was able to classify 72.9% of cases overall in accuracy.

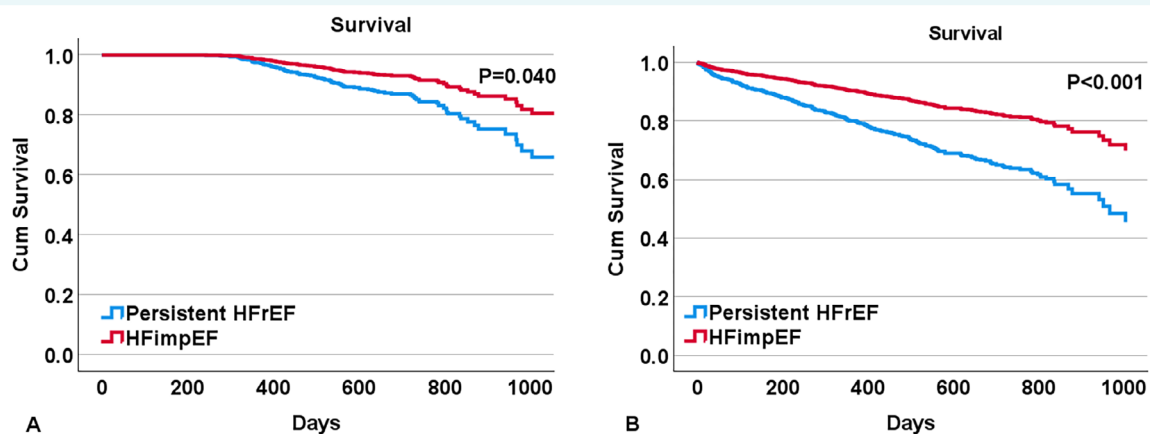


Figure 3 Clinical outcomes according to heart failure with improved ejection fraction (HF_{imp}EF) and persistent heart failure with reduced ejection fraction (HF_rEF) in BIOSTAT-CHF. (A) Cox regression survival curves for all-cause mortality according to HF_{imp}EF and persistent HF_rEF (792 patients [95.9%] were eligible for the Cox regression model). (B) Cox regression survival curves for the composite of heart failure rehospitalization or all-cause mortality according to HF_{imp}EF and persistent HF_rEF (781 patients [94.6%] were eligible for the Cox regression model).

Predictive models for improvement of left ventricular ejection fraction in BIOSTAT-CHF and validated in the ASIAN-HF registry

We found six common predictors in BIOSTAT-CHF and the ASIAN-HF registry for HFimpEF prediction in patients with HFrEF, including female sex, absence of IHD, higher LVEF, smaller LVESD and LVESD, and lower rate of MRA use at baseline. A predictive model for HFimpEF was developed by combining five of these common predictors (except for lower rate of MRA use) using logistic regression analysis. The performance of this model for the predictive probability of HFimpEF in patients with HFrEF achieved an AUC of 0.702 (95% CI 0.648–0.757, $p < 0.001$) in BIOSTAT-CHF (online supplementary Figure S3D) that was also validated in ASIAN-HF with an AUC of 0.682 (95% CI 0.629–0.736, $p < 0.001$) (online supplementary Figure S3E).

Comparisons of clinical outcomes between a $\geq 5\%$ threshold and a $\geq 10\%$ change from baseline left ventricular ejection fraction

Sensitivity analyses were performed to compare clinical outcomes between a ≥ 5 and 10-point increase from baseline LVEF. We found that, when using the 5% LVEF threshold for HFimpEF definition in the BIOSAT-CHF cohort, patients were also associated with a lower primary event rate of all-cause mortality (6.5% vs. 14.4%; HR 0.46, 95% CI 0.25–0.84, $p = 0.011$) and the composite endpoint of HF rehospitalization or all-cause mortality (14.5% vs. 33.1%; HR 0.41, 95% CI 0.28–0.61, $p < 0.001$) as compared to those with persistent HFrEF (online supplementary Figure S4). These results were similar to the clinical outcome results using the 10% LVEF threshold for HFimpEF classification. In addition, using the 5% LVEF threshold for HFimpEF classification, patients with HFimpEF in ASIAN-HF also had better prognosis for all-cause mortality (5.5% vs. 13.5%; HR 0.43, 95% CI 0.21–0.88, $p = 0.020$) and the composite endpoint of HF rehospitalization or all-cause mortality (12.7% vs. 38.4%; HR 0.30, 95% CI 0.19–0.48, $p < 0.001$) as compared to those with persistent HFrEF, and these results confirmed the findings in BIOSTAT-CHF.

Discussion

This study investigated the demographic and clinical characteristics, predictors and predictive models, and clinical outcomes in patients with HFimpEF in comparison with persistent HFrEF. Approximately 20% of patients with HFrEF in BIOSTAT-CHF developed HFimpEF within 9 months as compared to 30% at 1 year in the ASIAN-HF registry. More patients in ASIAN-HF had a LVEF improvement as compared to BIOSTAT-CHF, possibly due to the longer follow-up time before LVEF re-assessment (*Graphical Abstract*). In a recent study presented at the Heart Failure Society of America 2021 Annual Scientific Meeting on a cohort of 131 patients with HFrEF in the Middle East-Gulf Region, Alsindi *et al.*²⁰ reported that 27.5% of

HFrEF patients became HFimpEF after a follow-up of 12 months. These authors also found that patients with HFimpEF developed a significantly higher LVEF at 12-month follow-up ($48.6 \pm 7.2\%$ vs. $28.7 \pm 8.7\%$, $p < 0.001$). In a systematic review including 9491 HF patients from nine studies by He *et al.*,⁵ 22.6% of patients with HFrEF became HFimpEF during an average follow-up of 3.8 years, indicating a prevalence similar to BIOSTAT-CHF. Liu and colleagues also reported a prevalence of LVEF improvement of 37.2% in patients with HFrEF during a median follow-up of 17 months.⁶

Predictors and predictive models for heart failure with improved ejection fraction

In this study, we found five common predictors (excluding lower rate of MRA use that might be a confounding variable) that were the same in BIOSTAT-CHF and ASIAN-HF registry for prediction of a LVEF improvement (HFimpEF) in patients with HFrEF at baseline. The predictors were female sex, absence of IHD, higher LVEF, smaller LVESD and LVESD. Previous reports also showed similar results regarding these predictors for LVEF improvement in patients with HFrEF.^{1–3,6,21} In addition, Alsindi *et al.*²⁰ reported that patients with HFimpEF were less likely to have IHD. Kong and colleagues also found that patients with HFimpEF had a higher prevalence of female sex in a cohort of 230 HF patients.⁴ These predictors of HFimpEF would provide important information that could be used for LVEF improvement prediction, risk stratification and treatment guidance in patients with HFrEF in order to customize therapy, thus maximizing the treatment benefits in patients with HF. Moreover, patients with HFimpEF in our study also showed a reverse in cardiac remodelling, whereas patients with persistent HFrEF did not. The evidence for this was demonstrated by a significant reduction in LVESD, LVESD and LA diameter. LA reverse remodelling may occur across all stages of progression of HF after initiation of medical therapy and be associated with better clinical outcomes, as reported in a review by Inciardi *et al.*²² These authors suggested that the left atrium should be a target of treatment or rather a surrogate measurement of the severity of cardiac dysfunction.

Heart failure is a syndrome that involves many pathophysiological processes. In addition, due to the heterogeneity of clinical populations (age, sex, ethnicity and comorbidity), it is unlikely that a single clinical variable could identify patients with HFimpEF from those with HFrEF. Therefore, we developed a model combining only five clinical variables (absence of IHD and LBBB, smaller LVESD and LA diameter, and higher platelet count) in the BIOSTAT-CHF study that provided better prediction of HFimpEF for patients with HFrEF as compared to each single clinical variable with an AUC of 0.772. However, the parameters of LA diameter and platelet count were not available in the ASIAN-HF registry. Therefore, the validation of this predictive model with missing LA diameter and platelet count only yielded an AUC of 0.688 in the ASIAN-HF cohort. The absence of IHD in the predictive model could be a very strong predictor for HFimpEF that was also reported in previous studies.^{2,3,6,20,21} The LVESD and LA diameter in the predictive

model suggest that it is difficult to reverse once remodelling occurs. This predictive model would be easily applied to clinical practice to predict patients with HF_rEF who will improve LVEF to customize therapy to individuals.

Prognosis in patients with heart failure with improved ejection fraction

Patients with HF_{imp}EF had a better prognosis than those with persistent HF_rEF in this study, as evidenced by a highly reduced risk of all-cause mortality and the composite endpoint of HF rehospitalization or all-cause mortality. In addition, both cardiovascular and non-cardiovascular mortality rates were lower in patients with HF_{imp}EF as compared to persistent HF_rEF. These results were similar in both the BIOSTAT-CHF study and the ASIAN-HF registry. Our findings are consistent with previous reports that demonstrated a superior long-term clinical prognosis in patients with HF_{imp}EF.^{1–3} Patients with HF_{imp}EF had a lower mortality rate (116 deaths, 16.1%) as compared with those with persistent HF_rEF (270 deaths, 34.2%), HF with mildly reduced ejection fraction (214 deaths, 33.5%), and HF with preserved ejection fraction (149 deaths, 31.6%) during 4-year follow-up in Park et al.'s study.³ Florea and colleagues also reported that 397 (11.3%) patients died during a median (IQR) of 2 (1.6–2.4) years and the mortality rate ratio was 0.49 (0.31–0.76, $p = 0.002$) for patients with HF_{imp}EF.² Patients with HF_{imp}EF showed lower rate of HF hospitalization or all-cause mortality as a primary endpoint as compared to those with persistent HF_rEF in a study of 230 patients by Kong et al.⁴ (6.2% vs. 22.4%; HR 0.24, 95% CI 0.13–0.46, $p < 0.001$). Moreover, He and colleagues reported a lower risk of mortality (HR 0.44, 95% CI 0.33–0.60), and the composite endpoint of hospitalization and mortality (HR 0.56, 95% CI 0.44–0.73) in patients with HF_{imp}EF as compared to those with HF_rEF.⁵ In a study by Liu et al.,⁶ patients with HF_{imp}EF showed lower all-cause mortality (22.1% vs. 31.1%, $p = 0.019$; HR 0.67, 95% CI 0.47–0.97) as compared to patients without HF_{imp}EF. In a recent study (a pre-specified analysis of the DELIVER trial), Vardeny et al.²³ reported that patients with HF_{imp}EF (previous LVEF $\leq 40\%$) had similar event rates to those with a LVEF consistently $>40\%$ (prior LVEF $>40\%$) in terms of primary composite endpoint (cardiovascular mortality or worsening HF, HR 0.99, 95% CI 0.85–1.15), cardiovascular mortality (HR 0.94, 95% CI 0.75–1.19), HF hospitalization (HR 1.01, 95% CI 0.84–1.21), all-cause mortality (HR 1.03, 95% CI 0.87–1.20) and the composite of cardiovascular mortality and recurrent HF events (rate ratio 0.98, 95% CI 0.82–1.17). However, in their study HF_{imp}EF was defined as patients whose LVEF improved from $\leq 40\%$ to $>40\%$ and compared to patients with a LVEF consistently $>40\%$ (prior LVEF $>40\%$, not persistent HF_rEF).

Was a ≥ 5 -point increase as good as the 10% change from baseline left ventricular ejection fraction?

One of our findings in this study was that using the 5% LVEF improvement threshold for HF_{imp}EF definition in both BIOSTAT-CHF and ASIAN-HF was as good as using the $\geq 10\%$

change from baseline LVEF in terms of a lower primary event rate of all-cause mortality and the composite endpoint of HF rehospitalization or all-cause mortality. However, the 5% LVEF threshold is the margin of measurement error using echocardiography that may be a limitation to its utility.

Future perspectives

Five common predictors (female sex, absence of IHD, higher LVEF, smaller LV_{EDD} and LV_{ESD}) could be used for prediction of a LVEF improvement (HF_{imp}EF) in patients with HF_rEF. The predictive model combining absence of IHD and LBBB, smaller LV_{ESD} and LA diameter, and higher platelet count in this study could predict HF_{imp}EF in patients with HF_rEF with more accuracy and would be easily applied to clinical practice for prediction of LVEF improvement in patients with HF_rEF. Instead of the traditional one-size-fits-all treatment recommendation, early identification and intervention of HF_{imp}EF and persistent HF_rEF would provide useful information to allow clinicians to customize therapy to individuals that will not only require less frequent visits for patients at low risk (HF_{imp}EF) but also allow management efforts to be focused on high-risk patients (persistent HF_rEF), thus maximizing the treatment benefits in patients with HF.

Strengths and limitations

This study has several limitations. First, some confounding factors might not have been assessed because this study is a post hoc analysis of a prospective cohort study. Second, there may be survivor bias because only patients with HF who were still alive and had an echocardiographic assessment of LVEF at 9 months were selected for the study. Therefore, many HF patients with poor outcomes who died before 9 months were already excluded from the study. Third, only Caucasian patients were included in the BIOSTAT-CHF study design. In addition, the ASIAN-HF registry was a prospective multinational study from 11 Asian regions^{10,11} that was employed for validation of BIOSTAT-CHF findings. There are differences in genetic background, body mass index, pharmacokinetics and drug response between Caucasian and Asian populations. Therefore, this was also a limitation for validating the findings from the BIOSTAT-CHF cohort. Moreover, the number of patients in the ASIAN-HF registry that met inclusion criteria for comparison with BIOSTAT-CHF was smaller ($n = 499$) as well as missing several clinical variables such as LA diameter and platelet count, so these may limit the validity of complex predictive models including multiple variables. Fourth, the BIOSTAT-CHF project and ASIAN-HF registry were conducted between 2010–2015 and 2012–2015, respectively, so standard therapies were based on the ESC guidelines of 2008 that recommended the use of MRAs only for patients who had a NYHA class IV in the past 6 months (level B evidence) and no specific up-titration strategy for MRAs. In addition, new drugs such as sodium–glucose cotransporter 2 inhibitors were not prescribed for HF patients at that particular time.¹⁹ Therefore, the findings in this study should be interpreted in that scenario.

This study also has specific strengths. The BIOSTAT-CHF project is a well-designed, multinational, prospective clinical study

in which patients had echocardiography assessments at baseline and 9-month follow-up. Echocardiographic assessment of LVEF at 9 months may be the appropriate time for the detection of HFimpEF after initiation or up-titration of medications.²⁴

Conclusions

To our knowledge, this was the first large international study using the universal definition and classification of HF for HFimpEF by Bozkurt *et al.*⁷ HFimpEF is a distinct HF phenotype with better clinical outcomes than persistent HFref. The predictive model with clinical predictors (absence of IHD and LBBB, smaller LVESD and LA diameter, and higher platelet count) could more accurately predict HFimpEF in patients with HFref. Early identification of HFimpEF and persistent HFref in this study would allow customization of therapy to individuals, instead of the traditional one-size-fits-all treatment recommendation.

Supplementary Information

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

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