ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 1107–1117
Published online 5 February 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13779

ORIGINAL ARTICLE

Echocardiographically defined haemodynamic categorization predicts prognosis in ambulatory heart failure patients treated with sacubitril/valsartan

Frank L. Dini[1]*, Erberto Carluccio[2], Roberto Bitto[3], Michele Ciccarelli[4], Michele Correale[5], Andreina D'Agostino[1], Giuseppe Dattilo[3], Marco Ferretti[6], Arianna Grelli[7], Stefania Guida[7], Francesca Jacoangeli[2], Laura Lupi[8], Lorenzo Luschi[9], Daniele Masarone[10], Valentina Mercurio[11], Giuseppe Pacileo[10], Nicola Riccardo Pugliese[1], Antonella Rispoli[4], Laura Scelsi[7], Carlo Gabriele Tocchetti[11], Natale Daniele Brunetti[5], Alberto Palazzuoli[9], Massimo Piepoli[12], Savina Nodari[8], Giuseppe Ambrosio[2,13] and Working Group on Heart Failure of the Italian Society of Cardiology

[1]*Cardiac, Thoracic and Vascular Department, University of Pisa, Pisa, Italy;* [2]*Cardiology and Cardiovascular Pathophysiology, University of Perugia, Perugia, Italy;* [3]*Department of Clinical and Experimental Medicine Section of Cardiology, University of Messina, Messina, Italy;* [4]*Chair of Cardiology, Department of Medicine, Surgery and Dentistry, University of Salerno, Salerno, Italy;* [5]*Department of Cardiology, University Hospital Foggia, Foggia, Italy;* [6]*Department of Cardiology, University Hospital of Parma, Parma, Italy;* [7]*Division of Cardiology, Fondazione I.R.C.C.S. Policlinico San Matteo, Pavia, Italy;* [8]*Department of Cardiology, University of Brescia and ASST Spedali Civili di Brescia, Brescia, Italy;* [9]*Cardiovascular Diseases Unit, Department of Internal Medicine, University of Siena, Siena, Italy;* [10]*Heart Failure Unit, AORN dei Colli, Monaldi Hospital, Naples, Italy;* [11]*Department of Translational Medical Sciences, Federico II University, Naples, Italy;* [12]*Heart Failure Unit, Cardiology Department, Guglielmo da Saliceto Hospital, AUSL, Piacenza, Italy; and* [13]*CERICLET-Centro Ricerca Clinica e Traslazionale, University of Perugia, Perugia, Italy*

Abstract

Aim Echo-derived haemodynamic classification, based on forward-flow and left ventricular (LV) filling pressure (LVFP) correlates, has been proposed to phenotype patients with heart failure and reduced ejection fraction (HFrEF). To assess the prognostic relevance of baseline echocardiographically defined haemodynamic profile in ambulatory HFrEF patients before starting sacubitril/valsartan.

Methods and results In our multicentre, open-label study, HFrEF outpatients were classified into 4 groups according to the combination of forward flow (cardiac index; CI:$<$ or $\geq$2.0 L/min/m^2) and early transmitral Doppler velocity/early diastolic annular velocity ratio (E/e': $\geq$ or $<$15): *Profile-A*: normal-flow, normal-pressure; *Profile-B*: low-flow, normal-pressure; *Profile-C*: normal-flow, high-pressure; *Profile-D*: low-flow, high-pressure. Patients were started on sacubitril/valsartan and followed-up for 12.3 months (median). Rates of the composite of death/HF-hospitalization were assessed by multivariable Cox proportional-hazards models. Twelve sites enrolled 727 patients (64 ± 12 year old; LVEF: 29.8 ± 6.2%). Profile-D had more comorbidities and worse renal and LV function. Target dose of sacubitril/valsartan (97/103 mg BID) was more likely reached in Profile-A (34%) than other profiles (B: 32%, C: 24%, D: 28%, $P < 0.001$). Event-rate (per 100 patients per year) progressively increased from Profile-A to Profile-D (12.0%, 16.4%, 22.9%, and 35.2%, respectively, $P < 0.0001$). By covariate-adjusted Cox model, profiles with low forward-flow (B and D) remained associated with poor outcome ($P < 0.01$). Adding this categorization to MAGGIC-score and natriuretic peptides, provided significant continuous net reclassification improvement (0.329; $P < 0.001$). Intermediate and high-dose sacubitril/valsartan reduced the event's risk independently of haemodynamic profile.

Conclusions Echocardiographically-derived haemodynamic classification identifies ambulatory HFrEF patients with different risk profiles. In real-world HFrEF outpatients, sacubitril/valsartan is effective in improving outcome across different haemodynamic profiles.

Keywords heart failure; ejection fraction; haemodynamic; prognosis; sacubitril/valsartan

Received: 27 May 2021; Revised: 6 November 2021; Accepted: 5 December 2021
**Correspondence to: Frank L. Dini, Cardiac, Thoracic and Vascular Department, University of Pisa, Via Paradisa, 2. 56124 Pisa, Italy. Phone: 0039 (050) 995231; Fax: 0039 (050) 995308. Email: franklloyddini@gmail.com*
Erberto Carluccio share first authorship.

Introduction

Heart failure (HF) is a clinical syndrome accounting for a significant burden of death and cardiac-related hospitalizations. It is caused by structural and functional abnormalities resulting in reduced cardiac output (CO) and/or elevated left ventricular (LV) filling pressure (LVFP) and pulmonary congestion.[1] LV ejection fraction (EF) represents a universally used index to characterize patients with HF.[2] However, LVEF has also relevant limitations related to the inconsistency with the real LV cardiac contractility, inter-observer variability and modest accuracy compared with other imaging techniques (i.xe. cardiac magnetic resonance and single-photon emission computerized tomography -SPECT). Therefore, it is poorly related with patients' symptoms[3]; furthermore, appropriate risk stratification of HF patients with reduced EF (HFrEF) based only on LVEF may be imprecise, and it may oversimplify the haemodynamic status of those patients, whose better definition frequently requires addition of further evaluations tools.[4,5] To overcome the limitations of LVEF, haemodynamic categorization of HF patients has recently been proposed, based on combined evaluation of LV forward flow and LVFP.[6–8] However, accomplishing this categorization using cardiac catheterization is difficult in clinical practice, and obviously impossible in the outpatient setting. On the other hand, echocardiography can now easily provide quantitative and feasible assessment of CO and surrogate measures of LVFP, such as the ratio between transmitral *E* peak velocity to averaged tissue Doppler-derived *e'* velocity (E/e'). Yet although proposed and emphasized,[7,8] such an approach has not been applied to large series of ambulatory HFrEF patients.

The recent introduction of angiotensin-receptor neprilysin-inhibitors [ARNI, the prototype of which being sacubitril/valsartan (S/V)] has been a breakthrough in the management of patients with HF.[9] This novel class of drugs interferes with several key pathogenetic steps in HF progression through their powerful anti-remodelling and anti-fibrotic properties. The recent PROVE-HF study provided evidence that in HFrEF patients S/V can promote LV reverse remodelling (RR), with an increase in LV ejection fraction (LVEF) and a significant reduction of LV volumes as well as an amelioration of LV diastolic parameters.[10] Nevertheless, mechanisms underpinning the beneficial effects of S/V are still poorly understood, and investigated only in small studies.

The present analysis aimed to identify possible differences in baseline clinical and echocardiographic characteristics, treatments, and outcomes, among ambulatory HFrEF patients stratified according to well-specified echocardiographically defined haemodynamic profiles before starting S/V therapy, and to evaluate the effects of S/V therapy on outcome according to these haemodynamic profiles in a real-world setting.

Methods

Ambulatory HFrEF patients with optimized standard-of-care therapy for chronic HFrEF, were prospectively included in this multicentre, open-label study from 12 Italian academic hospitals, before starting S/V therapy (NCT04397302—study protocol is depicted in *Figure* S1). Entry criteria were as follows: LVEF $\leq$40% within the preceding 6 months (according to local measurement), clinical stability on a stable dose of loop diuretic since at least 2 weeks preceding study start, optimized medical therapy [defined as treatment for more than 6 months on maximum tolerated dose of an ACE-inhibitor or angiotensin receptor antagonists (ARBs), a beta-blocker, possibly in association with a mineralocorticoid-receptor antagonist (MRA)], suitability for on-label S/V treatment as per standard of care, and availability to undergo repeat echocardiographic examinations 8–12 months afterwards. Exclusion criteria were as follows: history of hypersensitivity/allergy, or suspected contraindication, to ACE-inhibitors/angiotensin receptor blockers, congenital heart disease, severe valvular disease, restrictive physiology, valvular surgery, recent (within the previous three months) acute coronary syndromes revascularization, or cardiac resynchronization therapy, history of stroke, and poor acoustic windows. Patients lost prior to follow-up evaluation or who underwent cardiac surgery, coronary, or mitral interventions before echocardiographic re-evaluation at follow-up were excluded from final analysis. Patients in whom follow-up data were incomplete/missing were also excluded. The Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score[11] was calculated at baseline and at the time of the second echocardiography. The study was conducted according to institutional guidelines, national legal requirements, European standards, and the revised Declaration of Helsinki. All patients provided written informed consent for anonymous collection and publication of their clinical data.

Study protocol

Detailed information on patients' medical history, including medications, and laboratory data [including B-type natriuretic peptide (BNP) and/or amino-terminal pro-type B-natriuretic peptide (NT-proBNP)], were recorded for each patient at the time of the first echocardiogram in the week before starting S/V therapy (*Figure* S1). Patients' functional status was determined according to the New York Heart Association (NYHA) classification. The estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease formula.[12]

A washout period of 36 h was used to allow switching from an ACE-inhibitors to S/V, which was preferentially started at 49/51 mg b.i.d., or 24/26 mg b.i.d. in patients taking a low dose of ACE-inhibitors. At each site, S/V dose was tentatively doubled every 2–3 weeks to reach the target maintenance dose of 97/103 mg b.i.d., except in patients with systolic BP less than 100 mmHg or who developed drug-related adverse events (symptomatic hypotension, hyperkalaemia>5.5 mEq/L, or a decrease in eGFR to <60 mL/min). S/V therapy was discontinued in case of non-adherence to treatment, persistent drug-related adverse event, and unwillingness to continue treatment.

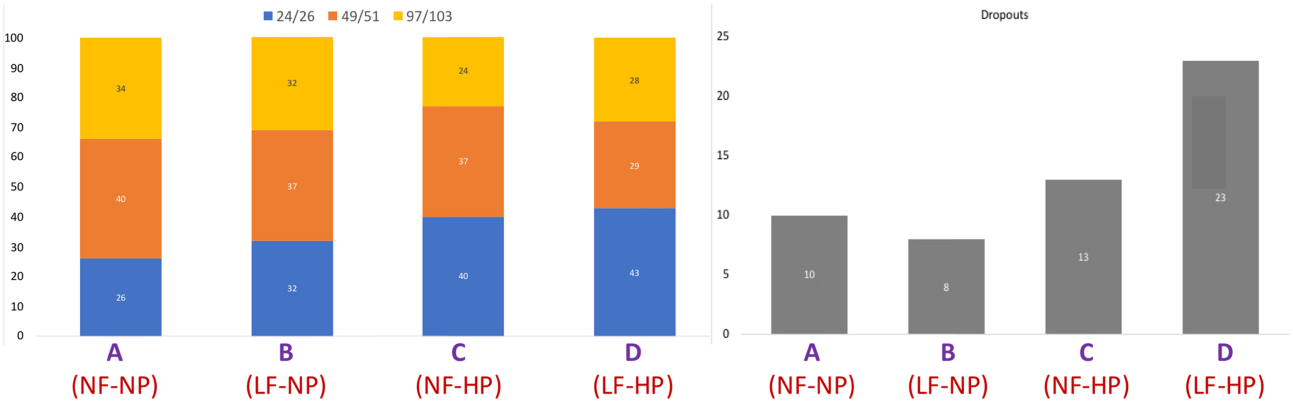
Then, patients were followed-up by periodical clinical visits and telephone calls. The primary end-point of this study was the composite of all-cause mortality (recorded by chart review, telephone contact, and electronic files of death certificates) and HF-related hospitalization. For patients without events, the date of last contact was used for survival analysis. Patients who received cardiac resynchronization therapy (CRT) with or without defibrillator therapy (CRT-P/CRT-D) during follow-up were censored at the time of device implantation.

Echocardiography and non-invasive haemodynamic profiling

Patients underwent baseline two-dimensional echocardiography in the week before starting S/V. LV end-diastolic (LVEDV) and end-systolic volumes (LVESV) were calculated according to the biplane Simpson's method according to the recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging (ASE-EACVI 2016 Recommendations).[13] Doppler examinations included assessment of early diastolic filling velocity (E wave) and early diastolic mitral annular velocity (e'); an averaged $E/e' \geq 15$ was considered a surrogate marker of increased LVFP.[14] Mitral regurgitation severity was assessed using colour, continuous-wave Doppler, as well as other conventional quantitative parameters. LV stroke volume (LVSV) was calculated as the product of LV outflow tract area and the time-velocity integral of the aortic flow velocity.[7,13] The LVSV index was estimated as LVSV divided by body surface area. CO was measured as stroke volume multiplied by heart rate. CI was estimated by dividing CO by body surface area.

By combining E/e' ratio and CI from baseline echocardiography, patients were classified into four haemodynamic profiles: (*Profile-A*) normal-flow and normal-pressure ($CI \geq 2.0$ L/min/m^2; $E/e' < 15$); (*Profile-B*) low-flow, normal-pressure ($CI < 2.0$ L/min/m^2; $E/e' < 15$); (*Profile-C*) normal-flow, high-pressure ($CI \geq 2.0$ L/min/m^2; $E/e' \geq 15$); (*Profile-D*) low-flow, high-pressure ($CI < 2.0$ L/min/m^2; $E/e' \geq 15$), (*Figure* 1).

Figure 1 Final dosage of sacubitril/valsartan (S/V) according to echo-defined haemodynamic profile (left panel). Maximal dosage (97/103 mg BID) was more likely reached in Profile-A, than in other profiles ($P = 0.009$). (Right panel) Prevalence of patients who withdrew S/V therapy during follow-up, according to echo-defined haemodynamic profiles.



Statistical analysis

For the present study, analyses were performed according to the intention-to-treat principle, and repeated according to the per-protocol principle, excluding patients who had a protocol deviation or those who discontinued S/V. Continuous measures were expressed as the mean value ± SD or median and interquartile range (IQR) for normally and non-normally distributed variables, respectively. Continuous data were compared using independent samples Student *t* test or ANOVA when appropriate with subgroup comparisons performed by means of Bonferroni post-hoc test. Mann–Whitney, Kruskal–Wallis, and Wilcoxon tests were used to analyse non-normally distributed variables. Categorical variables were presented as percentages and compared using the χ^2 and McNemar tests.

Because available natriuretic peptide (NP) levels in this registry could be a mixture of BNP or N-terminal pro-BNP (NT-proBNP), to assess the association of haemodynamic profiles with NP levels, we combined these data by calculating the Z-score of the log-transformed BNP or NT-proBNP level for each patient with available data.[15]

For survival analyses, Cox proportional hazards regression was used to evaluate the unadjusted relationship between exposure variables (haemodynamic profiles and S/V dosage) and the composite end-point of all-cause mortality/HF-related hospitalization. Event-rates (per 100 patients per year) were also calculated. Model was then adjusted for covariates chosen based on a combination of clinical relevance and association with adverse outcomes in univariable analysis (*Table* S2) such as MAGGIC score, atrial fibrillation, heart rate, NPs and LVESV index. In addition, interaction terms between echo-profile categories and S/V dosage were also tested. Survival was depicted by Kaplan–Meier curves. Proportional-hazards assumption was verified by inspecting the log–log plot of survival and using Schoenfeld residuals test. Continuous net reclassification improvement was estimated to evaluate the incremental value of echo-derived haemodynamic classification added to a risk model including MAGGIC-score and NP, using a set time of 3 years.[16] All differences were considered significant at the $P = 0.05$ level. Data were analysed with STATA 15 (StataCorp MP) and R statistics (version 4.0).

Results

From December 2016 to October 2019, 727 HFrEF patients were enrolled in this registry. Baseline clinical and echocardiographic characteristics of the study population are shown in *Tables 1* and *2*, respectively. The majority of patients were males, and median LVEF was 30% (IQR 25–35%). Two-hundred-thirty-six patients (32%) were in NYHA Class >II.

The dose of S/V was 50 mg (24/26 mg) B.I.D. in 251 (35%), 100 mg (49/51 mg) B.I.D in 263 (36%), and 200 mg (97/103 mg) B.I.D. in 213 (31.4%). Ninety-seven (13.3%) patients discontinued S/V during the study. Drop-outs for adverse events were 72, and included systemic hypotension (7%), worsening renal function (4%), and other reasons (2%). No patients were lost at follow up.

Echocardiographically derived haemodynamic profiles

At baseline, Profile-A was found in 226 (31%) patients, Profile-B in 146 (20%) patients, Profile-C in 187 patients (26%), and Profile-D in 168 (23%) (*Figure* 2A). Comparison of clinical and echocardiographic characteristics among echo-derived haemodynamic profiles are reported in *Tables* 1 and 2, respectively. Patients in Profile-C were the oldest ($P < 0.001$) and, along with those in profile-D, they more frequently had a history of HF-related hospitalization ($P = 0.001$). Patients in profile-D had lower systolic BP values, more comorbidities, advanced NYHA class, as well as worse renal function and greater values of NPs levels than other profiles (*Table* 1). Accordingly, Profile-D patients showed the highest MAGGIC risk score ($P = 0.0001$, *Table* 1). Profile-D also accounted for a higher prevalence of loop-diuretics as well as lower prevalence of previous treatment with ACE-inhibitors/angiotensin-receptors blockers (*Table* 1).

With regard to echocardiographic data, patients in Profile-C showed the highest indexed LV volumes ($P < 0.001$); EF was lower in Profile-D compared with other profiles (*Table* 2). By study design, non-invasive estimation of LVFPs and CI differed significantly across the haemodynamic profiles ($P < 0.001$, *Table 2*).

Final dose of S/V prescribed was significantly related to baseline echo-defined haemodynamic profiles (Spearman's rho = −0.12, $P = 0.0009$): the prevalence of the targeted S/V dose (97/103 mg BID) progressively decreased from Profile-A to Profile-D, in which low dose of S/V (24/26 mg BID) was prevalent (*Figure* 1, left panel, $P < 0.0009$). Profile-D also accounted for the higher prevalence of patients who withdrew S/V therapy compared with other profiles (*Figure* 1, right panel, $P < 0.0001$; *Table* S1).

Haemodynamic profiles and prognosis

During a median follow-up time of 12.3 months (IQR 6.5–16.6), 155 (21.3%) patients experienced the composite end-point of all-cause death/HF-related hospitalization, with an incidence-rate of 20.3 per 100 patients per year. Incidence-rate of the end-point progressively increased from Profile-A to Profile-D [A: 12.0%, 95% confidence interval (CI): 8.6–16.9; B: 16.4%, 95% CI: 10.9–24.7; C: 22.9%, 95% CI:

Table 1 Clinical characteristics of the study population according to haemodynamic profiles at baseline

	Overall (n = 727)	Profile-A (n = 226)	Profile-B (n = 146)	Profile-C (n = 187)	Profile-D (n = 168)	P value
Demographics						
Age (years)	64.1 ± 11.8	62.6 ± 11.8	62.2 ± 12.8	66.4 ± 11.2*†	65.1 ± 11.2	0.0011
Female gender, (%)	112 (15)	35 (16)	23 (16)	28 (15)	26 (16)	0.998
Weight (kg)	80.8 ± 16.6	80.7 ± 16.7	83.6 ± 16.2	79.4 ± 17.2	80.4 ± 16.1	0.1277
Body mass index	27.9 ± 5.6	27.9 ± 6.9	28.9 ± 4.9	27.4 ± 4.9	27.4 ± 4.9	0.0641
NYHA Class >2, (%)	233 (32)	48 (21)	35 (24)	70 (37)	80 (48)	<0.0001
Previous HF hospitalization	319 (44)	94 (42)	42 (29)	96 (51)	87 (52)	<0.0001
Ischemic aetiology	369 (51)	99 (44)	73 (50)	94 (50)	103 (61)	0.008
Physical features						
Systolic BP (mmHg)	122 ± 16	123 ± 14	121 ± 16	123 ± 17	119 ± 17	0.0963
Diastolic BP (mmHg)	74 ± 10	74 ± 9	74 ± 10	74 ± 10	72 ± 10	0.2008
Heart rate (beats/minute)	69 ± 12	70 ± 12	64 ± 10*	74 ± 14*†	67 ± 9*‡	<0.0001
Comorbidities						
History of hypertension, (%)	435 (60)	118 (52)	96 (66)	106 (57)	115 (68)	0.004
eGFR <60 mL/min/1.73 m^2	242 (33)	61 (27)	43 (29)	73 (39)	65 (39)	0.019
Diabetes, (%)	235 (32)	63 (28)	43 (29)	62 (33)	67 (40)	0.071
Atrial fibrillation, (%)	144 (20)	40 (18)	22 (15)	41 (22)	41 (24)	0.141
COPD, (%)	162 (22)	47 (21)	27 (19)	42 (22)	46 (27)	0.259
MAGGIC risk score, median (IQR)	20 (15–25)	18 (13–22)	19 (14–23)	22 (17–26)	24 (18–29)	0.0001
Laboratory analyses						
Creatinine (mg%), median [IQR]	1.07 [0.90–1.35]	1.00 [0.86–1.27]	1.04 [0.90–1.30]	1.10 [0.90–1.40]	1.13 [0.94–1.47]*	0.0225
B-type NP assessment, n (%)	252 (35)	92 (41)	39 (27)	81 (43)	40 (24)	<0.001
B-type NP (pg/mL), median [IQR]	227 [119–433]	165 [72–263]	281 [123–420]	270 [150–510]*	368 [189–938]*†	0.0001
NT-proBNP assessment, n (%)	479 (66)	143 (63)	93 (64)	121 (65)	121 (72)	0.212
NT-proBNP (pg/mL), median [IQR]	1272 [678–2856]	873 [498–1421]	871 [480–1365]	1890 [964–3800]*†	2550 [1356–3732]*†	0.0001
Therapy						
Loop diuretics, (%)	633 (87)	181 (80)	124 (85)	170 (91)	158 (94)	<0.0001
Beta-blockers, (%)	678 (93)	212 (94)	139 (95)	172 (92)	155 (92)	0.628
ACEI/ARBs, (%)	629 (87)	199 (88)	128 (88)	170 (91)	132 (79)	0.005
Aldosterone antagonists, (%)	502 (69)	136 (60)	110 (75)	131 (70)	125 (74)	0.004
Ivabradine, (%)	126 (17)	41 (18)	27 (19)	22 (12)	36 (21)	0.100
CRT, (%)	190 (26)	53 (24)	34 (23)	50 (27)	53 (32)	0.257
ICD, (%)	485 (67)	147 (65)	90 (62)	121 (65)	127 (76)	0.041

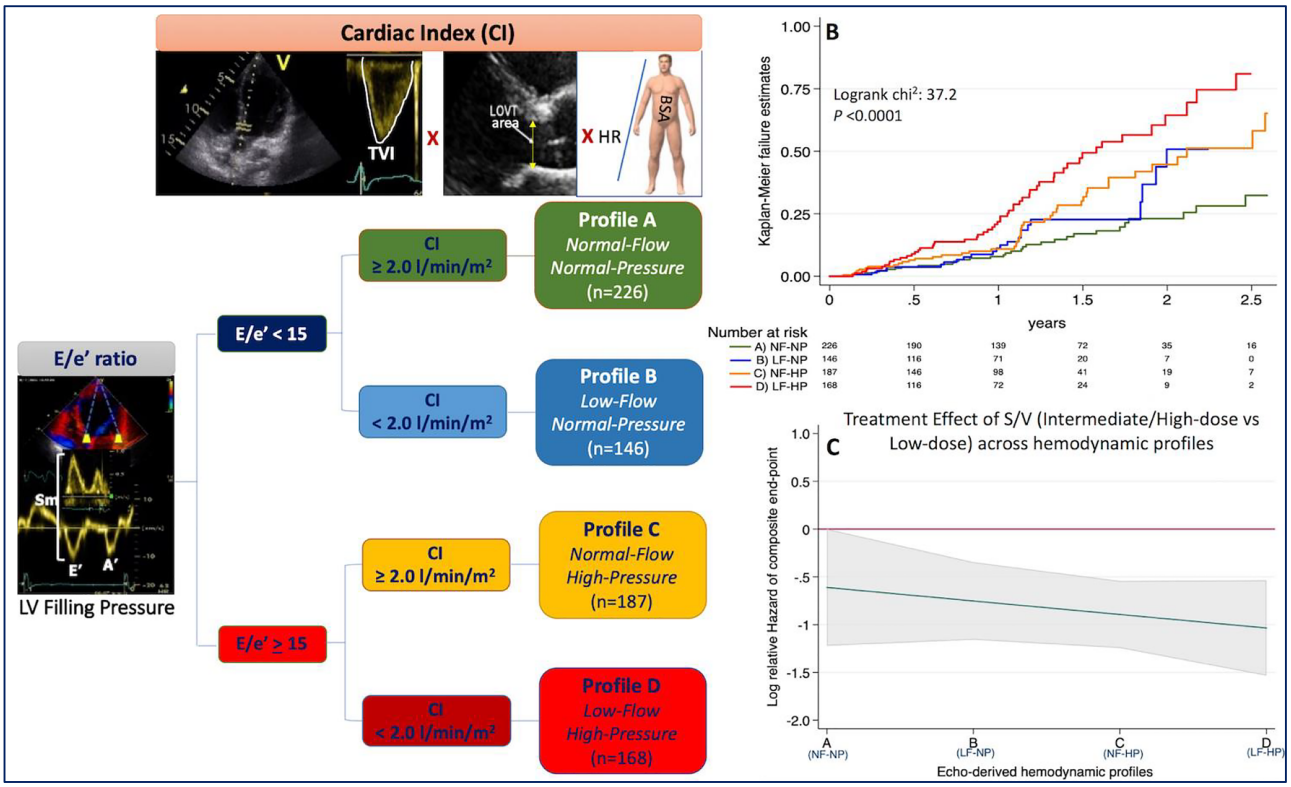
ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BP, blood pressure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator.
Legend: Values are n (%), mean ± SD, or median (interquartile range, IQR). The P values by Kruskal–Wallis or one-way ANOVA for non-Gaussian-distributed and Gaussian-distributed continuous variables, respectively.
*Bonferroni correction: $P < 0.05$ vs. Profile-A.
†Bonferroni correction: $P < 0.05$ vs. Profile-B.
‡Bonferroni correction: $P < 0.05$ vs. Profile-C.
§Bonferroni correction: $P < 0.05$ vs. Profile-D.

Table 2 Echocardiographic characteristics of the total population and according to haemodynamic profiles at baseline

	Overall (n = 727)	Profile-A (n = 226)	Profile-B (n = 146)	Profile-C (n = 187)	Profile-D (n = 168)	P value
LV EDVI (mL/m^2)	106.9 ± 33.4	111.7 ± 33.8†‡§	88.3 ± 22.8*‡§	123.1 ± 38.4*‡§	96.7 ± 22.7*†‡	<0.0001
LV ESVI (mL/m^2)	75.9 ± 27.5	75.9 ± 27.3†‡	63.0 ± 21.4*‡§	87.4 ± 32.2*†§	74.2 ± 21.1†‡	<0.0001
LV EF, median [IQR]	30 [25–35]	35 [30–35]†‡§	30 [25–35]*§	30 [25–35]*§	25 [20–30]*†‡	0.0001
Mitral regurgitation†, (%)	285 (39)	59 (26)	45 (31)	79 (42)	102 (61)	<0.0001
E/e' ratio, median [IQR]	13.3 [10–17]	10.0 [8.0–12.0]‡§	10.0 [8.0–12.0]‡§	18.0 [16.0–21.0]*†	16.0 [16.0–20.0]*†	0.0001
LV SV index (mL/m^2)	31.8 ± 9.8	37.8 ± 8.8†§	25.6 ± 5.6*‡	36.5 ± 9.2†§	24.0 ± 4.9*‡	<0.0001
Cardiac index (L/min/m^2)	2.17 ± 0.71	2.61 ± 0.60†§	1.61 ± 0.29*‡	2.61 ± 0.56†§	1.58 ± 0.28*‡	<0.0001

ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BP, blood pressure; COPD, chronic obstructive pulmonary disease, E/e', averaged ratio of early diastolic filling velocity and early diastolic mitral velocity; eGFR, estimated glomerular filtration rate; LV, left ventricular; RR, reverse remodelling; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator.
[a]Mild-to-moderate.
Legend: Values are n (%), mean ± SD, or median (interquartile range, IQR). The P values by Kruskal–Wallis or one-way ANOVA for non-Gaussian-distributed and Gaussian-distributed continuous variables, respectively.
[*]Bonferroni correction: $P < 0.05$ vs. Profile-A.
[†]Bonferroni correction: $P < 0.05$ vs. Profile-B.
[‡]Bonferroni correction: $P < 0.05$ vs. Profile-C.
[§]$P < 0.05$ vs. Profile-D.

Figure 2 Echo-defined haemodynamic profiles and effects of sacubitril/valsartan (S/V) dosages. (A) Distribution of echo-defined haemodynamic profiles based on presence/absence of elevated E/e' ratio and hypoperfusion. CI, cardiac index; *E/e'*, averaged ratio of early diastolic filling velocity to early diastolic mitral velocity; LVFP, left ventricular filling pressure. (B) Kaplan–Meier failure estimates according to echo-derived profiles. (C) Treatment effects of S/V therapy according to echo-defined haemodynamic profiles. Shaded areas represent the 95% confidence intervals for the log-relative hazard at each baseline echo-profile.



17.1–30.7; D: 35.2%, 95% CI: 26.9–45.9; $P < 0.0001$; *Figure* 3, left panel]. By univariable analysis, compared with Profile-A, Profile-B, Profile-C, and Profile-D were progressively associated with a significant increased risk of the composite end-point (*Figure* 3, right panel). Kaplan–Meier failure curves for each echo-derived profile are depicted in *Figure* 2 (Panel

Figure 3 *Left panel*: Incidence rate (per 100 patients per year) for the composite of all-cause death/HF-related hospitalization, according to echo-defined haemodynamic profiles. *Right panel*: univariable hazard ratios (HRs) and 95% confidence intervals for each haemodynamic profile.

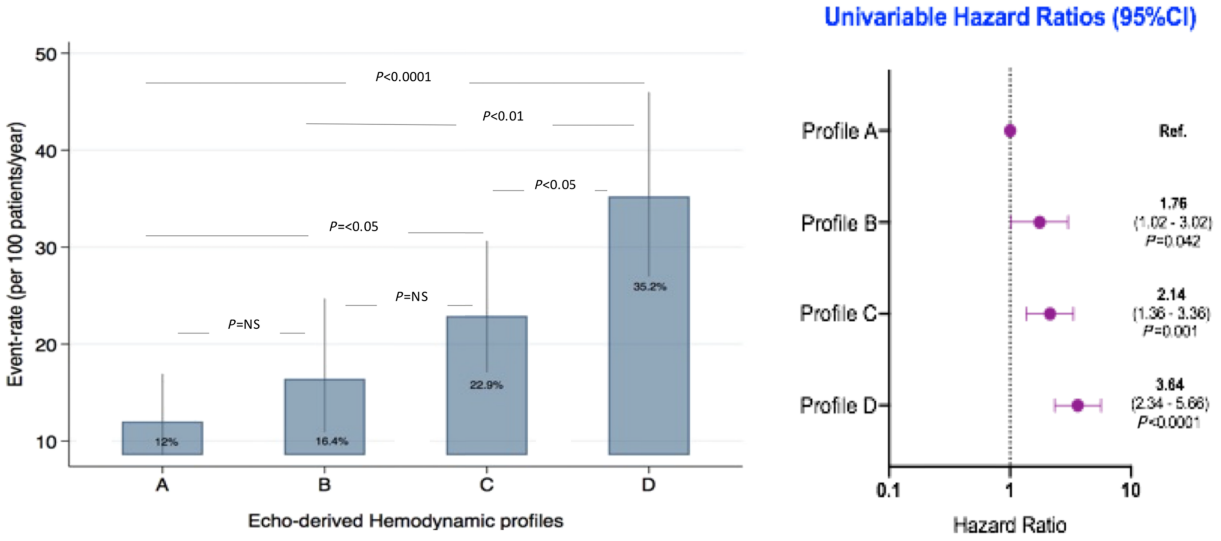


Table 3 Multivariable Cox regression models (intention-to-treat analysis)

	Hazard ratio (95%CI)	*P*
MAGGIC score (continuous)	1.04 (1.02—1.07)	<0.0001
Atrial fibrillation, yes/no	1.07 (0.79–1.46)	0.660
Heart rate, (per 10 bpm)	1.21 (1.00–1.47)	0.050
Natriuretic peptides (*Z*-scores)	1.25 (1.09–1.44)	0.002
LVESV index, per 10 mL/m^2	1.06 (1.02–1.11)	0.003
Sacubitril/valsartan dosage		
24/26 mg	Reference	
49/51 mg	0.47 (0.34–0.63)	<0.0001
97/103 mg	0.34 (0.18–0.64)	0.001
Haemodynamic profile*		
• A: *Normal-flow, normal-pressure*	Reference	
• B: *Low-flow, normal-pressure*	1.88 (1.25–2.83)	0.003
• C: *Normal-flow, high-pressure*	1.19 (0.67–2.13)	0.544
• D: *Low-flow, high-pressure*	2.23 (1.31–3.80)	0.003

CI, confidence interval; LVESV, left ventricular end-systolic volume; S/V, sacubitril/valsartan.

B). After adjustment for MAGGIC score, atrial fibrillation, heart rate, NPs, LVESV index, and S/V dosage, only Profile-B and Profile-D (haemodynamic profiles with low forward flow) remained independently associated with poor outcome (*Table* 3). Adding this categorization to MAGGIC-score and NPs provided significant continuous net reclassification improvement (0.329; $P < 0.001$), suggesting improvement in prognostic prediction. These results were replicated when patients who withdrew S/V were excluded from the analysis (*Table* S3).

Sacubitril/valsartan and prognosis

Incidence rate of the end-point (per 100 patients per year) progressively decreased as S/V dosage increased, from 37.2% with 24/26 mg dose, to 16.6% with 49/51 mg, and to 9.2% with the high-dose S/V (*Figure* 4, Left panel, $P < 0.0001$). By univariable analysis, compared with low dose (24/26 mg), intermediate dose (49/51 mg), and high dose (97/103 mg) of S/V were associated with 61% and 78% risk reduction of the composite end-point, respectively ($P < 0.0001$ for both; *Figure* 4, central panel). Kaplan–Meier failure curves for each S/V dosage are depicted in the right panel in *Figure* 4. By multivariable analysis, after adjusting for MAGGIC risk score, atrial fibrillation, heart rate, NPs, LVESV index, and echo-derived haemodynamic profiles, treatment with S/V remained significantly associated with a low risk of the composite end-point (*Table 3*).

Figure 5 shows the treatment effect of S/V according to haemodynamic profiles. The benefits of S/V therapy both at intermediate and high-dose were consistent across all the echo-defined haemodynamic profiles.

Discussion

Our study shows that (i) in HFrEF outpatients, a comprehensive echocardiographic examination comprising estimates of forward flow and LVFP is helpful in identifying specific haemodynamic phenotypes that are matched by different clinical profiles; (ii) patients exhibiting worse

DOI: 10.1002/ehf2.13779

Figure 4 *Left panel*: Incidence rate (per 100 patients per year) for the composite of all-cause death/heart failure (HF)-related hospitalization, according to sacubitril/valsartan (S/V) dosages. *Central panel*: univariable hazard ratios (HRs) and 95% confidence intervals for each S/V dosage; *Right panel*: Kaplan–Meier failure estimates according to S/V dosages.

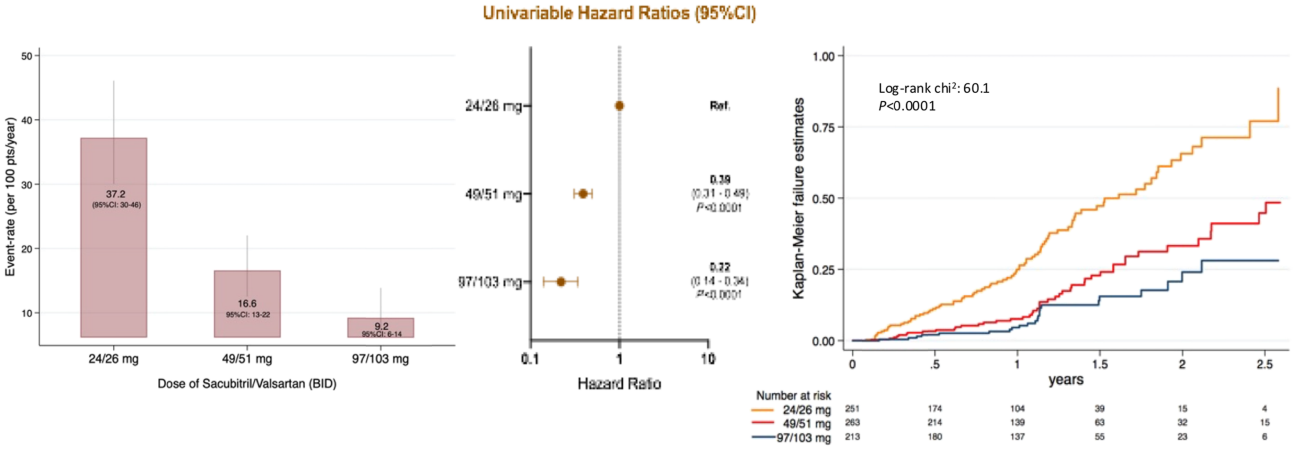
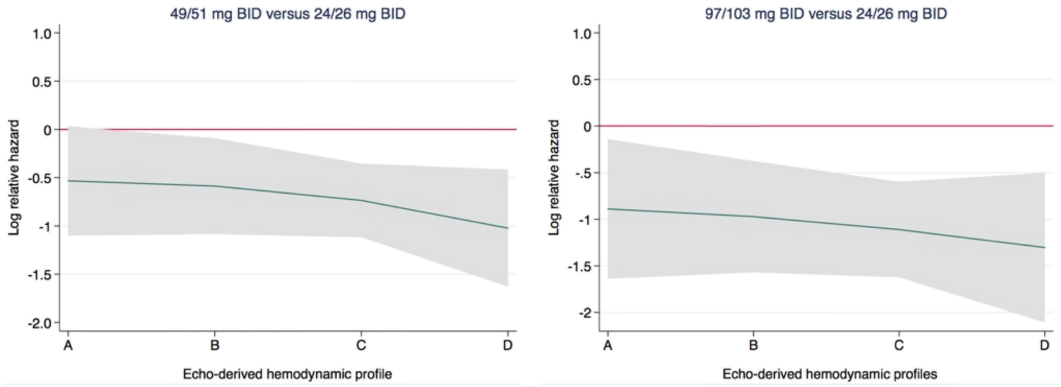


Figure 5 Treatment effects of intermediate (left) and high (right) compared with low-dosage sacubitril/valsartan therapy according to echo-defined haemodynamic profiles. Shaded areas represent the 95% confidence intervals for the log-relative hazard at each baseline echo-profile.



haemodynamic profiles, that is, those characterized by reduced forward flow, exhibit the worst prognosis independently from EF; (iii) patients with increased E/e' and reduced forward flow (i.e. Profile-D) less likely undergo treatment with full dose of S/V and more often discontinued S/V therapy; (iv) intermediate and high-dose S/V on top of conventional therapy may significantly reduce the risk of composite event, across different haemodynamic profiles.

Baseline characteristics of the patients enrolled in this real-world study match well with those of previous randomized trials which have enrolled a broadly generalizable high-risk population of chronic HFrEF despite very good HF therapy.[17]

Comparison with previous studies

Reduced ventricular forward flow and increased ventricular filling pressure represent the two main features of HFrEF, being responsible for the signs and symptoms of this syndrome. In clinical practice, LVEF is the most widely employed parameter to evaluate patients with HF and for clinical decision making as well.[2] However, reduced LVEF does not necessarily imply decreased LV forward flow, even when it may be associated with increased LVFP, as could be the case of dilated LV where LV cavity enlargement may allow LV forward flow to be within normal range despite a marked reduction of LVEF. On the contrary, a normal LVEF may be associated with reduced LV forward flow, as it

happens in the case of marked concentric hypertrophy, because of small LV cavity size. From this perspective, an adequate and comprehensive pathophysiological understanding of HF patients may require that both LV forward flow and LVFP be assessed in addition to LVEF.[7] Unlike simple LVEF measurements, a haemodynamic-based approach might better correlate with symptoms and might improve prognostication of HFrEF.

Recent evidences support the addition of LV output evaluation to LVEF for the assessment of HF patients. Tan *et al*., in patients with HFrEF, found that the stroke distance (SD, i.e. a simplified measure of LV forward flow volume) was an independent predictor of death and LV assist device implantation.[18] Abbas et al applied an echo-directed haemodynamic classification of HF to patients admitted with HF with either reduced (HFrEF, n = 123) or preserved EF (HFpEF, n = 53).[6] They found clear haemodynamic differences in patients with HFrEF vs. those with HFpEF, with a higher prevalence of patients in Profile-D among HFrEF cohort in the acute setting. Moreover, as in our study, in the HFrEF subgroup echo-directed haemodynamic classification was able to better discriminate among different degrees of diastolic dysfunction, and it was associated with increasing values of NPs. However, in their study assessment of prognosis was limited by the small sample size.[6] More recently, Mele *et al*. assessed the prognostic role of a classification based on combined non-invasive evaluation of LV forward flow, filling pressure, and right ventricular function in a large consecutive series of hospitalized patients with HF.[8] They found that such a categorization strongly predicted all-cause mortality independently of LVEF.[8]

In the present study, we extended the echocardiography-directed haemodynamic classification approach to the outpatient setting. In a large series of ambulatory patients with chronic HFrEF in optimized medical therapy, we found a relatively low prevalence of patients with isolated reduced forward-flow (Profile-B), whereas the remaining patients were almost equally distributed in the other groups. After accounting for clinical and laboratory differences among them, profiles characterized by reduced forward-flow remained independently associated with outcome during follow-up. Interestingly, echo-derived haemodynamic profiles seem to affect the titration process of S/V: the proportion of patients reaching the targeted dose of 97/103 mg BID progressively decreased from Profile-A to Profile-D, in which there was also a higher prevalence of patients who discontinued therapy. Higher prevalence of comorbidities and low blood pressure values in Profile-D might have contributed. Anyway, S/V therapy was able to reduce the risk of the composite event in the whole population. This effect was significantly seen across all haemodynamic profiles. Since this was not a trial of low-dose vs. high-dose S/V, the apparent dose-related response of outcome to S/V therapy should be rather viewed as a consequence of the fact that patients who tolerate higher dose have more cardiac reserve and better clinical profile.

Clinical implications

The definition of stable HF is mostly based on the absence of typical signs and symptoms, but clinical stability does not equate disease stability.[19] Therefore, identification of stable HF patients by clinical criteria may be sometimes problematic. Doppler echocardiographic measures of pulmonary congestion and tissue perfusion can better inform clinical judgement. Current approach, associated with clinical evaluation and NP measurement could provide future insights to better identify haemodynamic profile and its relation with congestion/perfusion status. A wider application of this screening could indicate whether the proposed method may be applicable for risk stratification in all HF patients. Excessive use of diuretics and subsequent hypotension could be prevented by better evaluation of the patients' haemodynamic status. ARNI have demonstrated a favourable effect on indirect measures of cardiac haemodynamics, and assessment of the haemodynamic profiles may also serve as a guide to titrate diuretic dosage in patients switched from ACE-inhibitors or angiotensin receptor antagonists to S/V.

Limitations

These real-world observations in unselected, non-randomized patients should be regarded as a hypothesis-generating experience, to be confirmed in larger populations with an appropriate protocol. Although E/e' is widely used to estimate LVFP, its sensitivity is generally low. Concomitant assessment of transmitral PW Doppler and pulmonary venous flow parameters may improve diagnostic accuracy.[20] Although our study design included a second echocardiographic assessment approximately 1 year thereafter, the present work was a pre-specified analysis of the prognostic role of echocardiographically defined haemodynamic profiles assessed at baseline in ambulatory HF patients before starting S/V.

Future perspectives

Further important information on the beneficial effect of S/V on outcome could come from the analysis of the follow-up echocardiographic assessment: indeed, further analyses are planned in the near future, with particular attention to cardiac remodelling following the introduction of S/V, that could confirm and further support the conclusions of the current study.

Conclusion

Echo-derived haemodynamic classification may be useful to identify ambulatory HF patients with different risk profiles and those who better tolerate S/V therapy. In this real-world HFrEF outpatient population, S/V therapy was effective in reducing the risk of events across all haemodynamic profiles.

Conflict of interest

There are no relationships with industry and financial associations from within the past 2 years that might pose a conflict of interest in connection with the submitted article for all the authors.

Funding

This work has been funded in part by Progetto NET-2016-02363853 (Performance evaluation and value assessment for cardiovascular and oncological care paths in a regional network context: challenges and opportunities), *Ricerca Finalizzata Ministero della Salute*, Italy.

Supporting information

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

Table S1. Number and percentage of dropouts and relative reasons in the overall population and each hemodynamic profile.
Table S2. Univariable Cox Regression Model: Baseline Predictors of Composite Outcome (All-cause death/rehospitalization for worsening HF).
Table S2. Multivariable Cox regression models (excluding patients who withdrew sacubitril/valsartan).
Figure S1. Study protocol.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Group ESCSD. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.
2. Konstam MA, Abboud FM. Ejection fraction: misunderstood and overrated (changing the paradigm in categorizing heart failure). *Circulation* 2017; **135**: 717–719.
3. Ambrosio G, Carluccio E. Prognostic role of left ventricular ejection fraction in heart failure: back to the future? *Int J Cardiol* 2018; **273**: 189–190.
4. Carluccio E, Dini FL, Biagioli P, Lauciello R, Simioniuc A, Zuchi C, Alunni G, Reboldi G, Marzilli M, Ambrosio G. The 'Echo Heart Failure Score': an echocardiographic risk prediction score of mortality in systolic heart failure. *Eur J Heart Fail*. 2013; **15**: 868–876.
5. Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. *JACC Cardiovasc Imaging* 2018; **11**: 260–274.
6. Abbas AE, Khoury Abdulla R, Aggrawal A, Crile J, Lester SJ, Boura J. A novel echocardiographic hemodynamic classification of heart failure based on stroke volume index and left atrial pressure. *Echocardiography* 2017; **34**: 1417–1425.
7. Mele D, Andrade A, Bettencourt P, Moura B, Pestelli G, Ferrari R. From left ventricular ejection fraction to cardiac hemodynamics: role of echocardiography in evaluating patients with heart failure. *Heart Fail Rev* 2020; **25**: 217–230.
8. Mele D, Pestelli G, Dini FL, Dal Molin D, Smarrazzo V, Trevisan F, Luisi GA, Ferrari R. Novel echocardiographic approach to hemodynamic phenotypes predicts outcome of patients hospitalized with heart failure. *Circ Cardiovasc Imaging* 2020; **13**: e009939.
9. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371**: 993–1004.
10. Januzzi JL Jr, Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, Camacho A, Piña IL, Rocha RA, Shah AM, Williamson KM, Solomon SD, Investigators ftP-H. Association of change in N-terminal pro–B-type natriuretic peptide following initiation of sacubitril–valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA* 2019; **322**: 1085–1095.
11. Pocock SJ, Ariti CA, McMurray JJV, Maggioni A, Køber L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J*. 2013; **34**: 1404–1413.
12. Kidney Disease: Improving Global Outcomes Diabetes Work G. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int* 2020; **98**: S1–S115.
13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 233–270.
14. Andersen OS, Smiseth OA, Dokainish H, Abudiab MM, Schutt RC, Kumar A, Sato K, Harb S, Gude E, Remme EW, Andreassen AK, Ha JW, Xu J, Klein AL, Nagueh SF. Estimating left ventricular

filling pressure by echocardiography. *J Am Coll Cardiol* 2017; **69**: 1937–1948.
15. Santos AB, Roca GQ, Claggett B, Sweitzer NK, Shah SJ, Anand IS, Fang JC, Zile MR, Pitt B, Solomon SD, Shah AM. Prognostic relevance of left atrial dysfunction in heart failure with preserved ejection fraction. *Circ Heart Fail* 2016; **9**: e002763.
16. Uno H, Tian L, Cai T, Kohane IS, Wei LJ. A unified inference procedure for a class of measures to assess improvement in risk prediction systems with survival data. *Stat Med* 2013; **32**: 2430–2442.
17. Pieske B, Patel MJ, Westerhout CM, Anstrom KJ, Butler J, Ezekowitz J, Hernandez AF, Koglin J, Lam CSP, Ponikowski P, Roessig L, Voors AA, O'Connor CM, Armstrong PW, Group VS. Baseline features of the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial. *Eur J Heart Fail* 2019; **21**: 1596–1604.
18. Tan C, Rubenson D, Srivastava A, Mohan R, Smith MR, Billick K, Bardarian S, Thomas Heywood J. Left ventricular outflow tract velocity time integral outperforms ejection fraction and Doppler-derived cardiac output for predicting outcomes in a select advanced heart failure cohort. *Cardiovasc Ultrasound* 2017; **15**: 18.
19. Butler J, Gheorghiade M, Metra M. Moving away from symptoms-based heart failure treatment: misperceptions and real risks for patients with heart failure. *Eur J Heart Fail* 2016; **18**: 350–352.
20. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD, Houston, Texas, Oslo, Norway, Phoenix, Arizona, Nashville, Tennessee, Hamilton, Ontario, Canada, Uppsala, Sweden, Ghent and Liège, Belgium, Cleveland, Ohio, Novara, Italy, Rochester, Minnesota, Bucharest, Romania, St. Louis, Missouri. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016; **17**: 1321–1360.