Multiparametric prognostic scores in chronic heart failure with reduced ejection fraction: a long-term comparison

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Aims

Risk stratification in heart failure (HF) is crucial for clinical and therapeutic management. A multiparametric approach is the best method to stratify prognosis. In 2012, the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score was proposed to assess the risk of cardiovascular mortality and urgent heart transplantation. The aim of the present study was to compare the prognostic accuracy of MECKI score to that of HF Survival Score (HFSS) and Seattle HF Model (SHFM) in a large, multicentre cohort of HF patients with reduced ejection fraction.

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Methods and results We collected data on 6112 HF patients and compared the prognostic accuracy of MECKI score, HFSS, and SHFM at 2- and 4-year follow-up for the combined endpoint of cardiovascular death, urgent cardiac transplantation, or ventricular assist device implantation. Patients were followed up for a median of 3.67 years, and 931 cardiovascular deaths, 160 urgent heart transplantations, and 12 ventricular assist device implantations were recorded. At 2-year follow-up, the prognostic accuracy of MECKI score was significantly superior [area under the curve (AUC) 0.781] to that of SHFM (AUC 0.739) and HFSS (AUC 0.723), and this relationship was also confirmed at 4 years (AUC 0.764, 0.725, and 0.720, respectively).

Conclusion In this cohort, the prognostic accuracy of the MECKI score was superior to that of HFSS and SHFM at 2- and 4-year follow-up in HF patients in stable clinical condition. The MECKI score may be useful to improve resource allocation and patient outcome, but prospective evaluation is needed.

Keywords Heart failure • Risk score • Prognosis • MECKI score • HFSS • SHFM

Introduction

Chronic heart failure (HF) is a major clinical and public health problem.[1] Despite advances in treatment, HF patients remain at high risk of death, and the course of the disease is often insidious and uncertain.[1,2] Prognostic stratification in HF is of paramount importance to guide clinical management and treatment strategy. Several single variables have proven to be implicated in the prognostic stratification of HF, but all of them have failed to demonstrate a robust correlation with adverse events. Considering the aging of the population and heterogeneity in clinical presentation, a clinical-epidemiological multiparametric approach has been advocated as the best strategy to predict HF outcome.

In recent years, a number of risk stratification models have been proposed in large cohorts of patients,[2–11] but the available algorithms have multiple limitations. In 2012, the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score was suggested to assess the risk of cardiovascular (CV) mortality and urgent heart transplantation.[12] A MECKI score calculator is also available online.[13] The score was built from a cohort of 2715 HF patients with reduced left ventricular ejection fraction (LVEF) followed in several HF units. Starting from 80 variables derived from clinical, laboratory, echocardiographic, and exercise evaluations, only six were independently related to prognosis: haemoglobin (Hb), sodium (Na^+), kidney function evaluated by means of the Modification of Diet in Renal Disease (MDRD) equation, LVEF by echocardiography, percentage of predicted peak oxygen consumption (VO_2%), and minute ventilation/carbon dioxide production (VE/VCO_2) relationship slope. It is recognized, however, that both MDRD and VO_2% require multiple, albeit easy available, data to be calculated. The MECKI score was later successfully validated in another population of HF patients on optimal pharmacological and non-pharmacological treatment and with a comparatively lower event rate.[14] Moreover, the MECKI score database is constantly updated, and additional HF units have contributed to the database by sharing their results.[14–20]

The cardiopulmonary exercise test (CPET) is a well-recognized, valuable, accurate tool for risk stratification in HF. At present, apart from MECKI score, only HF Survival Score (HFSS)[19] and HF-ACTION predictive risk score model[8] include analyses of exercise performance. The Seattle Heart Failure Model (SHFM),[20] based on 24 clinical variables that do not include exercise evaluation, has also been proposed to assess survival rate in HF patients and, at present, is probably the most frequently used HF prognostic score.

In this study, we aimed to compare the prognostic accuracy of MECKI score to HFSS and SHFM in a large, multicentre cohort of patients affected by HF at 2 and 4 years.

Methods

Population and study procedures

We collected data on a cohort of 6112 patients with a history of HF with reduced LVEF, enrolled and prospectively followed in 23 Italian HF centres. Data were derived from an update of the MECKI score database.[12,14] The present research protocol complies with the Declaration of Helsinki, and it was approved by the Ethics Committee of Centro Cardiologico Monzino, IRCCS (CCM-127).

Inclusion criteria at enrollment were previous or present HF symptoms [New York Heart Association (NYHA) functional class I–IV, stage B and C of the American College of Cardiology/American Heart Association classification] and former documentation of LVEF <40%, unchanged HF medications for at least 3 months, ability to perform a CPET, and no major CV treatment or intervention scheduled. We considered the following as exclusion criteria: history of pulmonary embolism, moderate-to-severe aortic and mitral stenosis, pericardial disease, severe obstructive lung disease, exercise-induced angina and significant ECG alterations, or presence of any clinical co-morbidity interfering with exercise performance.

At enrollment, clinical history was recorded, and physical examination, laboratory analyses, ECG, transthoracic echocardiography, and CPET were performed as previously described.[12] Moreover, additional data required to calculate HFSS and SHFM were collected. Specifically, dose equivalent for different diuretic molecules was calculated according to Levy *et al.*[20] CPET was performed using a ramp protocol on an electronically braked cycle ergometer or a modified Bruce protocol on a treadmill. Peak VO_2 data measured at treadmill exercise were reduced by 10% to allow an appropriate comparison between the two different procedures[21]; the CPET protocol was set to reach peak exercise in 8–12 minutes, but tests were stopped as patients reported maximal effort, regardless of the

respiratory quotient reached.[12] Peak VO_2 was calculated as the 20 s average of the highest recorded VO_2, while VE/VCO_2 slope was calculated as the slope of the linear relationship between VE and VCO_2 from 1 minute after the beginning of loaded exercise to the end of the isocapnic buffering period. Peak VO_2% of the predicted value was calculated according to Hansen *et al.*[22]

Follow-up and comparison among risk scores

Follow-up was carried out according to the local HF programme and ended with the last clinical evaluation in the centre where the patient had been enrolled.[12] The primary study endpoint was CV death and urgent cardiac transplantation defined as UNOS status 1[23] or left ventricular assist device (LVAD) implantation. The secondary endpoint was the composite of all-cause death, urgent cardiac transplantation, or LVAD implantation.[12] We compared the prognostic accuracy of MECKI score, HFSS, and SHFM at 2- and 4-year follow-up.

Statistical analysis

Quantitative variables were reported as mean ± standard deviation or median and interquartile range (IQR) as appropriate. Variables with skewed distributions were presented as median and IQR. Categorical variables were reported as frequency and percentage. Missing imputation was performed by replacing the missing value with the mean value of the entire data set. Receiver operating characteristic (ROC) curves were calculated, and the area under the ROC curve (AUC) with 95% confidence interval (CI) was used to compare the ability of the scores to predict the main endpoint at 2 and 4 years. To avoid a possible bias related to the use, albeit updated, of the original population from which MECKI score was derived, reclassification techniques were also employed in the newly enrolled population ($n = 3397$), because of their higher statistical power as compared with ROC analysis.[24] Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to assess the potential of MECKI score to improve risk prediction in comparison to SHFM and HFSS.[24,25] In the absence of widely recognized cut-offs for defining low-, medium- and high-risk categories, we employed the tertiles of the estimated risk (at 2 and 4 years) over the entire sample. Plot calibration of the three scores was performed by using the Hosmer–Lemeshow test and applying the coefficients derived in the validation cohort. For MECKI and SHFM scores we also performed calibration by computing in each decile of the validation cohort the median probabilities of events as predicted by the scores using the coefficients obtained in the derivation cohorts and using the appropriate endpoints: CV mortality, urgent heart transplant and LVAD for MECKI and all-cause mortality, urgent heart transplant and LVAD for SHFM. *P*-values of <0.05 were considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). The SAS macros published by Cook and Ridker[25] were employed in reclassification analysis.

Results

A total of 6112 HF patients (82% males) were enrolled from January 1993 to December 2015 (*Table 1*) (48 patients/year from 1993 to 1998, 191 patients/year from 1999 to 2004, 442 patients/year from 2005 to 2010, and 397 patients/year from 2011 to 2015). NYHA classification was available in 6109 of the 6112 patients. Fifteen percent of patients ($n = 919$) were in NYHA class I, 57% ($n = 3456$) in NYHA class II, 27% ($n = 1659$) in NYHA class III, and 1% ($n = 75$) in NYHA class IV. At enrollment, all patients were on optimized medical treatment (*Table 2*); 1905 patients (31.2%) had an implantable cardioverter-defibrillator and 748 (12.3%) were on cardiac resynchronization therapy. From a metabolic point of view, 4319 patients (71%) performed a maximal exercise as defined by a respiratory quotient of ≥ 1.05. Patients were followed up for a median period of 3.67 years (1341 days, IQR 630–2353 days), and 931 CV deaths, 160 heart transplantations, and 12 LVAD implantations occurred during the study period. Non-CV death occurred in 434 patients. Overall, 808 patients were lost to follow-up. Of the entire population, average MECKI score, SHFM and HFSS were 0.09 ± 0.11, 0.89 ± 0.10, and 9.91 ± 0.81, respectively.

The event rate at 2 years of the primary study endpoint was 39.6/1000 person-years, 55.2/1000 person-years, and 25.8/1000 person-years in the entire population, in the original MECKI score database ($n = 2715$), and in the more recent database ($n = 3397$), respectively. The event rate of the same endpoint at 4 years was 39.1/1000 person-years, 49.1/1000 person-years, and 28.8/1000 person-years, respectively.

Score comparison

Analysis of 2-year follow-up data showed that the prognostic accuracy of MECKI score (AUC 0.781) was superior to that of SHFM (AUC 0.739) and HFSS (AUC 0.723; $P < 0.001$ for both; *Figure 1a*). The superior prognostic value of MECKI score was also confirmed at 4-year follow-up (AUC 0.764, 0.725, 0.720, respectively; $P < 0.001$ for both; *Figure 1b*). Considering patients with the most severe HF, i.e. NYHA class III–IV ($n = 1734$), at 2 years MECKI score AUC was 0.737, compared to 0.678 for SHFM and 0.682 for HFSS ($P < 0.01$ and $P < 0.001$, respectively). At 4 years, MECKI score AUC was 0.750, compared to 0.684 and 0.706 for SHFM and HFSS, respectively ($P < 0.001$ and $P < 0.01$). Moreover, MECKI score AUC (0.781) was significantly higher than the AUC of each one of its component variables (peak VO_2% of predicted value 0.727, VE/VCO_2 slope 0.695, Hb 0.586, Na^+ 0.577, LVEF 0.692, and MDRD 0.633) (see Supplementary material online, *Figure S1*). MECKI, SHFM, and HFSS AUCs for the secondary endpoint were 0.741, 0.715, and 0.695 at 2 years and 0.744, 0.720, and 0.701 at 4 years, respectively. Imputation of missing data was necessary in 805 (13%), 2035 (33%), and 940 (15%) patients for MECKI score, SHFM, and HFSS, respectively.

A further analysis was performed to evaluate whether the use of patients from the original MECKI score development study introduced a statistical bias influencing our analysis. The follow-up of patients who were part of the original MECKI score database was updated and increased from a median of 1041 (513–1811) to 2315 (1085–3257) days. We assessed MECKI score AUC separately considering the original population ($n = 2715$) and the more recent one ($n = 3397$) at 2-year follow-up. The AUCs were very similar (*Figure 2*). We also analysed the Kaplan–Meier survival curves in the more recent population for each analysed model, MECKI, HFSS and SHFM, dividing the population into risk tertiles (*Figure 3*). All scores showed a notable capability to stratify patient

Table 1 **Population characteristics: total population, population who reached the primary study endpoint, and population who did not**

	Total population ($n = 6112$)		Endpoint + ($n = 1103$)		Endpoint – ($n = 5009$)	
	n	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD
Age, years	6093	61.4 ± 12.8	1101	63.0 ± 12.8	4992	61.0 ± 12.7
BMI, kg/m^2	6094	26.8 ± 4.4	1097	26.0 ± 4.4	4997	26.9 ± 4.3
Weight, kg	6099	77 ± 15	1092	75 ± 15	5007	78 ± 15
Male sex	6112	5000 (82%)	1103	964	5009	4037
LVEF, %	6067	33.2 ± 10.5	1097	28.3 ± 9.6	4972	34.3 ± 10.4
Idiopathic aetiology	2399 (40%)		395 (33%)		2004 (40%)	
Ischaemic aetiology	2794 (46%)		571 (52%)		2223 (44%)	
Other aetiology	867 (14%)		129 (12%)		738 (15%)	
Atrial fibrillation	965 (16%)		217 (20%)		748 (15%)	
Resting HR, b.p.m.	5400	71 ± 12	858	72.9 ± 13.3	4542	70.4 ± 12.3
QRS, ms	5036	117 ± 34	766	124 ± 36	4270	116 ± 33
SBP, mmHg	5398	117 ± 17	857	114 ± 17	4541	118 ± 17
DBP, mmHg	5401	73 ± 10	858	70 ± 11	4543	73 ± 10
Peak VO_2, mL/min	6104	1148 ± 433	1099	956 ± 346	5005	1191 ± 438
Peak VO_2, mL/kg/min	6099	14.8 ± 4.9	1099	12.8 ± 4.0	5000	15.3 ± 4.9
Peak VO_2, %	6093	56 ± 17	1097	47 ± 14	4996	58 ± 17
Peak workload, W	5735	83 ± 34	969	70 ± 28	4766	86 ± 35
VE/VCO_2 slope	5928	32.8 ± 7.8	1042	35.8 ± 8.6	4886	32.1 ± 7.4
Na^+, mmol/L	5792	139.3 ± 3.2	1065	138.8 ± 3.7	4727	139.4 ± 3.1
Hb, g/dL	5615	13.5 ± 1.6	977	13.2 ± 1.7	4638	13.5 ± 1.6
Lymphocytes, %	4872	28.9 ± 9.4	791	26.5 ± 9.9	4081	29.4 ± 9.2
Uric acid, mg/dL	4432	6.4 ± 1.9	641	6.8 ± 2.1	3791	6.3 ± 1.9
Total cholesterol, mg/dL	4851	179 ± 43	782	178.7 ± 43.6	4069	179.0 ± 43.2
MDRD	5804	71.4 ± 23.9	1065	64.2 ± 23.8	4739	73.1 ± 23.7

BMI, body mass index; DBP, diastolic blood pressure; Hb, haemoglobin; HR, heart rate; LVEF, left ventricular ejection fraction; Na^+, sodium; MDRD, Modification of Diet in Renal Disease; NYHA, New York Heart Association; Peak VO_2, oxygen uptake at peak exercise; SBP, systolic blood pressure; SD, standard deviation; VE/VCO_2 slope, slope of the relation between ventilation and carbon monoxide production during exercise.

risk. *Figure 4* shows the calibration plot, calculated in the present population and applying as study endpoint the composite of CV death, urgent heart transplant and LVAD, of the three analysed scores. At visual inspection HFSS shows the best calibration. In the calibration plots (Supplementary material online, *Figure S2*), the predicted probabilities were computed using the coefficients obtained in the derivation cohort. Data for the entire population, along with old and new subpopulations, are presented in the Supplementary material online, *Figure S3*.

We evaluated the more recent HF population by comparing MECKI score to SHFM and HFSS by means of a reclassification analysis using IDI and NRI methodology at 2 and 4 years (*Table 3*). We assessed score differences by analysing patients who had all the data needed to build the scores. Specifically, to assess the quality of reclassification, HF patients were arbitrarily divided into three risk groups according to tertiles of risk. Notably, at 2 years, MECKI score reclassified 449 (24.3%) subjects into a higher risk category than SHFM and 278 (13.3%) subjects into a higher risk category than HFSS (*Table 4*), while 566 (30.6%) and 403 (19.3%) subjects were reclassified into a lower risk category than those assigned by SHFM and HFSS, respectively. At 4 years, MECKI score reclassified 124 (11.9%) and 130 (11.3%) subjects into a higher risk category than SHFM and HFSS, respectively, and 271 (26%) and 174 (15.1%) subjects into a lower risk category (*Table 4*).

Discussion

The results of this study demonstrate that MECKI score exhibits greater prognostic accuracy than SHFM and HFSS in terms of hard endpoints such as the combination of CV death, urgent heart transplantation, and LVAD implantation in a large HF population. The superior prognostic value of MECKI score was evident both at 2- and 4-year follow-up.

The population we studied consists of HF patients recruited over a long time span. Regardless, patients were receiving optimal medical treatment according to the most recent HF guidelines.[26] Owing to the large database, HF severity, patient management, and therefore prognostic outcomes may have been heterogeneous among the different recruiting centres. However, when the HF centre where patients were recruited was analysed as an independent variable, it was found not to influence the findings. The multicentre recruitment represents a strength of this study by mimicking

Table 2 **Medical treatment of the total population, of the population who reached the primary study endpoint and the population who did not**

	Total population ($n = 6112$)	Endpoint + ($n = 1103$)	Endpoint – ($n = 5009$)
ACE-inhibitors	4565 (74.7)	857 (77.7)	3708 (74.0)
ARBs	1135 (18.6)	158 (14.3)	977 (19.5)
Beta-blockers	5302 (86.8)	895 (81.1)	4407 (88.0)
Aldosterone antagonists	3191 (52.2)	636 (57.7)	2555 (51.0)
Diuretics	4900 (80.2)	993 (90.0)	3907 (78.0)
Diuretic equivalent dose, median (IQR)	25 (12.5–50)	50 (25–125)	25 (12.5–50)
Statins	2724 (44.9)	377 (34.2)	2347 (46.8)
Allopurinol	1574 (25.9)	323 (29.3)	1251 (25.0)
Antiplatelets	3284 (53.8)	538 (48.8)	2746 (54.8)
Anticoagulants	1810 (29.6)	434 (39.3)	1376 (27.5)
Digitalis	1228 (20.1)	449 (40.7)	779 (15.6)
Amiodarone	1498 (24.5)	348 (31.6)	1150 (23.0)

Values are given as number (%) unless otherwise indicated.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; IQR, interquartile range.

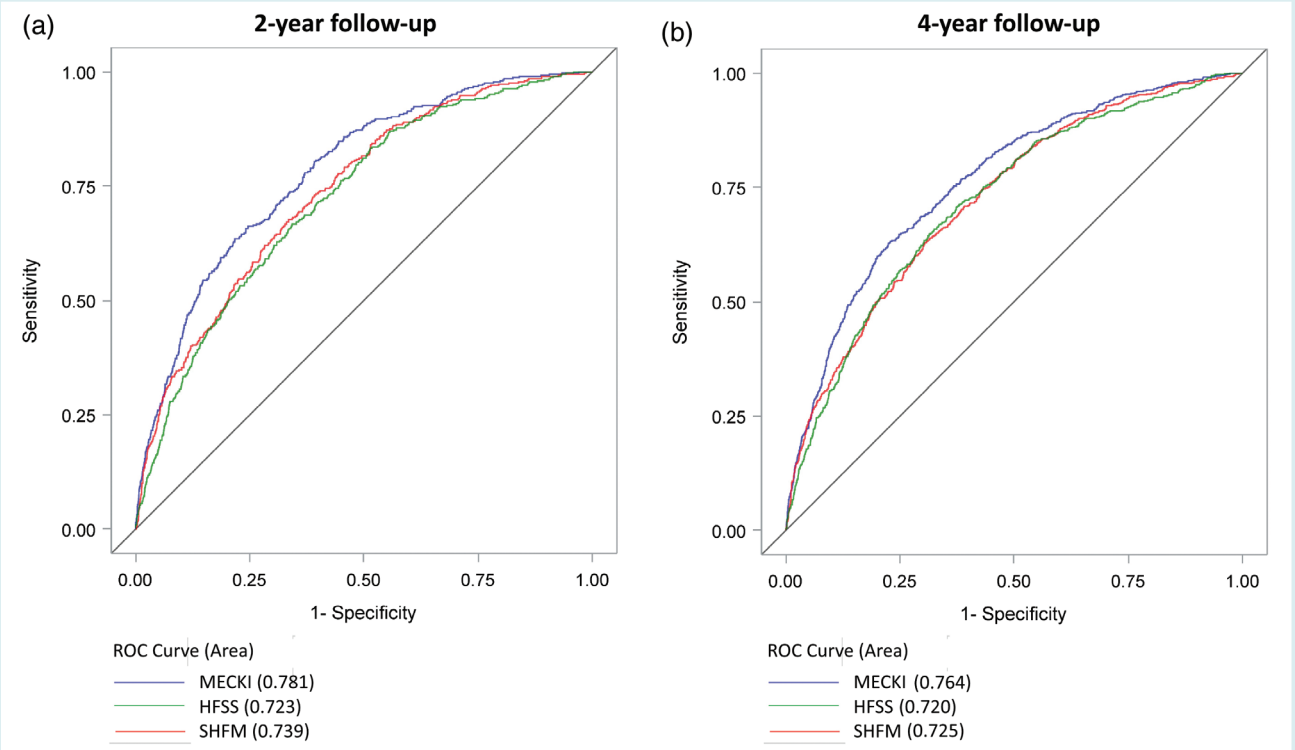

Figure 1 Receiver operating characteristic (ROC) curves at 2- and 4-year follow-up. At 2 years (*a*), the prognostic accuracy of the MECKI score (blue line) was significantly superior ($P < 0.001$ for both) to that of SHFM (red line) and HFSS (green line). The better prognostic value of MECKI score was confirmed at 4-year follow-up (*b*) ($P < 0.001$ for both). MECKI, Metabolic Exercise test data combined with Cardiac and Kidney Indexes; SHFM, Seattle Heart Failure Model; HFSS, Heart Failure Survival Score.

real-life conditions as much as possible. The MECKI score research project analysed low-LVEF HF patients in stable clinical condition capable of performing a CPET. Moreover, patients with frequent HF co-morbidities such as anaemia, renal insufficiency, and diabetes were evaluated in the study, while patients with co-morbidities able to strongly affect exercise performance *per se*, including severe lung disease, pulmonary embolism, idiopathic pulmonary artery hypertension, orthopaedic deficiencies, connective tissue disease, or neurological diseases were excluded. Therefore, our population is representative of HF patients frequently seen in daily clinical

Table 3 Net reclassification improvement and integrated discrimination improvement analysis of newly enrolled patients at 2- and 4-year follow-up

	Index	Estimate	SE	95% CI	*P*-value
2-year follow-up ($n = 1847$; n events 128)					
MECKI vs. SHFM	NRI	0.144	0.056	0.0349–0.2523	0.01
MECKI vs. SHFM	IDI	0.019	0.006	0.003–0.0346	0.002
MECKI vs. HFSS	NRI	0.139	0.045	0.0506–0.2281	0.002
MECKI vs. HFSS	IDI	0.016	0.004	0.0054–0.0263	<0.001
4-year follow-up ($n = 1042$; n events 217)					
MECKI vs. SHFM	NRI	0.1350	0.0388	0.0590–0.2110	<0.001
MECKI vs. SHFM	IDI	0.0569	0.012	0.0259–0.0879	<0.001
MECKI vs. HFSS	NRI	0.0749	0.0286	0.0188–0.1309	0.009
MECKI vs. HFSS	IDI	0.014	0.0081	−0.0069–0.0348	0.084

CI, confidence interval; HFSS, Heart Failure Survival Score; IDI, integrated discrimination improvement; MECKI, Metabolic Exercise test data combined with Cardiac and Kidney Indexes; NRI, net reclassification improvement; SE, standard error; SHFM, Seattle Heart Failure Model.

practice. It is of note that event rates decline substantially in the new population compared to the original one but the accuracy of the model remains. This datum confirms the high quality of MECKI score recruiting centres, which always have the most updated HF therapies and follow-up strategies.

In recent years, several HF risk scores have been built and validated, including a number of different parameters. HFSS was proposed in 1997 and it is composed by seven variables, including peak VO_2.[19] In 2006, Levy *et al.*[20] presented the SHFM, which requires several variables to estimate HF patients' survival. Notably, the AUCs we observed in the present population for SHFM and HFSS were similar to previously reported values.[27] Since the publication of the SHFM, other scores have been developed,[8–10] in particular the HF-ACTION,[8] built on a cohort of 2331 HF patients, which also includes exercise parameters at CPET, the MAGGIC risk score,[9] presented in 2013 as a meta-analysis of individual patient data from 30 studies, the 3C-HF score (6274 patients),[11] proposed to predict all-cause 1-year mortality, and the MUSIC risk score[10] derived from 992 ambulatory HF patients. The population we studied is among the largest to employ a long follow-up to evaluate HF risk scores, and it is certainly the largest in which exercise-derived parameters were considered.

The MECKI score was developed based on a population of 2715 HF patients able to perform a CPET[12] and successively validated in a new population.[14] In the present study, we confirmed that the MECKI score performed better than the six variables from which it is derived, reaffirming the usefulness of a multiparametric approach. We compared the prognostic accuracy of MECKI score to that of two other previous scores, HFSS and SHFM, the former chosen because it includes exercise parameters such as peak VO_2, making it similar to our score, and the latter due to its widespread adoption for the prognostic assessment of HF. We were not able to compare MECKI score with other risk scores because the required parameters were not all available in our database. The superior prognostic capability of MECKI score was also observed when the analysis was limited to patients with the most severe HF, NYHA class III–IV.

The addition of peak VO_2 (mL/kg/min) and VE/VCO_2 slope to SHFM, and the combined use of HFSS and SHFM demonstrated statistically significant improvements in risk stratification compared to SHFM, particularly in patients with moderate risk.[27–29] However, the clinical meaning of adding peak VO_2 and VE/VCO_2 slope has been questioned.[28] Nevertheless, the use of peak VO_2% of predicted value will likely add prognostic power to peak VO_2 expressed in mL/kg/min due to the heterogeneity of the HF population studied.

The population used to compare the risk scores was in part ($n = 2715$) derived from MECKI score development study.[12] However, the prognostic accuracy of MECKI score was similar in the old population with updated follow-up data and in the newly enrolled patients (*Figure 2*). Moreover, MECKI score provided a proper reclassification at 2-year follow-up in 14% of cases vs. both SHFM and HFSS, and at 4-year follow-up in 13.5% and 7.5% of cases vs. SHFM and HFSS, respectively (*Table 3*). Notably, as in the original analysis,[12] we only evaluated subjects with a complete set of data, avoiding any implementing procedure that might have diluted the efficacy of each tested method and particularly of those that require the assessment of a large number of variables, as the SHFM (*Table 3*). Altogether, these data show that all three analysed scores provide reliable prognostic information. However, MECKI score is superior to HFSS and SHFM in predicting HF patients' prognosis. Notably, as an average, MECKI score reclassification at 2 years was to a lower risk category in 25% of cases and to a higher risk category in 19% of cases compared to both HFSS and SHFM. At 4 years, MECKI score reclassification was to a lower risk category in 21% of cases and to a higher risk category in 12% of cases compared to both HFSS and SHFM. It is of note that very recently, albeit in a small population, Freitas *et al.*[30] confirmed the superiority of MECKI score compared to HFSS, MAGGIC and SHFM in predicting prognosis in HF patients with reduced LVEF. Consequently, if extensively applied in the clinical field, MECKI score should be able to improve resource allocation and patient outcome. However, this possibility needs to be confirmed by dedicated studies.

Table 4 **Observed risk and risk reclassification comparing 2- and 4-year risk according to MECKI vs. SHFM and MECKI vs. HFSS in newly enrolled patients**

2 years					% reclassified into new risk category		
SHFM	**MECKI**			**Total (%)**	**Lower**	**Higher**	**Total**
	<1.8%	**1.8–7.5%**	**>7.5%**				
<1.8%							
n (%)	216 (49.0%)	184 (41.7%)	41 (9.3%)	441	–	51.02	51.02
Observed risk	0.46	1.63	4.88	5.0			
n events	1	3	4	22			
1.8–7.5%							
n (%)	265 (35.4%)	259 (34.6%)	224 (30.0%)	748	35.43	29.95	65.38
Observed risk	0.38	4.25	9.82	4.55			
n events	1	11	22	34			
>7.5%							
n (%)	122 (18.5%)	179 (27.2%)	357 (54.3%)	658	45.74	–	45.74
Observed risk	0.51	4.9	16.7	13.4			
n events	3	14	71	88			
Total							
n (%)	603 (32.6%)	622 (33.7%)	622 (33.7%)	1847			
Observed risk	8.3	4.5	15.6	7.0			
n events	5	28	97	130			
HFSS	**MECKI**						
	<1.8%	**1.8–7.5%**	**>7.5%**				
<1.8%					–	22.53	22.53
n (%)	392 (77.5%)	102 (20.1%)	12 (2.4%)	506			
Observed risk	0.51	4.9	16.7	1.8			
n events	2	5	2	9			
1.8–7.5%							
n (%)	260 (29.6%)	455 (51.8%)	164 (18.7%)	879	29.58	18.66	48.24
Observed risk	1.15	4.4	7.9	4.1			
n events	3	20	13	36			
>7.5%							
n (%)	21 (3.0%)	176 (25.2%)	502 (71.8%)	699	28.18	–	28.18
Observed risk	No events	6.25	15.74	2.7			
n events	0	11	8	19			
Total							
n (%)	673 (32.3%)	733 (35.2%)	678 (32.5%)	2084			
Observed risk	0.7	4.9	3.4				
n events	5	36	23	64			
4 years					**% reclassified into new risk category**		
SHFM	**MECKI**			**Total (%)**	**Lower**	**Higher**	**Total**
	<8.0%	**8.0–11.0%**	**>11.0%**				
<8.0%							
n (%)	122 (51.5%)	22 (9.3%)	93 (39.2%)	237 (22.7%)	–	48.52	48.52
Observed risk	1.64	9.09	11.83	6.33			
n events	2	2	11	15			
8.0–11.0%							
n (%)	42 (37.2%)	12 (10.6%)	9 (52.2%)	113 (10.8%)	37.17	52.21	89.38
Observed risk	No events	8.33	16.95	9.73			
n events	0	1	2	11			
>11.0%							
n (%)	175 (25.3%)	54 (7.8%)	463 (66.9%)	692 (66.4%)	33.09	–	33.09
Observed risk	7.43	12.96	36.93	27.6			
n events	13	7	171	191			
Total							
n (%)	339 (32.5%)	88 (8.4%)	615 (59.0%)	1042 (100%)			
Observed risk	4.43	11.36	31.22	20.82			
n events	15	10	192	217			

Table 4 Continued

4 years					% reclassified into new risk category		
HFSS	**MECKI**			**Total (%)**	**Lower**	**Higher**	**Total**
	<8.0%	**8.0–11.0%**	**>11.0%**				
<8.0%							
n (%)	252 (74.3%)	23 (6.8%)	64 (18.9%)	339 (29.5%)	–	25.67	25.67
Observed risk	4.36	17.39	15.62	7.37			
n events	11	4	10	25			
8.0–11.0%							
n (%)	44 (41.5%)	19 (17.9%)	43 (40.6%)	106 (9.2%)	41.51	40.57	82.08
Observed risk	4.55	No events	4.65	3.77			
n events	2	0	2	4			
>11.0%							
n (%)	72 (10.2%)	58 (8.2%)	574 (81.5%)	704 (61.3%)	18.47	–	18.47
Observed risk	4.17	10.34	34.5	29.4			
n events	3	6	198	207			
Total							
n (%)	368 (32.0%)	100 (8.7%)	681 (59.37%)	1149 (100%)			
Observed risk	4.35	10	30.84	20.54			
n events	16	10	210	236			

MECKI, Metabolic Exercise test data combined with Cardiac and Kidney Indexes; SHFM, Seattle Heart Failure Model; HFSS, Heart Failure Survival Score.

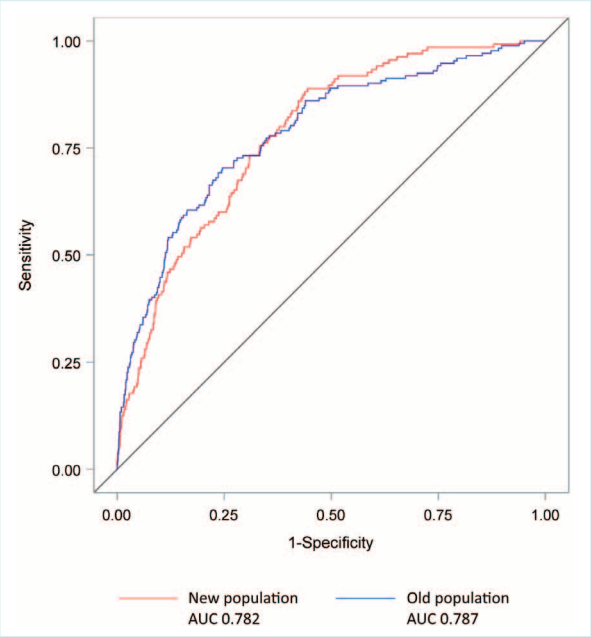

Figure 2 Receiver operating characteristic (ROC) curves for MECKI score in the original population and in newly enrolled patients. Comparison of areas under the curves at 2-year follow-up between the original MECKI score population (blue line) and newly enrolled patients (red line). AUC, area under the ROC curve; MECKI, Metabolic Exercise test data combined with Cardiac and Kidney Indexes.

Limitations

Our study has some important limitations. First, we only enrolled HF patients able to perform a CPET excluding subjects with more severe HF. Indeed, our population is relatively young and, consequently, represents only a section of the HF population seen in the clinical setting. Second, our patients were in stable clinical condition and HF patients with preserved LVEF were not evaluated; consequently, our results cannot be extrapolated to these patient populations. Similarly, we excluded HF patients with co-morbidities that *per se* influence CPET results. All variables used for risk calculation were collected at enrollment, giving a static picture of the patients without accounting for possible changes in clinical status and management with potential prognostic impact, such as device implantation and changes in HF medications. Both HFSS and MECKI include peak VO_2 among the prognostic parameters, which was obtained from a maximal test on a treadmill or cycle ergometer.[12,19] Peak VO_2 is reported in mL/kg/min for the HFSS and as percentage of predicted value for MECKI. In the original MECKI score analysis, the percentage of predicted value was superior to the absolute value for determining prognosis in a HF population that included overweight subjects[31] and patients of different ages and sexes. It is likely that the use of percentage of predicted value in the MECKI score overcame the differences in ergometer choice, but it is unknown whether the use of the percentage of predicted value instead of mL/kg/min in the HFSS could further improve HFSS prognostic capacity.

Finally, it is recognized that, albeit several variables were analysed when building the MECKI score, some, which have recognized prognostic power in chronic HF such as natriuretic peptides, left atrial volume and diuretic doses, were not available

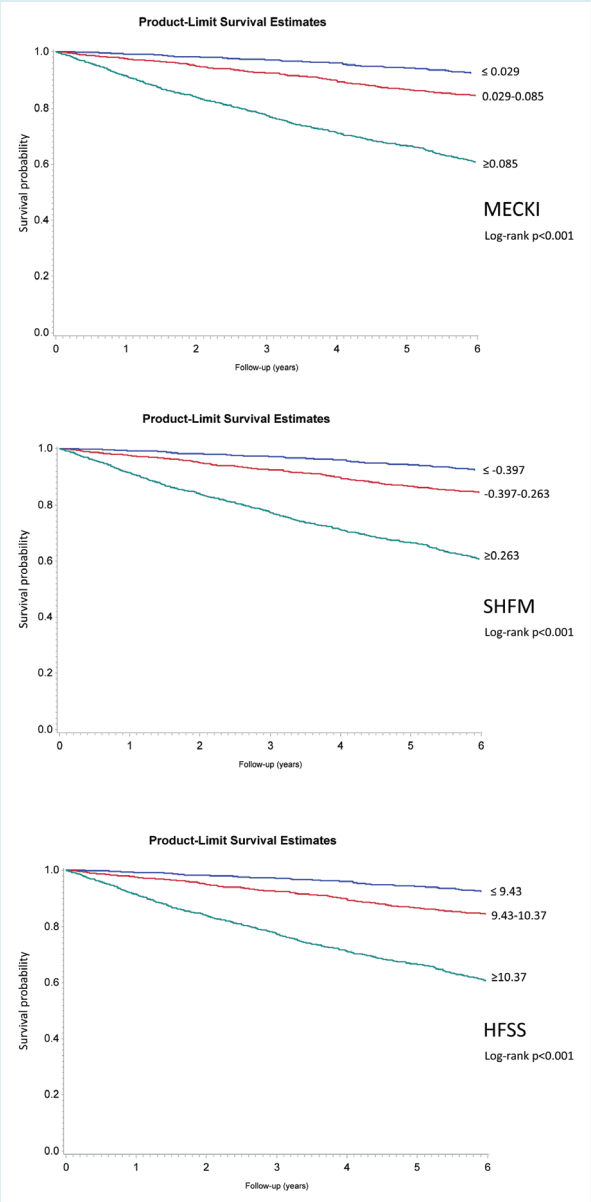

Figure 3 Survival rate by tertiles for each model in the newly enrolled patients. Kaplan–Meier curves according to tertiles for each model: MECKI score (upper panel), SHFM (middle panel), and HFSS (lower panel). MECKI, Metabolic Exercise test data combined with Cardiac and Kidney Indexes; SHFM, Seattle Heart Failure Model; HFSS, Heart Failure Survival Score.

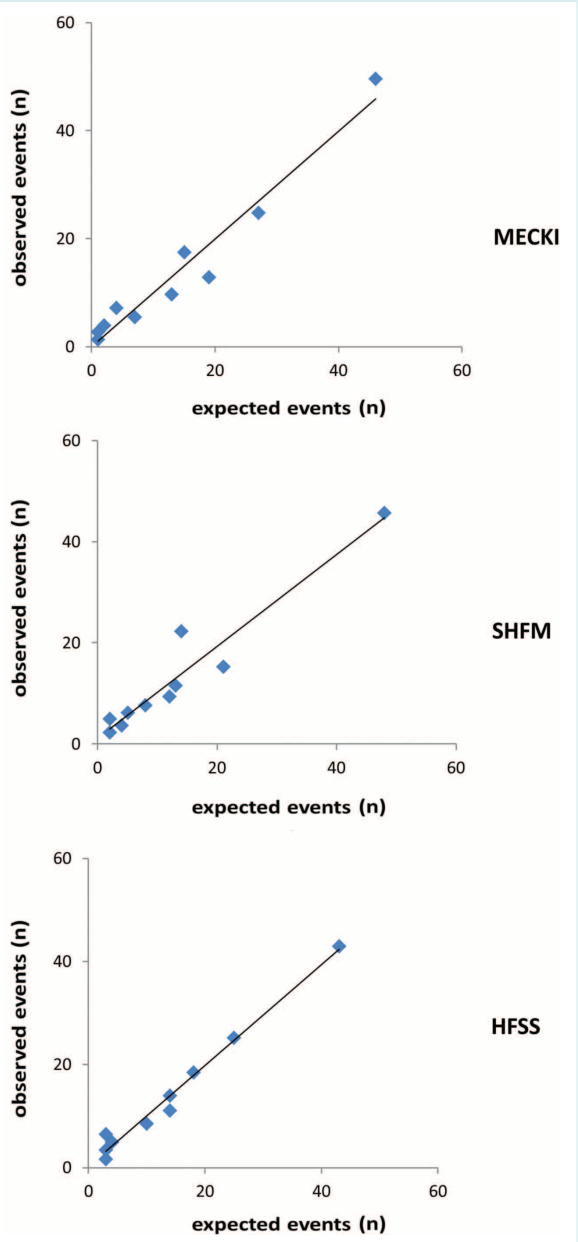

Figure 4 Calibration plot of the three scores in the newly enrolled patients. Calibration plot of each model: MECKI score (upper panel), SHFM (middle panel), and HFSS (lower panel). MECKI, Metabolic Exercise test data combined with Cardiac and Kidney Indexes; SHFM, Seattle Heart Failure Model; HFSS, Heart Failure Survival Score.

when the original MECKI score was built, and as such are not considered.

Conclusion

Using a very large HF database of patients in stable clinical condition and capable of performing a CPET, several multiparametric scores are able to provide reliable prognostic information, but the MECKI score exhibits superior discrimination ability for events at 2- and 4-year follow-up.

Figure S1. Univariate receiver operating characteristic (ROC) analysis for MECKI score and each variable used to generate it.
Figure S2. Predicted and observed calibration plot of MECKI and SHFM scores in the new subpopulation.
Figure S3. Calibration plot of the three scores for the entire population, along with old and new subpopulations.

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References

1. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009;**119**:480–486.
2. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, Ostergren J, Michelson EL, Pieper KS, Granger CB. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J* 2006;**27**:65–75.
3. Abraham WT, Fonarow GC, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB; OPTIMIZE-HF Investigators and Coordinators. Predictors of in-hospital mortality in patients hospitalized for heart failure: Insights from the organized program to initiate lifesaving treatment in hospitalized patients with heart failure (OPTIMIZE-HF). *J Am Coll Cardiol* 2008;**52**:347–356.
4. O'Connor CM, Hasselblad V, Mehta RH, Tasissa G, Califf RM, Fiuzat M, Rogers JG, Leier CV, Stevenson LW. Triage after hospitalization with advanced heart failure: the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) risk model and discharge score. *J Am Coll Cardiol* 2010;**55**:872–878.
5. Levy WC, Linker DT. Prediction of mortality in patients with heart failure and systolic dysfunction. *Curr Cardiol Rep* 2008;**10**:198–205.
6. O'Connor CM, Abraham WT, Albert NM, Clare R, Gattis Stough W, Gheorghiade M, Greenberg BH, Yancy CW, Young JB, Fonarow GC. Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J* 2008;**156**:662–673.
7. Lewis EF, Velazquez EJ, Solomon SD, Hellkamp AS, McMurray JJ, Mathias J, Rouleau JL, Maggioni AP, Swedberg K, Kober L, White H, Dalby AJ, Francis GS, Zannad F, Califf RM, Pfeffer MA. Predictors of the first heart failure hospitalization in patients who are stable survivors of myocardial infarction complicated by pulmonary congestion and/or left ventricular dysfunction: a VALIANT study. *Eur Heart J* 2008;**29**:748–756.
8. O'Connor CM, Whellan DJ, Wojdyla D, Leifer E, Clare RM, Ellis SJ, Fine LJ, Fleg JL, Zannad F, Keteyian SJ, Kitzman DW, Kraus WE, Rendall D, Pina IL, Cooper LS, Fiuzat M, Lee KL. Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction: the HF-ACTION predictive risk score model. *Circ Heart Fail* 2012;**5**:63–71.
9. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Kober L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN; Meta-Analysis Global Group in Chronic Heart Failure. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J* 2013;**34**:1404–1413.
10. Vazquez R, Bayes-Genis A, Cygankiewicz I, Pascual-Figal D, Grigorian-Shamagian L, Pavon R, Gonzalez-Juanatey JR, Cubero JM, Pastor L, Ordonez-Llanos J, Cinca J, de Luna AB; MUSIC Investigators. The MUSIC Risk score: a simple method for predicting mortality in ambulatory patients with chronic heart failure. *Eur Heart J* 2009;**30**:1088–1096.
11. Senni M, Parrella P, De Maria R, Cottini C, Bohm M, Ponikowski P, Filippatos G, Tribouilloy C, Di Lenarda A, Oliva F, Pulignano G, Cicoira M, Nodari S, Porcu M, Cioffi G, Gabrielli D, Parodi O, Ferrazzi P, Gavazzi A. Predicting heart failure outcome from cardiac and comorbid conditions: the 3C-HF score. *Int J Cardiol* 2013;**163**:206–211.
12. Agostoni P, Corrà U, Cattadori G, Veglia F, La Gioia R, Scardovi AB, Emdin M, Metra M, Sinagra G, Limongelli G, Raimondo R, Re F, Guazzi M, Belardinelli R, Parati G, Magri D, Fiorentini C, Mezzani A, Salvioni E, Scrutinio D, Ricci R, Bettari L, Di Lenarda A, Pastormerlo LE, Pacileo G, Vaninetti R, Apostolo A, Iorio A, Paolillo S, Palermo P, Contini M, Confalonieri M, Giannuzzi P, Passantino A, Dei Cas L, Piepoli MF, Passino C; MECKI Score Research Group. Metabolic exercise test data combined with cardiac and kidney indexes, the MECKI score: a multiparametric approach to heart failure prognosis. *Int J Cardiol* 2013;**167**:2710–2718.
13. MECKI score calculator. Available at: https://www.Cardiologicomonzino.It/en/mecki-score (11 August 2017).
14. Corrà U, Agostoni P, Giordano A, Cattadori G, Battaia E, La Gioia R, Scardovi AB, Emdin M, Metra M, Sinagra G, Limongelli G, Raimondo R, Re F, Guazzi M, Belardinelli R, Parati G, Magri D, Fiorentini C, Cicoira M, Salvioni E, Giovannardi M, Veglia F, Mezzani A, Scrutinio D, Di Lenarda A, Ricci R, Apostolo A, Iorio AM, Paolillo S, Palermo P, Contini M, Vassanelli C, Passino C, Giannuzzi P, Piepoli MF, Antonioli L, Segurini C, Bertella E, Farina S, Bovis F, Pietrucci F, Malfatto G, Roselli T, Buono A, Calabro R, De Maria R, Santoro D, Campanale S, Caputo D, Bertipaglia D, Berton E. The Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score and prognosis in heart failure. A validation study. *Int J Cardiol* 2016;**203**:1067–1072.
15. Corrà U, Agostoni P, Piepoli MF; MECKI Score Research Group. Metabolic exercise data combined with cardiac and kidney indexes: MECKI score. Predictive role in cardiopulmonary exercise testing with low respiratory exchange ratio in heart failure. *Int J Cardiol* 2015;**184**:299–301.
16. Corrà U, Agostoni P, Giordano A, Cattadori G, Battaia E, La Gioia R, Scardovi AB, Emdin M, Metra M, Sinagra G, Limongelli G, Raimondo R, Re F, Guazzi M, Belardinelli R, Parati G, Magri D, Fiorentini C, Cicoira M, Salvioni E, Giovannardi M, Veglia F, Mezzani A, Scrutinio D, Di Lenarda A, Ricci R, Apostolo A, Iorio AM, Paolillo S, Palermo P, Contini M, Vassanelli C, Passino C, Giannuzzi P, Piepoli MF; MECKI Score Research Group. Sex profile and risk assessment with cardiopulmonary exercise testing in heart failure: propensity score matching for sex selection bias. *Can J Cardiol* 2016;**32**:754–759.
17. Carubelli V, Metra M, Corrà U, Magri D, Passino C, Lombardi C, Scrutinio D, Correale M, Cattadori G, Piepoli MF, Salvioni E, Giovannardi M, Raimondo R, Cicoira M, Belardinelli R, Guazzi M, Limongelli G, Clemenza F, Parati G, Scardovi AB, Di Lenarda A, Bussotti M, La Gioia R, Agostoni P; MECKI Score Research Group. Exercise performance is a prognostic indicator in elderly patients with chronic heart failure—application of Metabolic Exercise Cardiac Kidney Indexes score. *Circ J* 2015;**79**:2608–2615.
18. Scrutinio D, Agostoni P, Gesualdo L, Corrà U, Mezzani A, Piepoli M, Di Lenarda A, Iorio A, Passino C, Magri D, Masarone D, Battaia E, Girola D, Re F, Cattadori G, Parati G, Sinagra G, Villani GQ, Limongelli G, Pacileo G, Guazzi M, Metra M, Frigerio M, Cicoira M, Mina C, Malfatto G, Caravita S, Bussotti M, Salvioni E, Veglia F, Correale M, Scardovi AB, Emdin M, Giannuzzi P, Gargiulo P, Giovannardi M, Perrone-Filardi P, Raimondo R, Ricci R, Paolillo S, Farina S, Belardinelli R, Passantino A, La Gioia R; MECKI Score Research Group. Renal function and peak exercise oxygen consumption in chronic heart failure with reduced left ventricular ejection fraction. *Circ J* 2015;**79**:583–591.
19. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation* 1997;**95**:2660–2667.
20. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL, Packer M. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation* 2006;**113**:1424–1433.
21. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. Philadelphia: Lippincott Williams & Wilkins; 2005. p138–139.
22. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis* 1984;**129**:S49–55.
23. US Department of Health & Human Services. Organ Procurement and Transplantation Network – Policies. Available at: https://optn.Transplant.Hrsa.Gov/media/1200/optn_policies.Pdf#nameddest=policy_06 (11 August 2017).
24. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;**27**:157–172.
25. Cook NR, Ridker PM. Advances in measuring the effect of individual predictors of cardiovascular risk: the role of reclassification measures. *Ann Intern Med* 2009;**150**:795–802.
26. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Veli-Pekka Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM,

Ruschitzka F, Rutten FH, van der Meer P. 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 J Heart Fail* 2016;**18**:891–975.

27. Goda A, Williams P, Mancini D, Lund LH. Selecting patients for heart transplantation: comparison of the Heart Failure Survival Score (HFSS) and the Seattle Heart Failure Model (SHFM). *J Heart Lung Transplant* 2011;**30**: 1236–1243.
28. Dardas T, Li Y, Reed SD, O'Connor CM, Whellan DJ, Ellis SJ, Schulman KA, Kraus WE, Forman DE, Levy WC. Incremental and independent value of cardiopulmonary exercise test measures and the Seattle Heart Failure Model for prediction of risk in patients with heart failure. *J Heart Lung Transplant* 2015;**34**: 1017–1023.
29. Levy WC, Aaronson KD, Dardas TF, Williams P, Haythe J, Mancini D. Prognostic impact of the addition of peak oxygen consumption to the Seattle Heart Failure Model in a transplant referral population. *J Heart Lung Transplant* 2012;**31**: 817–824.
30. Freitas P, Aguiar C, Ferreira A, Tralhao A, Ventosa A, Mendes M. Comparative analysis of four scores to stratify patients with heart failure and reduced ejection fraction. *Am J Cardiol* 2017;**120**:443–449.
31. Piepoli MF, Corrà U, Veglia F, Bonomi A, Salvioni E, Cattadori G, Metra M, Lombardi C, Sinagra G, Limongelli G, Raimondo R, Re F, Magri D, Belardinelli R, Parati G, Mina C, Scardovi AB, Guazzi M, Cicoira M, Scrutinio D, Di Lenarda A, Bussotti M, Frigerio M, Correale M, Villani GQ, Paolillo S, Passino C, Agostoni P; MECKI Score Research Group. Exercise tolerance can explain the obesity paradox in patients with systolic heart failure: data from the MECKI Score Research Group. *Eur J Heart Fail* 2016;**18**:545–553.