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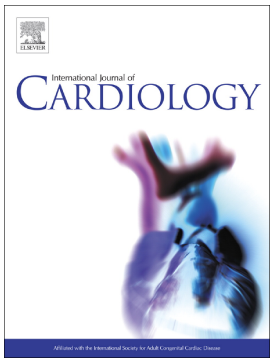

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THE IMPORTANCE OF RE-EVALUATING THE RISK SCORE IN HEART FAILURE PATIENTS: AN ANALYSIS FROM THE METABOLIC EXERCISE CARDIAC KIDNEY INDEXES (MECKI) SCORE DATABASE.

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Abstract

Background. The role of risk scores in heart failure (HF) management has been highlighted by international guidelines. In contrast with HF, which is intrinsically a dynamic and unstable syndrome, all its prognostic studies have been based on a single evaluation. We investigated whether time-related changes of a well-recognized risk score, the MECKI score, added prognostic value. MECKI score is based on peak VO_2, VE/VCO_2 slope, Na^+, LVEF, MDRD and Hb.

Methods. A multi-centre retrospective study was conducted involving 660 patients who performed MECKI re-evaluation at least 6 months apart. Based on the difference between II and I evaluation of MECKI values (MECKI II – MECKI I = Δ MECKI) the study population was divided in 2 groups: those presenting a score reduction (Δ MECKI <0, i.e. clinical improvement), vs. patients presenting an increase (Δ MECKI >0, clinical deterioration).

Results. The prognostic value of MECKI score is confirmed also when re-assessed during follow-up. The group with improved MECKI (366 patients) showed a better prognosis compared to patients with worsened MECKI (294 patients) ($p<0.0001$). At 1st evaluation, the two groups differentiated by LVEF, V_E/VCO_2 slope and blood Na^+ concentration, while at 2nd evaluation they differentiated in all 6 parameters considered in the score. The patients who improved MECKI score, improved in all components of the score but hemoglobin, while patients who worsened the score, worsened all parameters.

Conclusions. This study shows that re-assessment of MECKI score identifies HF subjects at higher risk and that score improvement or deterioration regards several MECKI score generating parameters confirming the holistic background of HF.

Key words: heart failure, prognosis, risk stratification, exercise capacity, hemoglobin, renal function

Introduction

Heart failure (HF) is currently one of the most relevant challenges in public health, occurring in 1-2% of developed countries adult population.[1] Despite significant treatment and management advances,[1] HF patients still have high mortality[2] and rehospitalization rates,[3] thus a precise and individually tailored prognosis estimation is of main relevance to establish the appropriate treatment and patients' follow-up strategies. However, risk stratification in HF still remains a challenge mainly due to HF complex pathophysiology, presence of comorbidities, limited access to expensive and novel pharmacological and device therapies, and to sophisticated examinations such as cardiac magnetic resonance and genetic assessment.

Cardiopulmonary exercise test (CPET) is a well-recognized, easy to perform, cheap and accurate tool for risk stratification in HF. Among several CPET variables, peak VO_2,[4,5] V_E/VCO_2 slope,[10,6,7,8] and their combination[9,10] have been identified as strong and independent HF prognosis predictors.

Albeit several prognostic markers of death and/or HF hospitalization have been identified, it is currently recognized that the best strategy to predict HF prognosis or re-hospitalization is by multiparametric evaluation.[1] For this purpose, several multivariable prognostic risk scores have been developed.[11,12,13,14,15,16]

Among the numerous HF prognostic score, the Metabolic Exercise Cardiac Kidney Indexes (MECKI) score[17] is the only one integrating CPET prognostic parameters of both cardiovascular and ventilatory response to effort with established clinical, laboratory and echocardiographic risk factors. MECKI score has been built and validated in a robust database derived from leading HF clinics in Italy. At present, MECKI score is indicated by ESC guidelines among useful HF prognostic scores[1] and, actually, a few reports showed its superiority compared to other scores such as Seattle HF model, HFSS, MAGICC,[18,19] at least in an HF population in whom CPET can be performed.

The MECKI score is built considering the combination of the following parameters: peak oxygen uptake (VO_2) % of predicted value, V_E/VCO_2 slope, left ventricular ejection fraction (LVEF by cardiac ultrasounds Simpson method), hemoglobin (Hb), blood sodium value (Na^+), and glomerular filtration rate as estimated by MDRD formula.[17]

The major limitation of all the observational prognostic studies in HF, including MECKI, is that they have been exclusively based on parameters evaluated once, i.e. at the beginning of the follow-up, both for incident and prevalent patients. The information of the role of a second evaluation during follow-up assessment is generally lacking with the exception of HFSS.[20] HF is a dynamic

condition where the clinical outcome can change dramatically over the course of the syndrome, related to cardiac and not cardiac factors. So repeated evaluations are of main relevance, allowing to update the risk profile and to monitor HF evolution, thereby improving the therapeutic strategy.

The purpose of this study was to investigate whether a second MECKI score evaluation and the analysis of MECKI score changes present an added prognostic value for HF morbidity and mortality prediction.

Study Design and Methods

The MECKI group registry

The MECKI group registry includes at present 7,700 consecutive systolic HF patients, recruited and prospectively followed in 24 Italian HF centers since 1993, with mean follow-up > 3 years.[21]

Currently a similar registry with > 1,000 patients is ongoing in other European countries and China.[22]

MECKI score database inclusion/exclusion criteria have been previously reported in detail.[17] In brief, inclusion criteria are: previous or present HF symptoms (NYHA classes I-III, stage C of ACC/AHA classification) and documentation of left ventricular systolic dysfunction (LVEF <40%), clinical stability with unchanged therapy for at least 3 months, ability to perform CPET, no major cardiovascular treatment or intervention scheduled. Exclusion criteria: history of pulmonary embolism, moderate-to-severe aortic and mitral stenosis, pericardial disease, severe BPCO, exercise-induced angina and significant ECG alterations, presence of any clinical co-morbidity interfering with exercise performance.

Study protocol

We asked all MECKI score centers if they were able to retrospectively retrieve data of patients who performed a second MECKI score evaluation and three centers replied positively. Only patients who performed 2 MECKI score evaluations (MECKI I and II) at least 6-month apart were included. After the MECKI II estimation, the follow-up lasted up to 2 years to detect any morbidity and mortality event reported in the registry during this time period. All patients were regularly re-evaluated at the recruiting center. At the time of MECKI II, all patients included in the study were still able to perform CPET.

The study endpoint was the combination of death of any cause, hospitalization for HF, hospitalization for cardiovascular causes other than HF, left ventricular assist device (LVAD)

implantation and urgent heart transplantation. The first event occurred during follow-up was taken into consideration.

The investigation was approved by local Ethical Committee (notification n CCM 04-21 - RE 3635). All participants signed an informed consent. The study was conducted in compliance with the declaration of Helsinki.

Cardiopulmonary exercise test

All CPETs were performed using a cycle-ergometer, and a personalized ramp protocol was applied. The exercise was preceded by at least three minutes of rest gas exchange monitoring and by a short unloaded warm-up period. During the exercise test, 12-lead ECG, blood pressure, and heart rate were recorded, and oxygen saturation was monitored through a pulse oximeter. The participants either wore a nose clip and breathed through a mouthpiece, or used a facemask connected to a mass flow-meter as they preferred. CPET was carried out and interpreted using a standard technique.[23] The exercise protocol was set to achieve peak exercise in ~10 min.[24] In the absence of clinical events, CPET was interrupted when patients stated that they had reached maximal effort. Breath-by-breath analysis of expiratory gases and ventilation was performed. Anaerobic threshold was measured by V-slope analysis of VO_2 and VCO_2, and it was confirmed by ventilatory equivalents and end-tidal pressures of CO_2 and O_2. VO_2/work slope was measured throughout the entire exercise. V_E/VCO_2 slope was calculated as the slope of the linear relationship between V_E and VCO_2 from 1 min after the beginning of the loaded exercise and the end of the isocapnic buffering period. Peak exercise O_2 pulse was calculated as peak VO_2/peak heart rate.

The MECKI score was calculated with the following algorithm: exp (k) / (1 + exp (k)) where k = 10.3464 - 0.0262 x Peak VO_2 (% pred) +0.0472 x V_E/VCO_2 slope - 0.1086 x Hb (g/dL) - 0.0615 x Na^+ (mmol / L) - 0.0699 x LVEF (%) - 0.0136 x MDRD (mL/min).[17]

Statistical analysis

Continuous variables were expressed as mean ± SD, categorical variables as counts and proportions. The study population was divided in two groups based on the difference between II and I evaluation of MECKI score values (MECKI II – MECKI I = Δ MECKI). The paired t test was used to compare the means of the variables at baseline and at the second assessment of the MECKI score; the unpaired t test was used to compare the population groups divided by Δ MECKI score < or > 0 at baseline and at the second evaluation. The chi-square test was used for the analysis of categorical variables. Kaplan-Meier curves were used to assess event-free survival during follow-up. A p value <0.05 was considered statistically significant.

All statistical analyzes were performed using SAS statistical package v. 9.4 (SAS Institute Inc, Cary, NC).

Results

Study population

Six hundred and sixty patients were enrolled: the main clinical, laboratory, echocardiographic, ergospirometric and treatment characteristics at the time of MECKI I and MECKI II are shown in Table 1. Average time between MECKI I and MECKI II determination was 2.02 ± 1.18 years, while median value was 2.03 years (1.34-3). Most of patients were male (81%) and had an ischemic etiology of HF (47%); the mean age at MECKI I was 60.7 ± 12.2 years. Enrolled patients largely received the most up-to-date evidence-based medical therapy for HF at the time of both first and second evaluation.

Follow-up

The average follow-up after MECKI II was 1.5 ± 0.7 years, when 262 events were observed: 220 patients (84% of events, 33% of total study population) were hospitalized for HF and 22 (8% of events) for cardiovascular causes other than HF; 6 patients (2% of events) died from cardiovascular causes, 13 (5% of events) died from non-cardiovascular or unknown causes, 1 patient underwent LVAD implantation (0.4% of events). No patient underwent heart transplantation.

As above described, study population was divided in two groups based on the difference between MECKI II and MECKI I score values: 366 subjects presented a reduction of MECKI score (Δ MECKI < 0, follow-up after MECKI II = 1.6 ± 0.6 years), suggesting prognosis improvement, while 294 patients presented an increase, implying a worse prognosis (Δ MECKI < follow-up 1.3 ± 0.7 years).

The main clinical, laboratory, echocardiographic, ergospirometric and therapy-related characteristics of the two groups at the time of the baseline (MECKI I) and of the second evaluation (MECKI II) are shown in Table 2. In the group with Δ MECKI < 0, the MECKI score reduced from 7.73 ± 9.54 to 3.93 ± 5.75 ($p > 0.0001$), or 4.34 (2-9.15 IQR) to 2.01 (0.92-4.11), while in the group with Δ MECKI > 0 MECKI score increased from 5.64 ± 6.61 to 12.04 ± 12.77 ($p > 0.0001$) or from 3.48 (1.78-6.89) to 7.77 (3.19-15.44).

Table 3 highlights the differences between patients who improved vs. those who worsened MECKI score in the first and the second evaluation for the MECKI score and for each of the parameters

included in the score taken individually. At the first evaluation a small but statistically significant difference was observed for MECKI score, which was slightly lower in those who subsequently increased the score. Statistically significant differences were observed only for LVEF, V_E/VCO_2 slope and Na^+, while at second evaluation significant differences were found for all the 6 parameters.

Without considering MECKI score parameters, there was no significant difference between improved and worsened patient at baseline evaluation concerning demographic, clinical and treatment characteristic, excluded MRA and ICD, more used in improved patients (See Table 5 in Supplemental Materials).

Analyzing the changes at follow-up compared to baseline of each single parameter of the MECKI score, we observed that the patients who improved the MECKI score also showed a significant improvement in all components of the score except for Hb, while patients who worsened the score, showed a significant worsening of all parameters (Table 4).

Percent changes of the 6 MECKI score generating parameters are reported in Figure 1. In improved patients, the improvement of the parameters mainly regarded LVEF and peak VO_2 %, while patients who worsened the score presented changes > 10% for peak VO_2 % and V_E/VCO_2 slope.

Prognostic evaluation

Figure 2 shows the Kaplan-Meier curves of event-free survival for both study patients' groups in a 2-year follow-up: the subjects who have improved MECKI score during follow-up presented a better prognosis after MECKI II evaluation compared to patients with worsened MECKI ($p < 0.0001$).

Figure 3 shows the event-free survival of study population divided into two group according the Δ (worsened or improved) for each of the parameters included in the MECKI score: at post MECKI II follow-up, patients who had improved LVEF, % VO_2 peak and V_E/VCO_2 slope showed a better prognosis than patients who had presented a worsening of the three parameters compared to MECKI I, while there was no statistically significant difference in event-free survival between patients who had improved or worsened MDRD, Hb and Na^+.

In addition, we performed a 1:1 matching of our study population with a similar group from the MECKI registry. Patients from our study were matched by MECKI re-evaluation with patients from the registry by first MECKI evaluation. It follows from the results that there were no significant differences on the survival of the two populations considered (p=0.992). The latter information

confirms that on the average patients who underwent the second MECKI score evaluation represent a typical sample of MECKI score patients.

Discussion

The results of our study first confirm the usefulness of the MECKI score for the prognostic evaluation of patients with HFrEF, showing that also the second MECKI score determination has, *per se*, a strong prognostic power. But most importantly we showed that the time-dependent MECKI score changes bear a very important prognostic information. Specifically, when MECKI score indicates a prognostic improvement, i.e. its value falls, all parameters improved but Hb, while when MECKI score indicates a prognosis worsening, i.e. MECKI increases, all parameters increased. Of note, the MECKI score changes were driven by peak VO_2 % for both worsening and improvement, by LVEF for improvement and by V_E/VCO_2 slope for worsening. Finally, only changes of peak VO_2 %, V_E/VCO_2 slope and LVEF had an independent prognostic power.

The MECKI score is the only HF prognostic model which integrates both peak VO_2 % and V_E/VCO_2 slope with established clinical, laboratory and echocardiographic risk factors. The CPET derived MECKI score parameters are among those which most importantly drive time related prognostic changes, suggesting a key role of functional capacity, assessed by CPET, in HF prognosis.[25]

A few other insights of our data should be underlined. Firstly, we can observe that the patients who had worsened MECKI score compared to the patients who had improved it, have only slight differences in the parameters included in the score taken individually and it is not possible to pre-identify patients who will worsen HF. Of note, all patients have moderate HF at MECKI I analysis. MECKI I score correctly characterized patients' prognosis for a given amount of time. Of note, patients with worsened MECKI even presented a slightly better score at baseline compared to patients who had subsequently improved the score. This means that patients starting from similar basal conditions can have a different disease trajectory which only the repetition of MECKI score can identify.

Secondly, we observed that the patients who improved the score, also improved in all single parameters, except Hb, while the worsened patients showed a significant worsening of all six score parameters. However, for the former group, the improvement was mainly driven by LVEF and peak VO_2 %, while for the latter the worsening was mainly attributable to peak VO_2 and V_E/VCO_2 slope (Figure 1). This finding above all confirms that HF as a multiorgan disease which must be assessed

as such, notwithstanding variables, related to functional/exercise capacity, play a predominant role in determining diseases evolution and prognosis.

Finally, by analyzing event-free survival in the study population divided into two groups according to improvement or worsening of each individual MECKI parameter, it can be observed that only peak VO_2 %, V_E/VCO_2 slope and LVEF show a value in prognostic stratification, while MDRD and Hb do not reach significance, and Na^+ curves are almost superimposed for the entire duration of the follow-up. This confirms the importance of the multiparametric holistic approach of evaluation of HF, but also it confirms the prognostic power of CPET. It is interesting to note that the variables affecting the prognosis even if taken individually, are the same ones that drive the worsening or improvement of the score, and notably peak VO_2 significantly impacts both the improvement and the worsening of MECKI score. Accordingly, as regards peak VO_2 changes with time, our data are in line with those of Lund et al[20] who confirmed, albeit in a smaller population, the need to repeat the prognostic assessment in HF patients.

Study limitations

This study has some relevant limitations that need to be acknowledged.

First, it is a retrospective study, so definitive conclusions cannot be derived. Specifically, we do not know how often MECKI score should be repeated and if re-evalaution time varies with HF severity as it seems to be reasonable but not tested in the present study.

Secondly, the number of patients is rather small when considering the prevalence of HF in the general population. Moreover, the population we studied is characterized by relatively low risk HFrEF patients mainly in NYHA class II able to perform CPET, so the generalization of the reported findings to more severe population or with different phenotypes such as preserved ejection fraction HF patients should not be done. Moreover, due to the present sample size, we did not attempt to group our population in more ΔMECKI classes albeit this would have been desirable. The present, therefore, must be considered as a first approach to the dynamic evaluation of HF prognosis through the MECKI score.

Conclusions

The results of our study confirm the value of the MECKI score in the prognostic assessment of patients with HFrEF and highlights the rationale and the usefulness of a re-evaluation of the score during the follow-up, which allow to identify those subjects at increased risk of morbidity and mortality. This could help physicians to improve tailored patients' follow-up strategies, risk stratification, and resources allocation.

Figure 1. Percent changes of the 6 MECKI score generating parameters: left ventricular ejection fraction (LVEF), peak oxygen uptake (Peak VO_2) as a percent of predicted value, V_E/VCO_2 slope, glomerular filtration rate by MDRD formula (MDRD), hemoglobin (Hb), sodium concentration (Na^+). In red patients who reduced MECKI score, ΔMECKI < 0, i.e. clinical improvement, in blue those who increased MECKI score, Δ MECKI > 0, i.e. clinical worsening.

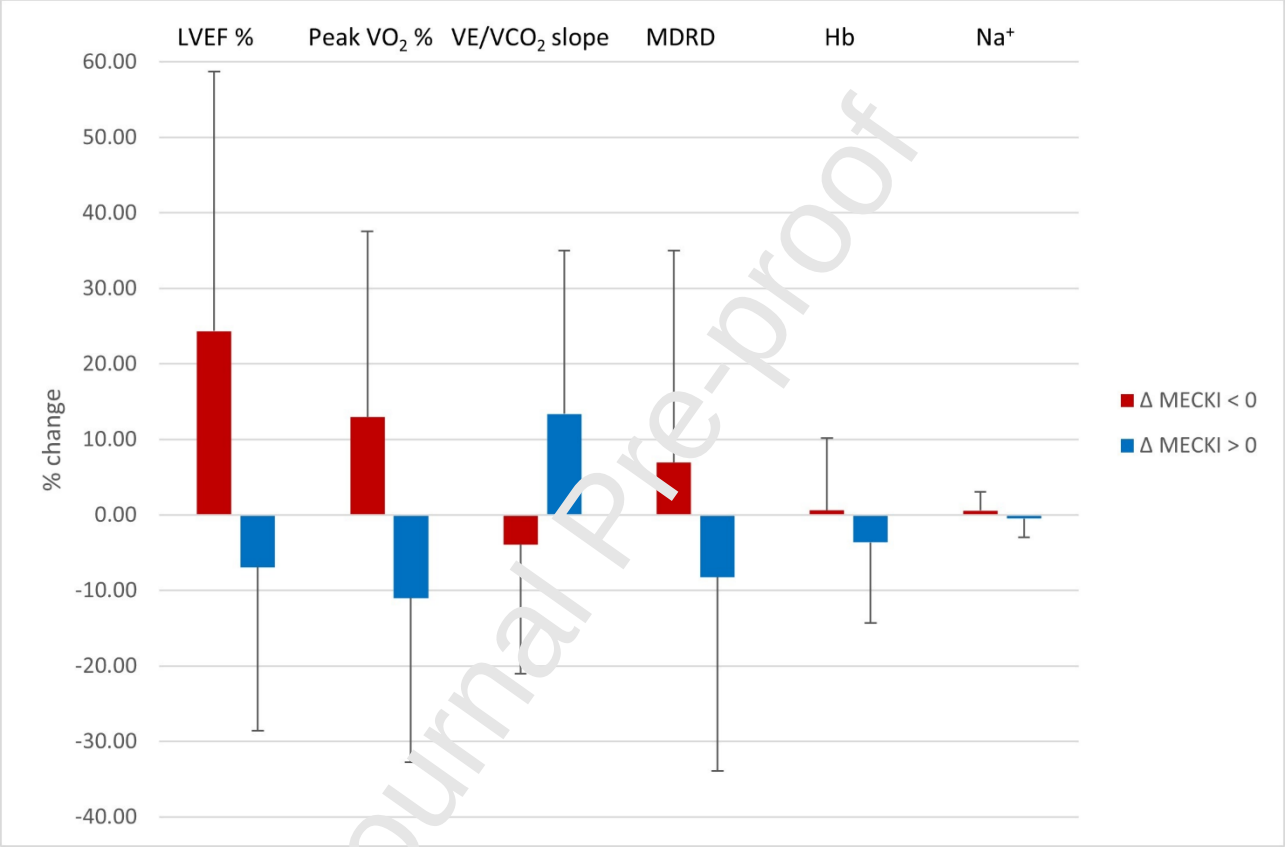


Figure 2. Kaplan-Meier curves of event-free survival in 2-year follow-up for patients with improved (Δ MECKI < 0) and worsened (Δ MECKI > 0) MECKI score value at II evaluation compared to baseline.

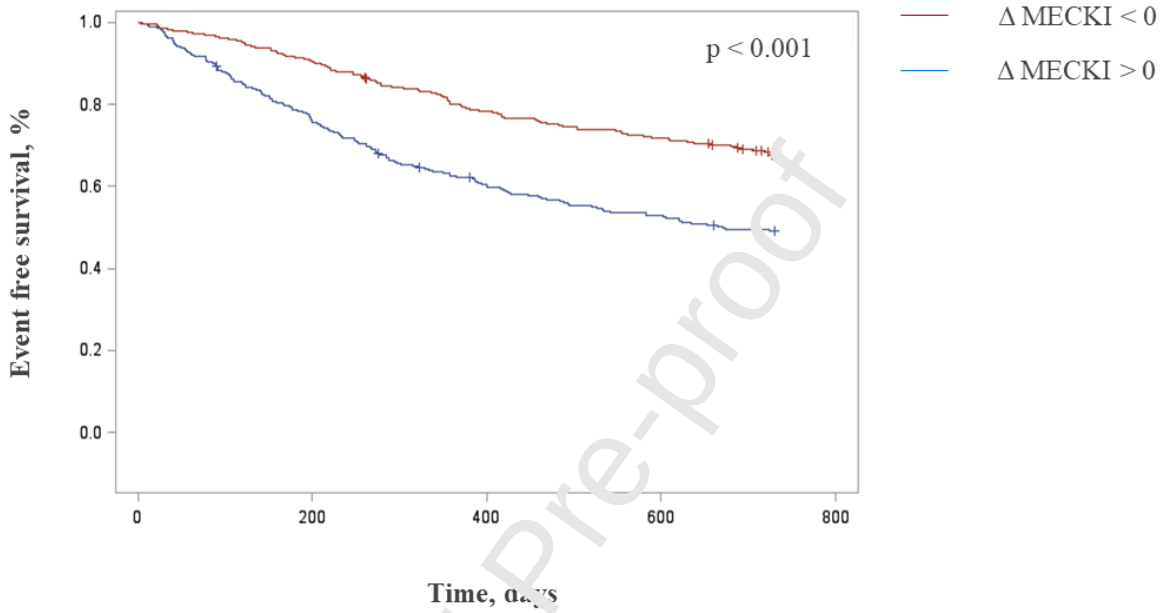
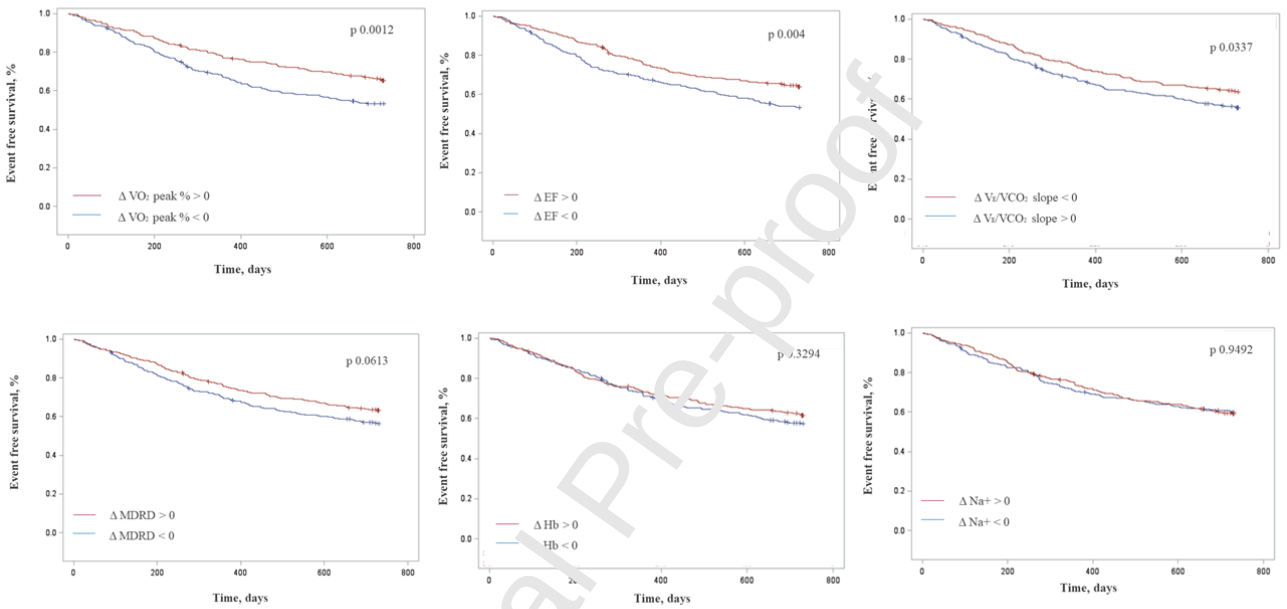


Figure 3. Kaplan-Meier curves of event-free survival in 2-year follow-up for patients with improving and worsening of each MECKI score parameter taken individually at II evaluation compared to baseline. Hb: hemoglobin; MDRD: Modification of Diet in Renal Disease; MECKI: Metabolic Exercise Cardiac Kideney Indexes; Na^+: serum sodium; Peak VO_2 %: percentage of predicted peak oxygen uptake; V_E/VCO_2 slope: ventilation to carbon dioxide production slope; Δ MECKI: MECKI II - MECKI I.



	I MECKI evaluation (baseline)	II MECKI evaluation (follow-up)	P value

Age, years	60.7 ± 12.2	63.3 ± 12.1	<0.0001
Gender, M/F (%)	534 (81) / 126 (19)		
BMI, Kg/m^2	26.8 ± 4.5	27.1 ± 4.5	NS
NYHA, class	2.1 ± 0.7	2.1 ± 0.7	NS
Ischemic etiology, n (%)	310 (47)		
MECKI score, %	6.8 ± 8.4	7.5 ± 10.4	0.05
Δ MECKI score, %		0.7 ± 9	
LVEF, %	33.5 ± 8.9	35.8 ± 10.4	<0.0001
Peak VO_2, % predicted	61.5 ± 15.7	61.5 ± 15.7	NS
V_E/VCO_2, slope	31.7 ± 7	32.3 ± 7.6	0.05
MDRD, $ml/min/1.73m^2$	71.2 ± 22.8	70.2 ± 27.1	NS
Na^+, mmol/L	139.4 ± 3	139.5 ± 2.8	NS
Hb, g/dL	13.9 ± 1.5	13.6 ± 1.6	<0.0001
AF, n (%)	126 (19)	110 (17)	NS
LBBB, n (%)	179 (27)	166 (25)	NS
PM, n (%)	139 (21)	118 (18)	NS
ICD, n (%)	224 (34)	304 (46)	<0.0001
CRT, n (%)	98 (15)	157 (24)	<0.0001
Beta-blockers, n (%)	554 (84)	603 (91)	<0.0001
ACE-I, n (%)	419 (63)	347 (53)	<0.0001
ARB, n (%)	161 (24)	123 (19)	0.01
MRA, n (%)	367 (56)	389 (59)	NS
ARNI, n (%)	0	141 (21)	<0.0001
Diuretics, n (%)	486 (74)	490 (74)	NS
Anti-platelet, n (%)	338 (51)	341 (52)	NS
VKA, n (%)	205 (31)	222 (34)	NS
NOAC, n (%)	2 (0.3)	12 (2)	0.01
Amiodarone, n (%)	233 (35)	259 (39)	NS
Digoxin, n (%)	59 (9)	41 (6)	NS
SGLT2i, n (%)	0	22 (3)	<0.0001

Table 1. Clinical, laboratory, echocardiographic, ergospirometric and treatment characteristics of the global study population at I and II evaluation of MECKI score.

Data are expressed as mean ± standard deviation, unless otherwise specified.

ACE-I: inhibitors of angiotensin-converting enzyme; AF: atrial fibrillation; ARB: angiotensin II receptor blockers; ARNI: angiotensin receptor neprilysin inhibitor; BMI: body mass index; CRT: cardiac resynchronization therapy; F: female; Hb: hemoglobin; ICD: intracardiac defibrillator; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; M: male; MDRD: Modification of Diet in Renal Disease; MECKI: Metabolic Exercise Cardiac Kidney Indexes; MRA: mineralocorticoid receptor antagonists; n: number; Na^+: serum sodium; NYHA: New York Heart Association; NOAC: non-vitamin K antagonist oral anticoagulant; PM: pacemaker; SD: standard deviation; SGLT2i: sodium-glucose co-transporter 2 inhibitors; Peak VO_2 %: percentage of predicted peak oxygen uptake; V_E/VCO_2 slope: ventilation to carbon dioxide production slope; VKA: vitamin K antagonists; Δ: MECKI II - MECKI I.

Table 2. Clinical, laboratory, echocardiographic, ergospirometric and treatment characteristics of

the two groups of study patients (Δ MECKI < 0 and Δ MECKI > 0) at I and II evaluation of the score.

Data are expressed as mean ± standard deviation, unless otherwise specified.

	Δ MECKI < 0			**Δ MECKI > 0**		
	MECKI I	**MECKI II**	**P value**	**MECKI I**	**MECKI II**	**P value**
Age, years	60.5 ± 12.2	62.9 ± 11.8	<0.0001	61 ± 12.1	63.7 ± 12.4	<0.0001
Gender, M/F (%)	299/68 (81/19)			234/ 59 (80/20)		
BMI, Kg/m^2	26.7 ± 4.2	27 ± 4.3	NS	26.9 ± 4.9	27.1 ± 4.7	NS
NYHA, class	2.1 ± 0.7	2 ± 0.7	0.01	2.1 ± 0.7	2.2 ± 0.7	<0.0001
Ischemic etiology, n (%)	165 (50)			145 (55)		
MECKI score, %	7.7 ± 9.5	3.9 ± 5.7	<0.0001	5.6 ± 6.6	12 ± 12.8	<0.0001
Δ **MECKI score**, %		-3.8 ± 5.9			-3.8 ± 5.9	
LVEF, %	32.6 ± 9	39 ± 9.8	<0.0001	34.[illegible] ± 8.8	31.7 ± 9.6	<0.0001
Peak VO$_2$, % predicted	60.9 ± 16	67.6 ± 18.9	<0.0001	62.2 ± [illegible].4	54.2 ± 15.7	<0.0001
V$_E$/VCO$_2$, slope	32.3 ± 7.6	30.3 ± 5.9	<0.0001	[illegible].0 ± 6.2	34.9 ± 8.7	<0.0001
MDRD, ml/min/1.73m^2	71.4 ± 22.9	75.5 ± 28.6	0.0002	7[illegible] ± 22.3	63.6 ± 23.6	<0.0001
Na$^+$, mmol/L	139.1 ± 3.1	139.8 ± 2.5	<0.0001	13[illegible].8 ± 2.9	139.1 ± 3	0.0005
Hb, g/dL	13.9 ± 1.5	13.9 ± 1.4	NS	13.9 ± 1.5	13.4 ± 1.7	<0.0001
AF, n (%)	79 (22)	60 (16)	NS	47 (16)	50 (17)	NS
LBBB, n (%)	104 (30)	92 (25)	NS	75 (27)	74 (25)	NS
PM, n (%)	66 (21)	52 (14)	0.01	73 (26)	66 (23)	NS
ICD, n (%)	113 (31)	142 (39)	0.05	111 (38)	162 (55)	<0.0001
CRT, n (%)	58 (16)	82 (22)	0.05	40 (14)	75 (26)	0.0003
Beta-blockers, n (%)	306 (83)	330 (90)	0.01	248 (85)	273 (93)	0.001
ACE-I, n (%)	235 (69)	185 (50)	0.0005	184 (69)	162 (55)	NS
ARB, n (%)	85 (23)	60 (16)	0.05	76 (26)	63 (2)	NS
MRA, n (%)	220 (60)	219 (60)	NS	147 (50)	170 (58)	NS
ARNI, n (%)	0	98 (27)	<0.0001	0	43 (15)	<0.0001
Diuretics, n (%)	261 (71)	261 (71)	NS	225 (77)	229 (78)	NS
Anti-platelet, n (%)	178 (49)	186 (51)	NS	160 (55)	155 (53)	NS
VKA, n (%)	119 (32)	121 (33)	NS	86 (29)	101 (34)	NS
NOAC, n (%)	0	6 (2)	0.01	2 (100)	6 (2)	NS
Amiodarone, n (%)	122 (33)	123 (34)	NS	122 (33)	136 (46)	0.036
Digoxin, n (%)	35 (10)	28 (8)	NS	35 (10)	13 (4)	NS
SGLT2i, n (%)	0	11 (3)	0.001	0	11 (4)	0.0008

ACE-I: inhibitors of angiotensin- converting enzyme; AF: atrial fibrillation; ARB: angiotensin II receptor blockers; ARNI: angiotensin receptor neprilysin inhibitor; BMI: body mass index; CRT: cardiac resynchronization therapy; F: female; Hb: hemoglobin; ICD: intracardiac defibrillator; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; M: male; MDRD: Modification of Diet in Renal Disease; MECKI: Metabolic Exercise Cardiac Kidney Indexes; MRA: mineralocorticoid receptor antagonists; n: number; Na^+: serum sodium; NYHA: New York Heart Association; NOAC: non-vitamin K antagonist oral anticoagulant; PM: pacemaker; SD: standard deviation; SGLT2i: sodium-glucose co-transporter 2 inhibitors; Peak VO_2 %: percentage of predicted peak oxygen uptake; V_E/VCO_2 slope: ventilation to carbon dioxide production slope; VKA: vitamin K antagonists; Δ MECKI: MECKI II - MECKI I.

Table 3. Comparison between improved and worsened patients at I e II MECKI evaluation for global score and for included parameters taken individually.

	MECKI I			**MECKI II**		
	Improved	**Worsened**	**P value**	**Improved**	**Worsened**	**P value**
	Δ MECKI < 0	Δ MECKI > 0		Δ MECKI < 0	Δ MECKI > 0	
Patients, n				366	294	
MECKI score, %	7.73±9.54	5.64±6.61		3.93±5.75	12.04±12.77	
MECKI score, % (median value)	4.34 (2-9.15)	3.48 (1.78-6.89)	0.0073	2.01 (0.92-4.11)	7.77 (3.19-15.44)	<.0001
LVEF, %	32.6±9	34.6±8.8	0.0049	39±9.8	31.7±9.6	<.0001
Peak VO_2, % predicted	60.9±16	62.2±15.4	NS	67.6±18.9	54.2±15.7	<.0001
V_E/VCO_2, slope	32.3±7.6	31±6.2	0.0186	30.3±5.9	34.8±8.7	<.0001
MDRD, ml/min/1.73m^2	71.4±22.9	70.8±22.3	NS	75.5±28.6	63.6±23.6	<.0001
Na^+, mmol/L	139.1±3.1	139.8±2.9	0.0025	139.8±2.5	139.1±3	0.0007
Hb, g/dL	13.9±1.5	13.9±1.5	NS	13.9±1.4	13.4±1.7	<.0001

Data are expressed as mean ± standard deviation, unless otherwise specified.

Hb: hemoglobin; LVEF: left ventricular ejection fraction; n: number; MDRD: Modification of Diet in Renal Disease; MECKI: Metabolic Exercise Cardiac Kidney Indexes; Na^+: serum sodium; NS: non significant; Peak VO_2 %: percentage of predicted peak oxygen uptake; V_E/VCO_2 slope: ventilation to carbon dioxide production slope; Δ MECKI: MECKI II - MECKI I.

Table 4. Changes of 6 MECKI parameters at II from I evaluation for improved and worsened patients.

	Improved patients (Δ MECKI < 0)				Worsened patients (Δ MECKI > 0)			
	MECKI I	**MECKI II**	**Δ**	**P**	**MECKI I**	**II MECKI**	**Δ**	**P**
LVEF, %	32.6 ± 9	39 ± 9.8	6.43±8.28	<.0001	34.6 ± 8.8	31.7 ± 9.6	-2.86±6.75	<.0001
Peak VO_2, % predicted	60.9 ± 16	67.6 ± 18.9	6.75±13.21	<.0001	62.2 ± 15.4	54.2 ± 15.7	-7.98±13.51	<.0001
V_E/VCO_2, slope	32.3 ± 7.6	30.3 ± 5.9	-1.98±6.12	<.0001	31 ± 6.2	34.9 ± 8.7	3.86±6.49	<.0001
MDRD, ml/min/1.73m^2	71.4 ± 22.9	75.5 ± 28.6	4.1±20.8	0002	71 ± 22.3	63.6 ± 23.6	-7.25±19.37	<.0001
Na^+, mmol/L	139.1 ± 3.1	139.8 ± 2.5	0.75±3.39	<.0001	139.8 ± 2.9	139.1 ± 3	-0.69±3.47	0.0007
Hb, g/dL	13.9 ± 1.5	13.9 ± 1.4	0.01±1.29	NS	13.9 ± 1.5	13.4 ± 1.7	-0.56±1.47	<.0001

Data are expressed as mean ± standard deviation.

Hb: hemoglobin; LVEF: left ventricular ejection fraction; MDRD: Modification of Diet in Renal Disease; MECKI: Metabolic Exercise Cardiac Kideney Indexes; Na^+: serum sodium; NS: non significant; Peak VO_2 %: percentage of predicted peak oxygen uptake; V_E/VCO_2 slope: ventilation to carbon dioxide production slope; Δ MECKI: MECKI II - MECKI I.

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THE IMPORTANCE OF RE-EVALUATING THE RISK SCORE IN HEART FAILURE PATIENTS: AN ANALYSIS FROM THE METABOLIC EXERCISE CARDIAC KIDNEY INDEXES (MECKI) SCORE DATABASE.

Highlights

- International guidelines have highlighted the role of risk scores in heart failure (HF).
- MECKI score is one of the prognostic models recommended by the European HF guidelines.
- Although HF is a dynamic syndrome, prognostic studies have been based on a single evaluation.
- The prognostic power of MECKI score is confirmed at a II evaluation during follow up.
- Re-evaluation of MECKI score during follow up identifies HF subjects at higher risk.

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