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Incremental value of biomarkers to clinical variables for mortality prediction in acutely decompensated heart failure: The Multinational Observational Cohort on Acute Heart Failure (MOCA) study

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ABSTRACT

Aim: This study aims to evaluate the incremental value of plasma biomarkers to traditional clinical variables for risk stratification of 30-day and one-year mortality in acutely decompensated heart failure (ADHF).
Methods and results: Through an international collaborative network, individual patient data on 5306 patients hospitalized for ADHF were collected. The all-cause mortality rate was 11.7% at 30 days and 32.9% at one year. The clinical prediction model (age, gender, blood pressure on admission, estimated glomerular filtration rate <60 mL/min/1.73 m^2, sodium and hemoglobin levels, and heart rate) had a c-statistic of 0.74 for 30-day mortality and 0.73 for one-year mortality. Several biomarkers measured at presentation improved risk stratification when added to the clinical model. At 30 days, the net reclassification improvement (NRI) was 28.7% for mid-regional adrenomedullin (MR-proADM; $p<0.001$) and 25.5% for soluble (s)ST2 ($p<0.001$). At one year, sST2 (NRI 10.3%), MR-proADM (NRI 9.1%), amino-terminal pro-B-type natriuretic peptide (NT-proBNP; NRI 9.1%), mid-regional proatrial natriuretic peptide (MR-proANP; NRI 7.4%), B-type natriuretic peptide (NRI 5.5%) and C-reactive protein (CRP; NRI 5.3%) reclassified patients with ADHF ($p<0.05$ for all). CRP also markedly improved risk stratification of patients with ADHF as a dual biomarker combination with MR-proADM (NRI 36.8% [$p<0.001$] for death at 30 days) or with sST2 (NRI 20.3%; [$p<0.001$] for one-year mortality).

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Conclusion: In this study, biomarkers provided incremental value for risk stratification of ADHF patients. Biomarkers such as sST2, MR-proADM, natriuretic peptides and CRP, reflecting different pathophysiologic pathways, add prognostic value to clinical risk factors for predicting both short-term and one-year mortality in ADHF.

1. Introduction

The care of patients with acutely decompensated heart failure (ADHF) is complex, involving clinical assessment and risk prediction as integral parts of daily clinical practice. Indeed, ADHF is associated with a very high mortality rate, and clinical risk stratification after hospitalization for ADHF remains a relevant challenge, in order to best identify those patients likely to encounter serious complications, and to potentially better allocate resources in order to mitigate this considerable risk. Several demographic and clinical factors, co-morbidities, and biochemical variables are associated with short- or mid-term mortality in ADHF, including measures of renal function and blood pressure as well as other relevant predictors [1–6]. In recent years, a growing focus has been given to novel blood-based biomarkers for their ability to risk stratify patients with ADHF, and with this, an abundance of different assays has emerged, many reportedly associated with increased mortality in heart failure [7,8].

Over the past several years, B-type natriuretic peptide (BNP) and its N-terminal precursor fragment (NT-proBNP) have become the biomarker "gold standards" for predicting risk, with studies demonstrating value of either test for risk stratification of ADHF [5,9–12]. Importantly, the value of natriuretic peptides as well as other novel markers has however been studied with variable depth. Indeed, the value of any biomarker for risk prediction in ADHF, analyzed in an unbiased and thorough manner, should clearly depend on the degree to which it adds to the prognostic information provided by standard risk factors and other available markers [13–15].

Accordingly, the purpose of this study was to equitably assess the individual and added value of various novel biomarkers to traditional clinical variables and to each other for risk stratification of patients with ADHF, using data from a large, collaborative global, multicenter patient cohort. Furthermore, we used the most recent and appropriate statistical tools, including reclassification and discrimination analyses.

2. Material and methods

The Multinational Observational Cohort on Acute heart failure (MOCA) study was performed in accordance with the ethical guidelines of the declaration of Helsinki and all patients provided written consent to the individual studies. In the MOCA database, individual patient data was coded without possibility of person identification. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.1. Study cohort

The study population comprised patients hospitalized for ADHF with at least one biomarker measured at presentation. Data and biomarker results were obtained either from participants enrolled in earlier studies and registries (n = 4323) [6,10,16–22] or from previously unpublished cohorts (n = 983). Patients presenting in emergency room (ED) or in cardiac care unit (CCU) with ADHF defined using standard criteria [23,24] and requiring hospitalization were eligible. Individual patients were included in the analysis if clinical parameters and biomarker data were available from presentation. In addition, mortality data at one year of follow-up was required for inclusion. Patients in this analysis were consecutively enrolled at the different sites, and all had ADHF confirmed for inclusion.

Twelve cohorts from 11 countries (Austria [n = 137], Czech Republic [n = 1917], Finland [n = 620], France [n = 199], Netherlands [n = 367], Italy [n = 213], Japan [n = 144], Spain [n = 107], Switzerland [n = 609], Tunisia [n = 187], and the United States [n = 597 for Cleveland, n = 209 for Boston]) provided individual patient data that were assembled for the study database, resulting in a large, global, and multicenter ADHF cohort.

2.2. Biomarker analysis

The database included available measurements of several plasma biomarkers reflecting different pathophysiological pathways in heart failure: cardiac stretch (BNP [various vendors], NT-proBNP [Roche Diagnostics], mid regional pro-atrial natriuretic peptide [MR-proANP, Thermo-Fisher Diagnostics]), vascular stress (mid-regional pro-adrenomedullin [MR-proADM, Thermo-Fisher Diagnostics]), inflammation (C-reactive protein [CRP, various vendors]), myocardial damage and remodeling (soluble [s]ST2, last generation of Presage ST2, Critical Diagnostics), and necrosis (Troponin [cTn] I, various vendors; cTnT, Roche Diagnostics). Biomarkers were either measured on admission by the local laboratory (at least one natriuretic peptide, CRP and one troponin) or in plasma generally stored at −80° (natriuretic peptides and all MR-proANP, MR-proADM and sST2).

2.3. Statistical methods and biomarker analysis

Clinical variables known to affect prognosis (age, gender, systolic [SBP] or diastolic [DBP] blood pressure, heart rate, impaired renal function [glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 estimated by the MDRD equation], sodium, and hemoglobin levels) were used to build a baseline model for mortality risk prediction in ADHF ("clinical model"), adding also a variable accounting for any difference between centers. As the increase in cardiovascular morbidity and mortality associated with renal dysfunction occurs mostly at eGFR-levels < 60 mL/min/1.73 m^2, this was selected as cut-off [25]. Gender, co-morbidities, impaired renal function and hyponatremia

Table 1
Characteristics of the study population (n = 5306).

	Value
Variables	
Age (years)	75 (65–81)
Male gender n = (%)	3002 (56.6)
Biological and hemodynamic status at admission	
RR (cpm)	23 (18–28)
SBP (mm Hg)	138 (117–160)
DBP (mm Hg)	80 (68–91)
Heart rate (bpm)	88 (73–106)
LVEF (%)	40 (26–55)
Co-morbidities n = (%)	
Diabetes mellitus	1832 (37.6)
COPD	807 (16.6)
Hypertension	3386 (68.1)
Chronic HF	2289 (47.4)
Atrial fibrillation	1292 (28.6)
Coronary artery disease	2814 (55.6)
Medication at admission n = (%)	
β-Blocker	2035 (50)
ACE inhibitor	1601 (46)
ARB	702 (20)
Diuretics	2016 (55)
Nitrates	980 (26)
Low dose aspirin	1495 (42)
Statins	922 (30)
Causes of ADHF (%)	
Acute coronary syndrome	36
Atrial fibrillation	12
Infection	23
Non-compliance	7
Not specified	22
Outcome n = (%)	
30-day mortality	611 (11.7)
One-year mortality	1745 (32.9)

Data given as mean numbers (n =), percentages (%) or median with interquartile range. NYHA = New York Heart Association, RR = respiratory rate, cpm = counts per minute, SBP = systolic blood pressure, DBP = diastolic blood pressure, bpm = beats per minute, LVEF = left ventricular ejection fraction, COPD = chronic obstructive pulmonary disease, HF = heart failure, ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, eGFR = estimated glomerular filtration rate by modification of diet in renal disease formula.

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Table 2
Studied biomarkers and plasma levels at admission.

	Number of subjects with available data	Median value (IQR)	Reference values
BNP (ng/L)	2457	902 (442–1621)	<100
NT-proBNP (ng/L)	1588	4636 (2000–10,345)	<300
MR-proANP (pmol/L)	846	384 (244–594)	<120
Troponin T (μg/L)	1626	0.02 (0.01–0.10)	<0.01
Troponin I (μg/L)	1235	0.02 (0.0–0.10)	<0.01
MR-proADM (nmol/L)	850	1.36 (0.93–2.10)	<0.5
sST2 (ng/mL)	728	76 (44–121)	<35
CRP (mg/L)	2155	13 (5–39)	<3
Nt-proBNP, MR-proANP, MR-proADM, sST2 and CRP	441	–	–
Hb (g/dL)	4257	13.0 (11.5–14.3)	
K (mmol/L)	4450	4.2 (3.8–4.6)	
Na (mmol/L)	5192	139 (136–141)	
Creatinine (μmol/L)	5197	103 (80–137)	
eGFR (mL/min/1.73 m^2)	5188	53 (37–70)	

Hb = hemoglobin, K = potassium, Na = sodium, eGFR = estimated glomerular filtration rate by modification of diet in renal disease formula. Biomarker levels as median with interquartile range (IQR).

(Na<135 mmol/L) were entered as discrete variables, whereas age, blood pressure and hemoglobin where modeled as continuous variables. The discriminative ability of the model was evaluated by the c-statistic, identical to the area under the receiver operating characteristics (ROC) curve, with an end-point of interest 30-day and one-year all-cause mortality.

The ability of each biomarker to improve risk prediction on top of the clinical model was evaluated. First, each biomarker was added to the previously built prediction model and the c-statistic, or area under the curve (AUC), of the model with the biomarker was compared to the clinical model alone using the DeLong test. Analyses were always performed without imputations for missing variables, and the number of subjects included in each model therefore varies depending on which biomarker was added. Biomarkers were included as continuous variables in the models. Log-linearity of the effect of the quantitative variables was tested using generalized additive models and log-transformation was performed as required (more precisely BNP, NT-proBNP, MR-proADM, sST2, CRP were log-transformed). Correlations between different biomarkers were also assessed by estimating the Pearson correlation coefficient and its 95% confidence interval (CI).

The clinical benefit in risk prediction of adding a biomarker to the clinical model was further assessed by reclassification analysis, including both the net reclassification improvement (NRI) and the integrated discrimination index (IDI) [26,27]. In the reclassification analysis, cut-offs for low-, intermediate- and high-risk classes were defined based on the observed overall mortality in the study cohort. Patients were regarded to be at high-risk if the predicted risk of death was approximately two-fold the observed mortality, whereas a predicted risk around half the observed mortality was considered low-risk category. For 30-day mortality, cut-offs were defined as a predicted risk of <5%, 5–25%, and >25% for low-, intermediate-, and high-risk categories. Corresponding cut-offs for one-year predicted mortality risk were <20%, 20–60%, and >60%. Finally, a combination of two biomarkers that individually improved reclassification was entered together in the model to test a multimarker approach in risk stratification. Statistical analyses were performed using R-statistical software (http://www.r-project.org/). A two-sided p-value <0.05 was considered statistically significant.

3. Results

Clinical characteristics of the study population are in Table 1, and data on the original cohorts are in Supplemental Table 1. In MOCA,

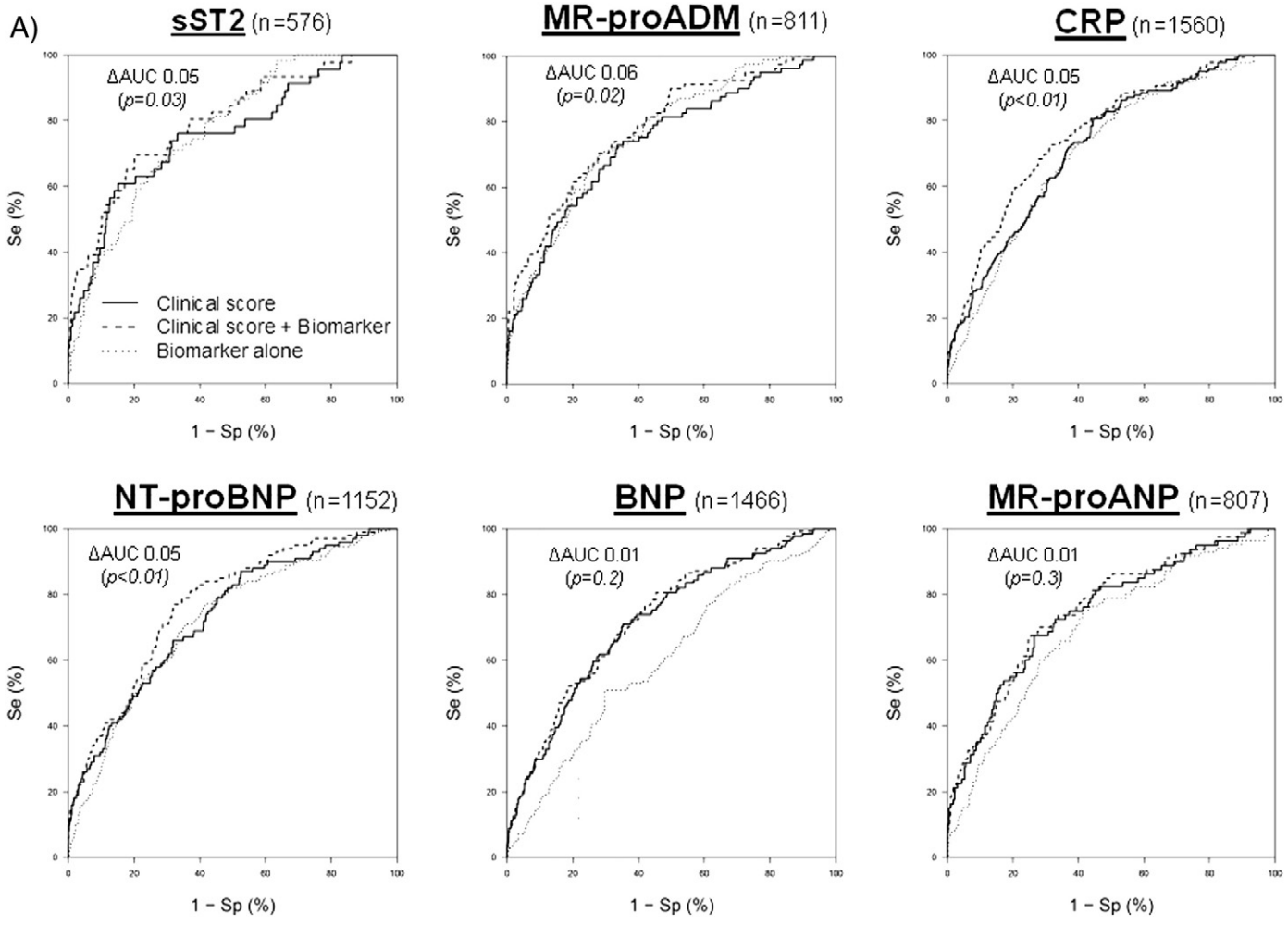

Fig. 1. ROC curves for 30-day (panel A) and one-year mortality (panel B) prediction for the studied biomarkers and the clinical model. Dotted line denotes receiver operating characteristics (ROC) curve of the biomarker alone. ΔAUC refers to the change in area under the curve (AUC) between the clinical model alone (full line) and biomarker + clinical model (dashed line).

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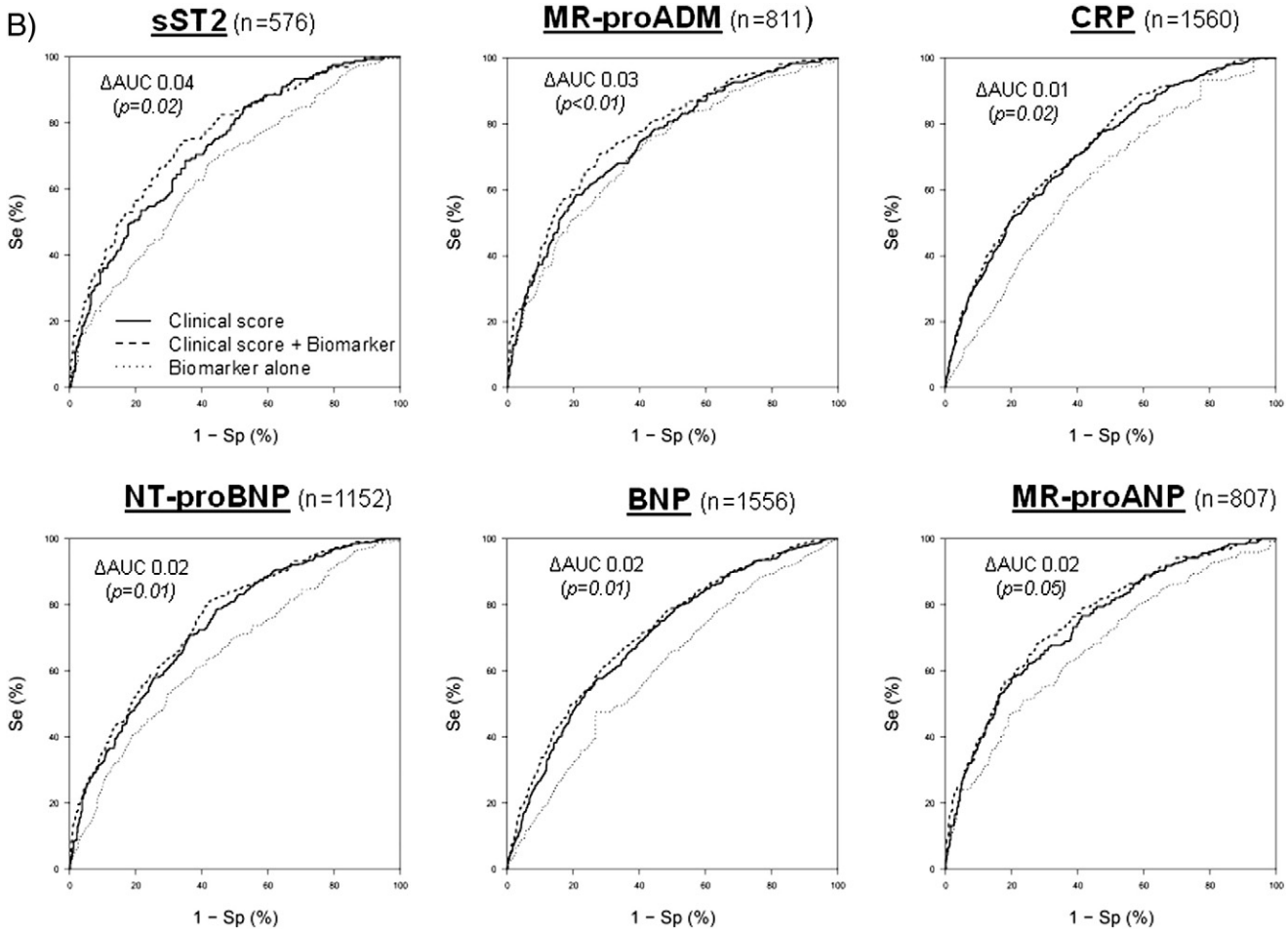

Fig. 1 (*continued*).

the mean age of the study population was 75 years and 43% were women. Prior history of heart failure was present in fewer than half of the subjects, and an ischemic cause of heart failure was present in approximately 56%. Consistent with the de novo presentation in a majority of patients, medications such as β-adrenergic blockers, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), or diuretics were used in only about half of the subjects at enrollment. The median left ventricular ejection fraction was 40% (interquartile range [IQR] 26–55%).

Baseline biomarker concentrations are detailed in Table 2; Supplemental Table 2 shows measured biomarkers and their levels in the original cohorts. Among the biomarkers studied, a natriuretic peptide result was available in the majority, while either cTnT or cTnI was measured in just over half the cohort and CRP was available in somewhat fewer. Novel biomarkers such as MR-proANP, MR-proADM and sST2 were available in 846, 850 and 728 patients, respectively. The concentrations of each of the biomarkers measured at presentation were all considerably elevated, consistent with the acuity of the patient population (see Table 2 for reference values). Correlation analyses revealed significant associations among biomarkers. A relatively strong correlation was observed between MR-proADM and sST2 ($R = 0.59$, $p < 0.001$), with moderate correlations found also between NT-proBNP and sST2 ($R = 0.42$, $p < 0.001$) and between NT-proBNP and MR-proADM ($R = 0.44$, $p < 0.001$). CRP showed only weak associations with NT-proBNP, MR-proADM or sST2 (Supplemental Fig. 1). As expected, the natriuretic peptides were strongly intercorrelated.

3.1. Outcomes

The number of deaths was 611 (11.7%) at 30 days and 1745 (32.9%) at one year. The c-statistic of the clinical model ($n = 3815$), which included age, gender, SBP and DBP on admission, eGFR < 60 mL/min/1.73 m^2, sodium and hemoglobin levels as well as heart rate, were 0.74 (95% CI: 0.71–0.74) for 30-day mortality and 0.73 (95% CI 0.71–0.73) for one-year mortality.

Fig. 1 shows that, when assessed alone, most of the studied biomarkers had worse predictive performance than the clinical model. Especially for the prediction of one-year mortality the clinical model clearly outperformed individual biomarkers (Fig. 1B). On the other hand, when biomarkers were added to the clinical model, NT-proBNP, CRP, MR-proADM and sST2 resulted in significantly higher c-statistic for the prediction of 30-day mortality (Fig. 1A). For death at one year (Fig. 1B), there was a modest but statistically significant improvement in the c-statistic above the clinical model with all markers but the troponins.

Following, we then considered reclassification with both NRI and IDI. Biomarkers of four different pathophysiological pathways resulted in significant reclassification of 30-day mortality risk (Fig. 2A): MR-proADM, with an NRI of 28.7% ($p < 0.001$) and sST2 with an NRI of 25.5% ($p < 0.001$) both reclassified more than one fourth of the patients. Similarly, significant improvement in IDI was noted. Each of the natriuretic peptides (BNP, NT-proBNP, MR-proANP) as well as CRP had lower reclassification rates (Fig. 2A).

Considering one-year mortality, several biomarkers also improved individual risk prediction in reclassification analyses. When added to

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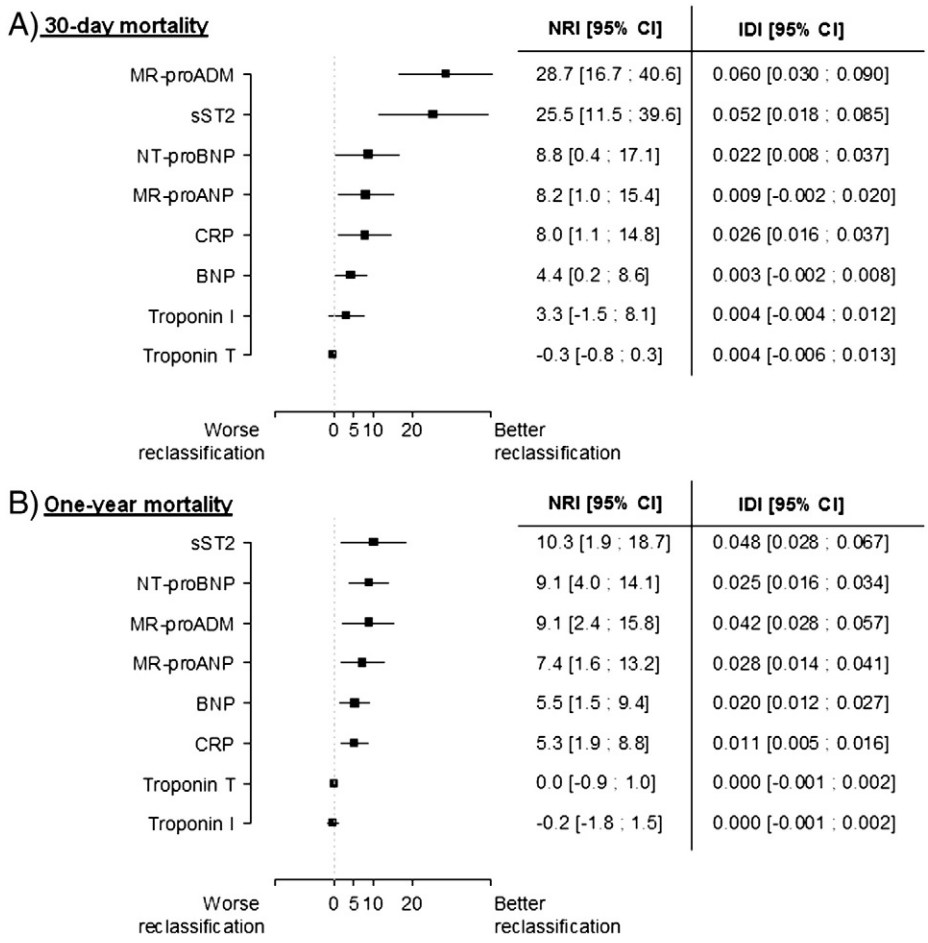

Fig. 2. Reclassification of 30-day (A) and one-year (B) risk of death in patients hospitalized for ADHF with addition of the studied biomarkers to the clinical model. Adding a biomarker is beneficial for risk stratification on the right side of the y-axis. The net reclassification improvement (NRI) point estimate and 95% confidence intervals (horizontal bars) are shown in the figure. The NRI and the integrated discrimination index (IDI) with corresponding 95% CI are shown in the columns on the right. For number of patients of each biomarker refer to Fig. 1.

the clinical model, sST2 reclassified 10.3% ($p=0.02$), MR-proADM 9.1% ($p=0.008$), NT-proBNP 9.1% ($p<0.001$), MR-proANP 7.4% ($p=0.01$), BNP 5.5% ($p=0.007$) and CRP 5.3% ($p=0.003$) of patients, resulting in significantly better one-year mortality risk prediction (Fig. 2B). IDI confirmed the results of the reclassification analysis for the significant biomarkers (Fig. 2B). The improved mortality risk prediction, especially at 30 days, was predominantly driven by improved reclassification of patients with an event, as seen in the reclassification Table 3A and B. Of note, consistent results were found in a sensitivity analysis in patients with acutely decompensated chronic heart failure and in patients with de novo acute heart failure (Table 4).

The use of dual biomarker combinations for risk stratification in ADHF was also explored. Though MR-proADM and sST2 were by far the biomarkers with the best individual performance at 30 days, the combination did not further improve risk stratification. Interestingly, CRP in combination with MR-proADM (36.8%; $p<0.001$), sST2 (30.8%; $p<0.001$) or NT-proBNP (27.1%; $p<0.001$) showed significantly higher reclassification indices (Fig. 3A). For death at one year, all dual combinations reclassified more patients than any single biomarker (Fig. 3B). Combining CRP and sST2 resulted in the greatest reclassification (NRI 20.3%, IDI 0.076; both $p<0.001$), improving risk stratification in one fifth of patients. Using the median of each biomarker as cut-off, Kaplan–Meier analyses also showed significant separation of survival curves for patients with low and/or high levels of CRP and MR-proADM for 30-day survival and CRP and sST2 for one-year survival (Fig. 4).

Finally, the analyses were repeated in the sub-group of 441 patients (see Supplemental Table 3 for characteristics) which had data available on the five biomarkers of interest: NT-proBNP, MR-proANP, CRP, MR-proADM and sST2. Of note, this sub-group represents 20% of patients with CRP measurements, 28% with NT-proBNP and up to 60% of patients with sST2. The biomarkers showed similar performance pattern in the complete-case cohort as in the entire study population, with sST2, MR-proADM, and natriuretic peptides showing the greatest reclassification and improving risk prediction in patients hospitalized for ADHF, either individually or in combination with CRP (Supplemental Table 4).

4. Discussion

Numerous reports of biomarker testing for prognosis have suggested potential utility of a wide array of assays when measured in patients with heart failure. With the growing number of manuscripts in this subject area, clinicians and investigators alike are left with uncertainty about the leading candidates for clinical use in this arena. Recent statements call for, among other things, a more standardized, thorough, and rigorous approach to evaluating heart failure biomarkers, including assessing them in a wide range of patients, and using contemporary, comprehensive, standardized and fair statistical methods when comparing biomarkers to each other and to clinical variables [15].

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Table 3
Risk prediction and reclassification for all-cause death in ADHF with a biomarker combination.

Panel A Reclassification of 30-day mortality risk

Alive		Clinical + biomarker (CRP+MR–proADM)model			
	Predicted mortality	**Low < 5%**	**Intermediate 5 – 25%**	**High > 25%**	**Total**
Clinical model	**Low < 5%**	**242**	**46**	**1**	289
	Intermediate 5 – 25%	**135**	**233**	**31**	399
	High > 25%	**2**	**17**	**12**	31
	Total	379	296	44	719

Dead		Clinical + biomarker (CRP+MR–proADM)model			
	Predicted mortality	**Low < 5%**	**Intermediate 5 – 25%**	**High >25%**	**Total**
Clinical model	**Low < 5%**	**8**	**4**	**0**	12
	Intermediate 5 – 25%	**1**	**29**	**20**	50
	High > 25%	**0**	**2**	**16**	18
	Total	9	35	36	80

NRI [95% CI]: 36.8%[23.4–50.2] ; p–value: 0.002, NRI alive 10.6%; NRI dead26.3%

IDI [95% CI]: 0.08[0.05–0.11] ; p–value<0.001

Panel B Reclassification of one-year mortality risk

Alive		Clinical + biomarker (CRP+sST2) model			
	Predicted mortality	**Low < 20%**	**Intermediate 20 – 60%**	**High > 60%**	**Total**
Clinical model	**Low < 20%**	**121**	**15**	**0**	136
	Intermediate 20 – 60%	**50**	**111**	**13**	174
	High > 60%	**0**	**6**	**4**	10
	Total	171	132	17	320

Dead		Clinical + biomarker (CRP+sST2) model			
	Predicted mortality	**Low < 20%**	**Intermediate 20 – 60%**	**High > 60%**	**Total**
Clinical model	**Low < 20%**	**14**	**5**	**0**	19
	Intermediate 20 – 60%	**8**	**73**	**22**	103
	High > 60%	**0**	**3**	**13**	16
	Total	22	81	35	138

NRI [95% CI]: 20.3[9.9–30.7], p–value: <0.001; NRI alive 8.8% ; NRI dead11.6%

IDI [95% CI]: 0.08[0.05–0.10]; p–value: <0.001

Comparing the clinical model versus the clinical+biomarker (CRP+MR-proADM) model, the green numbers are patients who changed risk category in a benificial direction with addition of biomarkers to the model, while light blue numbers are patients who were reclassified in the inappropriate direction. Patients in the diagonal boxes (grey) have the same predicted risk with both models.

It is in this context that we report a unique, global, multicenter analysis of patients hospitalized for ADHF, which provided an exceptional opportunity to assess multiple biomarkers for prediction of mortality risk with modern statistical methods for their comparison. The study includes patients from several different countries and continents. We found that several biomarkers reflecting different pathophysiological pathways may play an important role in assessing mortality risk after hospitalization for ADHF. Markers of inflammation (CRP), ventricular remodeling/fibrosis (sST2) and of cardiac or vascular stress (NT-proBNP, BNP, MR-proANP, MR-proADM), separately or in combination, showed the potential to improve prediction of individual patient risk beyond a model with established clinical variables.

Patients hospitalized for ADHF are at the distal end of the cardiovascular continuum and at high risk of death as we observed in the current study. For prediction of such outcome, interestingly, in this analysis, the clinical model had a better c-statistic than the studied biomarkers alone, but adding biomarkers to the clinical model showed mostly modest improvement in c-statistic for prediction of mortality. To be fair, c-statistic analyses often suffer from calibration issues, and such analyses tend to favor those variables entered as the 'base model', above the added variables, such as biomarkers. Thus it is worthwhile to point out that reclassification analysis demonstrated that several biomarkers have the potential to improve risk stratification of short- and long-term outcome in patients with ADHF. In particular, novel biomarkers such as sST2 and MR-proADM (as well as natriuretic peptides) reclassified a significant proportion of patients on top of a model with recognized clinical prognostic factors. Of note, we also found that widely used non-highly sensitive versions of cardiac troponin methods do not add to mortality prediction compared to conventional risk markers or other biomarkers. The prognostic ability of a biomarker may in part be dependent on whether the outcome is all-cause or cardiovascular mortality. CRP, a marker of inflammation, has previously associated with higher mortality in heart failure.[6,28,29] To our surprise, adding CRP to the biomarkers that had the best performance on their own, markedly improved the risk stratification of patients both for 30-day and one-year all-cause mortality.

The strongest biomarkers in this analysis were sST2 and MR-proADM, and this is the first study in ADHF which included a comparison of these two promising biomarkers for risk prediction in heart failure. It is intriguing to think that these biomarkers may predict increased risk reflected by different pathways. For example, sST2, a soluble "decoy" receptor from the IL-1 receptor superfamily, is involved in the regulation of fibrosis through interactions with IL-33. When dysregulated in patients with HF, concentrations of sST2 reflect a more decompensated profile and a more remodeled heart [30]. On the other hand, MR-proADM, a marker of cardiovascular and renal stress appears to provide information that is different than that by sST2, while natriuretic peptides mainly reflect cardiac hemodynamic perturbations and myocardial stretch. In addition, inflammation as measured by CRP, which displayed a weaker association to the other markers in this study, may represent yet another pathophysiological aspect not mirrored by the cardiac and vascular biomarkers. The biomarkers, measured at presentation, were strong predictors of short-term mortality and could be particularly useful for early risk stratification. The results of this study suggest that in patients with ADHF, markers such as sST2 and MR-proADM have the best potential to improve risk stratification and should be included in future risk prediction models, individually or in combination with CRP or a natriuretic peptide.

Limitations of our analysis include the fact that no established or externally validated clinical risk prediction model exists in ADHF.

Table 4
Sensitivity analysis in patients with acutely decompensated chronic heart failure and de-novo acute heart failure.

Subgroups	30-day mortality			One-year mortality		
	MR-proADM			sST2		
	n	NRI [95% CI]	IDI [95% CI]	n	NRI [95% CI]	IDI [95% CI]
Acutely decompensated chronic HF	433	18.9% [1.5; 36.2]	0.07 [0.03; 0.11]	336	15.4% [5.4; 25.4]	0.04 [0.02; 0.06]
de novo acute HF	378	13.9% [−0.4; 31.4]	0.08 [0.02; 0.13]	240	8.5% [−0.6; 23.4]	0.06 [0.02; 0.09]

NRI: net reclassification improvement, IDI: integrated discrimination index, HF: heart failure CI: confidence interval.

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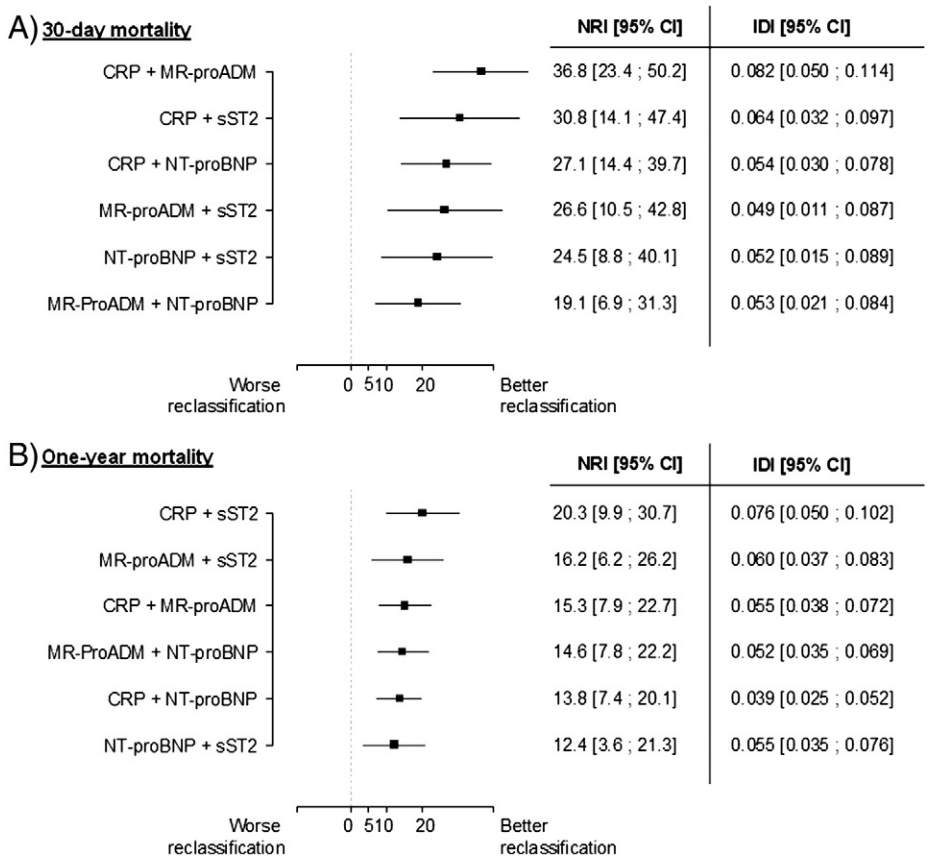

Fig. 3. Reclassification of 30-day (A) and one-year (B) risk of death in patients hospitalized for ADHF with addition of a dual biomarker combination to the clinical model. The net reclassification improvement (NRI) point estimate and 95% confidence intervals (horizontal bars) are shown in the figure. The NRI and the absolute integrated discrimination index (IDI) with corresponding 95% CI are shown in the columns on the right. Number of patients in each analysis: MR-proADM + NT-proBNP n = 758; MR-proADM + sST2 n = 447; MR-proADM + CRP n = 799; NT-proBNP + sST2 n = 556; NT-proBNP + CRP n = 876; sST2 + CRP n = 458. Cardiac troponins (which individually did not improve risk prediction) and BNP (very similar to NT-proBNP) were excluded from the tested combinations.

Nevertheless, the clinical model in this study comprises variables repeatedly found to have independent prognostic significance in this setting and provided a strong c-statistic. Reclassification analysis is dependent on predefined risk categories that enable categorization of patients within these strata. In the absence of such established risk categories in ADHF, low- and high-risk thresholds were defined based on the observed mortality in this large cohort. Furthermore, the risk strata used in MOCA are also well in line with those suggested in a previously published population with ADHF [4]. Lastly, while our cohort allowed for comparisons of various markers across multiple countries, uniform inclusion criteria were not applied in all the included cohorts. Heterogeneity between cohorts would probably dilute the results, which nevertheless were positive and consistent. We also included a variable to account for differences between centers in multivariable analyses. Biomarkers were not analyzed in a centralized laboratory and each of the biomarkers was not available in all patients. At least one natriuretic peptide was measured in the majority of the study cohort, while more recent biomarkers (MR-proADM [n = 850], MR-proANP [n = 846], and sST2 [n = 728]) were available in a smaller proportion of patients. Nevertheless, the MOCA study so far represents among the highest number of patients with these biomarkers measured in AHF. Although some heterogeneity in methods is present for CRP and natriuretic peptides; MR-proADM, MR-proANP and sST2 were measured using a homogeneous approach in the present study. This might have participated to the relatively better reclassification performance of the latter compared to the other biomarkers. While the number of patients is somewhat different for each biomarker, the study had enough power to identify that these central biomarkers improve risk stratification. Importantly, analysis of the cohort with all five biomarkers of interest (n = 441) supports the general findings of this study.

The MOCA study is clinical relevant for various reasons. It demonstrates that clinical variables, mostly measured at admission, cannot hereafter be used alone to predict outcome in ADHF patients. Various plasma biomarkers, alone or in combination, measured at presentation of ADHF, improve risk stratification to predict 30-day and one-year mortality. In many countries, NT-proBNP and CRP are already readily available to markedly improve risk stratification of ADHF patients. Furthermore, novel biomarkers, such as MR-proADM or sST2, are becoming increasingly available for clinical use and will provide additional alternatives to accurately assess ADHF patients' mortality risk. The latter will allow cardiologists, ED physicians or intensivists to optimize available resources and the intensity of follow-up.

In conclusion, this study demonstrates that biomarkers can provide considerable additive value to clinical parameters for risk stratification in ADHF. Novel biomarkers such as sST2 and MR-proADM detect features of risk not identified by conventional risk markers and improve risk prediction models of both short-term (30-day) and one-year mortality in ADHF.

Conflicts of interest

JL speaker's honoraria from Abbott, consultant fees from Roche Diagnostics; JLJ grants from Roche Diagnostics, Siemens Diagnostics, Critical Diagnostics, Thermo-Fisher Diagnostics, consultant fees from

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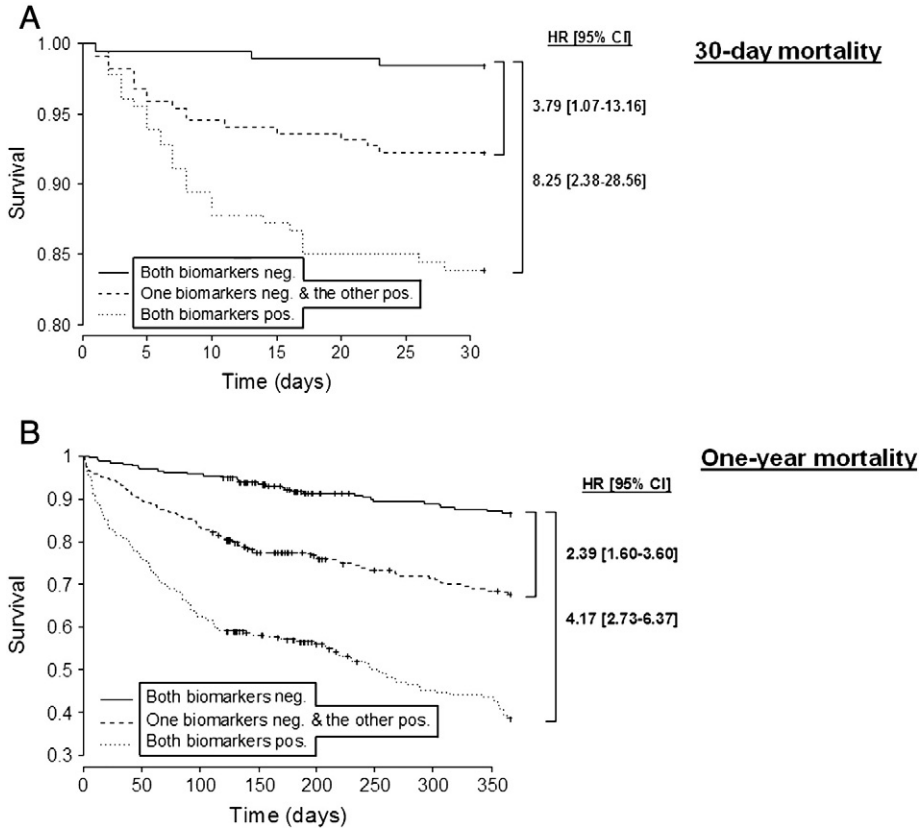

Fig. 4. Survival curves for patients risk stratified by dual biomarker levels. Panel A for the combination of CRP and MR-proADM and 30-day mortality, panel B for the combination of CRP and sST2 and one-year mortality. Survival curves for patients with both biomarkers below median (both negative), both biomarkers above median (both positive) or either marker above median (one positive/one negative). The median values were 76 ng/mL for sST2, 13 mg/L for CRP and 1,36 nmol/L for MR-proADM. NB. Y-axis does not start from zero.

Roche Diagnostics, Critical Diagnostics; V-PH consultant fees from Roche Diagnostics; WFP research grants from Abbott, Alere, Baxter, Brahms, Novartis, The Medicine's Company; consultant fees from Abbott, Alere, Lily, The Medicine's Company, speaker's honoraria from Abbott, Alere; ownership interest in Comprehensive Research Associates LLC, Vital Sensors, Emergencies in Medicine LLC, DP-F grants from Roche Diagnostics; CM research support and speaker's honoraria from BRAHMS, Alere, Abbott, and Critical Diagnostics; TM speaker's honoraria Abbott Diagnostics, B.R.A.H.M.S AG, and Roche Diagnostics, SdS consultant fees for Alere and Thermo-Fisher Diagnostics; AM speaker's honoraria from Alere, BRAHMS, Edwards, Orion, Bayer.

Appendix A. Study collaborators from the included studies

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Appendix B. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2013.01.228.

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