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Comparison of the diagnostic and prognostic values of B-type and atrial-type natriuretic peptides in acute heart failure

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ABSTRACT

Background: We compared diagnostic and prognostic properties of brain natruiretic peptide (BNP), proBNP, NT-proBNP and MR-pro-atrial natriuretic peptide (ANP) in patients admitted with shortness of breath (SOB).
Methods: All 4 NPs were measured in patients admitted to the emergency unit with SOB (in 2 centers) or acute heart failure (AHF) (1 FINN-AKVA cohort) and in a control population of stable chronic HF. Follow-up was 1 (2 centers) and 5 years (1 FINN-AKVA cohort). Area under the curve (AUC) was used to assess diagnostic properties. AUC, multivariate Cox regression, net reclassification improvement (NRI), and Kaplan–Meier analyses were used to assess mortality.
Results: We included 710 patients ("Biomarcoeurs" cohort n = 336; FINN-AKVA study, n = 306; stable chronic HF, n = 68). Pro-BNP was almost as powerful as BNP to diagnose AHF (AUC 0.953 vs 0.973 respectively, p = 0.003), NT-proBNP also performed well (0.922, p < 0.001 vs BNP). MR-proANP performed less well (0.901). AUC over time showed greater MR-proANP values over the first year. At 5 years, MR-proANP had the best prognostic value (AUC 0.668 vs 0.604 for BNP, p = 0.042). Kaplan Meier analysis confirmed better survival with MR-proANP ≤ 416.8 pmol/L at 5 years. NRI at 5 years was greater for MR-proANP (0.23, p < 0.05) than for proBNP, BNP or NTproBNP (p = NS).
Conclusion: Our study provides firm evidence that all NPs perform equally well for diagnostic purposes, and that MR-proANP has long term prognostic value in patients with acute heart failure.

1. Introduction

Shortness of breath (SOB, or acute dyspnea) is a chief complaint of many patients admitted to the emergency room or to coronary care units (CCUs). Plasma BNP and NT-proBNP are recommended in patients admitted with SOB when clinical diagnosis in uncertain, as both have been proven to have good discriminant value for distinguishing between acute heart failure (AHF) and non-AHF [1–3]. Indeed, in AHF patients, increased filling pressures raise cardiac wall stress leading to the release of BNP or NT-proBNP from cardiac myocytes into the plasma, whereas no such release occurs in patients admitted with non-HF related SOB.

In addition to BNP and NT-proBNP, which have been commercially available for clinical use for many years, mid-regional pro-atrial natriuretic peptide (MR-proANP) is a new biomarker that has recently become available to clinicians. MR-proANP, mainly synthesized by atrial sites, has been reported to have potential diagnostic and prognostic utility in AHF, comparable to that of BNP and NT-proBNP [4,5].

Pro-BNP, the precursor of BNP and NT-proBNP can also be measured in human plasma though no kit is currently available for clinical use. Pro-BNP is cleaved by corin or furin, mainly in the cytoplasm of cardiac myocytes, to yield to N-terminal (NT-proBNP) and C-terminal (BNP) portions of proBNP. Pro-BNP is also released from cardiac myocytes and plasma Pro-BNP has been shown, in a small cohort of patients with SOB, to yield diagnostic performance similar to

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that of BNP and NT-pro-BNP [6]. However, the prognostic value of pro-BNP in AHF remains unknown.

The aim of the present study was to compare the diagnostic and prognostic properties of the 4 natriuretic peptides (NPs) in patients admitted with SOB, a time of major release of NPs into the plasma. Plasma concentrations of NPs at admission were analyzed according to the presence or not of heart failure. We also compared the prognostic value of the 4 NPs for long term survival.

2. Methods

2.1. Study population

The present study analyzed the plasmatic values of 4 NPs (proBNP, BNP, NT-proBNP and MR-proANP) with acute dyspnea (of cardiac or non-cardiac origin or stable chronic heart failure).

NP measurements were performed on the plasma of patients included in the "Biomarcoeurs" cohort (n = 336); namely patients admitted to the emergency room of 2 centers (Monastir University Hospital in Tunisia (n = 131) and Lariboisière University Hospital in Paris, France (n = 205)) with shortness of breath (SOB) as their primary complaint upon presentation. In all patients, plasma was withdrawn at admission and kept at −80 °C for further analysis. The diagnosis of the cardiac or non-cardiac origin of shortness of breath was first performed by the emergency physician in charge on clinical examination and based on BNP concentrations obtained at admission to the emergency department. The diagnosis was also independently performed after patient discharge, by a senior cardiologist, and an intensivist, both heart failure experts based on patient files and BNP concentrations. In the very few cases with divergent diagnosis (n = 70), a third cardiology adjudicator was assigned to determine the final diagnosis. The 4 NPs were also measured in the plasma of patients admitted for acute heart failure in the FINN-AKVA study (n = 306), previously described elsewhere [7]. Follow-up was performed by phone contact at one year in the "Biomarcoeurs" cohort and 5 years in the FINN-AKVA cohort.

In addition, plasma was also drawn in 68 stable chronic heart failure patients in the cardiology outpatient center of Lariboisière Hospital (Paris).

This study was registered in clinical trials.gov and the identifier is NCT01374880. All patients gave informed consent. The study was approved by the institutional review board of each center.

2.2. Biomarkers testing

During initial patient examination at the emergency department, blood samples were collected in plastic tubes containing ethylenediaminetetra-acetic acid (EDTA). BNP32 (BNP) was measured within 4 h after admission in emergency department, on an Abbott Architect system (Abbott laboratories, Abbott Park, IL, USA). Aliquots of EDTA-plasma samples were stored at −80 °C for further analysis. These samples were used for the determination of plasma NT-proBNP, proBNP and MR-proANP. NT-proBNP$_{1-76}$ (NT-proBNP) was measured on a Roche Cobas analyser (Roche, Basel, Switzerland). ProBNP$_{1-108}$ (proBNP) was measured with a specific Bio-Rad assay: this assay is based on the monoclonal antibody mAb Hinge 76, that recognizes the cleavage site of proBNP$_{1-108}$ (Arg^{76}–Ser^{77}), an epitope present only in the precursor form [8]. MR-proANP was measured using available immunoluminometric assays by B.R.A.H.M.S. (B.R.A.H.M.S. AG, Hennigsdorf, Germany).

2.3. Statistical analysis

Values are expressed as mean ± standard deviation or number and percentage as appropriate. Diagnosis groups were compared with independent sample t-test and chi-square test as appropriate. The relationship of the four NPs was assessed using Spearman correlation coefficient.

To determine the diagnostic accuracy of the 4 NPs for the diagnosis of AHF, operating characteristics of the 4 NPs for diagnosis were evaluated using receiver operating characteristic curves (ROC), with calculation of the area under the curve (AUC) [9]. AUCs were compared according to the method of Hanley and McNeil [10].

To determine the prognostic value of plasma proBNP, BNP, NT-proBNP and MR-proANP, time-dependant AUC analyses were performed to assess the ability of the 4 NPs to discriminate mortality at various time points after index hospitalization (30 days, 1 and 5 years in the FINN-AKVA cohort). ROC curves were analyzed and the AUCs compared according to the method of Hanley and McNeil [10].

For both diagnostic and prognostic analyses, biomarkers were all included in the models as continuous variables.

Survival analyses were performed using Cox regression models. Median of MR-proANP was included in multivariate Cox proportional hazard models and the following variables were incorporated in the model: age, gender, systolic blood pressure, diastolic blood pressure, heart rate, hemoglobin, eGFR and BNP. Kaplan Meier curves for survival at different time points were constructed and compared using the log-rank test, with MR-proANP.

The clinical benefit on risk prediction of adding MR-proANP status to the clinical model was further assessed by reclassification analysis, using the continuous net reclassification improvement (NRI) [11]. Clinical variables used to build the baseline model for mortality risk prediction were: age, gender, systolic [SBP] and diastolic [DBP] blood pressure, heart rate, estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 in MDRD [12], hemoglobin level and sodium <136 mmol/l, atrial fibrillation, all recorded at admission.

Statistical analyses were performed using R-statistical software (http://www.r-project.org/) and MEDCALC version 11.2.1.0. A two-sided p value < 0.05 was considered statistically significant.

3. Results

Over the study period, 710 patients were included. The flowchart of the study population is shown in Fig. 1.

3.1. Comparison of plasma concentration of the 4 natriuretic peptides

Table 1 shows clinical, demographic and biochemical characteristics of the study population. Table 1 also shows that long lasting HF treatment, including ACE inhibitors/ARB, mineralocorticoids and beta-blockers, was optimized during the index hospitalization in AHF patients. Plasma concentrations of all NPs were 3 to 10-fold greater in patients admitted for AHF (n = 479) than patients admitted for acute dyspnea of non-AHF origin (n = 163): median ProBNP (1 344 pg/ml versus 89 pg/ml), median BNP (916 pg/ml versus 71 pg/ml), median NT-proBNP (4 728 pg/ml versus 50 pg/ml), median MR-proANP (953 pmol/l versus 50 pmol/l) (p < 0.0001 for all NPs) (Fig. 2A). In AHF patients, plasma concentrations of all NPs were higher in patients with previous history of HF (acute decompensated HF, ADHF) versus patients without previous history of HF (de novo AHF) (Fig. 2B).

Fig. 2A also shows that plasma concentrations of pro-BNP, BNP and NT-proBNP were 2-fold greater in AHF than in CHF patients (n = 68) while MR-proANP was only 20% greater in AHF than in CHF patients.

Fig. S1 further shows that BNP best correlated with proBNP (r = 0.947, p < 0.0001), in patients admitted with acute dyspnea (n = 642) and that NT-proBNP was well correlated with BNP and proBNP (r = 0.861 and 0.825 respectively). MR-proANP was slightly less well correlated with the 3 other NPs (r < 0.710) (Fig. S1 in Supplementary material).

Fig. 3A shows that the median proBNP/BNP ratios were greater than 1 for all studied groups, with the lowest proBNP/BNP ratio in AHF patients (median [25–75%]; 1.3 [1–1.7]) compared to non-AHF (1.6 [1.1–2]) or CHF (1.9 [1.2–2.6]) populations (p < 0.05 between AHF and non-AHF patients and between AHF and CHF patients). The median proBNP/NT–proBNP ratios were below 1 in all studied groups, with a lower proBNP/NT–proBNP ratio in AHF (0.43) and CHF (0.52) than in non-AHF (0.8) patients, (p < 0.05 between AHF and non-AHF patients, non-AHF versus CHF patients) (Fig. 3B). Fig. 3C represents the proportion of pro-BNP, NT-proBNP and BNP in AHF patients, and shows that in this population, there was more NT-proBNP than proBNP, and more proBNP than BNP.

3.2. Diagnostic performance

The accuracy of the 4 NPs to discriminate AHF from non-AHF was tested in the "Biomarcoeurs" cohort. Fig. 4 compares the diagnostic accuracy of the 4 NPs when the diagnosis of AHF or non-AHF was adjudicated with the knowledge of BNP. Fig. 5 shows that pro-BNP was almost as powerful as BNP to diagnose AHF in patients with SOB with an AUC of 0.953 and 0.973 respectively (p = 0.003 pro-BNP versus BNP). NT-proBNP also performed well with an AUC of 0.922 (p < 0.001 versus BNP). Though still very good, the diagnostic performance of MR-proANP was slightly lower (AUC of 0.901) than the other 3 NPs. AUC for all NPs were slightly greater in the subgroup of ADHF patients versus de novo patients (Fig. S2 in Supplementary material).

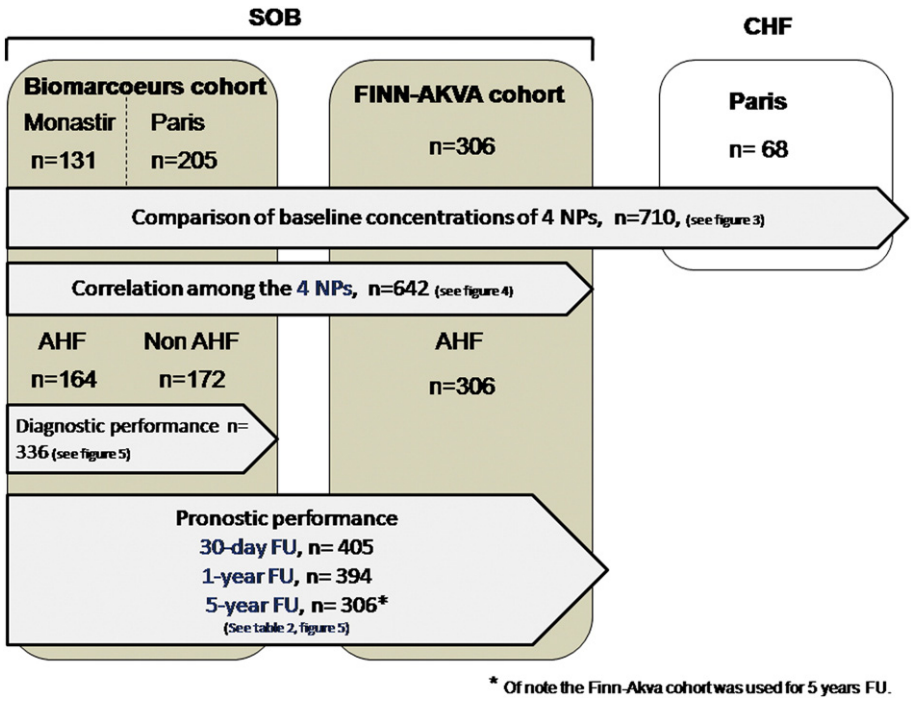


Fig. 1. Flowchart of the study population.

Table 1
Clinical, demographic and biological features for the "Biomarcoeurs", FINN-AKVA and CHF cohorts.

	Biomarcoeurs cohort (n = 336)		FINN-AKVA cohort	p*	Stable CHF
	Non-AHF n = 163	AHF n = 173	AHF n = 306		n = 68
Men n, (%)	83(50.9)	111(64.5)	160(52.3)	0.122	48(70.6)
Age years, (SD)	69(13)	73(13)	76(10)	0.011	58(12)
History of					
Arterial hypertension n, (%)	112(68.7)	120(69.3)	175(57.2)	0.28	25(36.4)
Diabetes mellitus n, (%)	77(46.2)	75(43.4)	103(33.7)	0.30	9(13.2)
CAD n, (%)	67(41.1)	65(37.6)	176(57.5)	0.052	28(41.3)
Myocardial infarction n, (%)	13(7.9)	16(9.2)	85(27.8)	0.0031	16(23.5)
Severe valvular disease n, (%)	16(9.8)	28(16.2)	1(0.3)	0.0007	0
CHF n, (%)	18(11.2)	88(50.9)	179(58.4)	0.560	68(100)
Atrial fibrillation n, (%)	31(19)	61(35.3)	92(30)	0.62	20(30)
Causes of current AHF episodes					–
Infection n, (%)	–	52(30)	74(24.2)	0.49	–
Acute coronary syndrome n, (%)		35(20.2)	79(25.8)	0.55	–
Arrhythmia n, (%)	–	34(19.6)	96(31.4)	0.16	
Hemodynamic parameters					
LVEF (%)	55(17)	45 (16)	44(14)	0.716	31(10)
HR (bpm)	96(23)	94(26)	91(29)	0.183	74(16)
SBP (mm Hg)	139(27)	134(26)	150(34)	<0.001	102(20)
DBP (mm Hg)	77(14)	80(16)	84(20)	0.028	80(20)
Biochemical markers					
Serum creatinine (μmol/l)	93(53)	127 (89)	112(52)	0.087	101(24)
Treatment at arrival					
ACE inhibitors or ARB n, (%)	92(60.1)	110(63.6)	158(51.6)	0.35	65(95)
Beta blockers n, (%)	28(17.2)	56(32.4)	109(35.6)	0.8	68(100)
Mineralocorticoids n, (%)	12(7.3)	16(9.3)	28(9.2)	1	37(54.4)
Treatment at discharge					
ACE inhibitors or ARB n, (%)	75(46)	118(68)	216(70.5)	0.86	–
Beta blockers n, (%)	55(34)	82(47.5)	239(78.1)	0.098	–
Mineralocorticoids n, (%)	21(13)	31(18)	57(18.6)	0.79	–

Data are presented as mean (standard deviation (SD)).
AHF, acute heart failure; CHF, chronic heart failure; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers.
p*: p values between AHF subgroup of «Biomarcoeurs» cohort and FINN-AKVA cohort.

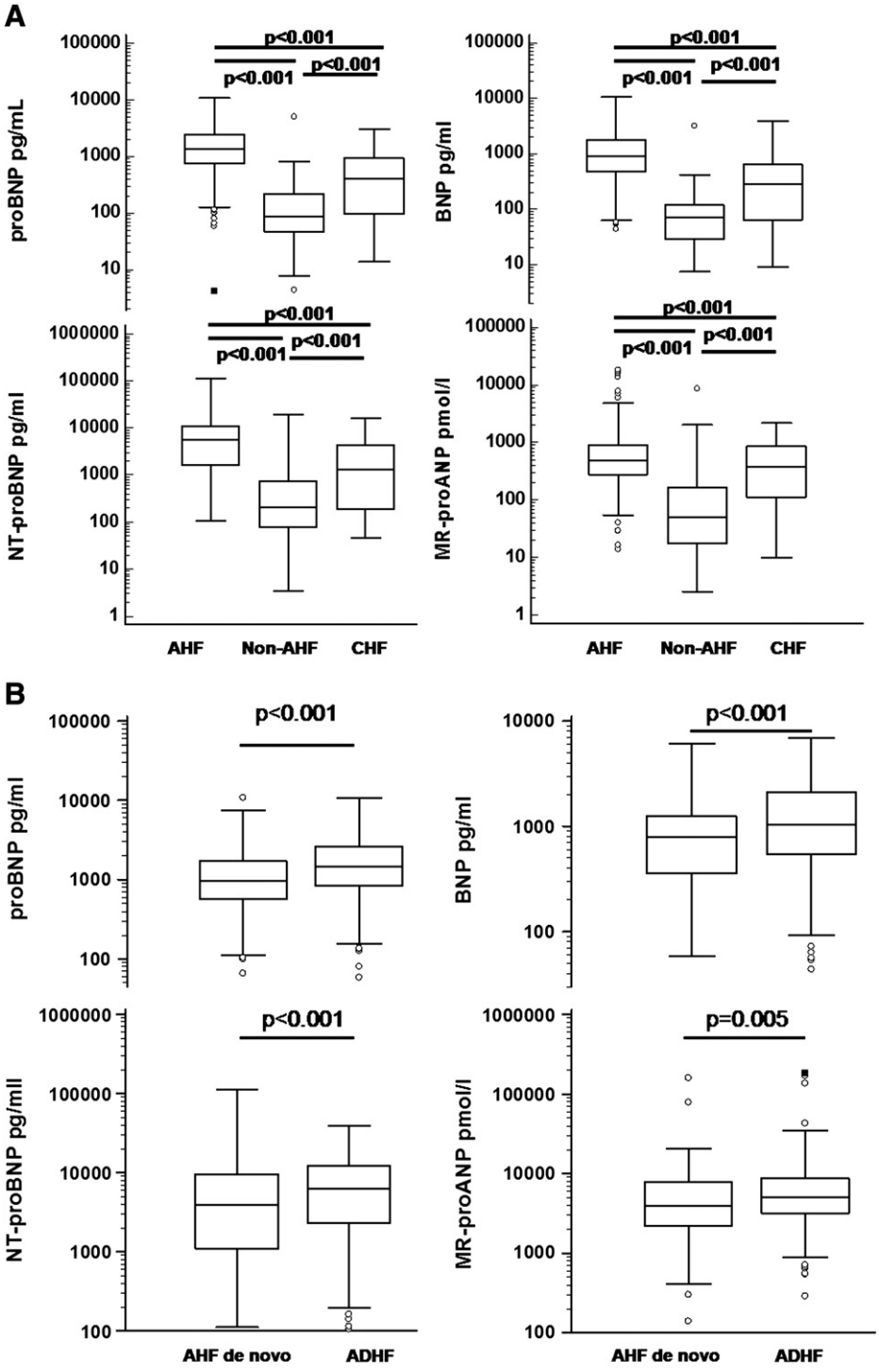


Fig. 2. Comparison of plasma levels of 4 natriuretic peptides in heart failure patients. (A) Patients admitted with acute dyspnea related to acute heart failure (AHF) or non-acute heart failure (non-AHF) and chronic heart failure (CHF) patients. (B) Comparison among AHF patients between de novo AHF (no previous history of HF) and acute decompensated HF (ADHF). Note that the Y axis uses a logarithmic scale.

3.3. Short and long-term prognostic performance of NPs in AHF patients

Mortality was 9.2% at 30 days, 28.7% at one year and 64.7% at 5 years (Table 2). Plasma BNP was consistently and significantly elevated at admission in AHF patients that subsequently died at 30 days, one year or 5 years.

Table 2 shows that the other NPs were similar at admission in AHF patients that subsequently died at 30 days or one year (the same findings were observed for proBNP/BNP and proBNP/NT–proBNP ratios, data not shown).

The representation of AUC over time showed a greater AUC for MR-proANP over the first year (Fig. S3 in Supplementary material).

Regarding 5 year outcome, NT-proBNP and MR-pro-ANP were also greater in patients who died versus those who survived (Table 2). The latter is confirmed by the representation of AUC over time for each of the 4 NPs (Fig. 5A). MR-proANP had the best prognostic value at five years with an AUC at 0.668 versus BNP (AUC = 0.604, p = 0.042) and versus NT-proBNP (AUC = 0.564, p = 0.004). Of note, the MR-proANP AUC was influenced neither by LVEF nor by the presence of AF (data not shown).

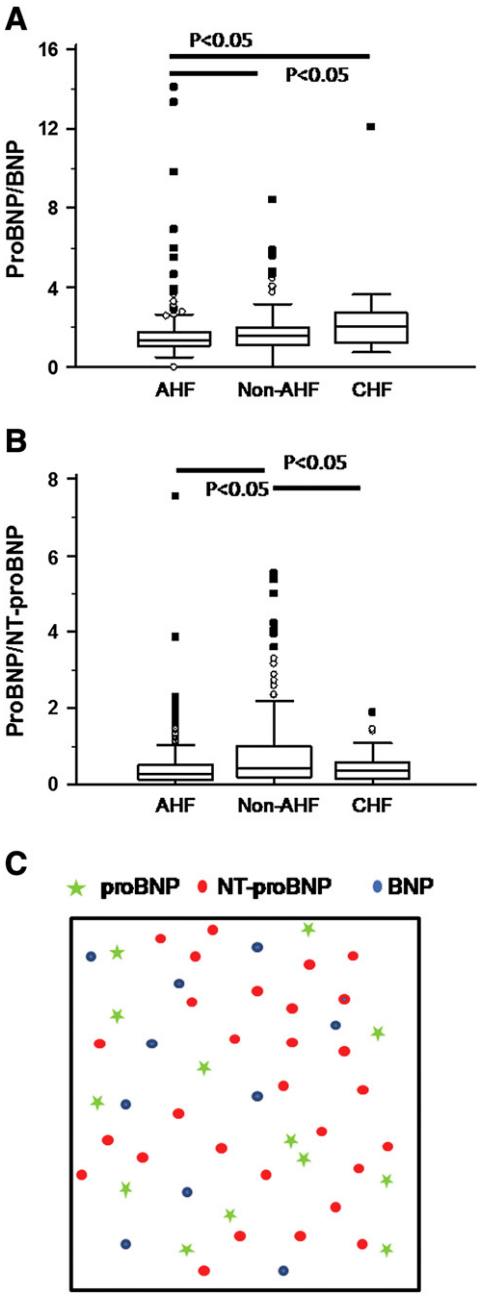


Fig. 3. 3A: ProBNP/BNP ratios in AHF, non-AHF, and CHF patients. 3B: ProBNP/NT–proBNP ratios in AHF, non-AHF, and CHF patients. 3C: Graphic representation of the proportion of plasma concentrations of BNP, proBNP and NT-proBNP.

Kaplan Meier survival analysis (Fig. 5B) confirmed that patients with low MR-proANP (≤median i.e. 416.8 pmol/l) at admission had a better survival rate over 5 years as compared to patients with MR-proANP > median with an HR of 2.2 (1.65–2.93) ($p < 0.0001$). Of note, HR for low versus high MR-proANP was 1.55 [1.05; 2.29] ($p = 0.0274$) when adjusted for age, gender, atrial fibrillation, systolic blood pressure, diastolic blood pressure, heart rate, hemoglobin, eGFR and BNP (Supplementary table S1).

We further analyzed the impact of adding biomarker information to the clinical model to predict 5-year mortality. Goodness-of-fit of the clinical model alone and the four models including NPs were similar (data not shown). The net reclassification improvement (NRI) of the 4 biomarkers was calculated, and we found an NRI of 23% [0.01–0.36] ($p < 0.05$) for MR-ProANP, much greater than the NRI of the 3 B-type NPs (NRI) for proBNP = 0.04 [−0.11–0.19] (NS); for BNP = 0.04 [−0.16–0.17] (NS); for NT-proBNP = 0.11 [−0.01–0.25] (NS). Sensitivity analyses were conducted in subgroups of patients with reduced and preserved LVEF (Supplementary table S2a and S2b) and showed similar results, though non-significant.

4. Discussion

Our study shows that 1) all NPs performed very well in the diagnosis of AHF with BNP and pro-BNP being the best performers, and 2) high MR-proANP was best associated with 5-year mortality.

4.1. Plasma concentration of NPs and correlations

As expected, our study shows that concentrations of all NPs were 3 to 10-fold greater at admission in AHF than in non-AHF patients and 2-fold greater in AHF than in CHF patients. In addition, plasma concentration of all NPs was greater in AHF patients with a history of HF than in patients with de novo AHF. This is possibly related to a greater release of all NPs during an acute episode in patients with history of heart failure and/or greater levels of NPs at baseline in CHF patients. Our study suggests that high levels of NPs in AHF patients admitted in acute conditions indicate ADHF rather than de novo AHF. We further measured proBNP/BNP and proBNP/NT–proBNP ratios in our studied patients. We confirmed previous findings in CHF patients that median proBNP/BNP was >1 and median proBNP/NT–proBNP < 1 indicating that NT-proBNP was more abundant than pro-BNP, which in turn was more abundant than BNP in our patients. Furthermore, these ratios were lowest in AHF patients, suggesting that BNP or NT-pro-BNP plasma concentration rose more than the plasma concentration of pro-BNP in AHF patients [13,14].

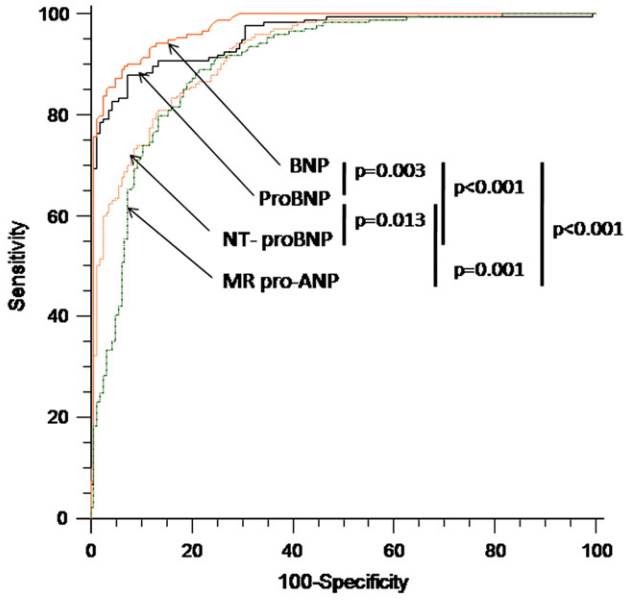
Our study further confirmed significant positive correlations among the 3 B-type NPs (proBNP, BNP and NT-proBNP) measured in the 642 patients admitted with acute dyspnea. BNP and proBNP are very well correlated ($r = 0.947$) while NT-proBNP was slightly less well correlated with pro-BNP ($r = 0.825$). This is in accordance with similar correlations found between pro-BNP and BNP in 3 monocentric studies that included respectively 156 patients admitted for SOB ($r = 0.95$) [6], 164 patients admitted for acute decompensated heart failure ($r = 0.92$) [15] and 756 chronic heart failure patients ($r = 0.87$) [16].

Our study further compared the atrial natriuretic peptide, MR-proANP, to the 3 B-type NPs. In our study, correlations between MR-proANP and each of proBNP, BNP and NT-proBNP were less striking than the correlations among B-type NPs and were all below 0.71. This contrasts with the correlation found in the BACH study between MR-proANP and BNP ($r = 0.919$) or NT-proBNP ($r = 0.920$) [4]. Another monocentric study measured MR-proANP in 251 patients with SOB and found the following correlations: between MR-proANP and BNP ($r = 0.835$) or between MR-proANP and NT-proBNP ($r = 0.832$) [17].

In summary, our study confirms that the 3 B-type NPs are very well correlated while the correlation between any B-type of natriuretic peptide and MR-proANP needs further confirmatory study.

4.2. Diagnostic performance of NPs

Our study compared plasma concentrations of the 4 NPs – 3 B-type NPs (proBNP, BNP and NT-proBNP) and MR-proANP – in 336 patients admitted with shortness of breath in the "Biomarcoeurs" cohort. The highest increase in plasma concentrations of all NPs was observed in AHF followed by CHF and non-AHF patients. Our study first compared the diagnostic performance of the 4 NPs in acute dyspneic patients; they all performed very well (AUC ≥ 0.90) with similar performances for proBNP and BNP in patients admitted with SOB (AUC at 0.953 and 0.973 respectively). Few studies have assessed the diagnostic performance of proBNP in acute conditions. For



n= 336	Pro BNP(pg/ml)	BNP (pg/ml)	NT-proBNP(pg/ml)	MR pro-ANP(pmol/l)
AUC	0.953	0.973	0.922	0.901
SE*	0.011	0.008	0.014	0.017
95% CI**	0.925 - 0.973	0.950 - 0.988	0.888 -0.948	0.864 - 0.931

*SE: Standard Error, ** CI confidence interval

Fig. 4. ROC curve analysis of the 4 NPs for diagnosis of acute heart failure.

instance, one monocentric study compared head-to-head pro-BNP with BNP and NT-proBNP in 156 patients admitted to the emergency department for SOB and found similar diagnostic performance for the 3 B-type NPs (pro BNP, BNP and NT-proBNP) (AUC at 0.92, 0.91 and 0.92 respectively) [6].

In our study, MR-proANP, although it had the lowest AUC (0.901), also performed well. A similar AUC for MR-proANP was observed in the prospective international BACH study (n = 1641; AUC for MR-proANP at 0.90) and in another monocentric study (the PRIDE population) (n = 560; AUC for MR-proANP: 0.90) [4,5]. Accordingly, our study confirmed that all NPs (B-type or MR-proANP) have similar diagnostic performance to identify or exclude acute heart failure in patients with SOB.

4.3. Prognosis

In the prognosis portion of our study, we compared the prognostic properties of the plasma levels of 4 NPs in acute heart failure patients. We confirmed that BNP was well associated with short-term mortality as shown in various published studies [3,18,19]. Most importantly, we observed that low MR-proANP was best associated with 5-year survival with an AUC of 0.67, a HR of 2.2 between low and high plasma levels of MR-proANP (and 1.72 after adjustments) and an NRI of 23%. In a previously published study of 137 patients hospitalized for acute decompensated heart failure, MR-ProANP had an AUC of 0.725, BNP of 0.716, proADM 0.708 and copeptine 0.688 to predict one-year all-cause mortality [20]. In another multicenter study with 797 stable chronic heart failure patients, MR-proANP showed similar AUC than NT-proBNP (0.79 and of 0.76 respectively) to predict 24-month mortality but MR-proANP was the only biomarker to be found an independent predictor of death, in addition to age, gender, NYHA, left ventricular ejection fraction and systolic blood pressure [21]. The prognostic value of MR-proANP was also confirmed at 4 years in patients hospitalized for SOB [5]. We further showed a striking improvement in the risk stratification (NRI of 23%) of long term outcome with the use of MR-proANP.

The reason for the long term prognostic superiority of high plasma levels of MR-ProANP compared to the 3 other B-type NPs in our study remains to be elucidated. It might be related to different biological properties of MR-proANP compared to B-type NPs, such as higher biological stability or the use of an assay directed at the mid-region of the molecule [22]. ProANP is an atrial natriuretic peptide and as such, is an index of the size of the atria. Our data might suggest that high plasma MR-ProANP is related to dilated atria, known to be a strong predictor of long term mortality, and suggesting chronicity of increased filling pressure with time. MR-proANP might also be related to atrial fibrillation or supra-ventricular tachycardia, known to lead to excessive release of ANP [23,24].

Our study has certain limitations. We combined data from two cohorts of patients admitted in 3 different countries for SOB or AHF to assess diagnostic and prognostic performances of the 4 NPs. The "Biomarcoeurs" cohort included patients from Monastir (n = 131) and Paris (n = 205) and made it possible to assess diagnostic performance. On the other hand, data from patients admitted in the Parisian center and the FINN-AKA cohort were used to assess the prognostic performance of all NPs. Despite the different origins of the patients, NP performances were similar among countries; this strengthens our results. Another limitation is the different follow-up time between Parisian patients (1 year) and Finnish patients (5 years). However, MR-proANP remained the best prognostic performer in Paris and in Finland both at one year and in Finland at 5 years. In addition, this confirms very recent results [5]. Accordingly, MR-proANP is the best NP to perform for long term outcome in AHF. Our study recorded LVEF in all patients but not other echocardiographic parameters including atrial size. A link between MR-proANP, atrial size and outcome should therefore be explored in future studies.

The present study brings new information that may change our clinical daily practice. Indeed, our study shows that all NPs and especially

Table 2
Comparison of biological status at admission between survivors and non-survivors in the AHF cohort.

	Survivors	Non-survivors	p value	AUC	95%CI
At 30 days	n = 368	n = 37			
Creatinine μmol/l	116(69)	146(86)	0.076	–	–
ProBNP pg/ml	1851(1694)	2429(2214)	0.056	0.594	0.544–0.642
BNP pg/ml	1341 (1263)	1894(1581)	0.014	0.615	0.565–0.662
NT-proBNP pg/ml	7797(6792)	8290(7699)	0.678	0.507	0.457–0.557
MR-proANP pmol/l	726(1172)	1017(1353)	0.158	0.615	0.566–0.663
At 1 year	n = 281	n = 113			
Creatinine μmol/l	110(59)	137(80)	<0.001	–	–
ProBNP pg/ml	1761(1654)	2113(1984)	0.09	0.552	0.501–0.602
BNP pg/ml	1275(1159)	1653(1609)	0.01	0.566	0.515–0.615
NT-proBNP pg/ml	7750(6407)	7654(7258)	0.897	0.524	0.473–0.574
MR-proANP pmol/l	650(741)	825 (1055)	0.063	0.582	0.532–0.631
At 5 years	n = 108	n = 198			
Creatinine μmol/l	96 (30)	124 (67)	<0.001	–	–
ProBNP pg/ml	1499(1662)	1971(1762)	0.5	0.610	0.553–0.665
BNP pg/ml	1036(1015)	1500(1380)	0.001	0.604	0.547–0.660
NT-proBNP pg/ml	6296(4954)	7742(6132)	0.015	0.564	0.507–0.621
MR-proANP pmol/l	402(309)	561(389)	0.009	0.668	0.612–0.721

AUC, area under the curve; 95%CI, 95% confidence interval; BNP, brain natriuretic peptide; MR-proANP, mid-regional pro-atrial natriuretic peptide.

the most widely used, namely BNP and NT-proBNP, are excellent diagnostic performers. Interestingly, the simultaneous measurement of the 3 B-type of NPs in 479 AHF patients indicates that the plasma concentration of NT-proBNP is roughly 3-fold greater and proBNP 1.3-fold greater than BNP, as shown in Fig. 3c. Furthermore, our study indicates that MR-proANP markedly improves risk stratification to predict long term outcome compared to standard clinical parameters in AHF patients; together with the data already published by Shah [5], our data strongly advocate use of MR-proANP as the NPs of choice to predict long-term (more than 2 years) outcome. This result may change the way AHF patients will be included in clinical trials with long term mortality as an endpoint.

In summary, our study shows firm evidence of similar diagnostic performances for all NPs and important long-term prognostic value for MR-proANP in patients with acute heart failure. Future studies should explore the significance of the prognostic performance of MR-proANP and favor its use in risk-stratifying HF patients.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2013.04.164.

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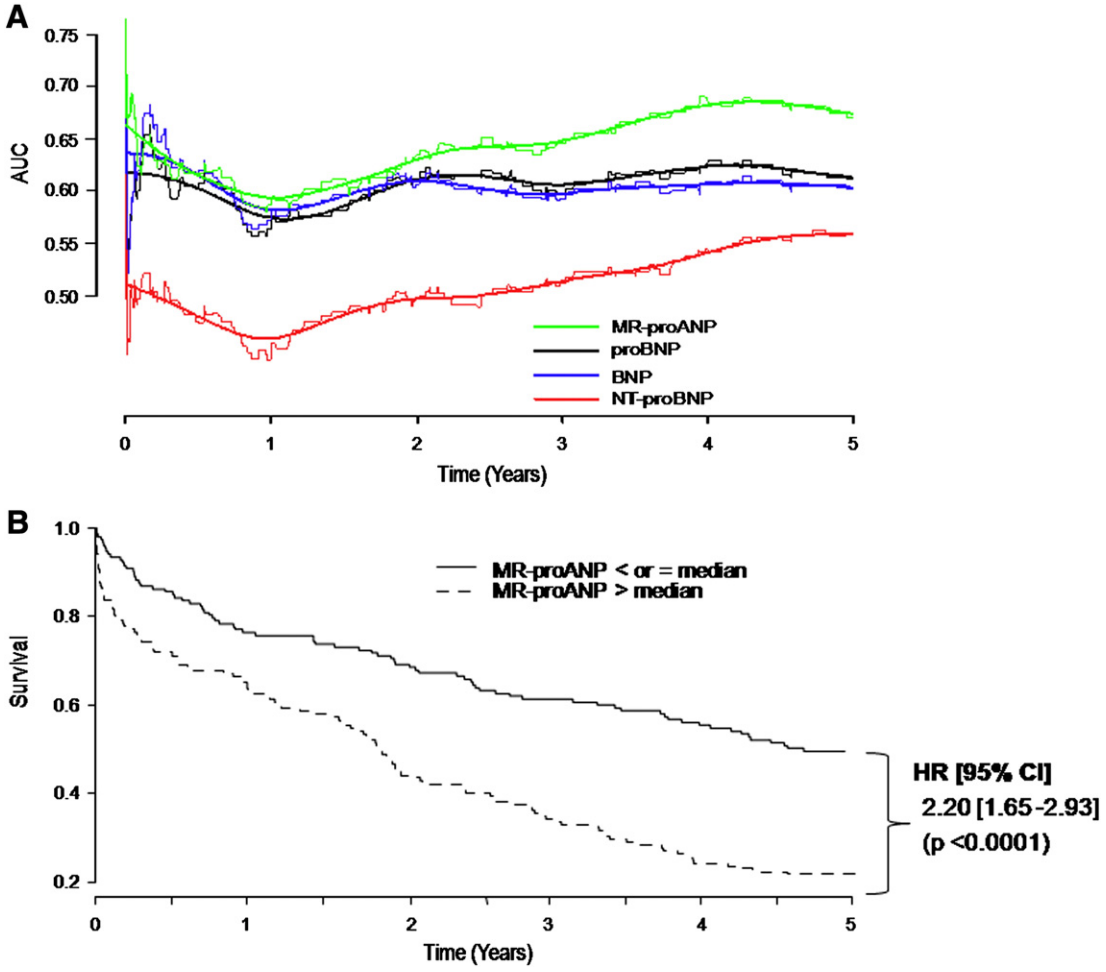

Fig. 5. A) Time dependent changes in area under the curve for multiple biomarkers in acute heart failure patients at 5 year follow up in FINN-AKVA (n = 306). B) Kaplan Meier survival curves according to plasma MR-proANP concentration. Analysis performed in the FINN-AKVA cohort (n = 306).

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