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Differential Associations of A-/B-Type Natriuretic Peptides With Cardiac Structure, Function, and Prognosis in Heart Failure

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ABSTRACT

BACKGROUND Natriuretic peptide (NP) elevations are prognostic in heart failure (HF), but relative atrial NP deficiency in acute HF has been suggested.

OBJECTIVES The authors compared plasma concentrations and relative strength of associations of A- and B-type NPs with cardiac structure/function and clinical outcomes in HF.

METHODS Midregional pro-atrial natriuretic peptide (MR-proANP), B-type natriuretic peptide (BNP), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were measured in patients with compensated HF in a prospective, multicenter study. The primary outcome was a composite of HF-hospitalization or all-cause mortality. Secondary outcomes included individual primary outcome components and cardiovascular admission.

RESULTS Among 1,278 patients (age 60.1 ± 12.1 years, 82% men, left ventricular ejection fraction [LVEF] 34% ± 14%), median concentrations of MR-proANP were 990 pg/mL (Q1-Q3: 557-1,563 pg/mL), NT-proBNP 1,648 pg/mL (Q1-Q3: 652-3,960 pg/mL), and BNP 291 pg/mL (Q1-Q3: 103-777 pg/mL). No subpopulation with inappropriately low MR-proANP (relative to BNP/NT-proBNP) was observed. Clinical event rates were similar for biomarker tertiles. Increments in MR-proANP exhibited steeper associations with concurrent shifts in left ventricular size, diastolic indexes and LVEF than BNP/NT-proBNP at baseline and serially ($P < 0.05$), and lower odds of beneficial left ventricular reverse remodeling: OR: 0.35 (95% CI: 0.18-0.70). In single-biomarker models, MR-proANP($\log_{10}$) was associated with the highest hazard (4 to 6 times) for each outcome. In multimarker models, independent associations were observed for the primary outcome (MR-proANP and NT-proBNP), HF-hospitalization and cardiovascular admission (MR-proANP only), and all-cause mortality (NT-proBNP only) ($P < 0.05$). The discriminative value of MR-proANP was superior to BNP/NT-proBNP (HF-hospitalization) and BNP (primary outcome) ($P < 0.05$).

CONCLUSIONS MR-proANP was not inappropriately low relative to concurrent BNP/NT-proBNP values. Proportional increments in MR-proANP were more pronounced than for B-peptides for given decrements in cardiac structure/function. MR-proANP offered greater independent predictive power overall. (J Am Coll Cardiol HF 2024;12:461–474)

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BNP = B-type natriuretic peptide

HF = heart failure

LVEF = left ventricular ejection fraction

MR-proANP = midregional pro-atrial natriuretic peptide

NT-proBNP = N-terminal pro-B-type natriuretic peptide

Elevation of plasma natriuretic peptides (NPs) is a hallmark of heart failure (HF). Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are secreted from cardiomyocytes in response to increased wall stress to regulate diuresis, natriuresis, and vasodilation, and exert antifibrotic and antihypertrophic effects in the heart.[1] Enzymatic cleavage of propeptide NP forms leads to concurrent release of the bioactive carboxypeptides ANP and BNP along with their respective amino terminal congeners N-terminal pro-A-type natriuretic peptide (NT-proANP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP). BNP and NT-proBNP are widely applied for diagnosis and prognosis in clinical heart failure.[2-4] To date, the ANPs have yielded less clinical utility, related in part to measurement reliability. Bioactive carboxy-terminal ANP with its short half-life is labile and is influenced by sampling methodology,[5] whereas peptide terminals of NT-proANP are subject to truncation.[6,7]

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To address these limitations, a sandwich immunoassay targeting the stable central portion of NT-proANP was developed. The performance of midregional pro-atrial natriuretic peptide (MR-proANP) in the diagnosis of acute heart failure (AHF) and non-AHF has been demonstrated to be comparable to that of BNP and NT-proBNP.[8,9] The prognostic value of MR-proANP remains less well-studied, but at least for all-cause mortality in HF, has been reported to perform as well as NT-proBNP and BNP.[10-16] However, the recent suggestion from Reginauld et al[17] of ANP deficiency among a subset of patients with acute HF has cast doubt on the performance of the cosecreted congener A-type NPs (ANP, NT-proANP, and MR-proANP) as diagnostic or prognostic biomarkers in HF. Any such relative ANP deficiency would potentially also affect the relationships of A-type NPs with the following: 1) concurrent B-type NP concentrations; 2) cardiac structure and function; and 3) prognosis.

The objectives of this study were therefore as follows: 1) to investigate if an ANP deficiency state relative to concurrent plasma B-type NPs exists; 2) to compare the associations of individual NPs with cardiac structural and functional parameters; and 3) to evaluate the prognostic performance of MR-proANP compared with NT-proBNP/BNP in a wider array of clinical outcomes than assessed hitherto, including HF-hospitalization and cardiovascular admission in addition to all-cause mortality.

METHODS

STUDY POPULATION. Participants were from 2 separate, prospectively designed, longitudinal cohorts of patients with HF recruited across 6 public hospitals in Singapore (Singapore Heart Failure Outcomes and Phenotypes study between 2010 and 2015, ACTRN12610000374066; and its extension, Asian neTwork for Translational Research and Cardiovascular Trials between 2015 and 2019, NCT02791009).[18] The inclusion and exclusion criteria have previously been described.[19] Briefly, participants (≥21 years of age) had a prior episode of acute HF and were enrolled in compensated states before discharge during hospital admission for AHF, or in hospital clinics for follow-up within 6 months of an episode of AHF. Ethics approval was obtained from the local Institutional Review Board. All participants provided informed consent, and the study complied with the Declaration of Helsinki.

Patients were assessed at baseline, at clinic follow-up (6 weeks and 6 months), and by phone at 1 and 2 years. Clinical comorbidities, standard 12-lead electrocardiogram, and blood samples were obtained at baseline. Transthoracic echocardiograms were performed to assess left ventricular (LV) dimensions, left ventricular ejection fraction (LVEF), left atrial volume index (LAVI), E/e′, peak tricuspid regurgitation jet velocity, and right ventricular systolic pressure according to the American Society of Echocardiography guidelines. Atrial fibrillation (AF) was defined as prior history or presence of AF/atrial flutter at recruitment. Heart failure with preserved ejection fraction (HFpEF) was defined as LVEF ≥50%, and heart failure with reduced ejection fraction (HFrEF) as LVEF <50%.

BIOMARKERS. Venous samples for assay of circulating peptides were obtained at baseline,[20] transported on ice in EDTA tubes with separation of

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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plasma within 1 hour, and stored at −80 °C before assay. NT-proBNP was sampled within 1 year of collection, while MR-proANP and BNP were sampled in 2021. All samples were subjected to no more than 2 freeze-thaw cycles. Plasma concentrations of MR-proANP were measured by immunoluminometric assays on the B.R.A.H.M.S KRYPTOR analyzer (Thermo Scientific GmbH). Interassay coefficient of variation (5.68% at 102 pmol/L; 5.69% at 507 pmol/L) was derived over 42 independent runs. Plasma NT-proBNP was measured by electrochemiluminescence immunoassays on a Cobas immunoanalyzer (Roche Diagnostics GmbH). Interassay coefficient of variation (low quality 141 pg/mL, 3.38%; high quality 4,759 pg/mL, 4.03%) was established over 56 independent runs. BNP was measured using the Siemens ADVIA Centaur* BNP assay (Siemens Healthcare Diagnostics). Mean and interassay coefficients of variation (n = 38) for low-, medium-, and high-quality control samples were 46.9 pg/mL (3.4%), 478 pg/mL (3.15%), and 1,754 pg/mL (2.78%), respectively.

OUTCOMES. The primary outcome was a composite of HF-hospitalization or all-cause mortality at 2 years. Secondary outcomes included individual components of the primary outcome and cardiovascular admission. Participants were followed up at public hospitals, which allowed the reliable ascertainment of clinical events through electronic health records and the National Death Registry within Singapore.

STATISTICAL ANALYSIS. Continuous variables were summarized as mean ± SD and categorical variables as n (%). Biomarker concentrations (pg/mL) were $\log_{10}$ transformed. Scatterplots of MR-proANP were plotted against NT-proBNP and BNP to assess for disproportionately low plasma MR-proANP concentrations relative to concurrent BNP levels. The associations of each biomarker with selected elements of cardiac structure and function were ascertained in linear regression analyses. The test for equality of regression coefficients[21] was performed to compare the steepness of the association of each NP with echocardiographic parameters at baseline, and change in NP levels with change in echocardiographic parameters at 6 months. Logistic regression was performed to evaluate NP associations with LV reverse remodeling. The prognostic value of each biomarker in primary and secondary outcomes was evaluated in Cox proportional hazard models adjusting for known prognostic clinical variables. With regard to time to HF-hospitalization and cardiovascular disease admission analyses, follow-up was censored at death or end of study duration in those without a secondary outcome event. Subgroup analyses and interactions with age (≤70 years vs >70 years), sex, NYHA functional class (I/II vs III/IV), body mass index (BMI) (≤30 kg/m^2 vs >30 kg/m^2), AF, LVEF (<50% vs ≥50%), and admission status (inpatient vs outpatient) were tested. Clinical event rates were evaluated by likelihood ratio tests, and Kaplan-Meier survival curves were plotted by

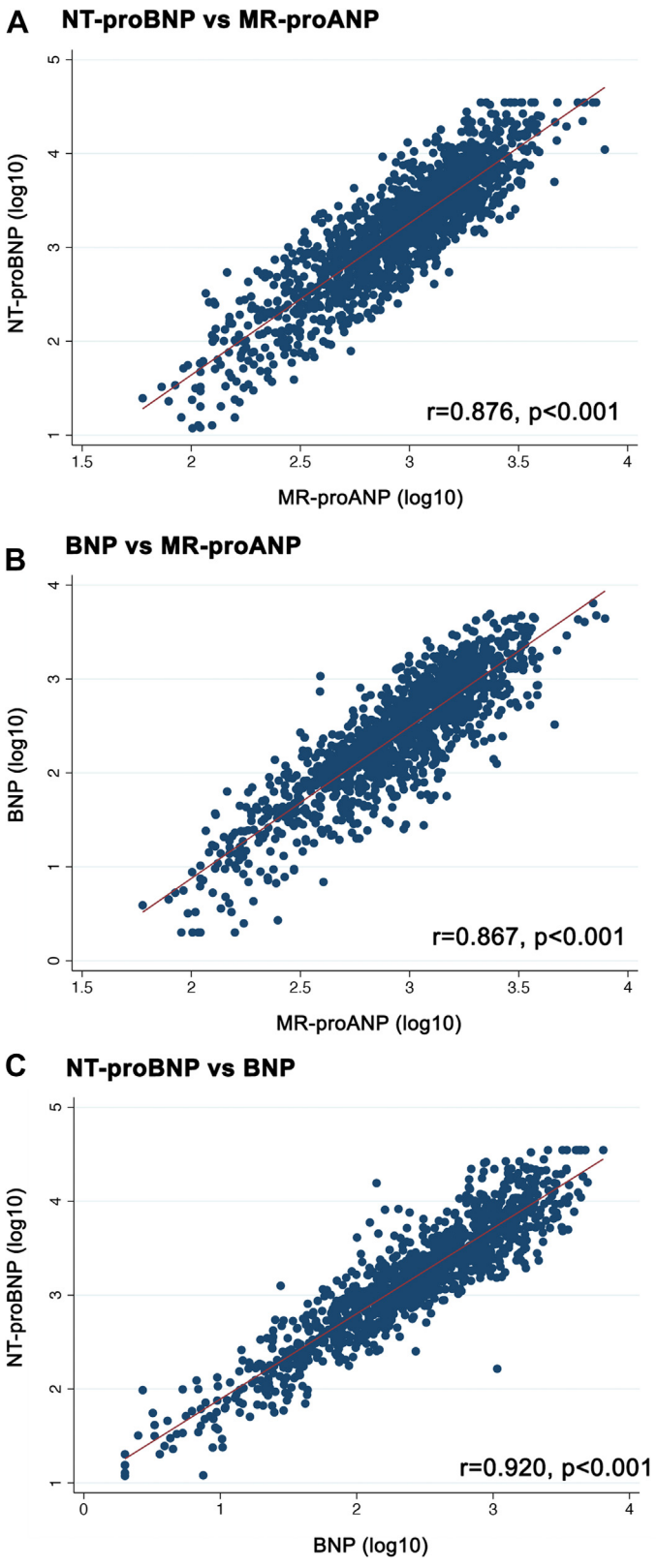
TABLE 1 Baseline Characteristics of Patients With HF (N = 1,278)

Age, y	60.1 ± 12.1
Male	1,049 (82.1)
NYHA functional class	
I/II	1,074 (85)
III/IV	185 (15)
Body mass index, kg/m^2	26.7 ± 5.6
Heart rate, beats/min	76.0 ± 13.8
Systolic blood pressure, mm Hg	124.9 ± 22.0
Diastolic blood pressure, mm Hg	71.6 ± 13.0
Smoker	709 (57.4)
Creatinine, μmol	114.8 ± 51.5
Ischemic etiology of HF	734 (57.4)
AF	281 (22)
Hypertension	872 (68.2)
Diabetes	699 (54.7)
Prior stroke	135 (10.6)
Peripheral vascular disease	56 (4)
Chronic respiratory disease	111 (9)
Liver disease	49 (4)
Cancer	45 (4)
Echocardiography indexes	
LVEF, %	33.9 ± 14.2
LAVI, mL/m^2	42.4 ± 17.2
LVEDD, mm	58.8 ± 9.6
LVESD, mm	47.2 ± 12.0
LVEDV, mL	144.8 ± 59.8
LVESV, mL	101.2 ± 55.6
Peak TR velocity, m/s	2.7 ± 0.6
RVSP, mm Hg	37.2 ± 15.3
E/e' ratio	16.7 ± 7.9
Baseline biomarkers[a]	
NT-proBNP, pg/mL	1,648 (652-3,960)
MR-proANP, pmol/L	291 (103-777)
MR-proANP, pg/mL[b]	990 (557-1,563)
BNP, pg/mL	291 (103-777)
Medications	
ACEI/ARB	963 (75.4)
Beta-blocker	1,107 (86.6)
Loop diuretic agent	1,093 (85.5)
MRA	658 (51.5)

Values are mean ± SD, n (%), or median (Q1-Q3). Mean N-terminal pro-B-type natriuretic peptide (NT-proBNP) 3,555 ± 5,358 pg/mL, mean B-type natriuretic peptide (BNP) 585 ± 771 pg/mL, mean midregional-pro atrial natriuretic peptide (MR-proANP) 1,165 ± 856 pg/mL. [a]Median (IQR). [b]MR-proANP converted from pmol/L to pg/mL for comparisons with BNPs.

ACEI = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; HF = heart failure; LAVI = left atrial volume index; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; MRA = mineralocorticoid receptor antagonist; RVSP = right ventricular systolic pressure; TR = tricuspid regurgitation.

FIGURE 1 Distributions of Circulating Natriuretic Peptides in HF



Scatterplots of natriuretic peptides show proportional increases in midregional pro-atrial natriuretic peptide (MR-proANP) and B-type natriuretic peptides (BNPs). A distinct group of low MR-proANP but high BNP/N-terminal pro-B-type natriuretic peptide (NT-proBNP) was not identifiable. HF = heart failure.

biomarker tertiles. The predictive ability of each biomarker for selected outcomes as binary events was determined by area under receiver-operating characteristics curve (AUROC). A 10-fold cross validation with random sampling of 80% of the observations for training and the rest for testing was performed. Statistical analyses were performed with STATA MP version 16 with 5% level of significance.

RESULTS

Among 1,548 patients with HF, 1,278 (age 60.1 ± 12.1 years, 82% male, BMI 26.7 ± 5.6 kg/m^2, 85% NYHA functional class I/II, LVEF 33.9% ± 14.2%) with measurements of all 3 NPs were included. Of those included (84% HFrEF, 16% HFpEF), 68% had hypertension, 55% diabetes, 57% ischemic HF etiology, and 22% had AF (Table 1). None were on angiotensin receptor/neprilysin inhibitors (ARNIs) at the time of study. Over a mean follow-up of 577 ± 261 days, 548 (35.4%) had a primary outcome event, with 420 (27.1%) HF-hospitalizations, 580 (37.5%) cardiovascular admissions, and 209 (13.5%) all-cause deaths.

CIRCULATING BIOMARKER PROFILE. Median biomarker concentrations were: MR-proANP 990 pg/mL (Q1-Q3: 557-1,563 pg/mL), NT-proBNP 1,648 pg/mL (Q1-Q3: 652-3,960 pg/mL), and BNP 291 pg/mL (Q1-Q3: 103-777 pg/mL). Strong correlations were seen between the 3 NPs (MR-proANP vs NT-proBNP: r = 0.876; $P < 0.001$; MR-proANP vs BNP: r = 0.867; $P < 0.001$; NT-proBNP vs BNP: r = 0.920; $P < 0.001$). Scatterplots of $\log_{10}$NP concentrations showed similar slope and density across the range of peptide concentrations with no anomalous subgroup of distinctly low MR-proANP concentrations relative to concurrent plasma concentrations of NT-proBNP or BNP (Figure 1). Similar event rates were observed between NPs across all tertiles, except marginally lower rates of the primary outcome and HF-hospitalization in the first tertile of MR-proANP relative to BNP ($P < 0.05$) (Supplemental Table 1). Notably, this modest trend is opposite in direction to that expected should ANP be inappropriately low.

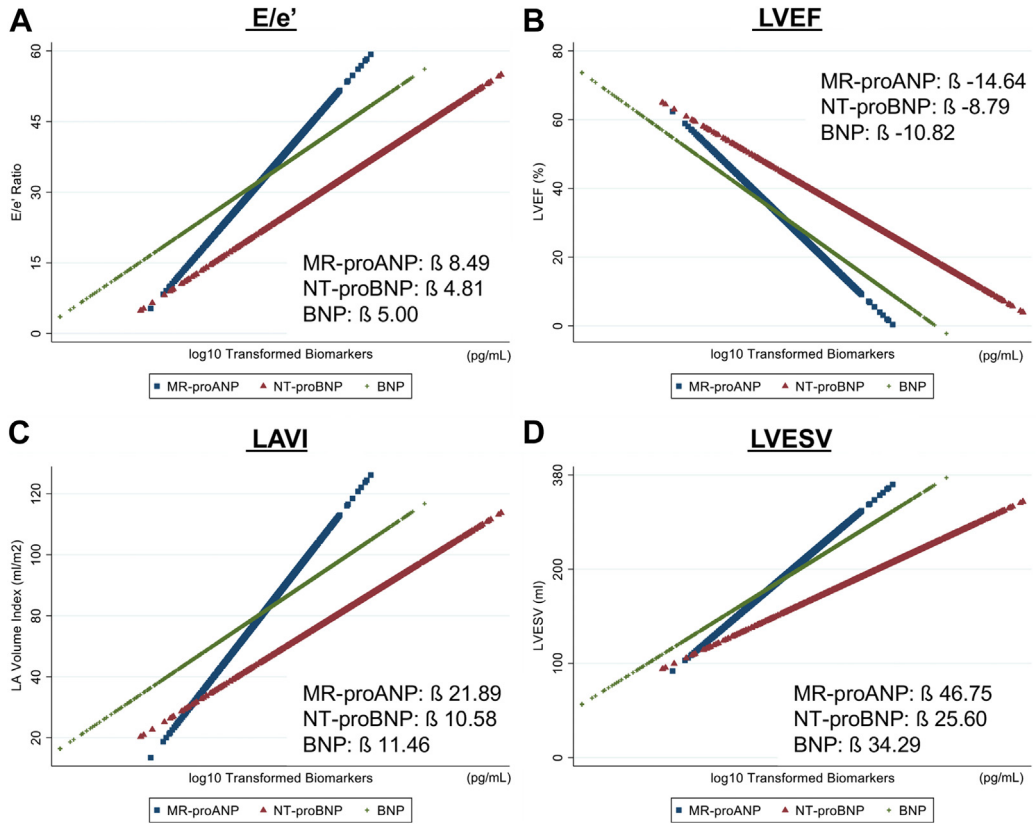
ASSOCIATION WITH CARDIAC STRUCTURE AND FUNCTION. The associations of individual NPs with LV size and systolic (LVEF) and diastolic function (LAVI, E/e′ right ventricular systolic pressure, peak tricuspid regurgitation velocity) at baseline are shown in Table 2 (scatterplots of correlations provided in Supplemental Figure 1). Any given proportional shift in each of the evaluated echocardiographic variables was associated with greater concurrent change (steeper association with highest beta-coefficient) in plasma concentration of MR-proANP than BNPs ($P < 0.001$) (Figure 2). In 769 patients with repeat TTE at 6 months, the associations of change in NP levels with echocardiographic parameters are shown in Table 2. MR-proANP (per unit increase) consistently showed a greater reduction in LVEF and greater increase in LAVI and LVESV when compared with either BNP ($P < 0.05$) (Table 2). LV reverse remodeling, defined as a >15% reduction in LV end-systolic volume indexed by body surface area,[22] occurred in 426 (60%) patients. Baseline MR-proANP ($\log_{10}$) was the only NP significantly associated with lower odds of reverse remodeling (adjusted OR: 0.35; 95% CI: 0.17-0.72; $P = 0.004$) adjusting for

TABLE 2 Association of Biomarkers With Cardiac Function and Structure

	Biomarker	Beta	95% CI	*P* Value[a]	R^2
Association of biomarkers and echocardiographic parameters at baseline					
LVEF	MR-proANP	−14.64	−16.84 to −12.64	Ref.	0.123
	NT-proBNP	−8.79	−9.89 to −7.69	<0.001	0.152
	BNP	−10.82	−11.83 to −9.80	<0.001	0.235
LAVI	MR-proANP	21.89	19.59 to 24.18	Ref.	0.19
	NT-proBNP	10.58	9.29 to 11.87	<0.001	0.151
	BNP	11.46	10.23 to 12.29	<0.001	0.183
LVEDD	MR-proANP	6.63	5.21 to 8.04	Ref.	0.056
	NT-proBNP	3.56	2.79 to 4.34	<0.001	0.055
	BNP	4.79	4.06 to 5.52	<0.001	0.101
LVESD	MR-proANP	9.56	7.83 to 11.28	Ref.	0.074
	NT-proBNP	5.37	4.43 to 6.32	<0.001	0.079
	BNP	7.12	6.27 to 7.98	<0.001	0.144
LVEDV	MR-proANP	38.62	29.09 to 48.15	Ref.	0.049
	NT-proBNP	21.36	16.26 to 26.47	<0.001	0.051
	BNP	29.58	24.54 to 34.61	<0.001	0.1
LVESV	MR-proANP	46.75	38.24 to 55.25	Ref.	0.082
	NT-proBNP	25.6	21.08 to 30.13	<0.001	0.084
	BNP	34.29	29.81 to 38.77	<0.001	0.155
TR velocity	MR-proANP	0.74	0.65 to 0.83	Ref.	0.172
	NT-proBNP	0.38	0.33 to 0.43	<0.001	0.154
	BNP	0.39	0.35 to 0.44	<0.001	0.169
RVSP	MR-proANP	19.83	17.12 to 22.53	Ref.	0.176
	NT-proBNP	9.88	8.30 to 11.46	<0.001	0.151
	BNP	10.59	9.18 to 11.99	<0.001	0.178
E/e′	MR-proANP	8.49	7.32 to 9.66	Ref.	0.137
	NT-proBNP	4.81	4.12 to 5.50	<0.001	0.148
	BNP	5	4.36 to 5.63	<0.001	0.164
Association of change in biomarkers and echocardiographic parameters at baseline					
LVEF (delta)	MR-proANP (delta)	−0.006	−0.007 to −0.005	Ref.	0.132
	NT-proBNP (delta)	−0.0006	−0.0008 to −0.0004	<0.001	0.065
	BNP (delta)	−0.004	−0.006 to −0.003	0.002	0.087
LAVI (delta)	MR-proANP (delta)	0.008	0.006 to 0.009	Ref.	0.1
	NT-proBNP (delta)	0.0005	0.0002 to 0.0007	<0.001	0.02
	BNP (delta)	0.004	0.003 to 0.006	<0.001	0.042
LVESV (delta)	MR-proANP (delta)	0.02	0.01 to 0.02	Ref.	0.056
	NT-proBNP (delta)	0.002	0.001 to 0.003	<0.001	0.029
	BNP (delta)	0.01	0.005 to 0.01	0.012	0.025

[a]The differences between coefficients were tested against that of MR-proANP (Ref.).
Ref. = Reference; other abbreviations as in Table 1.

FIGURE 2 Association of Natriuretic Peptides and Echocardiographic Parameters



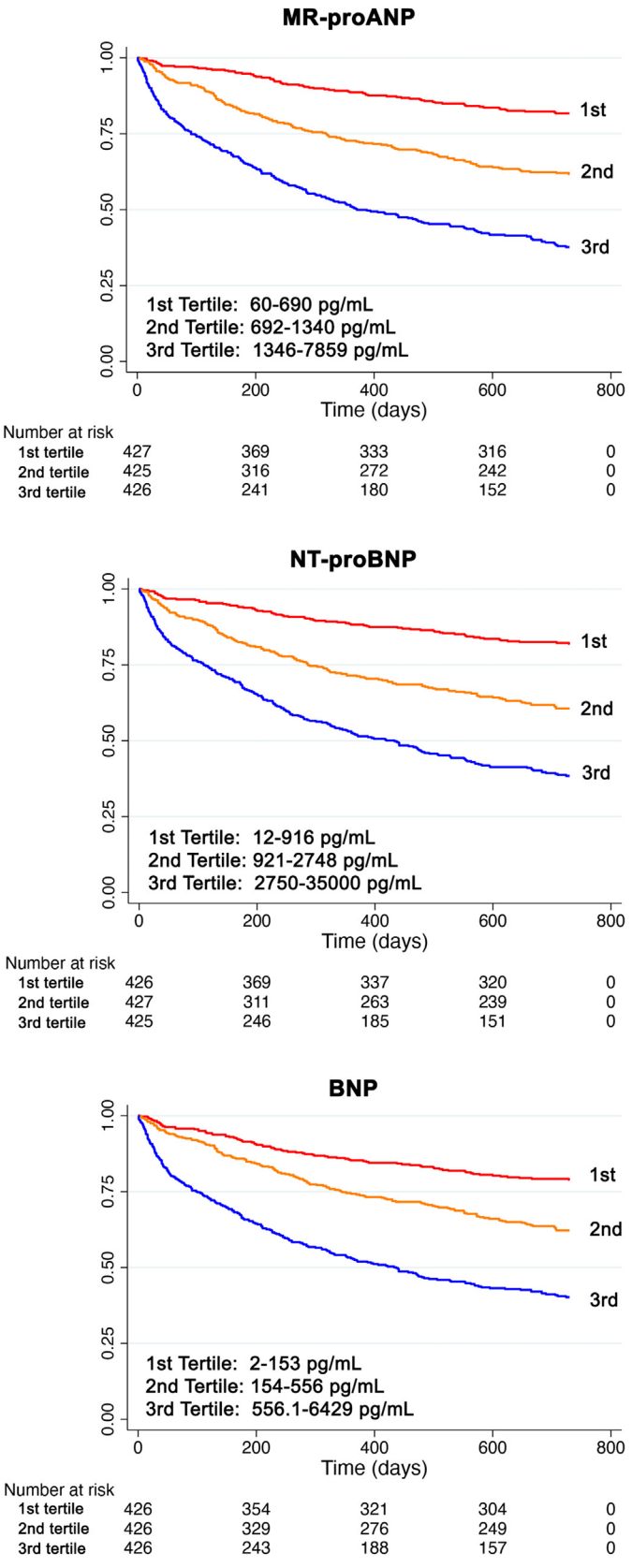
Associations between MR-proANP and echocardiographic parameters were steeper than for BNPs, with significantly higher beta-coefficients (*$P < 0.05$ in reference to MR-proANP). LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; other abbreviations as in Figure 1.

age, sex, BMI, hypertension, diabetes, ischemic etiology of HF, creatinine, LVEF, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists.

ASSOCIATION OF NPs WITH CLINICAL OUTCOMES. Univariable Cox regression analyses of NPs with clinical outcomes are shown in Supplemental Table 2, and Kaplan-Meier survival curves for the primary outcome according to NP tertiles are provided in Figure 3. Adjusting for age, gender, BMI, hypertension, diabetes, ischemic HF etiology, AF, heart rate, pulse pressure, creatinine, NYHA functional class (III/IV vs I/II), LVEF, LAVI, E/e′, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, loop diuretic agents, and mineralocorticoid receptor antagonists, all NPs were independently prognostic but MR-proANP consistently demonstrated the highest risk per proportional increment (log_{10}) across all clinical outcomes with a 6-times increased hazard of the primary outcome, HF-hospitalization and all-cause mortality, and a 4-times increased hazard of cardiovascular admission ($P < 0.05$) (Table 3), and consistently more than twice that observed for NT-proBNP and BNP. Multivariable modeling of the primary outcome incorporating clinical factors without NPs is shown in Supplemental Table 3.

In paired-biomarker models, MR-proANP retained its independent prognostic value with respect to the primary outcome, HF-hospitalization and cardiovascular admissions. MR-proANP attenuated the significance of both NT-proBNP and BNP with respect to HF-hospitalization, and of BNP with respect to the primary outcome ($P > 0.05$) (Table 3). By contrast, the prognostic value of MR-proANP for all-cause mortality was attenuated in models including either of the BNPs ($P > 0.05$). When all NPs were included, only

FIGURE 3 Kaplan-Meier Curves in Relation to the Primary Outcome



Biomarker concentrations in the highest tertile had the worst event-free survival compared with the lowest tertile. Abbreviations as in Figure 1.

TABLE 3 Associations of Biomarkers With Clinical Outcomes

	Primary Outcome		HF-Hospitalization		Cardiovascular Admission		All-Cause Mortality	
	AHR (95% CI)	*P* Value	AHR (95% CI)	*P* Value	AHR (95% CI)	*P* Value	AHR (95% CI)	*P* Value
Single-marker models								
MR-proANP	5.71 (3.48-9.37)	<0.001	5.54 (3.19-9.62)	<0.001	3.99 (2.53-6.32)	<0.001	7.57 (3.25-17.65)	<0.001
NT-proBNP	2.39 (1.86-3.08)	<0.001	2.17 (1.64-2.87)	<0.001	2.06 (1.62-2.60)	<0.001	3.50 (2.25-5.46)	<0.001
BNP	2.22 (1.72-2.85)	<0.001	2.06 (1.56-2.73)	<0.001	2.08 (1.64-2.64)	<0.001	3.00 (1.93-4.68)	<0.001
Paired-marker models								
MR-proANP + NT-proBNP								
MR-proANP	2.90 (1.45-5.81)	0.003	3.60 (1.64-7.90)	0.001	2.20 (1.13-4.30)	0.021	2.19 (0.72-6.71)	0.168
NT-proBNP	1.64 (1.15-2.33)	0.006	1.36 (0.91-2.04)	0.130	1.53 (1.08-2.16)	0.016	2.71 (1.53-4.82)	0.001
MR-proANP + BNP								
MR-proANP	3.73 (1.80-7.72)	<0.001	4.49 (1.98-10.20)	<0.001	2.11 (1.05-4.24)	0.037	2.83 (0.84-9.56)	0.094
BNP	1.35 (0.93-1.96)	0.115	1.16 (0.76-1.76)	0.497	1.55 (1.08-2.23)	0.017	2.05 (1.09-3.85)	0.025
NT-proBNP + BNP								
NT-proBNP	2.02 (1.29-3.18)	0.002	1.81 (1.08-3.01)	0.023	1.43 (0.92-2.23)	0.108	2.99 (1.39-6.43)	0.005
BNP	1.23 (0.78-1.94)	0.375	1.25 (0.75-2.09)	0.397	1.54 (0.99 -2.39)	0.057	1.22 (0.56-2.63)	0.618
Multimarker models								
MR-proANP	3.00 (1.42-6.33)	0.005	3.82 (1.64-8.91)	0.002	1.89 (0.92-3.90)	0.084	2,21 (0.66-7.44)	0.199
NT-proBNP	1.70 (1.08-2.69)	0.023	1.45 (0.86-2.45)	0.159	1.29 (0.82-2.04)	0.268	2.74 (1.28-5.88)	0.010
BNP	0.94 (0.58-1.52)	0.805	0.90 (0.52-1.55)	0.704	1.31 (0.81-2.10)	0.271	0.99 (0.43-2.23)	0.972

All models adjusted for age, gender, body mass index, hypertension, diabetes, ischemic etiology of HF, AF, heart rate, estimated glomerular filtration rate, pulse pressure (difference between systolic and diastolic blood pressure), NYHA functional class (III/IV vs I/II), LVEF, LAVI, E/e' ratio, and medication use (ACEI/ARB, beta-blocker, loop diuretic, MRA).

AHR = adjusted HR; other abbreviations as in Table 1.

MR-proANP (adjusted HR [AHR]: 3.08; 95% CI: 1.51-6.30) and NT-proBNP (AHR: 1.69; 95% CI: 1.08-2.63) were independently associated with the primary outcome. For secondary outcomes in triple-marker models, MR-proANP was the sole NP independently associating with higher risk of HF-hospitalization and cardiovascular admission, whereas NT-proBNP was the only NP associated with all-cause death ($P < 0.05$)

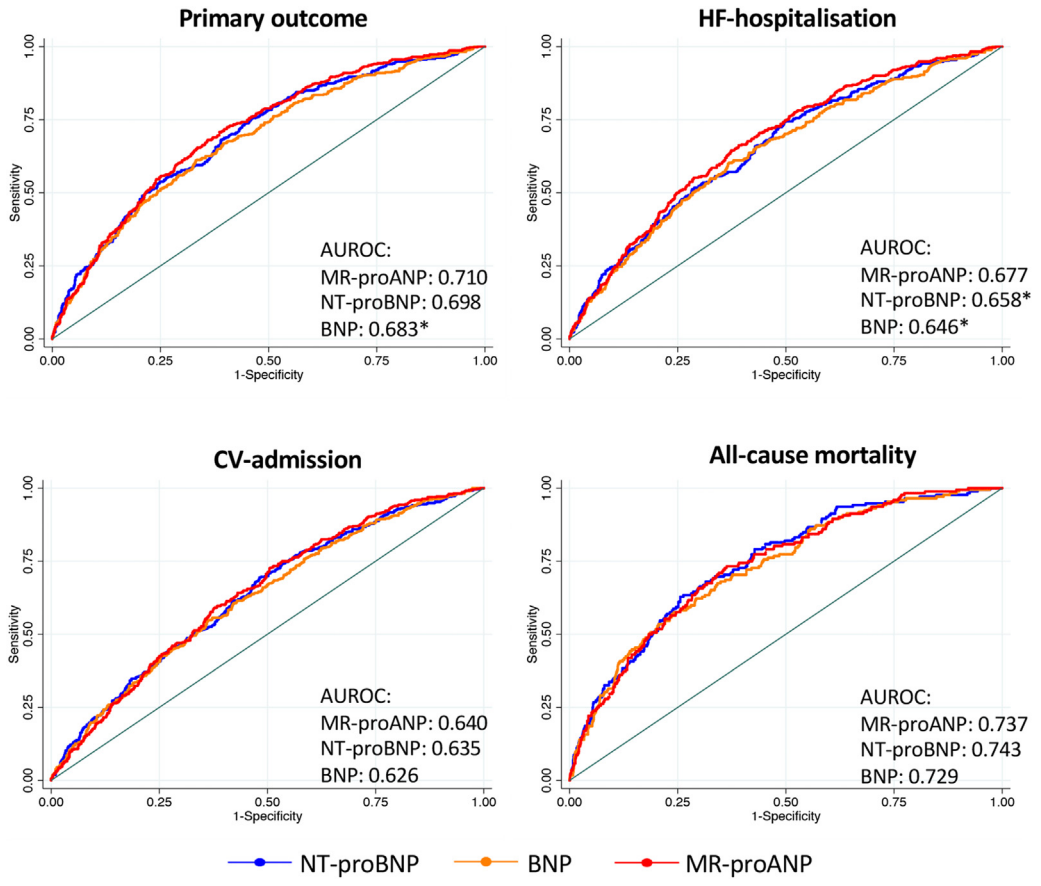
TABLE 4 Discriminative Value of NPs for Clinical Outcomes

	AUROC	95% CI	*P* Value[a]		AUROC	95% CI	*P* Value[b]	*P* Value[c]
Primary outcome								
Clinical model	0.721	0.69-0.75						
Clinical model + MR-proANP	0.750	0.72-0.78	<0.001	MR-proANP	0.710	0.68-0.74		
Clinical model + NT-proBNP	0.747	0.72-0.78	0.002	NT-proBNP	0.698	0.67-0.73	0.159	
Clinical model + BNP	0.742	0.71-0.77	0.007	BNP	0.683	0.65-0.71	0.002	0.029
HF-hospitalization								
Clinical model	0.689	0.65-0.72						
Clinical model + MR-proANP	0.717	0.68-0.75	0.003	MR-proANP	0.677	0.64-0.71		
Clinical model + NT-proBNP	0.708	0.67-0.74	0.030	NT-proBNP	0.658	0.62-0.69	0.035	
Clinical model + BNP	0.707	0.67-0.74	0.033	BNP	0.646	0.61-0.68	0.002	0.147
Cardiovascular admission								
Clinical model	0.661	0.63-0.69						
Clinical model + MR-proANP	0.688	0.65-0.72	0.003	MR-proANP	0.524	0.49-0.56		
Clinical model + NT-proBNP	0.685	0.65-0.72	0.010	NT-proBNP	0.560	0.52-0.60	0.600	
Clinical model + BNP	0.686	0.65-0.72	0.008	BNP	0.626	0.59-0.66	0.129	0.191
All-cause mortality								
Clinical model	0.764	0.72-0.81						
Clinical model + MR-proANP	0.787	0.75-0.83	0.008	MR-proANP	0.737	0.70-0.77		
Clinical model + NT-proBNP	0.799	0.76-0.84	0.004	NT-proBNP	0.743	0.70-0.78	0.611	
Clinical model + BNP	0.788	0.75-0.83	0.013	BNP	0.729	0.69-0.77	0.532	0.157

[a]Compared with clinical model. [b]Compared with MR-proANP. [c]Compared with NT-proBN.

AUROC = area under receiver-operating characteristics curve; all other abbreviations as in Table 1.

FIGURE 4 Area Under Operating Receiver-Operating Characteristics Curve of Natriuretic Peptides in Relation to Clinical Outcomes



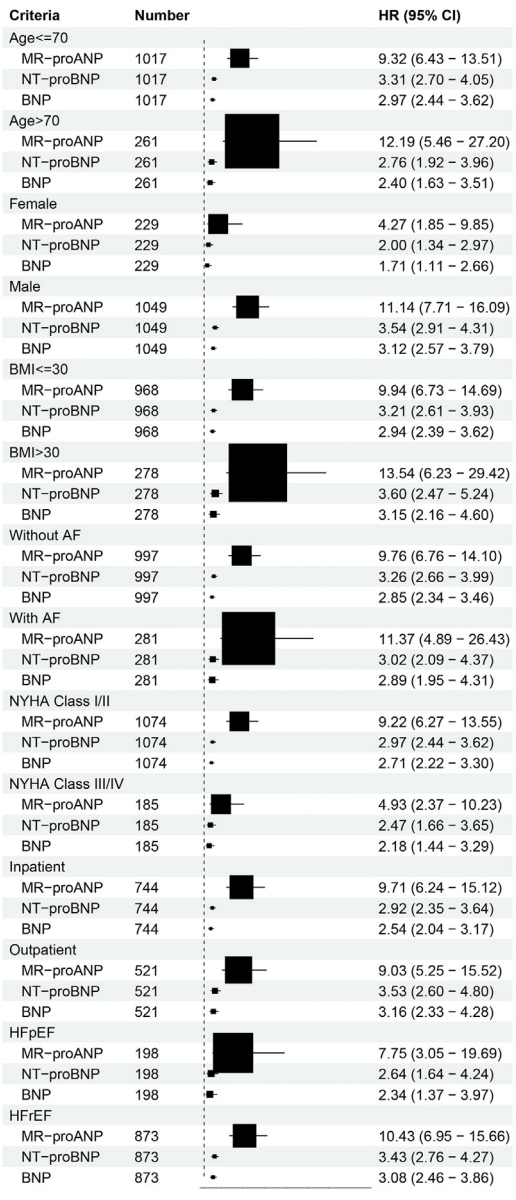
MR-proANP was superior to NT-proBNP and BNP for discriminating HF-hospitalization and was superior to BNP for the primary outcome, but was similar to BNPs for CV admission and all-cause mortality. *$P < 0.05$. Abbreviations as in Figure 1.

(Table 3). The stronger prognostic performance of MR-proANPs compared with either of the BNPs was confirmed on 10-fold cross validation.

DISCRIMINATIVE ABILITY OF NPs. AUROCs of each NP with respect to individual clinical outcomes are shown in Table 4 and Figure 4. All NPs added significantly to the discriminative value of the comprehensive clinical model across all clinical outcomes ($P < 0.05$) (Supplemental Figure 2). When considered singly, MR-proANP was superior in discriminating HF-hospitalization compared with NT-proBNP (AUROC 0.688 vs 0.658; $P = 0.035$) and BNP (AUROC 0.677 vs 0.646; $P = 0.002$), and additionally the primary outcome compared with BNP (AUROC 0.710 vs 0.683; $P = 0.002$). The discriminative values of NT-proBNP and BNP were generally similar for all outcomes, with NT-proBNP being modestly superior to BNP with regard to the primary outcome ($P = 0.029$).

SUBGROUP ANALYSES. Interaction testing and subgroup analyses by age, sex, obesity, NYHA functional class, AF status, HF etiology, LVEF, and admission status are shown in Supplemental Tables 4 and 5, and a Forest plot of univariable associations of each NP with the primary outcome is shown in Figure 5. Significant sex interactions were present for all NPs with respect to the primary outcome (MR-proANP: $P_{\text{interaction}} = 0.043$, NT-proBNP: $P_{\text{interaction}} = 0.013$, BNP: $P_{\text{interaction}} = 0.016$), and for NT-proBNP and BNP for HF-hospitalizations and cardiovascular admission (all $P_{\text{interaction}} < 0.05$), with higher hazards conferred by NPs in men than women (sex differences in baseline characteristics shown in Supplemental Table 6). There were no interactions with age, NYHA functional

FIGURE 5 Forest Plot of Natriuretic Peptides Associations With Primary Outcome in Subgroup Analyses



MR-proANP demonstrated the largest hazard of the primary outcome of HF-hospitalizations or all-cause mortality per $\log_{10}$ increment in natriuretic peptide concentrations. Significant interaction with sex was noted across all natriuretic peptides ($P_{interaction} < 0.05$), with higher hazards of the primary outcome per $\log_{10}$ increment in all natriuretic peptide concentrations in men than women. AF = atrial fibrillation; BMI = body mass index; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; other abbreviations as in Figure 1.

class status, AF, ischemic etiology, LVEF, and admission status ($P > 0.05$). Adjusting for clinical variables, the stronger prognostic performance of NPs persisted for MR-proANP (men: AHR: 9.68 [95% CI: 5.66-16.55]; women: AHR: 6.76 [95% CI: 1.98-23.08]), but became less pronounced for NT-proBNP/BNP (Table 5). Significant interactions were additionally noted for obesity with NT-proBNP and BNP ($P_{interaction} < 0.05$), with higher hazards of all-cause mortality in nonobese than obese patients (comparison of characteristics by obesity status in Supplemental Table 6), which persisted after multivariable adjustment (Table 5).

DISCUSSION

In this large HF cohort, cardiac-specific NPs exhibited differential circulating profiles and associations with cardiac structure/function and differing prognostic performance, additive to established risk factors. MR-proANP displayed consistent relationships to concurrent NT-proBNP and BNP without any subpopulation of inappropriately low MR-proANP mapping to relatively higher B-peptide values, thus providing no evidence of a relative ANP-deficiency state as suggested in a recent report.[17] Compared with BNPs, shifts in MR-proANP had the steepest associations with concurrent shifts in key components of cardiac structure and both systolic and diastolic functional indexes, and associated most strongly with worsening of LV function and structure longitudinally.

MR-proANP portended the highest risk of adverse outcomes per proportional increase in plasma concentrations and was superior in predicting recurrent HF, attenuating the significance of BNPs in multimarker prognostic models. Conversely, its prognostic significance for all-cause mortality was attenuated by the BNPs. These differential relationships to cardiac structure/function and prognosis suggest that, among NPs considered, MR-proANP offers the greatest value for risk stratification for adverse cardiovascular events in HF (Central Illustration).

DIFFERENTIAL NP PROFILES. In HF, ANP and BNP are released in response to myocardial stretch.[1] The pattern of circulating BNPs in our study mirrors other HF cohorts in approximating a 6:1 NT-proBNP/BNP ratio.[23] Despite 1:1 secretion after enzymatic cleavage of proBNP, BNP circulates at much lower levels due to its shorter half-life compared with NT-proBNP (20 minutes vs 120 minutes).[6] Predominantly produced in the atria under normal conditions, ANP

reverts to the fetal gene program with abundant ventricular expression in severe HF.[24] Proportionate ANP secretion, reflected by MR-proANP (due to their equimolar cosecretion), finds support in the comparable mean values of MR-proANP (246 pmol/L vs 241 pmol/L, respectively) and NT-proBNP (1,645 pmol/L vs 1,671 pg/mL) in our study and those reported in a chronic HF cohort.[11] When plotted against B-type peptides, an outlier group of MR-proANP levels disproportionately low relative to concurrent B-type peptides was not observed. This was further corroborated by the similar clinical event rates in the lowest tertiles of all 3 NPs. In the presence of a true ANP-deficient state, one might expect a higher incidence of clinical events in the lowest tertile of MR-proANP (with correspondingly high BNP levels) compared with those in the lowest tertile of BNP/NT-proBNP. Taken together, these data offer no support for a relative deficiency of circulating ANPs, as has been suggested.[17]

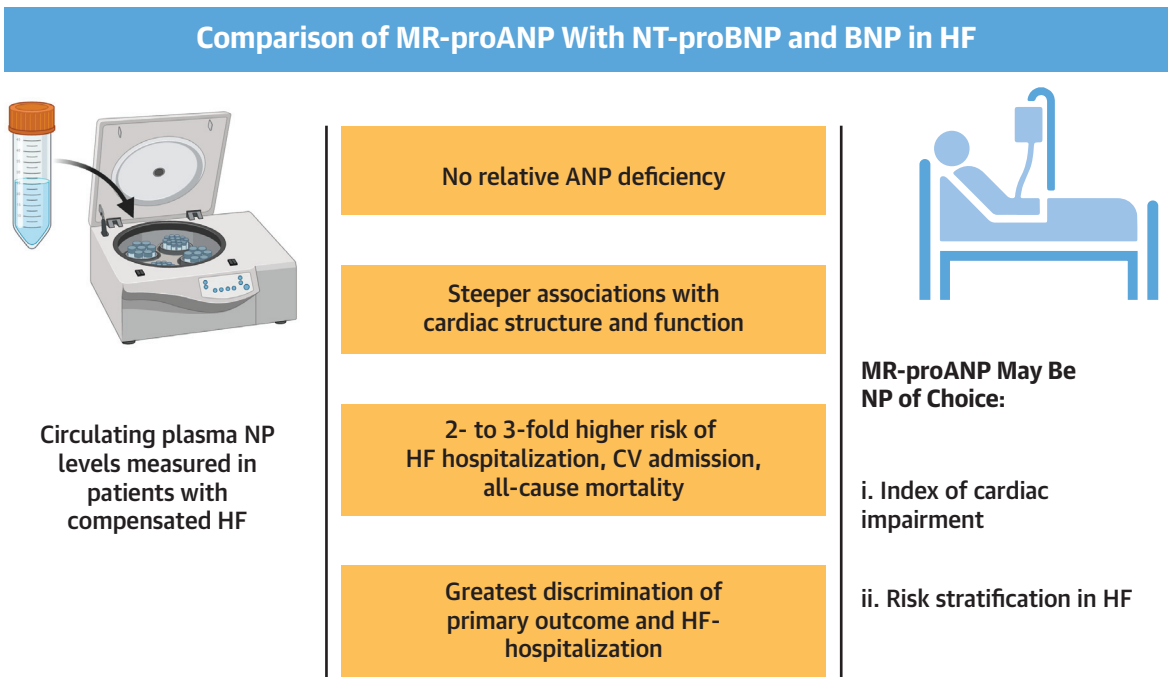
TABLE 5 Subgroup Analyses of Natriuretic Peptides With Significant Interactions With Clinical Outcomes

	Female[a]			Male[a]		
	AHR	95% CI	*P* Value	AHR	95% CI	*P* Value
Primary outcome						
MR-proANP	6.76	1.98-23.08	0.002	9.68	5.66-16.55	<0.001
NT-proBNP	2.39	1.36-4.22	0.003	2.93	2.24-3.83	<0.001
BNP	2.1	1.16-3.81	0.014	2.55	1.97-3.32	<0.001
HF-hospitalizations						
NT-proBNP	2.18	1.20-3.95	0.01	2.72	2.02-3.67	<0.001
BNP	1.9	1.00-3.58	0.048	2.35	1.76-3.15	<0.001
Cardiovascular admission						
NT-proBNP	1.66	1.02-2.70	0.042	2.45	1.91-3.16	<0.001
BNP	1.58	0.93-2.70	0.093	2.27	1.77-2.90	<0.001
	BMI ≤30 kg/m²[b]			BMI >30 kg/m²[b]		
All-cause mortality						
NT-proBNP	4.03	2.63-6.19	<0.001	2.79	1.69-8.50	0.001
BNP	4.02	2.52-6.40	<0.001	2.97	1.26-7.00	0.013

[a]Adjusted for age, BMI, diabetes, ischemic etiology HF, creatinine, LVEF, LAVI, LVESV, and MRA. [b]Adjusted for age, gender, HTN, ischemic HF, LVEF, LAVI, and E/e′.

Abbreviations as per Table 1.

CENTRAL ILLUSTRATION Differential Associations of A- and B-Type NPs in Relation to Cardiac Structure/Function and Prognosis



Tan ESJ, et al. J Am Coll Cardiol HF. 2024;12(3):461–474.

Measurements of circulating MR-proANP, NT-proBNP, and BNP concentrations in patients with HF was not consistent with an ANP deficiency state and showed steeper MR-proANP associations with cardiac structure and function and stronger prognostic value over NT-proBNP and BNP, suggesting a role for MR-proANP to be the natriuretic peptide of choice in risk stratifying HF. ANP = A-type natriuretic peptide; BNP = B-type natriuretic peptide; CV = cardiovascular; HF = heart failure; MR-proANP = midregional pro-atrial natriuretic peptide; NP = natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

ASSOCIATION WITH CARDIAC STRUCTURE AND FUNCTION. Although NP associations with left atrial size, LV diastolic indexes, and RV dimensions and function have been described in other cardiac conditions,[25-27] direct comparisons between the NPs, with regard to cardiac structure and function in HF, are sparse. MR-proANP associated more strongly with left atrial volume on computed tomography than NT-proBNP in patients without HF,[26] and MR-proANP but not BNP correlated with echocardiographic markers of congestion in AHF.[25] We extend current published reports by demonstrating that although all NPs correlated with multiple echocardiographic indexes of cardiac structure and function, the associations with MR-proANP were steeper in cross-sectional analysis, and over time with dynamic changes in echocardiographic parameters. MR-proANP was also the sole NP associated with absence of LV reverse remodeling.

These differential NP associations might in part be related to their biological properties. In natriuretic peptide receptor-A knockout mice, pressure overload induced by transverse aortic constriction led to 15-fold increased ANP, 55% increased LV weight and dilatation, and significant LV function decline.[28] It is hard to ascertain if this is due primarily to loss of ANP or BNP bioactivity, because both bind to natriuretic peptide receptor-A, but the sharp increase in ANP is consistent with the return to fetal gene profiles with increased ANP expression in failing hearts, and also a marker of pathologic hypertrophy, characteristic of HFpEF (concentric) and HFrEF (eccentric).[29,30] The closer relationship of ANP to cardiac hypertrophy and remodeling was demonstrated in ANP knockout mice subjected to pressure overload,[31] whereas BNP knockout mice subjected to pressure overload showed increased focal fibrosis without significant ventricular hypertrophy.[32] Steeper associations of MR-proANP with LV size (and hypertrophy) and indexes of diastolic and systolic dysfunction may reflect distinct NP responses to pathological stimuli, further highlighting differential biological roles in HF.

PROGNOSTIC EVALUATION OF NPs. Our findings affirm the known independent prognostic values of MR-proANP and B-type NPs in HF.[4,10-16,20] We extend beyond previous reports by demonstrating that the risk associated with MR-proANP was 2 to 3 times higher than that conferred by equivalent increments in NT-proBNP or BNP, and was superior in discriminating adverse outcomes compared with BNP/NT-proBNP. The mechanisms underlying this superior prognostication of cardiovascular events in HF by MR-proANP is uncertain but may be linked to its higher biological stability and close associations with atrial size and AF,[10,12] both of which were accounted for in our analyses. Likewise, the stronger relationship of MR-proANP to lower likelihood of LV reverse remodeling, diastolic dysfunction, and filling pressure may contribute to its predictive power for HF recurrence. Differential secretory patterns, in which BNP is rapidly expressed into the circulation suggesting an "emergency-rescue" role, compared with a regulatory role with more graduated changes in ANP expression,[33] may further underlie their different prognostic associations. Notably, NPs displayed stronger prognostic associations in men, which adds to the conflicting evidence on BNPs[34,35] and is novel in regard to MR-proANP,[11] despite accounting for sex-specific differences in clinical risk factors. Exact pathophysiological mechanisms merit further investigation, but the greater prognostic value and comparable diagnostic utility[8,9] afforded by MR-proANP suggest its role as the NP of choice for cardiovascular risk stratification in the clinical management of HF.

STUDY LIMITATIONS. The majority of subjects were men, in NYHA functional class I/II, and had HFrEF, which may limit comparability of our findings to other HF populations. Our results should be validated in an independent cohort to corroborate the differential prognostic associations of NPs in chronic HF and the performance of MR-proANP in prognostic risk scores in relation to NT-proBNP/BNP ascertained in future study. Participants were enrolled before routine use of ARNI, but because neprilysin inhibition does not alter metabolism of the amino-terminal NPs, MR-proANP would be expected to retain the observed relationships to cardiac structure/function and prognosis even in current cohorts exposed to ARNI.[36]

CONCLUSIONS

MR-proANP offered greater independent predictive power than BNP or NT-proBNP for key clinical endpoints. Proportional increments in plasma MR-proANP for given decrements in cardiac structure and function were more pronounced than observed for the BNPs. MR-proANP may be the NP of choice as a sensitive index of cardiac impairment and for cardiovascular risk stratification in HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The elevation of plasma NPs in HF underpins their guideline-endorsed incorporation in HF diagnosis and management. This study provides evidence of differential circulating profiles, associations with cardiac structure/function, and differing prognostic performance among circulating NPs. MR-proANP may be the NP of choice as a sensitive index of cardiac impairment and for risk stratification in HF.

TRANSLATIONAL OUTLOOK: Proportional increments in plasma MR-proANP for given decrements in cardiac structure and function were more pronounced and offered greater independent predictive power for key clinical endpoints than BNP or NT-proBNP. Further study into its role as the NP of choice in risk stratifying HF is required.

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KEY WORDS biomarkers, B-type natriuretic peptide, heart failure, midregional pro-atrial natriuretic peptide, N-terminal pro-BNP

APPENDIX For supplemental tables and figures, please see the online version of this paper.