ESC European Society of Cardiology

European Journal of Heart Failure (2024) **26**, 1480–1492
doi:10.1002/ejhf.3336

RESEARCH ARTICLE

Biologically active adrenomedullin as a marker for residual congestion and early rehospitalization in patients hospitalized for acute heart failure: Data from STRONG-HF

Geert Voordes[1], Beth Davison[2,3,4,5], Jan Biegus[6], Christopher Edwards[4], Kevin Damman[1], Jozine ter Maaten[1], Alexandre Mebazaa[2,3], Koji Takagi[4], Marianna Adamo[7], Andrew P. Ambrosy[8,9], Mattia Arrigo[10], Marianela Barros[4], Jelena Celutkiene[11], Kamilė Čerlinskaitė-Bajorė[11], Ovidiu Chioncel[12], Alain Cohen-Solal[13], Albertino Damasceno[14], Benjamin Deniau[2,3], Rafael Diaz[15], Gerasimos Filippatos[16], Etienne Gayat[2,3], Antoine Kimmoun[17], Carolyn S.P. Lam[18,19,20], Marco Metra[7], Maria Novosadova[4], Matteo Pagnesi[7], Peter Pang[21], Piotr Ponikowski[6], Hadiza Saidu[22], Karen Sliwa[23], Daniela Tomasoni[7], Gad Cotter[2,3,4,5], and Adriaan A. Voors[1]*

[1]Department of Cardiology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands; [2]Université Paris Cité, INSERM UMR-S 942 (MASCOT), Paris, France; [3]Department of Anesthesiology and Critical Care and Burn Unit, Saint-Louis and Lariboisière Hospitals, FHU PROMICE, DMU Parabol, APHP Nord, Paris, France; [4]Momentum Research, Durham, NC, USA; [5]Heart initiative, Durham, NC, USA; [6]Institute of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland; [7]Cardiology, Cardiology, ASST Spedali Civili and Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; [8]Department of Cardiology, Kaiser Permanente San Francisco Medical Center, San Francisco, CA, USA; [9]Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA; [10]Department of Internal Medicine, Stadtspital Zurich, Zurich, Switzerland; [11]Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [12]Emergency Institute for Cardiovascular Diseases 'Prof. C.C. Iliescu', University of Medicine 'Carol Davila', Bucharest, Romania; [13]APHP Nord, Department of Cardiology, Lariboisière University Hospital, Paris, France; [14]Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique; [15]Estudios Clínicos Latinoamérica, Instituto Cardiovascular de Rosario, Rosario, Argentina; [16]National and Kapodistrian University of Athens, School of Medicine, Attikon University Hospital, Athens, Greece; [17]Université de Lorraine, Nancy; INSERM, Défaillance Circulatoire Aigue et Chronique; Service de Médecine Intensive et Réanimation Brabois, CHRU de Nancy, Vandœuvre-lès-Nancy, France; [18]National Heart Centre Singapore and Duke-National University of Singapore, Singapore, Singapore; [19]Baim Institute for Clinical Research, Boston, MA, USA; [20]University Medical Centre Groningen, Groningen, The Netherlands; [21]Department of Emergency Medicine, Indiana University School of Medicine, Indianapolis, IN, USA; [22]Murtala Muhammed Specialist Hospital, Bayero University Kano, Kano, Nigeria; and [23]Division of Cardiology, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa

Received 15 April 2024; revised 6 May 2024; accepted 22 May 2024; online publish-ahead-of-print 14 June 2024

Aims

Biologically active adrenomedullin (bio-ADM) is a promising marker of residual congestion. The STRONG-HF trial showed that high-intensity care (HIC) of guideline-directed medical therapy (GDMT) improved congestion and clinical outcomes in heart failure (HF) patients. The association between bio-ADM, decongestion, outcomes and the effect size of HIC of GDMT remains to be elucidated.

*Corresponding author. Department of Cardiology, University Medical Center Groningen, Hanzeplein 1, P.O Box 30001, 9700 RB, Groningen HPC AB 31, The Netherlands. Tel: +31 50 3612355, Fax: +31 50 3614884, Email: a.a.voors@umcg.nl

Methods and results We measured plasma bio-ADM concentrations in 1005 patients within 2 days prior to anticipated discharge (baseline) and 90 days later. Bio-ADM correlated with most signs of congestion, with the exception of rales. Changes in bio-ADM were strongly correlated with change in congestion status from baseline to day 90 (gamma −0.24; $p = 0.0001$). Patients in the highest tertile of baseline bio-ADM concentrations were at greater risk than patients in the lowest tertile for the primary outcome of 180-day all-cause mortality or HF rehospitalization (hazard ratio [HR] 2.14, 95% confidence interval [CI] 1.42−3.22) and 180-day HF rehospitalization (HR 2.33, 95% CI 1.38−3.94). Areas under the receiver-operating characteristic curves were 0.5977 (95% CI 0.5561−0.6393), 0.5800 (95% CI 0.5356−0.6243), and 0.6159 (95% CI 0.5711−0.6607) for bio-ADM, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and their combination, respectively, suggesting that both bio-ADM and NT-proBNP provided similarly modest discrimination for this outcome. A trend towards better discrimination by combined bio-ADM and NT-proBNP than NT-proBNP alone was found ($p = 0.059$). HIC improved the primary outcome, irrespective of baseline bio-ADM concentration (interaction $p = 0.37$). In contrast to NT-proBNP, the 90-day change in bio-ADM did not differ significantly between HIC and usual care.

Conclusions Bio-ADM is a marker of congestion and predicts congestion at 3 months after a HF hospitalization. Higher bio-ADM was modestly associated with a higher risk of death and early hospital readmission and may have added value when combined with NT-proBNP.

Keywords Biologically active adrenomedullin • Acute heart failure • Residual congestion • Biomarker • STRONG-HF

Introduction

Heart failure (HF) hospitalizations present a significant clinical and economic burden worldwide. Due to the increasing prevalence of HF in the aging population, this burden is expected to increase.[1,2] Annual medical costs in the United States are projected to increase from $20.9 billion in 2012 to $53.1 billion in 2030 annually, of which 80% can be contributed to hospitalization practices.[2] Despite improving medical treatment for HF, rates for HF-specific short-term rehospitalization (90 days) are reported from 21.1% to 31.2% among adults with a diagnosis of HF.[1]

Residual congestion is one of the main drivers for HF rehospitalization. The majority of hospitalized HF patients still have signs of congestion 7 days after admission, which is associated with greater risk of death and hospital rehospitalization.[3] Assessing residual congestion is difficult and while there are multiple tools to assess residual congestion, none are currently guideline-recommended.[4,5] Therefore, improving diagnostics for residual congestion is essential to identify patients at risk for early readmissions after a hospitalization for HF.[6]

Biologically active adrenomedullin (bio-ADM) is a protein that has a prominent role in maintaining the barrier function of the vascular endothelium.[7–9] Bio-ADM is a promising marker for residual congestion.[10] Additionally, it is strongly associated with pulmonary capillary wedge pressure, right atrial pressure, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and elevated pre-discharge bio-ADM is strongly associated with HF rehospitalizations.[10–12]

Optimal treatment to relieve congestion is currently under discussion.[8,13] Although decongestion with loop diuretics remains the first choice during the early phases of a HF hospitalization, data from STRONG-HF have shown that early initiation and fast up-titration of GDMT before and shortly after discharge not only reduces congestion but improves clinical outcomes as well. However, the potential role of bio-ADM in the selection of patients that might need more aggressive decongestion remains to be established.[10]

We therefore explored the additional value of bio-ADM, on top of NT-proBNP in hospitalized HF patients who were randomized to rapid initiation and up-titration of GDMT or usual care (UC).

Methods

Study population

The methods and results of STRONG-HF have been published previously.[14] In short, STRONG-HF was a multinational, open-label, parallel-group randomized clinical trial that compared high-intensity care (HIC) comprising rapid up-titration of GDMT versus UC. The trial ended prematurely due to greater than expected between-group differences favouring the HIC group. Haemodynamically stable patients from 18 to 85 years old, admitted for acute HF were screened within 72 h of admission. Patients were required to have elevated NT-proBNP concentrations (>2500 pg/ml), a more than 10% decrease in concentration between screening and randomization (but still >1500 pg/ml) and not been treated with optimal doses of GDMT 2 days before anticipated discharge, when they were randomized to HIC or UC. Lastly, patients with clear intolerances for any high-dose GDMT were excluded from the trial. Ultimately, 1078 patients were randomized in STRONG-HF, before the trial was prematurely terminated for efficacy.

Biomarker assays

Plasma samples were obtained at baseline and day 90 and stored locally at −20°C or colder until shipped to a central laboratory (SphingoTec GmbH, Henningsdorf, Germany) for analysis. Immunoluminometric

assays were used to measure bio-ADM (sphingotest® bioADM®). In essence, the bio-ADM immunoassay is a single-step sandwich chemiluminescence technique utilizing acridinium NHS-ester labelling. The assay is designed for detecting human ADM directly in unprocessed plasma, requiring only 100 µl of plasma samples/calibrators and 220 µl of labelled detection antibody. The assay employs two mouse monoclonal antibodies, one targeting the mid-region and the other the amidated C-terminal moiety of ADM. EDTA plasma containing bio-ADM remains stable for 24 h at room temperature and can endure at least four freeze-thaw cycles without significant impact on sample integrity. Based on the manufacturer's instruction for use, the 97.5th percentile for sphingotest® bio-ADM® in healthy adult subjects is 29 pg/ml (90% confidence interval [CI] 27–38 pg/ml). Its specificity lies in its reactivity solely to the mature amidated C-terminus of ADM, distinguishing it form other (pro-ADM) variants.[15,16]

Values of NT-proBNP were obtained locally, at randomization and day 90 in both the HIC and UC groups, and additionally at visits 1, 2, 3, and 6 weeks following randomization in the HIC group, using either the Roche CARDIAC POC NT-proBNP on a cobas® h232 POC system or Elecsys® NT-proBNP (Roche Diagnostics GmbH, Mannheim, Germany). Physicians rated signs and symptoms of congestion at each in-person visit. Patients at sites where a protocol amendment extended the study to 180 days were followed up with a phone call at 180 days to assess outcomes. The study was approved by the appropriate competent authorities and ethics committees, and patients gave their written, informed consent to participate.

Statistical methods

Data as available are included in the analyses. Bio-ADM values less than the lower limit of quantitation (LLOQ; 10.8 pg/ml) were set to half the lower limit, and NT-proBNP values were set to the minimum upper limit of quantitation (9000 ng/L) among assays employed, for analysis. The cohort was split into tertiles based on the baseline bio-ADM concentration. Bio-ADM values <LLOQ are included in the lowest tertile. To compare the bio-ADM with NT-proBNP, analyses were replicated using tertiles of baseline NT-proBNP, where not previously published. Normally distributed continuous variables are reported as mean (± standard deviation [SD]) and non-normally distributed continuous variables are reported as median (interquartile range). Trends across tertiles were assessed using Cochran–Armitage tests for binary variables, Jonckheere's trend test for continuous variable, Cochran–Mantel–Haenszel (CMH) general association for categorical variables and CMH non-zero correlation for ordinal variables.

Goodman–Kruskal gamma was used as a measure of associations between ordinal variables.

Successful decongestion at baseline and day 90 was defined as no oedema, no rales, and jugular venous pressure (JVP) <6 cm on physical examination. To evaluate the association of change in bio-ADM with change in congestion status, patients' change in congestion status was categorized as improved, unchanged, or worsened. Changes in bio-ADM from baseline to day 90 were categorized as a decrease >40 pg/ml, a decrease 20–40 pg/ml, a change <20 pg/ml in either direction, an increase 20–40 pg/ml, and an increase >40 pg/ml. The categories were chosen because the SD of the change among patients with detectable values at both time points was approximately 40 pg/ml.

The ability of baseline bio-ADM as a continuous measure to predict successful decongestion at day 90, and its performance relative to NT-proBNP, was examined using logistic regression. Bio-ADM values imputed as half the LLOQ were included in these models along with an indicator for whether or not the value was below the LLOQ; final models excluded the indicator when non-significant. Values were modelled using restricted cubic splines with three knots, with a joint test of the non-linear effects serving as a test of non-linearity. To illustrate the ability of various models to discriminate between patients with and without successful decongestion, receiver-operating characteristic (ROC) curves were estimated. These curves were derived using predicted probabilities obtained from a logistic regression model incorporating baseline levels of bio-ADM, NT-proBNP, and an indicator denoting whether the bio-ADM value fell below the LLOQ. Subsequently, contrasts were employed for pairwise comparisons of the area under the ROC curves (AUCs) for bio-ADM, NT-proBNP, and their combination utilizing the method proposed by DeLong *et al.*[17] Plots of the ROC curves were generated using the R package 'pROC'.[18]

The ability of baseline bio-ADM to predict clinical outcomes and its performance relative to baseline NT-proBNP were also examined. The endpoints considered were time to the first event of all-cause mortality or HF hospitalization through day 180, and time to HF hospitalization through 180 days. Deaths were censored for the latter endpoint. Patients who were enrolled at sites who followed patients to 180 days were included in these analyses; results for patients enrolled prior to implementation of a protocol amendment changing the primary endpoint from 90 to 180 days were weighted proportional to half the initial cohort's sample size. Kaplan–Meier curves are provided for both the tertiles of bio-ADM and for NT-proBNP, and further classified by treatment group, where not previously published. Differences among biomarker tertiles and their interaction with treatment were compared using Cox regression. Cox regression was further used to evaluate the predictive value of baseline bio-ADM and NT-proBNP as continuous measures. Bio-ADM values imputed as half the LLOQ were included in these models along with an indicator for whether or not the value was below the LLOQ. Values were modelled using restricted cubic splines with three knots, with a joint test of the non-linear effects serving as a test of non-linearity. To illustrate the ability of various models to discriminate between patients with and without events, time-dependent ROC curves were estimated using the inverse probability of censoring weighting method,[19–21] using R package 'timeROC'[22]; AUCs were estimated using Uno's c-statistic.

The change in bio-ADM from baseline to day 90 was compared between HIC and UC using rank ANCOVA with adjustment for baseline bio-ADM. NT-proBNP changes were compared similarly.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) or with the R statistical computing software version 4.1.1 (R Core Team 2020; R Foundation for Statistical Computing, Vienna, Austria). A p-value <0.05 was considered statistically significant.

Results

Baseline

Of the 1078 patients randomized, 1005 (93.2%) had baseline bio-ADM, 1077 (99.9%) had baseline NT-proBNP, and 1005 (93.2%) had both values available. The median baseline concentration of bio-ADM was 20.2 (range 5–383) pg/ml, with 267 (26.6%) of the available values below the LLOQ. Baseline characteristics across tertiles of bio-ADM are presented in *Table 1*. Patients whose baseline bio-ADM levels were < LLOQ were more likely

Table 1 Baseline characteristics by tertiles of biologically active adrenomedullin

Parameter	Bio-ADM <13.32 pg/ml (*n* = 335)	Bio-ADM 13.32–28.40 pg/ml (*n* = 335)	Bio-ADM >28.40 pg/ml (*n* = 335)	*p*-value for trend[a]
Age, years	61.4 (14.76)	63.3 (13.08)	63.5 (12.97)	0.0760
Sex				0.2346
Female	145 (43.3)	116 (34.6)	130 (38.8)	
Male	190 (56.7)	219 (65.4)	205 (61.2)	
Self-reported race				<0.0001
Black	109 (32.5)	56 (16.7)	55 (16.4)	
Caucasian/White	222 (66.3)	276 (82.4)	275 (82.1)	
Other	4 (1.2)	3 (0.9)	4 (1.2)	
Pacific Islander	0 (0)	0 (0)	1 (0.3)	
Geographical region				<0.0001
Europe	218 (65.1)	268 (80.0)	270 (80.6)	
Non-Europe	117 (34.9)	67 (20.0)	65 (19.4)	
NT-proBNP at screening, ng/L, geom. mean (95% CI)	5590.5 (5283.6–5915.2)	6354.2 (5975.1–6757.4)	6171.4 (5792.2–6575.3)	0.0321
History of atrial fibrillation or atrial flutter or present at screening	111 (33.1)	159 (47.5)	180 (53.7)	<0.0001
Medical history				
Stroke or transient ischaemic attack	36 (10.7)	27 (8.1)	30 (9.0)	0.4380
Severe liver disease	1 (0.4)	1 (0.4)	3 (1.1)	0.2941
Psychiatric or neurological disorder	7 (2.1)	4 (1.2)	7 (2.1)	0.9999
Malignancies	9 (2.7)	12 (3.6)	7 (2.1)	0.6385
Diabetes	75 (22.4)	90 (27.0)	127 (38.0)	<0.0001
Diabetes control method				
Insulin	15 (4.5)	15 (4.5)	46 (13.8)	<0.0001
Diet only	49 (14.6)	52 (15.6)	88 (26.3)	0.0001
Oral antidiabetic agents	56 (16.7)	72 (21.6)	93 (27.8)	0.0006
Pulmonary embolism	9 (2.7)	4 (1.2)	5 (1.5)	0.3098
Acute coronary syndrome	84 (25.1)	103 (30.7)	115 (34.3)	0.0090
Coronary artery bypass surgery	19 (5.7)	13 (3.9)	21 (6.3)	0.7364
Percutaneous coronary intervention	40 (12.0)	41 (12.2)	61 (18.2)	0.0207
Angina Canadian Cardiovascular Society class ≥2	29 (8.7)	45 (13.5)	47 (14.0)	0.0338
Moderate or severe chronic obstructive pulmonary disease or asthma	7 (2.1)	10 (3.0)	7 (2.1)	0.9999
Sustained ventricular arrhythmia (with syncopal episodes in past 3 months)	0 (0)	0 (0)	1 (0.3)	0.6667
Cardiac resynchronization therapy	2 (0.6)	0 (0)	3 (0.9)	0.7896
Automatic internal cardiac defibrillator	1 (0.3)	2 (0.6)	5 (1.5)	0.1275
Anaemia	106 (31.6)	74 (22.1)	94 (28.1)	0.2978
Heart failure history				
History of heart failure	296 (88.4)	272 (81.2)	295 (88.1)	0.9117
NYHA class 1 month before hospital admission				<0.0001
I	7 (2.3)	30 (9.7)	16 (5.1)	
II	126 (40.9)	68 (21.9)	85 (27.2)	
III	147 (47.7)	128 (41.3)	119 (38.0)	
IV	28 (9.1)	84 (27.1)	93 (29.7)	
Ischaemic aetiology,	136 (40.6)	163 (48.9)	181 (54.0)	0.0005
Left ventricular ejection fraction, %	36.3 (11.45)	35.2 (12.58)	36.7 (13.23)	0.8265
Left ventricular ejection fraction category				0.2124
≤40%	233 (69.6)	237 (70.7)	218 (65.1)	
>40%	102 (30.4)	98 (29.3)	117 (34.9)	
Hospitalized for heart failure in the past year	78 (23.3)	73 (21.8)	105 (31.3)	0.0167
No. of heart failure hospitalizations in the past year	0.3 (0.60)	0.3 (0.55)	0.5 (1.79)	0.0160
History of atrial fibrillation or atrial flutter	116 (34.6)	162 (48.4)	184 (54.9)	<0.0001
Type of atrial fibrillation or atrial flutter				0.0912

Table 1 (Continued)

Parameter	Bio-ADM <13.32 pg/ml (n = 335)	Bio-ADM 13.32–28.40 pg/ml (n = 335)	Bio-ADM >28.40 pg/ml (n = 335)	p-value for trend[a]
Paroxysmal	38 (33.3)	40 (25.2)	35 (19.0)	
Permanent	61 (53.5)	93 (58.5)	120 (65.2)	
Persistent	15 (13.2)	26 (16.4)	29 (15.8)	
Baseline vital signs				
Systolic blood pressure at baseline, mmHg	124.6 (14.11)	121.7 (11.55)	122.3 (12.95)	0.0247
Pulse, bpm	80.0 (12.23)	78.2 (11.47)	78.2 (11.25)	0.0640
Respiratory rate, breaths/min	17.8 (2.39)	18.5 (6.04)	18.4 (4.94)	0.0261
Local laboratory				
Haemoglobin, g/L	133.9 (17.79)	140.8 (20.07)	134.5 (21.32)	0.3313
Lymphocytes, %	29.7 (9.96)	27.9 (9.34)	25.4 (9.24)	<0.0001
White blood cells, 10^9/L	6.8 (1.75)	7.0 (1.78)	7.1 (2.27)	0.0914
Glucose, mmol/L	5.9 (2.05)	6.2 (2.15)	6.5 (2.54)	0.0027
Creatinine, µmol/L	101.2 (24.08)	106.0 (27.49)	110.9 (31.46)	<0.0001
Potassium, mmol/L	4.2 (0.45)	4.3 (0.45)	4.2 (0.44)	0.8696
Sodium, mmol/L	140.2 (3.61)	140.6 (4.30)	140.3 (4.26)	0.2369
Urea, mmol/L	7.3 (2.72)	7.9 (3.32)	8.6 (3.94)	<0.0001
ALT, U/L	28.6 (41.96)	28.7 (27.04)	31.7 (57.91)	0.9432
Total bilirubin, µmol/L	15.8 (10.22)	17.2 (11.69)	18.7 (11.71)	0.0001
Total cholesterol, mmol/L	4.5 (1.13)	4.2 (1.06)	4.0 (1.03)	<0.0001
NT-proBNP, ng/L, geom. mean (95% CI)	2929.3 (2758.9–3110.3)	3259.6 (3043.7–3490.7)	3402.0 (3165.1–3656.6)	0.0123
Oral heart failure medications taken at Visit 2: pre-randomization				
ACEi/ARBs/ARNi	222 (66.5)	212 (63.3)	217 (64.8)	0.6474
Beta-blockers	108 (32.3)	127 (37.9)	115 (34.3)	0.5894
Mineralocorticoid receptor antagonists	320 (95.8)	315 (94.0)	319 (95.2)	0.7289
Loop diuretic	323 (96.7)	323 (96.4)	316 (94.3)	0.1243
Furosemide equivalence dose, mg	67.8 (52.31)	53.9 (30.85)	65.4 (50.99)	0.3098

Values are given as mean (standard deviation), or *n* (%), unless indicated otherwise.
ACEi, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; bio-ADM, biologically active adrenomedullin; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
[a]Jonckheere's trend test for continuous variables, Cochran–Armitage trend test for binary variables, CMH general association for categorical variables, and CMH non-zero correlation for ordinal variables.

to have been recruited outside of Europe (37.5% vs. 20.2%, $p = 0.050$) and their stored baseline samples had almost double the rate of overt haemolysis (5.6%) compared to patients in whom the bio-ADM levels were ≥ LLOQ (3.0%, $p < 0.0001$). Patients in the lowest bio-ADM tertile, including patients with values < LLOQ, had bio-ADM concentration <13.32 pg/ml, the middle tertile had bio-ADM concentrations of 13.32–28.40 pg/ml, and the highest tertile had bio-ADM concentrations of >28.40 pg/ml (*Table 1*). Patients with the highest concentration of bio-ADM had higher concentrations of NT-proBNP, more often a history of atrial fibrillation and acute coronary syndrome, a higher New York Heart Association (NYHA) class, lower lymphocyte count, higher creatinine and urea, and a lower amount of total cholesterol.Similar associations were found with NT-proBNP tertiles, where patients with higher baseline concentrations had a higher prevalence of a history of atrial fibrillation and acute coronary syndrome, lower lymphocyte count, higher creatinine and urea, and lower total cholesterol.[23] The median baseline NT-proBNP was 2859 (range 650–9000) ng/L, with 80 (7.43%) having reported values >9000 ng/L.

Associations between biologically active adrenomedullin and signs and symptoms of congestion

The association between plasma bio-ADM concentrations and physician-assessed signs and symptoms of congestion at baseline are presented in *Table 2*. Bio-ADM correlated strongly with NYHA class (gamma 0.22, $p < 0.0001$), oedema (gamma 0.25, $p < 0.0001$) and elevated JVP (gamma 0.24, $p = 0.0008$), but not with rales (gamma 0.00, $p = 0.99$), and was inversely associated with orthopnoea (gamma −0.14, $p = 0.0067$). Baseline NT-proBNP correlated strongly with NYHA class (gamma 0.23, $p < 0.0001$), rales (gamma 0.24, $p = 0.0003$) and JVP (gamma 0.32, $p < 0.0001$), but not with orthopnoea (gamma 0.07, $p = 0.18$) and oedema (gamma 0.08, $p = 0.10$) (*Table 3*). Similar associations were evident between

Table 2 Association between signs and symptoms of congestion and tertiles of biologically active adrenomedullin at baseline

Parameter	Bio-ADM <13.32 pg/ml (*n* = 335)	Bio-ADM 13.32–28.40 pg/ml (*n* = 335)	Bio-ADM >28.40 pg/ml (*n* = 335)	Goodman–Kruskal gamma	*p*-value
NYHA class				0.2222	<0.0001
I	17 (5.1)	18 (5.4)	9 (2.7)		
II	227 (67.8)	203 (60.6)	181 (54.0)		
III	90 (26.9)	113 (33.7)	141 (42.1)		
IV	1 (0.3)	1 (0.3)	4 (1.2)		
Orthopnoea				−0.1377	0.0067
None	177 (52.8)	226 (67.5)	217 (64.8)		
1 pillow (10 cm)	149 (44.5)	99 (29.6)	99 (29.6)		
2 pillows (20 cm)	9 (2.7)	9 (2.7)	17 (5.1)		
>30°	0	1 (0.3)	2 (0.6)		
Rales				0.0011	0.9887
No rales	289 (86.5)	295 (88.1)	289 (86.5)		
Rales <1/3	40 (12.0)	37 (11.0)	39 (11.7)		
Rales 1/3–2/3	5 (1.5)	2 (0.6)	6 (1.8)		
Rales >2/3	0	1 (0.3)	0 (0)		
Oedema				0.2536	<0.0001
0	216 (64.7)	201 (60.0)	156 (46.6)		
1+	110 (32.9)	118 (35.2)	144 (43.0)		
2+	8 (2.4)	13 (3.9)	32 (9.6)		
3+	0	3 (0.9)	3 (0.9)		
JVP				0.2359	0.0008
<6 cm	273 (88.1)	265 (85.5)	238 (78.3)		
6–10 cm	36 (11.6)	41 (13.2)	65 (21.4)		
>10 cm	1 (0.3)	4 (1.3)	1 (0.3)		

Values are given as *n* (%).
bio-ADM, biologically active adrenomedullin; JVP, jugular venous pressure; NYHA, New York Heart Association.

Table 3 Association between signs and symptoms of congestion and tertiles of NT-proBNP at baseline

Parameter	NT-proBNP <2159 ng/L (*n* = 359)	NT-proBNP 2160–4165 ng/L (*n* = 359)	NT-proBNP ≥4165 ng/L (*n* = 359)	Goodman–Kruskal gamma	*p*-value
NYHA class				0.2332	<0.0001
I	19 (5.3)	16 (4.5)	27 (7.5)		
II	247 (68.8)	233 (65.1)	161 (45.0)		
III	90 (25.1)	107 (29.9)	167 (46.6)		
IV	3 (0.8)	2 (0.6)	3 (0.8)		
Orthopnoea				0.0660	0.1778
None	225 (62.7)	223 (62.3)	213 (59.5)		
1 pillow (10 cm)	128 (35.7)	123 (34.4)	121 (33.8)		
2 pillows (20 cm)	4 (1.1)	12 (3.4)	23 (6.4)		
>30°	2 (0.6)	0 (0)	1 (0.3)		
Rales				0.2431	0.0003
No rales	320 (89.4)	309 (86.3)	286 (80.1)		
Rales <1/3	33 (9.2)	46 (12.8)	60 (16.8)		
Rales 1/3–2/3	5 (1.4)	3 (0.8)	10 (2.8)		
Rales >2/3	0 (0)	0 (0)	1 (0.3)		
Oedema				0.0770	0.1014
0	199 (55.4)	219 (61.2)	188 (52.7)		
1+	149 (41.5)	122 (34.1)	127 (35.6)		
2+	10 (2.8)	15 (4.2)	38 (10.6)		
3+	1 (0.3)	2 (0.6)	4 (1.1)		
JVP				0.3157	<0.0001
<6 cm	294 (90.2)	277 (84.7)	252 (77.5)		
6–10 cm	32 (9.8)	49 (15.0)	67 (20.6)		
>10 cm	0 (0)	1 (0.3)	6 (1.8)		

Values are given as *n* (%).
JVP, jugular venous pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

bio-ADM, and NT-proBNP, and HF signs and symptoms at day 90 (online supplementary *Tables S1* and *S2*). The correlation between baseline bio-ADM and NT-proBNP tertiles was modest but statistically significant (gamma 0.12; $p = 0.0035$).

The proportion of patients whose decongestion status improved between baseline and day 90 was associated with greater reductions in bio-ADM (gamma −0.24, $p = <0.0001$) (online supplementary *Table S3*). Among patients with residual congestion at baseline, patients in both the highest tertile of baseline bio-ADM and NT-proBNP were the least likely to be successfully decongested at day 90, with independent effects of the two biomarkers (interaction $p = 0.35$) (online supplementary *Figure S1*).

The association of bio-ADM with successful decongestion at day 90 was approximately linear ($p = 0.19$) and did not differ between treatment groups ($p = 0.54$); thus, results are presented for bio-ADM as a linear effect and for all patients combined. The ability to discriminate between patients successfully decongested at day 90 using baseline bio-ADM alone (AUC 0.5963, 95% CI 0.5546–0.6380) was similar that with baseline NT-proBNP alone (AUC 0.5795, 95% CI 0.5372–0.6217) ($p = 0.5628$), while including both bio-ADM and NT-proBNP (AUC 0.6078, 95% CI 0.5666–0.6490) was associated with numerically higher but not statistically significant better discrimination than NT-proBNP alone ($p = 0.15$) (*Figure 1*).

Baseline biologically active adrenomedullin as a predictor of clinical outcomes

Among the 1008 patients enrolled at sites who followed patients to day 180, 950 (94.2%), 1007 (99.9%), and 950 (94.2%) patients had bio-ADM, NT-proBNP, and both available at baseline, respectively. During 180 days of follow-up, 183 patients reached the primary endpoint of all-cause death or HF readmission. Patients in the highest tertile of bio-ADM had the highest risk of reaching the primary endpoint (hazard ratio [HR] 2.14, 95% CI 1.42–3.22 relative to tertile 1) while those in the lower two tertiles had similar risks (HR 1.05, 95% CI 0.66–1.68 tertile 2 vs. 1) (*Figure 2A*). Examination of the risk of the composite outcome as a function of baseline bio-ADM as a continuous measure suggests that the risk of experiencing the primary endpoint increased monotonically with increasing baseline bio-ADM level (online supplementary *Figure S2*). The association of baseline NT-proBNP tertiles with 180-day death or HF readmission showed a similar pattern, with similar risks in

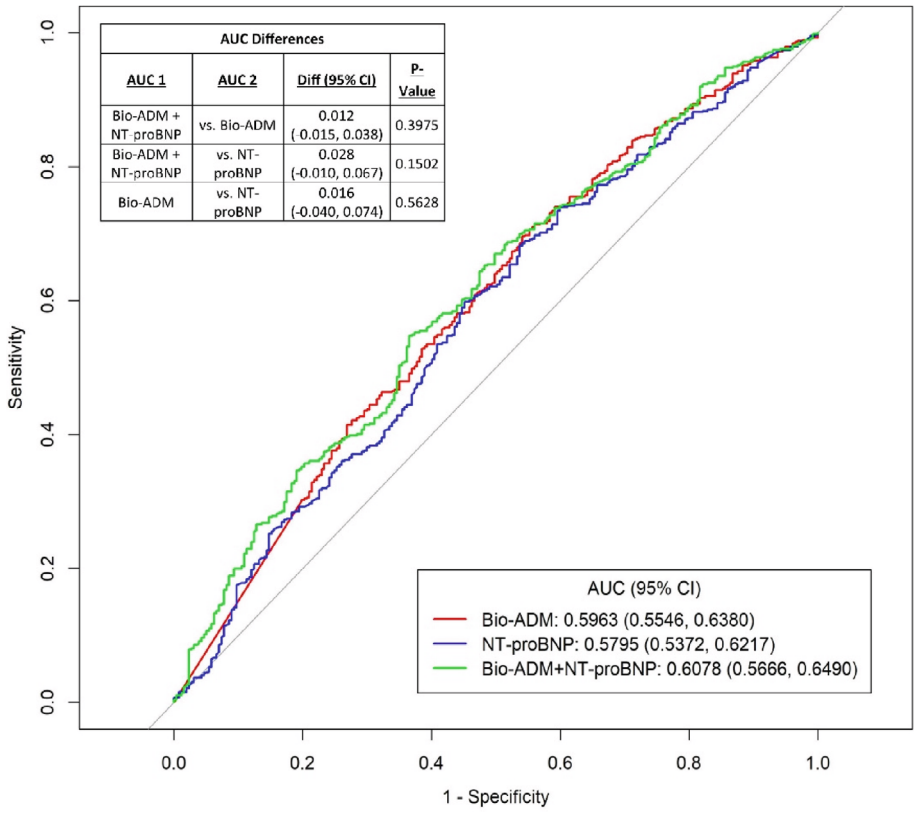

Figure 1 Receiver-operating characteristic curves comparing the ability of baseline biologically active adrenomedullin (bio-ADM), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and their combination to predict successful decongestion at day 90. AUC, area under the receiver-operating characteristic curve; CI, confidence interval.

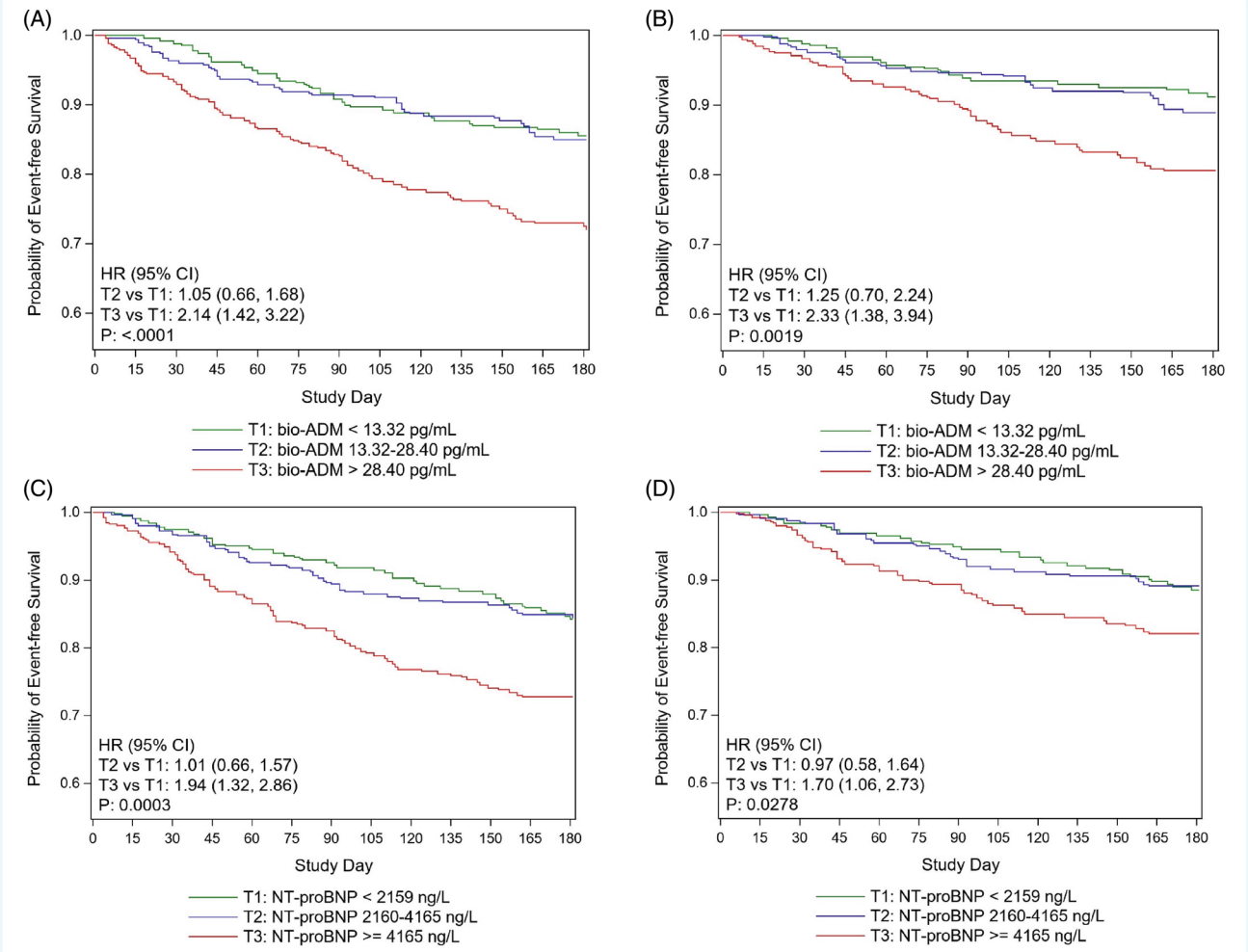

Figure 2 Kaplan–Meier estimates of cumulative incidence of (*A*) all-cause death or heart failure readmission by day 180 by tertiles of biologically active adrenomedullin (bio-ADM), (*B*) heart failure readmission by day 180 by tertiles of bio-ADM, (*C*) all-cause death or heart failure readmission by day 180 by tertiles of N-terminal pro-B-type natriuretic peptide (NT-proBNP), and (*D*) heart failure readmission by day 180 by tertiles of NT-proBNP. CI, confidence interval; HR, hazard ratio.

the lower two tertiles (<4165 pg/L) and higher risk among patients in the highest tertile of NT-proBNP (≥4165 pg/L) (*Figure 2C*). Taken together, patients in the highest tertile of baseline bio-ADM and NT-proBNP had the highest risk of the primary outcome, with independent effects of the two biomarkers (interaction $p = 0.63$) (online supplementary *Figure S3A*).

The associations of baseline bio-ADM and NT-proBNP with the primary composite outcome were not statistically significantly non-linear ($p = 0.26$ and 0.94, respectively), and were therefore modelled as linear relationships. The individual associations of baseline bio-ADM and NT-proBNP with 180-day death or HF readmission did not differ significantly between HIC and UC (interaction $p = 0.28$ and 0.85, respectively); thus, ROC curves are presented among all patients combined (*Figure 3A*). In a model including both biomarkers as predictors, the association of either biomarker did not depend significantly on the level of the other biomarker (interaction $p = 0.091$), and in a model not including the interaction, the effects of both baseline bio-ADM ($p = 0.041$) and baseline NT-proBNP ($p < 0.0001$) were statistically significant, indicating that each contributes to the predictive ability of the model. The AUCs were 0.5977 (95% CI 0.5561–0.6393), 0.5800 (95% CI 0.5356–0.6243), and 0.6159 (95% CI 0.5711–0.6607) for bio-ADM, NT-proBNP and their combination, respectively (*Figure 3A*). Baseline bio-ADM alone did not show better discrimination compared to NT-proBNP alone ($p = 0.52$). The combination of markers did not provide significantly better discrimination than bio-ADM alone ($p = 0.20$) but showed discrimination superior to NT-proBNP alone ($p = 0.059$). Examination of the AUCs for the endpoint over time indicate that the discrimination was strongest for earlier events before day 50 (online supplementary *Figure S4A*), with bio-ADM having slightly greater ability than NT-proBNP to discriminate between patients with and without early events (online supplementary *Figure S5A*).

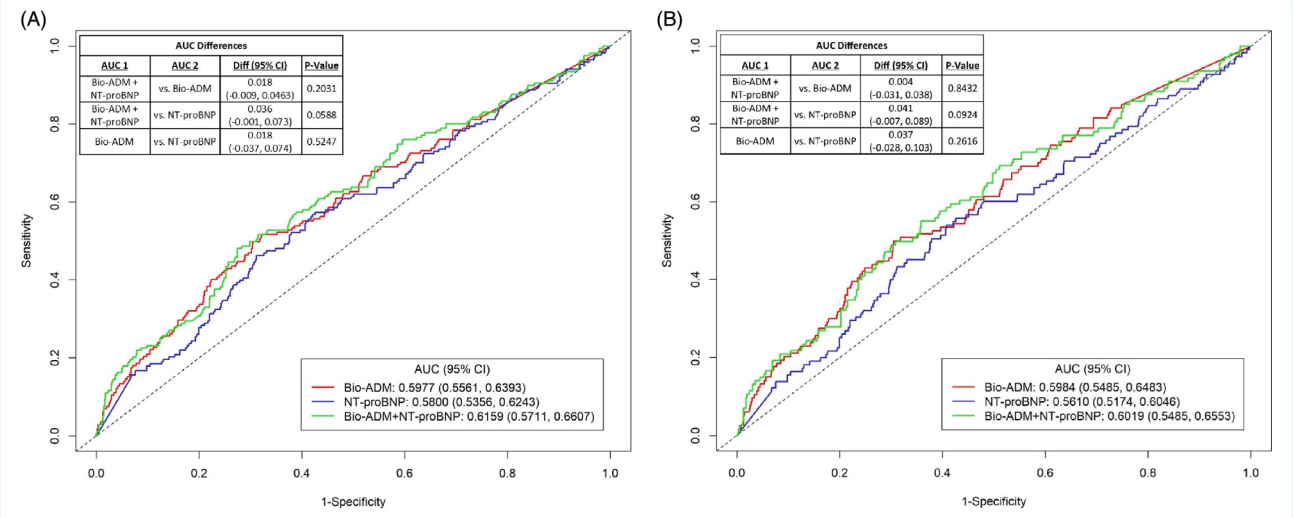

Figure 3 Receiver-operating characteristic curves comparing the ability of baseline biologically active adrenomedullin (bio-ADM), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and their combination to predict (*A*) death or heart failure readmission by day 180, and (*B*) heart failure readmission by day 180. AUC, area under the receiver-operating characteristic curve; CI, confidence interval.

Table 4 Change in biologically active adrenomedullin from baseline to day 90 by treatment group

Bio-ADM (pg/ml)	High-intensity care ($n = 542$)	Usual care ($n = 536$)	Total ($n = 1078$)
Baseline			
n	436	435	871
Mean (SD)	30.1 (34.86)	28.4 (30.99)	29.3 (32.98)
Median (min−max)	20.4 (5−370)	19.6 (5−290)	20.0 (5−370)
Day 90			
n	436	435	871
Mean (SD)	27.6 (33.94)	28.9 (36.15)	28.3 (35.05)
Median (min−max)	17.3 (5−288)	17.8 (5−374)	17.6 (5−374)
Change from baseline to day 90			
n	436	435	871
Mean (SD)	−2.5 (37.01)	0.5 (32.05)	−1.0 (34.63)
Median (min−max)	0.0 (−344 to 227)	0.0 (−245 to 323)	0.0 (−344 to 323)
p-value*	0.2689		

Summary statistics presented for subjects with both an available baseline and day 90 bio-ADM value.
bio-ADM, biologically active adrenomedullin; SD, standard deviation.
*p-value from rank ANCOVA with baseline bio-ADM as a covariate.

Results for HF readmission by day 180 reflected the same pattern as for the composite endpoint. Patients in the tertile with the highest concentration of bio-ADM had the highest risk of HF readmission by day 180 (HR 2.33 relative to tertile 1) with patients in the lower two tertiles exhibiting similar risk ($p = 0.0019$ comparing the three tertiles) (*Figure 2B*). Similarly, the risk of HF readmission was highest in the highest baseline NT-proBNP tertile, while risks in the lower two thirds were similar (*Figure 2D*). As a continuous measure, risk of HF readmission by day 180 appeared to increase monotonically with baseline bio-ADM (online supplementary *Figure S2B*). Taken together, patients in the highest tertile of bio-ADM and highest tertile of NT-proBNP had the highest risk for rehospitalization at 180 days (online supplementary *Figure S3B*), with independent effects of the two biomarkers (interaction $p = 0.42$).

Similar to results for the composite endpoint, associations of baseline bio-ADM and NT-proBNP with 180-day HF readmission were approximately linear and did not differ between treatment groups ($p = 0.61$ and 0.94, respectively). The bio-ADM-by-NT-proBNP interaction was not statistically significant (interaction $p = 0.092$), and in a model including both biomarkers but excluding the interaction, the effect of bio-ADM did not contribute significantly ($p = 0.070$) to NT-proBNP ($p = 0.0312$). The AUCs for the endpoint through 180 days were 0.5984 (95% CI 0.5485−0.6483), 0.5610 (95% CI 0.5174−0.6046), and 0.6019 (95% CI 0.5485−0.6553) for bio-ADM, NT-proBNP and their

Table 5 Change in NT-proBNP from baseline to day 90 by treatment group

NT-proBNP (pg/ml)	High intensity care ($n = 542$)	Usual care ($n = 536$)	Total ($n = 1078$)
Baseline			
n	476	475	951
Mean (SD)	3714.2 (2290.13)	3631.7 (2236.44)	3673.0 (2262.66)
Median (min–max)	2803.5 (725–9000)	2846.0 (650–9000)	2811.0 (650–9000)
Day 90			
n	476	475	951
Mean (SD)	2287.9 (2402.61)	2709.8 (2571.78)	2498.6 (2496.17)
Median (min–max)	1376.5 (38–9000)	1823.0 (49–9000)	1554.0 (38–9000)
Change from baseline to day 90			
n	476	475	951
Mean (SD)	−1426.3 (2620.91)	−921.9 (2794.17)	−1174.4 (2719.14)
Median (min–max)	−1301.0 (−8892 to 7790)	−962.3 (−8823 to 7674)	−1143.0 (−8892 to 7790)
p-value*	0.0003		

Summary statistics presented for subjects with both an available baseline and day 90 NT-proBNP value. Values truncated at 9000 pg/ml.
bio-ADM, biologically active adrenomedullin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation.
*p-value from rank ANCOVA with baseline bio-ADM as a covariate.

combination, respectively (*Figure 3B*). There was not a significant difference in AUCs between bio-ADM and NT-proBNP ($p = 0.26$) nor for the combined markers compared to bio-ADM alone ($p = 0.84$) with similar results as were seen for the composite endpoint. As for the primary endpoint, AUCs for the endpoint over time indicate that association was strongest for earlier events (online supplementary *Figure S4B*), with bio-ADM having greater ability than NT-proBNP to discriminate between patients with and without early events (online supplementary *Figure S5B*).

Responsiveness of biologically active adrenomedullin to treatment

High-intensity care was shown to significantly improve signs and symptoms of congestion including oedema, JVP, and NYHA class, as well as to reduce the 90-day change in NT-proBNP when analysed using ANCOVA on log-transformed values.[14] While the level of bio-ADM also numerically decreased more in the HIC than in the UC group between baseline and day 90, the difference did not reach statistical significance ($p = 0.27$) (*Table 4*). Comparing treatment groups with respect to the change in NT-proBNP using the same statistical methodology confirms that NT-proBNP decreased more in patients assigned to HIC than those assigned to UC ($p = 0.0003$) (*Table 5*).

Potential modification of high-intensity care effect by baseline biomarker level

As was the case for baseline NT-proBNP,[23] baseline bio-ADM did not significantly influence the effect of HIC on the composite of 180-day all-cause mortality or HF hospitalization examined either grouped in tertiles (interaction $p = 0.21$; online supplementary *Figure S6A*) or as a continuous measure (interaction $p = 0.37$; online supplementary *Figure S7A*). The effect of HIC relative to UC on HF hospitalization also did not vary significantly by baseline bio-ADM level, considered either in tertiles (interaction $p = 0.85$, online supplementary *Figure S7*) or as a continuous measure (interaction $p = 0.66$; online supplementary *Figure S7B*).

Discussion

In this analysis, we examined the predictive value of bio-ADM as a congestion marker for short-term rehospitalization and decongestion following discharge from a hospitalization for acute HF. The novelty of this study is the additional information bio-ADM provides as compared to NT-proBNP and the behaviour of these biomarkers during rapid up-titration of GDMT.

Baseline characteristics and correlations

The levels of bio-ADM in the current study were lower than those reported in other HF studies.[15,24] The possible reasons for this difference are multifactorial. First, the assay used in the current study differed from that used in other studies, with a LLOQ of 10.8 pg/ml compared to 2–3 pg/ml in previous studies. Second, a large proportion of patients (26.6%) had pre-discharge (baseline) bio-ADM levels < LLOQ. This is potentially related to the higher LLOQ of the assay used in the study but might also reflect issues with sample handling, as a higher proportion of patients with bio-ADM < LLOQ were recruited outside of Europe or their samples had overt haemolysis. In this analysis we found that patients in the highest tertile of bio-ADM have significantly more severe signs and symptoms of HF, with the exception of rales. This is consistent with other literature, as bio-ADM has been shown to be associated with vascular leakage and systemic and pulmonary oedema and has been found to be elevated in a sub-analysis of BIOSTAT-CHF and PROTECT[15,24] and is in line with the current theory reviewed by Boorsma *et al.*[7] that bio-ADM is strongly related to tissue congestion, while NT-proBNP is more related to intravascular congestion. Of note, both biomarkers correlated with

NYHA class and JVP at baseline, but only bio-ADM (in contrast to NT-proBNP) correlated with peripheral oedema and orthopnoea, which further supports this concept. Importantly, the residual dyspnoea (orthopnoea) has been shown to be associated with poor outcome and counterintuitively was not a 'simple' reflection of pulmonary rales.[25] On the other hand, NT-proBNP correlated with lung congestion (rales), unlike bio-ADM. Interestingly, the tertiles of bio-ADM did not show a correlation with left ventricular ejection fraction.

Additive value of biologically active adrenomedullin to NT-proBNP

Pre-discharge concentrations of bio-ADM and NT-proBNP levels were weakly but significantly correlated. Bio-ADM was associated with both signs of congestion at baseline, a few days before discharge from an acute HF hospitalization, and at day 90. Both NT-proBNP and bio-ADM were associated with better decongestion at day 90; however, the associations were comparable and the combination of bio-ADM and NT-proBNP did not add significantly to the information obtained by either biomarker alone. Patients with the highest baseline bio-ADM levels were at the highest risk of the primary endpoint of 180-day all-cause mortality or HF hospitalization and 180-day HF hospitalization. This is similar to findings from BIOSTAT-CHF, PROTECT and in the OptimaCC trial.[11,15,26] Patients with higher bio-ADM are generally sicker patients, showing more signs and symptoms of HF, which might partly explain the increased mortality and rehospitalization risk. The risk was especially high in patients with bio-ADM in the upper tertile, whose bio-ADM levels were mostly above the 97.5th percentile of healthy volunteers, suggesting that a cut-off of 29 pg/ml may be considered as a marker of higher risk for acute HF patients. Such elevated baseline bio-ADM might be a sign of limited response to treatment and/or signs of residual congestion. Since these patients are at the highest risk of all-cause mortality or HF hospitalization, they might benefit from more regular or intensive follow-up. The discriminative value for both HF readmission or death at 180 days or HF readmission alone at 180 days was similar for bio-ADM and NT-proBNP; however, there was a trend towards better discrimination when bio-ADM and NT-proBNP were combined. Both biomarkers had modest associations with these outcomes, with AUCs around 0.6. This result is in line with previous studies examining the role of biomarkers in the risk stratification of patients after an acute HF admission.[27] The reasons for such modest associations are not known; however, it is possible that congestion by itself is a symptom of HF but not its main pathophysiological cause and, therefore, the presence of congestion is not a strong predictor of adverse outcomes post-discharge from an acute HF admission.[13] Hence, bio-ADM and NT-proBNP, which are markers of congestion, are equally only modest predictors of adverse outcomes. This issue is compounded by the fact that HF readmissions are not always determined only by HF severity and some are related to socioeconomical and other non-cardiovascular causes (such as frailty) further reducing the association between congestion and its markers and outcomes after acute HF.[28]

Effect of rapid guideline-directed medical therapy up-titration

Although both bio-ADM and NT-proBNP decreased significantly during follow-up and numerically more so in the HIC arm, the effect of rapid up-titration of GDMT on bio-ADM levels did not reach statistical significance while the effect on NT-proBNP was highly statistically significant. There was no interaction between the level of bio-ADM at baseline and the effect of HIC. These observations are important, suggesting that serial measurements of NT-proBNP but not bio-ADM may be of value in the follow-up of patients during the post-acute HF period, especially when rapidly up-titrating GDMT.

Limitations

The current analysis is limited by the number of patients enrolled in the STRONG-HF study. This may render some of the analysis underpowered, especially tests of interactions and tests comparing the predictive value of bio-ADM, NT-proBNP and their combination on outcomes and decongestion.

Conclusion

Bio-ADM is a marker of (residual) tissue congestion and is associated with early and mid-term congestion as well as with HF hospital readmission or death after hospitalization for acute HF, particularly HF readmissions. Bio-ADM measurement adds prognostic information as compared to NT-proBNP alone, especially with regard to 180-day HF readmission or death. The effects of HIC on all-cause death and early rehospitalization is independent of baseline bio-ADM.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

We thank Dr. Gary Koch for his advice regarding statistical analysis.

Funding

Roche Diagnostics Int. Ltd., Rotkreuz Switzerland supported the study as an investigator initiated study.

Conflict of interest: G.V. reports receiving grants from RECONNEXT. B.D., C.E., K.T., M.B., M.N., and G.C. are employees of Momentum Research, which has received grants for research from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Corteria Pharmaceuticals, Heart Initiative, Sanofi, Windtree Therapeutics, and XyloCor Therapeutics. B.D. and G.C. are directors of Heart Initiative, a non-profit organization. K.D. reports speaker/consultancy fees to his institution from AstraZeneca, Abbott, Boehringer Ingelheim, Novartis, Echosense, FIRE1. J.T.M. reported receiving grants from Dekker, Netherlands Heart Foundation, and Off Road, outside the submitted work. A.M. has received grants from Roche Diagnostics, Abbott Laboratories, 4TEEN4, and Windtree Therapeutics; honoraria for lectures from Roche Diagnostics,

Bayer, and MSD; is a consultant for Corteria Pharmaceuticals, S-form Pharma, FIRE-1, Implicity, 4TEEN4, and Adrenomed; and is coinventor of a patent on combination therapy for patients having acute or persistent dyspnoea. M.Ad. has received speaker fees from Abbott Vascular and Medtronic. A.P.A. has received relevant research support through grants to his institution from the National Heart, Lung, and Blood Institute (K23HL150159), the American Heart Association (2nd Century Early Faculty Independence Award), The Permanente Medical Group, Northern California Community Benefits Programs, Garfield Memorial Fund, Abbott Laboratories, Amarin Pharma, Inc., Edwards Lifesciences LLC, Esperion Therapeutics, Inc., and Novartis. J.C. has received personal fees from Novartis, AstraZeneca, Boehringer Ingelheim, Roche Diagnostics, and Pfizer. O.C. received grants from Servier. A.C.S. has received honoraria for lectures or consultancy from AstraZeneca, Novartis, Vifor, Bayer, Merck, Sanofi, Abbott, and Boehringer Ingelheim. A.D. works for the Faculty of Medicine, Eduardo Mondlane University (Maputo, Mozambique), which received research grants from the Heart Initiative for their participation in this study. R.D. has received supporting fees for coordination of STRONG-HF trial activities. G.F. has received lecture fees or was a committee member for trials and registries sponsored by Bayer, Vifor, Boehringer Ingelheim, Medtronic, Servier and Amgen. C.S.P.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Novo Nordisk and Roche Diagnostics; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Alleviant Medical, Allysta Pharma, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, CardioRenal, CPC Clinical Research, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Quidel Corporation, Radcliffe Group Ltd, Recardio Inc, ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics, and Us2.ai; and serves as cofounder and non-executive director of Us2.ai. M.M. has received personal fees from Amgen, Livanova, and Vifor Pharma as a member of executive committees of sponsored clinical trials and from AstraZeneca, Bayer, Boehringer Ingelheim, Edwards Lifesciences, and Roche Diagnostics for participation in advisory boards or for speaking at sponsored meetings. M.P. has received personal fees from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim and Vifor Pharma. P.Pa. has received grants or research contracts from American Heart Association, Roche, Siemens, Ortho Diagnostics, Abbott, Beckman Coulter, and Siemens; consulting fees from Roche; honoraria from WebMD; and he has financial interest in The Heart Course. P.Po. reports grants and personal fees from Amgen, Servier, Boehringer Ingelheim, Vifor Pharma, Novartis, Bayer, Cibiem, AstraZeneca, BMS, Renal Guard Solutions, Impulse Dynamics, and Abbott Vascular, and personal fees from Berlin Chemie, outside of the submitted work. K.S. has received grants from Medtronic, Servier, and Amylam and honoraria from MSD, Novartis, and Sanofi. D.T. has received speaker fees from Boehringer Ingelheim, Alnylam Pharmaceuticals, and Pfizer. A.A.V. has received consultancy fees or research support from AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Cytokinetics, Myocardia, Merck, Novartis, Novo Nordisk, and Roche Diagnostics. All other authors have nothing to disclose.

References

1. Osenenko KM, Kuti E, Deighton AM, Pratik B, Szabo SM. Burden of hospitalization for heart failure in the United States: A systematic literature review. *J Manag Care Spec Pharm* 2022;**28**:157–167. https://doi.org/10.18553/jmcp.2022.28.2.157
2. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, *et al.* Forecasting the impact of heart failure in the United States: A policy statement from the American Heart Association. *Circ Heart Fail* 2013;**6**:606–619. https://doi.org/10.1161/HHF.0b013e318291329a
3. Rubio-Gracia J, Demissei BG, Ter Maaten JM, Cleland JG, O'Connor CM, Metra M, *et al.* Prevalence, predictors and clinical outcome of residual congestion in acute decompensated heart failure. *Int J Cardiol* 2018;**258**:185–191. https://doi.org/10.1016/j.ijcard.2018.01.067
4. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.*; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
5. Girerd N, Seronde MF, Coiro S, Chouihed T, Bilbault P, Braun F, *et al.*; INI-CRCT, Great Network, and the EF-HF Group. Integrative assessment of congestion in heart failure throughout the patient journey. *JACC Heart Fail* 2018;**6**:273–285. https://doi.org/10.1016/j.jchf.2017.09.023
6. Zhu Y, Li N, Wu M, Peng Z, Huang H, Zhao W, *et al.* Impact of B-lines-guided intensive heart failure management on outcome of discharged heart failure patients with residual B-lines. *ESC Heart Fail* 2022;**9**:2713–2718. https://doi.org/10.1002/ehf2.13988
7. Boorsma EM, Ter Maaten JM, Damman K, Dinh W, Gustafsson F, Goldsmith S, *et al.* Congestion in heart failure: A contemporary look at physiology, diagnosis and treatment. *Nat Rev Cardiol* 2020;**17**:641–655. https://doi.org/10.1038/s41569-020-0379-7
8. Voors AA, Kremer D, Geven C, Ter Maaten JM, ter Struck J, Bergmann A, *et al.* Adrenomedullin in heart failure: Pathophysiology and therapeutic application. *Eur J Heart Fail* 2019;**21**:163–171. https://doi.org/10.1002/ejhf.1366
9. Egerstedt A, Czuba T, Bronton K, Lejonberg C, Ruge T, Wessman T, *et al.* Bioactive adrenomedullin for assessment of venous congestion in heart failure. *ESC Heart Fail* 2022;**9**:3543–3555. https://doi.org/10.1002/ehf2.14018
10. Núñez J, de la Espriella R, Rossignol P, Voors AA, Mullens W, Metra M, *et al.* Congestion in heart failure: A circulating biomarker-based perspective. A review from the Biomarkers Working Group of the Heart Failure Association, European Society of Cardiology. *Eur J Heart Fail* 2022;**24**:1751–1766. https://doi.org/10.1002/ejhf.2664
11. Pandhi P, Ter Maaten JM, Emmens JE, Struck J, Bergmann A, Cleland JG, *et al.* Clinical value of pre-discharge bio-adrenomedullin as a marker of residual congestion and high risk of heart failure hospital readmission. *Eur J Heart Fail* 2020;**22**:683–691. https://doi.org/10.1002/ejhf.1693
12. Ahmed A, Kania K, Abdul Rahim H, Ahmed S, Rådegran G. Adrenomedullin peptides and precursor levels in relation to haemodynamics and prognosis after heart transplantation. *ESC Heart Fail* 2023;**10**:2427–2437. https://doi.org/10.1002/ehf2.14399
13. Cotter G, Davison B, Chioncel O. Enhanced decongestive therapy in patients with acute heart failure: JACC review topic of the week. *J Am Coll Cardiol* 2024;**83**:1243–1252. https://doi.org/10.1016/j.jacc.2024.01.029
14. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, *et al.* Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): A multinational, open-label, randomised, trial. *Lancet* 2022;**400**:1938–1952. https://doi.org/10.1016/S0140-6736(22)02076-1
15. Ter Maaten JM, Kremer D, Demissei BG, Struck J, Bergmann A, Anker SD, *et al.* Bio-adrenomedullin as a marker of congestion in patients with new-onset and worsening heart failure. *Eur J Heart Fail* 2019;**21**:732–743. https://doi.org/10.1002/ejhf.1437
16. Weber J, Sachse J, Bergmann S, Sparwaßer A, Struck J, Bergmann A. Sandwich immunoassay for bioactive plasma adrenomedullin. *J Appl Lab Med* 2017;**2**:222–233. https://doi.org/10.1373/jalm.2017.023655
17. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics* 1988;**44**:837–845. PMID: 3203132.
18. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, *et al.* pROC: An open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* 2011;**12**:77. https://doi.org/10.1186/1471-2105-12-77
19. Uno H, Cai T, Tian L, Wei LJ. Evaluating prediction rules for t-year survivors with censored regression models. *J Am Stat Assoc* 2007;**102**:527–537. https://doi.org/10.1198/016214507000000149
20. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics* 2000;**56**:337–344. https://doi.org/10.1111/j.0006-341x.2000.00337.x
21. Hung H, Chiang CT. Optimal composite markers for time-dependent receiver operating characteristic curves with censored survival data. *Scand J Stat* 2010;**37**:664–679. https://doi.org/10.1111/j.1467-9469.2009.00683.x
22. Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for

censored event times with competing risks. *Stat Med* 2013;**32**:5381–5397. https://doi.org/10.1002/sim.5958
23. Adamo M, Pagnesi M, Mebazaa A, Davison B, Edwards C, Tomasoni D, *et al.* NT-proBNP and high intensity care for acute heart failure: The STRONG-HF trial. *Eur Heart J* 2023;**44**:2947–2962. https://doi.org/10.1093/eurheartj/ehad335
24. Kremer D, Ter Maaten JM, Voors AA. Bio-adrenomedullin as a potential quick, reliable, and objective marker of congestion in heart failure. *Eur J Heart Fail* 2018;**20**:1363–1365. https://doi.org/10.1002/ejhf.1245
25. Garus M, Jura M, Guzik M, Zymliński R, Iwanek G, Ponikowski P, *et al.* Prognostic significance and clinical determinants of residual dyspnoea at discharge in acute heart failure: A single-centre, prospective observational study. *BMJ Open* 2023;**13**:e075302. https://doi.org/10.1136/bmjopen-2023-075302
26. Takagi K, Levy B, Kimmoun A, Miró Ò, Duarte K, Asakage A, *et al.* Elevated plasma bioactive adrenomedullin and mortality in cardiogenic shock: Results from the OptimaCC trial. *J Clin Med* 2021;**10**:4512. https://doi.org/10.3390/jcm10194512
27. Wettersten N. Biomarkers in acute heart failure: Diagnosis, prognosis, and treatment. *Int J Heart Fail* 2021;**3**:81–105. https://doi.org/10.36628/ijhf.2020.0036
28. Damiani G, Salvatori E, Silvestrini G, Ivanova I, Bojovic L, Iodice L, *et al.* Influence of socioeconomic factors on hospital readmissions for heart failure and acute myocardial infarction in patients 65 years and older: Evidence from a systematic review. *Clin Interv Aging* 2015;**10**:237–245. https://doi.org/10.2147/CIA.S71165