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RESEARCH ARTICLE

Clinical value of pre-discharge bio-adrenomedullin as a marker of residual congestion and high risk of heart failure hospital readmission

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Aims	Recently, bio-adrenomedullin (bio-ADM) was proposed as a congestion marker in heart failure (HF). In the present study, we aimed to study whether bio-ADM levels at discharge from a hospital admission for worsening HF could provide additional information on (residual) congestion status, diuretic dose titration and clinical outcomes.
Methods and results	Plasma bio-ADM was measured in 1236 acute HF patients in the PROTECT trial at day 7 or discharge. Median discharge bio-ADM was 33.7 [21.5−61.5] pg/mL. Patients with higher discharge bio-ADM levels were hospitalised longer, had higher brain natriuretic peptide levels, and poorer diuretic response (all $P < 0.001$). Bio-ADM was the strongest predictor of discharge residual congestion (clinical congestion score > 3) (odds ratio 4.35, 95% confidence interval 3.37−5.62; $P < 0.001$). Oedema at discharge was one of the strongest predictors of discharge bio-ADM ($\beta = 0.218$; $P < 0.001$). Higher discharge loop diuretic doses were associated with a poorer diuretic response during hospitalisation ($\beta = 0.187$; $P < 0.001$) and higher bio-ADM levels ($\beta = 0.084$; $P = 0.020$). High discharge bio-ADM levels combined with higher use of loop diuretics were independently associated with a greater risk of 60-day HF rehospitalisation (hazard ratio 4.02, 95% confidence interval 2.23−7.26; $P < 0.001$).
Conclusion	In hospitalised HF patients, elevated pre-discharge bio-ADM levels were associated with higher discharge loop diuretic doses and reflected residual congestion. Patients with combined higher bio-ADM levels and higher loop diuretic use at discharge had an increased risk of rehospitalisation. Assessment of discharge bio-ADM levels may be a readily applicable marker to identify patients with residual congestion at higher risk of early hospital readmission.
Keywords	Bio-adrenomedullin ● Loop diuretics ● Acute heart failure

Introduction

Acute heart failure (AHF) is characterised by fluid overload and signs and symptoms of congestion in 95% of the patients.[1] As a result, decongestive therapy using diuretics is the primary aim of treatment.[1] Despite receiving diuretic therapy, a significant number of patients are still discharged with one or more signs of residual congestion, which is independently associated with worse post-discharge outcomes.[2–4] However, pre-discharge assessment of residual congestion is notoriously difficult, and current clinical

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assessments such as rales, oedema, jugular venous pressure (JVP), and chest radiographs have high inter-observer variability.[4–6] Hence, there is an increasing need to assess congestion status objectively for better discharge planning including loop diuretic dose titration and post-discharge follow-up.

Recently, biologically active adrenomedullin (bio-ADM) was proposed as a congestion marker.[6–9] Adrenomedullin (ADM) is a 52-amino acid vasodilatory peptide hormone secreted by endothelial and smooth muscle cells of blood vessels and is involved in blood pressure regulation and maintenance of vascular integrity.[6,10] ADM is produced in an inactive glycine-extended form after proteolytic cleavage of a large precursor hormone pro-adrenomedullin (pro-ADM).[10] About 5−20% of this inactive hormone is converted into bio-ADM.[7,11] Bio-ADM levels are elevated in conditions that reflect fluid overload, vascular leakage, and oedema, such as sepsis, and AHF, and is predictive of adverse short-term outcomes.[6,8,9,12–15] Emerging evidence suggests that baseline bio-ADM levels are correlated with the severity of congestion at admission and during/after hospitalisation in AHF patients.[8,9,15] However, as a potential congestion marker, the role of using pre-discharge bio-ADM levels to monitor residual congestion status and accordingly optimize decongestive therapies remains undescribed. Therefore, in the present study we aimed to investigate the hypothesis that elevated discharge bio-ADM levels are associated with (residual) congestion and increased loop diuretic use at discharge. Furthermore, by assessing the additive prognostic value of bio-ADM on top of loop diuretic doses, we aimed to investigate their combined ability for identifying inadequately decongested patients at a higher risk of adverse outcomes.

Methods

Study design and procedures

Study design and main results of the Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial have been published elsewhere.[16,17] Briefly, in the multicentre, randomised, double-blind placebo-controlled PROTECT trial, 2033 patients with AHF were randomised to rolofylline or placebo in a 2:1 ratio. Eligible patients had brain natriuretic peptide (BNP) levels ≥500 pg/mL or N-terminal pro brain natriuretic peptide levels ≥2000 pg/mL, ongoing intravenous (IV) loop diuretic therapy and dyspnoea at rest or with minimal physical activity and impaired renal function. Overall study results were neutral.[17] All enrolled patients provided written informed consent. The trial was conducted according to the Declaration of Helsinki and all local and national ethics committees approved the protocol.

In the PROTECT trial, signs and symptoms of heart failure (HF) and other biochemical measurements are available at least at baseline, discharge and at days 2, 7 and 14. Body weight was measured from baseline until day 4. Creatinine clearance was calculated using the Cockcroft−Gault formula.[17] Plasma bio-ADM levels were measured in patient EDTA samples using a novel immunoassay (Sphingotec GmbH, Henningsdorf, Germany). Measurements were available at baseline (n = 1562) and at discharge (if discharge occurred before

day 7), otherwise it was measured on day 7 (n = 1236).[17,18] BNP levels were measured using a highly sensitive single molecule counting (SMC™) technology (RUO, Erenna® Immunoassay System; Singulex Inc., Alameda, CA, USA). Further information on biomarkers measured in the PROTECT trial has been described previously.[18,19]

Study population and assessments

The current study is a retrospective analysis of the PROTECT trial. A clinical congestion score (CCS) was calculated by adding up the individual scores of JVP (0 to 2), orthopnoea (0 to 3) and peripheral oedema (0 to 3), yielding a maximum score of 8.[2,20] Patients with missing CCS data at day 7 (n = 461) were excluded from all analyses involving this variable. Diuretic response was calculated as weight change (in kg) until day 4 per 40 mg of IV furosemide administered in the first 72 h of hospital admission (or equivalents − bumetanide: 1 mg, torsemide: 20 mg). Discharge loop diuretic doses were calculated by adjusting the doses according to frequency, route of administration and furosemide equivalents. Final discharge diuretic doses were calculated as [IV/2 = oral dose]. Total cumulative diuretic doses till day 7 were calculated as [IV + (0.5 x oral dose)], adjusting for bioavailability. Loop diuretic doses were available in 1497 subjects at discharge. From the initial intention-to-treat study population of 2033 subjects, patients who underwent dialysis through day 4, had weight loss >20 kg or had missing values for day 7 bio-ADM levels (total n = 803) were excluded, resulting in a final study population of 1230 patients (online supplementary *Figure S1*). The included patient population was comparable to the excluded patient population (online supplementary *Table S1*).

Statistical analysis

Continuous variables are summarised as means (± standard deviation) or as median [interquartile range] as appropriate, and categorical variables are presented as number (percentage). Differences between tertiles of bio-ADM were tested using analysis of variance (ANOVA) or Kruskal−Wallis test for continuous variables and Pearson χ^2 for categorical variables. Normality was assessed using histograms and normal quantile−quantile plots. Non-normally distributed variables were natural log-transformed. Associations between clinical variables and residual congestion (defined as CCS > 3) at discharge were assessed using a logistic regression model. Multivariable linear regression models were constructed using backward elimination to identify predictors of discharge bio-ADM levels and loop diuretic doses. All variables with a P-value <0.10 from univariable analyses were included.

Cox proportional hazards regression analysis was performed to investigate the prognostic ability of bio-ADM levels individually and combined with loop diuretic doses for endpoints. Multivariable models were adjusted in model 1 for rolofylline treatment and for baseline variables from the PROTECT model published previously.[21] This model includes age, previous HF hospitalisation, peripheral oedema, systolic blood pressure, serum sodium, log blood urea nitrogen, log creatinine and albumin. Model 2 was adjusted for baseline log bio-ADM levels and day 7 log BNP levels in addition to model 1. Proportional hazards assumptions were checked using Schoenfeld residuals and log−log plots. Kaplan−Meier survival estimates were used to investigate the prognostic ability of discharge bio-ADM levels combined with loop diuretic doses. Differences between groups were tested using a log-rank test. Two-tailed tests were used and a

P-value <0.05 was considered statistically significant. All analyses were performed using STATA/SE version 15.0 (StataCorp LLC, College Station, TX, USA).

Results

Baseline characteristics

Baseline characteristics according to tertiles of discharge bio-ADM levels are presented in *Table 1*. Median bio-ADM levels were 33.7 [21.5−61.5] pg/mL at discharge. Higher discharge bio-ADM levels were associated with a longer duration of hospitalisation, poorer diuretic response, worsening renal function and higher BNP levels at discharge (all *P* < 0.001). Furthermore, loop diuretic use and signs and symptoms of residual congestion, such as a high congestion score, orthopnoea, rales, JVP, and oedema were more prevalent across increasing tertiles of bio-ADM (all *P* < 0.006). To further elucidate the relation between bio-ADM levels and loop diuretic doses at discharge, patients were divided into groups based on the respective medians (*Table 2*). Patients with elevated discharge bio-ADM levels combined with increased loop diuretic usage reflected a more diseased profile, as indicated by elevated levels of BNP and worsening renal function biomarkers (all *P* < 0.001). Interestingly, only few patients with high bio-ADM levels were receiving lower doses of loop diuretics, as this was the smallest of the four groups. Similar patterns in clinical characteristics were observed when patients were divided according to change in bio-ADM levels from baseline to discharge in combination with loop diuretic dosing (online supplementary *Table S2*). Trends across tertiles of congestion score at discharge were comparable to that of bio-ADM (online supplementary *Table S3*).

Predictors of bio-ADM levels, loop diuretic doses, and residual congestion at discharge

Taking the initial population of 1230 patients, after dropping missing values for discharge bio-ADM levels, 691 patients out of 1230 (56.2%) were discharged after day 7. In a multivariable linear regression model for predictors of discharge bio-ADM levels, oedema ($\beta = 0.218$, *P* < 0.001) was the strongest predictor of bio-ADM (adjusted $r^2 = 0.312$) (*Table 3*). In this model, higher discharge bio-ADM levels were also associated with higher BNP levels and serum creatinine at discharge and a history of diabetes and atrial fibrillation. In a univariable logistic regression model, bio-ADM was the strongest predictor of residual congestion (as indicated by a CCS score > 3 at discharge) (odds ratio 4.35, 95% confidence interval (CI) 3.37−5.62; *P* < 0.001) (online supplementary *Table S4*). In a multivariable linear regression model for predictors of loop diuretics, higher loop diuretic use at discharge was independently associated with a poorer diuretic response during hospitalisation ($\beta = 0.187$; *P* < 0.001) and higher discharge bio-ADM levels ($\beta = 0.084$; *P* = 0.020) (adjusted $r^2 = 0.261$) (online supplementary *Table S5*).

Bio-ADM levels, residual congestion, and discharge diuretic doses as predictors of outcomes in acute heart failure

Log bio-ADM at discharge was independently associated with an increased risk of all-cause mortality (hazard ratio (HR) 1.58 per log increase, 95% CI 1.22−2.05; *P* = 0.001), and HF rehospitalisation (HR 1.42 per log increase, 95% CI 1.10−1.84; *P* = 0.008), in contrast to baseline bio-ADM levels (*Table 4*). The curves for 180-day mortality and 60-day readmission according tertiles of discharge bio-ADM levels have been presented in online supplementary *Figures S2* and *S3*. The Kaplan−Meier curves for 60-day readmission due to HF for the combined groups of bio-ADM and loop diuretic doses at discharge are presented in *Figure 1*. Higher loop diuretic doses were independently associated with increased HF rehospitalisation, irrespective of bio-ADM levels (high or low; *Figure 1* and online supplementary *Table S6*). Interestingly, higher bio-ADM levels combined with higher use of loop diuretics was associated with a four times higher risk of rehospitalisation compared to the reference group (HR 4.02 per log increase, 95% CI 2.23−7.26; *P* < 0.001). The association remained significant even after adjusting for the baseline PROTECT model, baseline log bio-ADM and day 7 log BNP levels (online supplementary *Table S6*).

Discussion

In this study, we showed that higher levels of pre-discharge plasma bio-ADM levels are associated with more signs and symptoms of residual congestion and increased use of loop diuretics at discharge. Elevated pre-discharge bio-ADM levels had additive prognostic value on top of higher doses of loop diuretics to predict risk of early HF hospital readmissions. Thus, bio-ADM levels measured before discharge may be a valuable indicator of those patients that were not sufficiently decongested and consequently have a higher risk of readmission due to HF.

Role of bio-ADM as a congestion marker

Release of ADM is stimulated by volume overload as a protective response to limit further vascular leakage and the resulting tissue and interstitial fluid accumulation, by maintaining the vascular endothelial barrier function.[6,10] Bio-ADM levels are elevated in AHF, a condition characterized by volume overload, and are reflective of congestion.[6,8,9,12] We recently showed that bio-ADM levels measured during hospital admission or an episode of worsening signs and/or symptoms of HF were independently associated with severity of congestion, even after adjusting for other variables associated with congestion.[8,9] In the current study, we expanded on these findings and studied the clinical correlates associated with elevated pre-discharge bio-ADM levels, increased use of loop diuretic doses and the prognostic ability of discharge bio-ADM levels combined with loop diuretic doses.

Recent studies have demonstrated that inadequate decongestion at the time of discharge still remains a prevalent issue in AHF

Table 1 Baseline characteristics according to tertiles of day 7 or discharge bio-adrenomedullin levels

Variables	Tertile 1	Tertile 2	Tertile 3	P-value
Patients, n	411	409	410	
Bio-ADM day 7 (pg/mL)	17.6 [12.7–21.5]	33.7 [29.0–40.3]	80.5 [60.5–124.3]	
Demographics				
Male sex	267 (65.0)	262 (64.1)	278 (67.8)	0.500
Age (years)	70.9 (11.1)	71.3 (11.1)	69.7 (11.1)	0.099
LVEF at baseline (%)	32.5 (12.3)	32.3 (12.1)	32.4 (13.8)	0.980
Clinical profile				
LOS (days)	7.0 [6.0–12.0]	8.0 [6.0–14.0]	10.0 [7.0–16.0]	<0.001
CCS[a]	1.0 [0.0–2.0]	1.0 [1.0–2.0]	2.0 [1.0–4.0]	<0.001
Improvement in dyspnoea	360 (95.5)	351 (91.4)	332 (85.8)	<0.001
NYHA class III/IV	134 (36.2)	169 (44.9)	214 (58.2)	<0.001
Orthopnoea ≥+2	88 (23.3)	86 (22.4)	131 (34.3)	<0.001
Rales ≥1/3 lung fields	2 (0.5)	6 (1.6)	14 (3.7)	0.006
JVP ≥6 cm	59 (16.6)	92 (26.8)	138 (41.6)	<0.001
Oedema ≥+2	8 (2.1)	19 (4.9)	91 (23.6)	<0.001
Patient history				
Hyperlipidaemia	220 (53.5)	195 (47.7)	204 (49.9)	0.240
DM	145 (35.3)	199 (48.7)	231 (56.3)	<0.001
Hypertension	325 (79.1)	327 (80.0)	337 (82.2)	0.510
AF/atrial flutter	190 (46.5)	221 (54.3)	252 (61.8)	<0.001
Stroke (beyond 2 years)	31 (7.5)	40 (9.8)	35 (8.5)	0.520
COPD/asthma/bronchitis	69 (16.8)	75 (18.3)	94 (22.9)	0.071
IHD	287 (70.0)	291 (71.1)	296 (72.2)	0.790
PCI	108 (26.3)	101 (25.2)	106 (25.9)	0.930
CABG	78 (19.1)	83 (20.6)	113 (27.7)	0.007
Pacemaker	32 (7.8)	48 (11.7)	57 (13.9)	0.019
Biventricular pacing	38 (9.2)	38 (9.3)	47 (11.5)	0.480
ICD	53 (12.9)	59 (14.4)	84 (20.5)	0.007
NYHA class				0.084
I/II	81 (20.8)	75 (19.0)	53 (13.5)	
III	197 (50.6)	203 (51.5)	209 (53.3)	
IV	111 (28.5)	116 (29.4)	130 (33.2)	
Prior medication use (2 weeks before admission)				
ACEi or ARB	323 (78.6)	310 (75.8)	297 (72.4)	0.120
Beta-blocker	306 (74.5)	321 (78.5)	302 (73.7)	0.230
CCB	52 (12.7)	64 (15.6)	56 (13.7)	0.450
AI	185 (45.0)	176 (43.0)	201 (49.0)	0.210
Digoxin	107 (26.0)	105 (25.7)	139 (33.9)	0.013
Study medications				
Rolofylline, [n(%)]	257 (62.5)	283 (69.2)	283 (69.0)	0.069
Dose at discharge				
Loop diuretics	40.0 [40.0–80.0]	41.6 [40.0–80.0]	80.0 [40.0–160.0]	<0.001
Metolazone	2.5 [2.5–2.5]	0.6 [0.6–0.9]	1.3 [0.6–1.3]	0.071
Chlorothiazide	25.0 [12.5–25.0]	25.0 [12.5–25.0]	25.0 [25.0–25.0]	0.110
Spironolactone	25.0 [25.0–50.0]	25.0 [25.0–50.0]	25.0 [25.0–50.0]	0.200
Total diuretics until day 7 (IV + oral)	360.0 [220.0–520.0]	360.0 [251.3–600.0]	560.0 [330.0–1120.0]	<0.001
Diuretic response (kg/40 mg furosemide)	−0.4 [−0.9 to −0.2]	−0.5 [−1.0 to −0.2]	−0.3 [−0.6 to −0.1]	<0.001
Laboratory values				
Sodium (mmol/L)	138.7 (3.7)	138.7 (4.0)	137.5 (4.6)	<0.001
Potassium (mmol/L)	4.5 (0.5)	4.5 (0.6)	4.5 (0.7)	0.330
Haemoglobin (g/dL)	13.2 (1.9)	12.9 (2.1)	12.2 (2.0)	<0.001
Total cholesterol (mg/dL)	165.5 [141.0–200.0]	156.0 [131.0–188.0]	134.0 [107.0–164.5]	<0.001
Biomarkers				
BNP (pg/mL)	192.0 [110.0–318.5]	284.0 [151.0–494.0]	344.0 [196.0–678.0]	<0.001
Creatinine (mg/dL)	1.2 [1.0–1.6]	1.4 [1.1–1.8]	1.6 [1.3–2.2]	<0.001
eGFR (mL/min/1.73 m^2)	50.0 [37.6–65.0]	45.1 [33.5–60.9]	40.7 [30.3–56.8]	<0.001
Albumin (g/dL)	4.0 [3.7–4.3]	3.9 [3.6–4.2]	3.8 [3.5–4.1]	<0.001
BUN (mg/dL)	28.0 [22.0–38.0]	33.0 [25.0–45.0]	40.0 [28.0–57.0]	<0.001

Values are presented as mean ($\pm$ standard deviation), median [interquartile range], or n (%) wherever appropriate.
Clinical variables and biomarkers presented were measured on day 7, unless stated otherwise.
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AI, aldosterone inhibitor; ARB, angiotensin receptor blocker; bio-ADM, bio-adrenomedullin; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CCB, calcium channel blocker; CCS, clinical congestion score; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; IHD, ischaemic heart disease; IV, intravenous; JVP, jugular venous pressure; LOS, length of stay; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.
[a]Maximum score 8, values are lower than usual as patients with missing values of components of the score were not dropped.

Table 2 Baseline characteristics according to combined groups of day 7 bio-adrenomedullin levels (high or low) and loop diuretic doses at discharge (high or low)

Variables	1: Low bio-ADM + low dose	2: Low bio-ADM + high dose	3: High bio-ADM + low dose	4: High bio-ADM + high dose	P-value
Patients, n	259	206	188	278	
Bio-ADM day 1 (pg/mL)	23.9 [16.0–33.7]	27.9 [19.2–40.1]	66.9 [42.6–99.5]	74.0 [45.9–121.1]	
Bio-ADM day 7 (pg/mL)	20.9 [14.4–26.1]	19.6 [14.2–25.1]	51.7 [37.9–72.2]	60.3 [43.0–90.6]	
Demographics					
Male sex	152 (58.7)	147 (71.4)	114 (60.6)	197 (70.9)	0.003
Age (years)	70.8 (10.9)	70.1 (11.6)	71.9 (10.7)	70.7 (11.0)	0.460
White	254 (98.1)	197 (95.6)	183 (97.3)	257 (92.4)	0.008
LVEF at baseline (%)	34.5 (12.6)	29.8 (12.0)	33.0 (11.6)	30.3 (13.7)	0.012
Clinical profile					
LOS (days)	7.0 [6.0–13.0]	7.0 [4.0–9.0]	8.0 [7.0–15.0]	8.5 [6.0–14.0]	<0.001
CCS[a]	1.0 [0.0–2.0]	1.0 [0.0–2.0]	2.0 [0.0–3.0]	2.0 [1.0–3.0]	<0.001
Improvement in dyspnoea	224 (96.1)	177 (93.7)	163 (92.6)	220 (85.6)	<0.001
NYHA class III/IV	92 (40.2)	60 (32.4)	81 (46.8)	131 (52.8)	<0.001
Study medications					
Rolofylline 30 mg	156 (60.2)	140 (68.0)	130 (69.1)	201 (72.3)	0.025
Loop diuretics at discharge	40.0 [40.0–40.0]	80.0 [80.0–120.0]	40.0 [24.5–40.0]	80.0 [80.0–160.0]	<0.001
Total diuretics until day 7 (IV + oral)	270.0 [180.0–399.4]	520.0 [370.0–760.0]	300.0 [200.0–480.0]	690.0 [440.0–1165.0]	<0.001
Diuretic response (kg/40 mg furosemide)	−0.5 [−1.0 to −0.2]	−0.3 [−0.6 to −0.1]	−0.6 [−1.0 to −0.3]	−0.3 [−0.6 to −0.1]	<0.001
Biomarkers					
BNP (pg/mL)	196.5 [108.0–333.0]	204.0 [132.0–389.0]	291.0 [147.5–557.5]	319.5 [193.0–660.5]	<0.001
Creatinine (mg/dL)	1.3 [1.0–1.5]	1.3 [1.1–1.7]	1.5 [1.1–2.0]	1.6 [1.3–2.1]	<0.001
eGFR (mL/min/1.73 m^2)	49.6 [37.0–65.6]	48.0 [34.2–62.0]	40.4 [30.6–57.5]	40.6 [31.2–55.6]	<0.001
Albumin (g/dL)	4.0 [3.7–4.3]	4.0 [3.7–4.3]	3.9 [3.6–4.1]	3.9 [3.6–4.1]	<0.001
BUN (mg/dL)	28.0 [22.0–36.0]	33.0 [25.0–42.0]	34.0 [25.0–46.0]	39.0 [29.0–55.0]	<0.001

Values are presented as mean (± standard deviation), median [interquartile range], or n (%) wherever appropriate.
Clinical variables and biomarkers presented were measured on day 7, unless stated otherwise.
bio-ADM, bio-adrenomedullin; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CCS, clinical congestion score; eGFR, estimated glomerular filtration rate; IV, intravenous; LOS, length of stay; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
[a]Maximum score 8, values are lower than usual as patients with missing values of components of the score were not dropped.

patients, which is associated with a higher risk of readmission and mortality.[2,3,20] Moreover, pre-discharge assessment of residual congestion is still suboptimal. Though measurement of right atrial pressure and pulmonary capillary wedge pressure using cardiac catheterisation is considered the gold standard, this technique is highly invasive and not used routinely.[4] Non-invasive assessments such as JVP, oedema, and rales are subject to inter- and intra-observer variability, lack standardisation, and a decreasing number of medical professionals are sufficiently skilled to assess them.[4–6] Thus, biomarkers are of interest for assessing congestion as they are objective, and easily measurable. Though natriuretic peptides are commonly used to assess congestion, their production is mainly triggered by increased cardiac stretch and pressure during a state of volume overload.[6,22,23] In contrast, bio-ADM is stimulated to maintain vascular integrity in response to tissue congestion. Therefore, though both markers provide information on congestion status, the distinct mechanisms of production suggest that BNP may be a marker better suited for circulatory congestion and bio-ADM for tissue congestion. In our study, bio-ADM at discharge was associated with BNP levels and loop diuretic doses

at discharge. However, BNP levels were not associated with loop diuretic doses; therefore, bio-ADM may be of additive value on top of natriuretic peptides to assess pre-discharge residual congestion status. The utility of bio-ADM further needs to be validated using more invasive diagnostics studies such as lung ultrasound and cardiac catheterisation, which were unfortunately not available in this study.

Bio-ADM, loop diuretics, and risk of rehospitalisation

In recent studies, bio-ADM was shown to be predictive of adverse short-term outcomes in conditions such as AHF and sepsis.[8,9,12–15] In the current study, higher bio-ADM levels combined with increased use of loop diuretics were associated with a four times higher risk of readmission compared to the reference group, even after adjusting for discharge BNP and baseline bio-ADM levels. When combined with congestion score and BNP levels, low bio-ADM levels may help to identify patients with resolved congestion and an even lower risk of readmission, who

Table 3 Multivariable model for predictors of discharge bio-adrenomedullin levels

Variables	Log bio-ADM at discharge[a]		
	Standardized β	T-value	P-value
Oedema	0.218	8.04	<0.001
Log BNP	0.209	7.61	<0.001
Log creatinine	0.169	6.40	<0.001
History of DM	0.111	4.27	<0.001
History of AF	0.113	4.22	<0.001
Dyspnoea on exertion	0.098	3.73	<0.001
Digoxin	0.062	2.31	0.021
History of COPD	0.053	2.09	0.037
Albumin	−0.060	−2.22	0.026
Sodium	−0.060	−2.32	0.021
Log total cholesterol	−0.143	−5.11	<0.001

Clinical variables and biomarkers presented were measured on day 7, unless stated otherwise.
AF, atrial fibrillation; bio-ADM, bio-adrenomedullin; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus.
[a]$n = 1080$, $r^2 = 0.319$, adjusted $r^2 = 0.312$.

Table 4 Cox regression analyses for bio-adrenomedullin levels for 180-day mortality and 60-day heart failure rehospitalisation

Outcome	Events, n (%)	Log bio-ADM levels	Univariable Cox		Model 1[a]		Model 2[b]	
			HR (95% CI) per log increase	P-value	HR (95% CI) per log increase	P-value	HR (95% CI) per log increase	P-value
180-day mortality	270/1556 (17.4)	Day 1	1.49 (1.30−1.70)	<0.001	1.25 (1.07−1.45)	0.004	–	–
	186/1230 (15.1)	Day 7	1.78 (1.53−2.08)	<0.001	1.47 (1.24−1.75)	<0.001	1.58 (1.22−2.05)	0.001
	186/1230 (15.1)	Difference day 1 to 7	1.44 (1.21−1.70)	<0.001	1.22 (1.02−1.45)	0.027	1.13 (0.94−1.35)	0.195
60-day HF rehospitalisation	230/1556 (14.8)	Day 1	1.10 (0.95−1.27)	0.199	1.02 (0.87−1.20)	0.783	–	–
	187/1230 (15.2)	Day 7	1.35 (1.16−1.58)	<0.001	1.28 (1.08−1.51)	0.005	1.42 (1.10−1.84)	0.008
	187/1230 (15.2)	Difference day 1 to 7	1.11 (0.96−1.29)	0.171	1.02 (0.87−1.19)	0.840	1.01 (0.86−1.20)	0.884

bio-ADM, bio-adrenomedullin; CI, confidence interval; HF, heart failure; HR, hazard ratio.
[a]Model 1 was adjusted for rolofylline treatment and for baseline variables from the PROTECT model published previously that included age, previous HF hospitalisation, peripheral oedema, systolic blood pressure, serum sodium, log blood urea nitrogen, log creatinine and albumin.
[b]Model 2 was adjusted for day 1 log bio-ADM levels and day 7 log BNP levels in addition to model 1.

could therefore be safely discharged. On the other hand, higher bio-ADM levels may help detect patients that are inadequately decongested, and if the patients are already receiving optimal loop diuretic doses or are resistant to diuretic therapy, re-assessment of treatment may be warranted. In these patients, the physician can then consider extending hospital stay and selecting an alternative treatment strategy, such as increasing the diuretic dose further, using IV loop diuretics, changing to another loop diuretic type (e.g. torsemide), or combination of loop diuretic with either a thiazide diuretic or an aldosterone antagonist.[24,25] After adjusting the diuretic strategy, bio-ADM can also be used in conjunction with other novel prognostic markers such as proenkephalin A 119−159 (PENK). Elevated PENK levels predict

worsening renal function, glomerular and tubular dysfunction, and are associated with a higher risk of in-hospital and post-discharge mortality in AHF patients.[15,26] As PENK levels rise faster than creatinine during renal damage, the marker can be used to identify patients who do not tolerate intensification of diuretic treatment based on bio-ADM levels.[15] In these patients, surrogate treatment strategies such as ultrafiltration, hypertonic saline infusion, rolofylline or vasopressin antagonist tolvaptan might be of benefit.[25]

Interestingly, patients with high bio-ADM levels receiving high loop diuretic doses formed the largest patient group in our study, while patients with high bio-ADM levels receiving lower doses of loop diuretics at discharge composed the smallest group. This
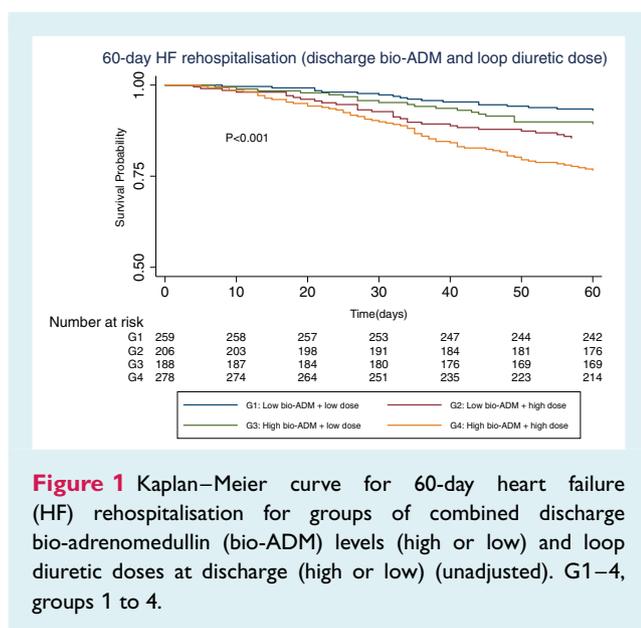
Figure 1 Kaplan−Meier curve for 60-day heart failure (HF) rehospitalisation for groups of combined discharge bio-adrenomedullin (bio-ADM) levels (high or low) and loop diuretic doses at discharge (high or low) (unadjusted). G1−4, groups 1 to 4.

supports the assumption that patients with high bio-ADM were already considered by the treating physician as more congested patients than those with lower bio-ADM levels. This patient group also reflected the presence of a more diseased profile, as they had higher BNP levels, worse New York Heart Association class, and a longer hospital stay compared to other groups. Thus, the higher doses may also be due to advanced HF, which is more likely to result in diuretic resistance and worsening renal function. The association of the combination of bio-ADM and loop diuretic doses with readmission but not with mortality is an important finding, since congestion is a prominent cause of readmission due to worsening HF, instead of mortality.[4] Therefore, this finding further supports the role of bio-ADM as a congestion marker. Moreover, though models predicting mortality in AHF perform reasonably well, models predicting readmission risk still remain poor.[6,27] Since this may be a preventable outcome, bio-ADM could be an easily measurable biomarker for identifying patients warranting diuretic therapy changes, or patients at lower risk of readmission due to HF. In addition to its value in detecting congestion status and high-risk patients, bio-ADM may also be a promising therapeutic target in HF patients. Adrecizumab is a humanized, non-neutralizing, monoclonal antibody targeted against the N-terminus of ADM.[28] The antibody increases intravascular ADM concentration in a dose-dependent manner, leading to improved vascular integrity of blood vessels and a decrease in tissue congestion and dyspnoea as a result. A phase II proof of concept study in patients with worsening HF is currently underway.[6]

Strengths and limitations

This is the first study evaluating the associations of discharge bio-ADM levels with (residual) congestion at discharge and its prognostic ability combined with discharge loop diuretics to predict outcomes in AHF. Since bio-ADM levels were available at different time points, we were able to study the effects of

changes in bio-ADM on clinical variables and congestion. However, our study is limited by its retrospective design, and all analyses are purely observational. The diagnostic and prognostic ability of bio-ADM needs to be supported by validation in prospective studies and by more sensitive imaging studies such as cardiac catheterisation or lung ultrasound. Furthermore, diuretic response was only available until day 4, as weight change was only measured from baseline until day 4 in the PROTECT trial. Additionally, the BNP assay used in the study was not standardised. Lastly, our results cannot be generalized to chronic HF patients, and applicability to patients with mild decompensated HF, or worsening HF cannot be conferred from this study, however we recently studied this in the BIOSTAT-CHF dataset.[8]

Conclusions

In hospitalised HF patients, elevated discharge bio-ADM levels were associated with higher discharge loop diuretic doses and reflected residual congestion. Patients with both higher bio-ADM levels and higher loop diuretic doses at discharge had an increased risk of early hospital readmission for worsening HF. Assessment of discharge bio-ADM may be a readily applicable marker to identify patients with residual congestion at higher risk of early hospital readmission. Future prospective studies need to establish whether bio-ADM can be used to guide time of discharge and loop diuretic doses pre- and post-discharge.

Supplementary Information

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

Figure S1. Diagram showing study populations after excluding patients.

Figure S2. Kaplan−Meier curve for 180-day mortality for tertiles of discharge bio-adrenomedullin levels (unadjusted).

Figure S3. Kaplan−Meier curve for 60-day rehospitalisation for tertiles of discharge bio-adrenomedullin levels (unadjusted).

Table S1. Baseline characteristics of included and excluded patients.

Table S2. Baseline characteristics according to combined groups of changes in bio-adrenomedullin levels day 1 to 7 (increase or decrease) and loop diuretic doses at discharge (high or low).

Table S3. Baseline characteristics according to groups of day 7 clinical congestion score.

Table S4. Univariable models for predictors of residual congestion at discharge.

Table S5. Multivariable model for predictors of discharge loop diuretic doses.

Table S6. Cox regression analyses for combined groups day 7 bio-adrenomedullin levels (high or low) with loop diuretic doses at discharge (high or low) for outcomes 180-day mortality and 60-day heart failure rehospitalisation.

Funding

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