Bioactive adrenomedullin for assessment of venous congestion in heart failure

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Abstract

Aims Bioactive adrenomedullin (bio-ADM) is a vascular-derived peptide hormone that has emerged as a promising biomarker for assessment of congestion in decompensated heart failure (HF). We aimed to evaluate diagnostic and prognostic performance of bio-ADM for HF in comparison to amino-terminal pro-B-type natriuretic peptide (NT-proBNP), with decision thresholds derived from invasive haemodynamic and population-based studies.

Methods and results Normal reference ranges for bio-ADM were derived from a community-based cohort (n = 5060). Correlations with haemodynamic data were explored in a cohort of HF patients undergoing right heart catheterization (n = 346). Mortality and decision cutoffs for bio-ADM was explored in a cohort of patients presenting in the ER with acute dyspnoea (n = 1534), including patients with decompensated HF (n = 570). The normal reference range was 8–39 pg/mL. The area under the receiver operating characteristic curve (AUROC) for discrimination of elevated mean right atrial pressure (mRAP) and pulmonary arterial wedge pressure (PAWP) was 0.74 (95% CI = 0.67–0.79) and 0.70 (95% CI = 0.64–0.75), respectively, with optimal bio-ADM decision cutoff of 39 pg/mL, concordant with cubic spline analyses. NT-proBNP discriminated PAWP slightly better than mRAP (AUROC 0.73 [95% CI = 0.68–0.79] and 0.68 [95% CI = 0.61–0.75]). Bio-ADM correlated with (mRAP, r = 0.55) while NT-proBNP correlated with PAWP. Finally, a bio-ADM decision cutoff of 39 pg/mL associated with 30 and 90 day mortality and conferred a two-fold increased odds of HF diagnosis, independently from NT-proBNP.

Conclusions Bio-ADM tracks with mRAP and associates with measures of systemic congestion and with mortality in decompensated HF independently from NT-proBNP. Our findings support utility of bio-ADM as a biomarker of systemic venous congestion in HF and nominate a decision threshold.

Keywords Heart failure; Biomarker; Congestion; Bioactive adrenomedullin; Haemodynamics; Prognosis

Introduction

Heart failure (HF) is the end-stage condition of all heart disease, characterized by inability of typically the left ventricle to maintain sufficient output of blood for the demands of the body at normal cardiac filling pressures. Elevated intraventricular pressure during diastolic filling is a hallmark of HF, that may result both from reduced blood ejection (systolic dysfunction), restrictive filling (diastolic dysfunction), and intravascular fluid expansion from retention of fluid and salt.¹² With increasing severity, elevated left ventricular pressures are transmitted retrogradely through the venous system (pulmonary venous congestion) and may be further transmitted across the pulmonary arteries and right ventricle resulting in systemic venous congestion.³ Pulmonary congestion may manifest with pulmonary fluid extravasation, pulmonary oedema, and
right ventricular (RV) failure, while subsequent systemic congestion may result in abdominal organ dysfunction and peripheral oedema.\(^3\)\(^,\)\(^4\) Episodes of acute decompensation of chronic HF occur when filling pressures are acutely further elevated, typically necessitating in-hospital care for dyspnoea and fluid accumulation, and represent a major determinant of quality of life and healthcare costs in HF. Furthermore, a large proportion of patients with decompensated HF are discharged with residual congestion which is associated with rehospitalization and death after discharge,\(^2\) and congestion remains a major hurdle in the care for all HF patients.\(^5\)

In clinical practice, decongestive therapy is often guided by symptoms of dyspnoea, peripheral oedema or weight gain, but many studies have established that elevated filling pressures often precede symptomatic decompensation by weeks, suggestive that intravascular congestion may represent an important target for decongestive therapy.\(^6\)\(^,\)\(^7\) Invasive pressure tracing from cardiac catheterization is the golden standard for assessment of filling pressures and intravascular congestion.\(^5\) Non-invasive measures to estimate filling pressures are available, particularly including ultrasound-based measures, but require highly specialized expertise and further scientific evaluation to establish clinical utility.\(^8\) Plasma proteins represent an attractive alternative for non-invasive assessment of congestion, given their objectivity, reproducibility, and ease of ascertainment from peripheral venous blood samples through standardized immunoassays.

Adrenomedullin (ADM), a peptide hormone released particularly from endothelial and vascular smooth muscle cells in response to intravascular volume overload, has recently emerged as a promising biomarker of venous congestion. ADM has vasodilating properties and a role in maintenance of endothelial barrier function, thus regulating intravascular volume and tissue oedema.\(^9\)\(^,\)\(^10\) The prohormone pro-ADM is proteolytically processed into biologically inactive ADM, before being converted to bioactive ADM (bio-ADM) through enzymatic C-terminal amidation. Several studies have described association of a specific bio-ADM assay\(^11\) with clinical manifestations of congestion\(^12\)\(^–\)\(^19\) but key aspects of bio-ADM kinetics remain unexplored. Two phase 2 trials have also demonstrated favourable safety for the therapeutic bio-ADM antibody Adrecizumab, opening for potential therapeutic intervention in patients with high levels.\(^20\)\(^,\)\(^21\)

Importantly, there is no consensus across studies on target bio-ADM levels, and no data are available on the distribution of bio-ADM in the general population or in relation to invasively measured pulmonary and systemic venous pressures in HF. Therefore, we first aimed to derive reference ranges for bio-ADM in the community. Secondly, we explored the relation with haemodynamic measures and derived a bio-ADM cutoff in HF patients. Finally, we aimed to evaluate these bio-ADM cutoffs for diagnostic and prognostic assessment of decompensated HF in a clinical acute setting including other causes of dyspnoea.

**Methods**

**Study samples**

**Malmö preventive project**

The Malmö preventive project (MPP) was a community-based lifestyle intervention program that started in the early 1970s, from which 18 240 participants were reexamined 2002–2006. Cardiovascular risk factors were evaluated and fasting plasma samples were obtained during the reexamination. From this cohort, a random sample of 5060 individuals was included in the current study. Estimated glomerular filtration rate (eGFR) was calculated from creatinine using the CKD-EPI formula. To explore the variation in reference intervals, depending on disease burden and risk factors, we identified a healthy subcohort of 1128 subjects after excluding subjects with history of HF, atrial fibrillation, stroke, ischemic heart disease, diabetes, smoking, BMI > 30 kg/m\(^2\), hypertension, and eGFR <60 ml/min/1.73 m\(^2\) (Supporting Information, Figure S1).

**Right heart catheterization cohort**

A cohort consisting of 346 patients with HF undergoing right heart catheterization (RHC) with insertion of a Swan Ganz catheter (Baxter Healthcare Corp., Santa Ana, CA, USA) for haemodynamic assessment at Skåne University Hospital in Lund, Sweden between August 2011 and January 2019, were asked to provide plasma samples as part of an ongoing biobanking project at Skåne University Hospital (Lund Cardio-pulmonary Register). Blood samples were drawn from central venous catheters, immediately centrifuged at 2000 g for 10 min and plasma extracted, aliquoted and stored at −80°C until the time of biochemical analysis without previous thawing. Patients from this cohort underwent RHC typically as part of a transplant assessment and occasionally as part of a HF workup, either in an outpatient or inpatient setting.

A subset of 47 patients underwent heart transplantation, after which a second sample was obtained using the same procedures in relation to the 6-month routine endomyocardial biopsy after transplantation. For these patients, a first sample was collected during RHC at a median of 142 days before transplantation (range 4–1218 days) and follow-up samples at a median of 167 days (~6 months) after transplantation (range 26–409 days). Among the 47 patients, four patients had a follow-up at 3 months and two patients had a 1 year follow-up. RHC was performed in the supine position under local anaesthesia, with the catheter introduced through the right internal jugular vein using the Seldinger technique. The catheter was advanced to the pulmonary artery guided by ultrasound and fluoroscopy, and the catheter position was verified by identifying the signature pressure curves. Pressure measurements were obtained in the pulmonary arterial wedge position (pulmonary arterial wedge pressure, PAWP), pulmonary artery (mean pulmonary arterial
pressure, mPAP), right ventricle (diastolic right ventricular pressure, RVPd), and atrium (mean right atrial pressure, mRAP). Cardiac output was measured by thermodilution as the average of three measurements and indexed to body surface area as cardiac index. Stroke volume index (SVI) was computed by dividing cardiac output by the heart rate. The mixed venous oxygen saturation (SvO₂) was measured in blood drawn from the pulmonary artery on an ABL 90 Flex (Radiometer Medical Aps, Copenhagen, Denmark). Elevated filling pressures were defined based on published studies as mRAP >10 mmHg and PAWP >15 mmHg, while pulmonary hypertension was defined as mPAP >25 mmHg in accordance with guidelines from the European Society of Cardiology.²² A cutpoint of PAWP >18 was also explored, as many patients in a chronic context have higher values.

**Acute dyspnoea cohort**

A total of 1710 patients aged ≥18 years seeking the emergency department (ED) of Skåne University Hospital in Malmö on weekdays, 8 a.m. to 5 p.m., between December 2013 and July 2018 were enrolled in a study of acute dyspnoea (ADYS) described previously.²³ A research nurse approached patients triaged as dyspnoea and collected written informed consent, clinical parameters through structured questions and review of patient records, and blood samples through peripheral venipuncture. Skåne University Hospital in Malmö serves a catchment area of 400 000 subjects from Malmö, the third largest city in Sweden, and the ED has up to 85 000 visits per year. Data on both bio-ADM and clinical parameters were available in 1539 patients.

The investigations conforms with the principles outlined in the Declaration of Helsinki and were approved by the local ethics committee in Lund. All subjects gave informed consent to participate in the study.

**Biomarker measurements**

Bio-ADM was measured using a sandwich immunoassay from SphingoTec GmbH (Hennigsdorf, Germany), by an external laboratory blinded to clinical characteristics.¹¹ This biomarker is unique in measuring bio-ADM, and was used in all previous studies of this biomarker.¹²⁻¹⁹ The lower limit of detection is 3 pg/mL and the limit of quantification is 8 pg/mL, with interassay and intraassay coefficients of variation of 5⁻¹⁰% and 4⁻⁸%, respectively.¹¹

N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured by a common clinical electrochemiluminescence sandwich immunoassay, in HF-RHC as part of routine clinical care through the department of clinical chemistry on the fully automated Elecsys E170 analyser, and in ADYS on a Cobas e411 analyser (both from Roche Diagnostics, Indianapolis, IN). Low intra-assay and individual variability have been described for both assays.²⁴

**Statistical analysis**

Firstly, the population distribution of bio-ADM in the MPP was explored in histograms and a truncated distribution was noted (Figure 1A), with many samples near the lower limit of quantification and nearly 10% of samples below the lower limit. Clinical covariates of log-transformed bio-ADM were therefore determined using Tobit regression type 1. Reference intervals were derived based on percentiles from bootstrap resampling in both the full cohort and the healthy subcohort.

Secondly, the distribution of bio-ADM in the HF-RHC cohort was explored and found less markedly truncated, but with considerable skewness (Figure 1B). General linear models and Pearson’s correlation coefficients of natural logarithm transformed bio-ADM were therefore used to explore haemodynamic correlates of bio-ADM and compared with logarithm transformed NT-proBNP. Whether bio-ADM tracked with such haemodynamic correlates over time was further explored in the subset of patients who underwent a second RHC 6 months after heart transplantation, using mixed-effects regression models. The relation of bio-ADM with venous pressures was also explored based on restricted cubic splines with knots placed at the five percentiles of congestion measures recommended by Harrel (5th, 25th, 50th, 75th, and 95th percentiles).²⁵ The area under the receiver-operating characteristic (AUROC) curve was computed to evaluate discrimination of elevated venous pressures according to derived bio-ADM cutoffs, maximization of sensitivity and specificity, and technical optimum obtained from maximization of Youden’s J statistic.

Finally, bio-ADM cutoffs derived from the general population and haemodynamic cohorts were explored in the ADYS cohort, in addition to bio-ADM quartiles from ADYS. Bio-ADM displayed a skewed distribution and was natural logarithm transformed (Figure 1C). The association of bio-ADM with a diagnosis of HF, measures of congestion, and with outcome in HF patients was explored both based on cutoffs and full distributions using logistic and Cox proportional hazards regression models. Models and areas under the ROC curve were compared with the corresponding models for NT-proBNP, and adjustment for NT-proBNP was performed in separate models. Differences in survival across bio-ADM thresholds were plotted based on the Kaplan–Meier estimator. All analyses were conducted in STATA SE 15 (StataCorp, College Station, TX, USA).

**Results**

**Bioactive adrenomedullin in the community**

Baseline characteristics of the community-based MPP cohort (n = 5060) and the healthy subcohort (n = 1128) are shown in

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Figure 1  Bio-ADM distribution across cohorts. Distribution of bioactive adrenomedullin (bio-ADM) in the three study cohorts. For all cohorts, the dashed line indicates the upper reference threshold based on the MPP cohort (39 pg/mL), which also corresponds to the decision cutoff for elevated mRAP. (A) The community-based MPP cohort distribution of bio-ADM in the entire cohort \( (n = 5060, \text{yellow}) \) and healthy subcohort \( (n = 1128, \text{blue}) \). Truncation of the distribution was observed at the lower limit of detection (8 pg/mL). A normal reference interval was derived from 2.5 and 97.5 percentiles through bootstrap resampling (8 [95% CI 8–8] to 39.1 [95% CI 36.5–41.8] for entire cohort, 8 [95% CI 8–8] to 29.5 [95% CI 25.6–33.7] in the healthy subcohort. Fourteen positive outliers were excluded from the plot (max. 283 pg/mL). The proportion of subjects over the cutoff of 39 pg/mL was 2.5% in the full cohort (127 subjects) and 1.1% (12 subjects) in the healthy subcohort. (B) Cohort of heart failure (HF) patients undergoing right heart catheterization (HF-RHC). Distribution of bio-ADM at baseline in the entire cohort \( (n = 346, \text{yellow}) \) and in a subset of patients after transplantation \( (n = 47, \text{blue}) \). The proportion of patients over the cutoff of 39 pg/mL was 27.5% (95 patients) in the entire cohort, 29.8% (14 patients) before transplantation, and 19.2% (nine patients) after transplantation. (C) Cohort of patients presenting with acute dyspnoea (ADYS). Distribution of bio-ADM in the entire cohort \( (n = 1534) \) (yellow) and in the subset with a final diagnosis of HF \( (n = 570) \) (blue). The proportion of patients over the cutoff of 39 pg/mL was 33.3% (510 patients) in the entire cohort and 54% (308 patients) in HF patients.
Table 1. The distribution and reference range for bio-ADM are shown in Figure 1A. The median bio-ADM plasma concentration was 14 pg/mL (interquartile range [IQR] 10–19 pg/mL), and the reference range was 8–39 pg/mL (95% confidence interval [CI] for upper limit 36–42 pg/mL) in the full cohort and 8–30 pg/mL (95% CI 26–34 pg/mL) in the healthy subcohort. Clinical covariates of bio-ADM from regression analysis are shown in Table 2. The strongest associations were observed with measures of body size (BMI, r = 0.41; and waist circumference, r = 0.38) followed by triglycerides (r = 0.26) and eGFR (r = −0.22). The ranges of BMI and eGFR were 15.8–54.5 kg/m² and 6.8–120.9 mL/min/1.72 m², and 1103 (22%) subjects had a BMI > 30 kg/m², 120 (2%) subjects BMI < 20 kg/m², 60 (1%) subjects eGFR <30 ml/min/1.72 m², and 1648 (33%) subjects eGFR 30–60 ml/min/1.72 m². Subjects with BMI > 30 kg/m² had a median bio-ADM of 19 pg/mL (IQR = 14–25 pg/mL), median bio-ADM of 10 pg/mL (IQR = 8–13 pg/mL) for BMI < 20 kg/m², median bio-ADM of 21 pg/mL (IQR = 15–31 pg/mL) for eGFR <30 ml/min/1.72 m², and median bio-ADM of 16 (IQR = 12–21) for eGFR of 30–60 ml/min/1.72 m² indicating small bio-ADM differences by major clinically relevant strata for these correlates.

Bioactive adrenomedullin and central haemodynamics

Baseline characteristics for the 346 patients in the HF-RHC cohort are shown in Table 1. Central haemodynamics were impaired in this cohort as shown in Supporting Information, Figure S2, with a hypokinetinc circulation (mean cardiac index of 2.32 L/min/m² and SvO₂ of 61%). Overall, venous pressures were mildly elevated both in the pulmonary veins (PAWP of 16 mmHg) and systemic veins (mRAP of 10 mmHg), but a substantial subset of patients had elevated pressures (179 [54%] of patients with PAWP >15 mmHg and 136 [41%] patients with mRAP >10 mmHg). Most patients with elevated mRAP also had elevated PAWP (n = 119), while pulmonary hypertension was present in 76% of the patients with mRAP >10 mmHg and a PAWP <15. Overall mPAP was mildly elevated (median 27 mmHg [IQR 18–35]). Most haemodynamic measures were at least modestly correlated (Supporting Information, Figure S3), with modest inverse correlations of both mRAP and PAWP with cardiac index (r = −0.3 and r = −0.4), SVI (r = −0.4 and r = −0.5), SvO₂ (r = −0.6 for both) and positive correlations with mPAP (r = 0.5 and r = 0.8) and RVpD (r = 0.7 and r = 0.5). NT-proBNP was markedly elevated, with a median of 2582 pg/mL. In the subset of 47 patients that underwent transplantation, cardiac function improved after transplantation and pressures declined towards normal reference values (Supporting Information, Figure S2).

The distributions of bio-ADM in HF patients and the subset who obtained a heart transplant are depicted in Figure 1B. Bio-ADM was most strongly correlated with mRAP (r = 0.6, Figure 2A), followed by SvO₂ (r = −0.5), PAWP (r = 0.4, Figure 2B), RVpD (r = 0.4) and mPAP (r = 0.4) as shown in Supporting Information, Figure S3. In contrast, NT-proBNP was most strongly correlated with SvO₂ (r = −0.6), followed by PAWP (r = 0.5), mPAP (r = 0.4), and SVI (r = 0.4) as shown in Supporting Information, Figures S3 and S4.

In the subset of HF patients who underwent heart transplantation, bio-ADM declined over time from a median of 28 pg/mL (IQR = 18.46–42.80) to 20 pg/mL (IQR = 11.89–30.43, P < 0.001), and the decline was accompanied by a significant decline in mRAP to normal levels (median from 11 to 3 mmHg, P < 0.001, Supporting Information, Figure S5). The change in bio-ADM was most strongly correlated with change in mRAP (r = 0.64, Supporting Information, Table S2), followed by SvO₂ (r = 0.60) and RVpD (r = 0.59). In multivariable-adjusted repeated-measures regression models, bio-ADM also decreased significantly after transplantation in parallel with these factors (Supporting Information, Table S2).

Discrimination of elevated mRAP was higher for bio-ADM compared with NT-proBNP (AUROC 0.74 [CI = 0.67–0.79] vs. 0.68 [CI 0.61–0.75]), while elevated PAWP was better recognized by NT-proBNP compared with bio-ADM (AUROC 0.73 [CI 0.68–0.79] vs. 0.70 [CI 0.64–0.75]) as shown in Figure 2C,D. In comparisons of several potential decision thresholds, the upper population reference from MPP (39 pg/mL) was found to provide optimal sensitivity while retaining specificity >0.8 for both mRAP and PAWP (Supporting Information, Table S2) as also indicated in Figure 2C,D. Restricted cubic spline analyses supported linear relationships of bio-ADM and corroborated 39 pg/mL as optimal threshold for detection of elevated RAP and PAWP (Supporting Information, Figure S6). This bio-ADM threshold also provided 80% specificity for PAWP >18 mmHg.

Bioactive adrenomedullin in acute dyspnoea

The ADYS cohort consists of 1534 patients with ADYS, of which 871 patients (57%) were hospitalized. In total, 570 patients were diagnosed with HF, of which 516 patients (91%) had a history of HF, while 54 patients (9%) received a first HF diagnosis. In patients with a history of HF, 390 patients (76%) had performed echocardiography, showing reduced ejection fraction (<50%) in 196 patients (50%), while in newly diagnosed HF only 7 patients (13%) performed echocardiography in-hospital, showing reduced ejection fraction in 4 patients. Overall, 439 (77%) of the HF patients were hospitalized. Baseline characteristics for the full ADYS cohort and the HF patients are shown in Table 1. The distribution of bio-ADM in the overall ADYS cohort and the subset with HF are shown in Figure 1C.

Bio-ADM was associated with a diagnosis of HF independently of NT-proBNP as shown in Table 3. Bio-ADM was also
Table 1  Baseline characteristics of study cohorts

|                         | Population-based (MPP, n = 5060) | Healthy sub-cohort (MPP, n = 1128) | Haemodynamic cohort (HF-RHC, n = 346) | Heart transplant recipients (HF-RHC, n = 47) | Dyspnoea (ADYS, n = 1534) | Decompensated HF (ADYS, n = 570) |
|-------------------------|-----------------------------------|------------------------------------|--------------------------------------|---------------------------------------------|--------------------------------|----------------------------------|
| Age (years)             | 68.6 (67.1–74.7)                  | 67.7 (66.0–70.6)                   | 57.3 (14.3)                          | 53.4 (10.8)                                 | 74.4 (62.2–84.1)              | 81.5 (73.4–88.2)                 |
| Sex, female             | 1467 (29)                         | 353 (31)                           | 108 (31)                             | 10 (21)                                     | 856 (56)                      | 279 (49)                        |
| Body mass index (kg/m²) | 27.2 (24.4–29.4)                  | 23.0 (23.7–27.5)                   | 26.0 (23.0–29.4)                     | 25.4 (22.0–29.0)                            | 25.5 (22.3–30.0)              | 26.6 (23.1–30.8)                |
| Systolic Blood pressure (mmHg) | 146.0 (20.8)                     | 142.7 (19.5)                       | 118.2 (22.0)                         | 142.2 (15.6)                                | 145.7 (27.9)                  | 143.4 (30.3)                    |
| Diastolic Blood pressure (mmHg) | 83.5 (10.8)                       | 82.9 (9.9)                         | 74.8 (12.1)                          | 90.1 (10.9)                                 | 81.8 (15.7)                   | 80.0 (16.8)                     |
| Heart rate (b.p.m.)     | 76.0 (12.5)                       | 71.4 (11.9)                        | 75.3 (14.7)                          | 78.6 (8.8)                                  | 91.0 (21.5)                   | 90.2 (21.8)                     |
| SaO₂ (%)                | N/A                               | N/A                                | N/A                                  | N/A                                         | 95.0 (90.0–98.0)              | 93.0 (88.0–96.0)                |
| Current smoking         | 955 (19)                          | 0 (0)                              | 19 (5)                               | 0 (0)                                       | 268 (17)                      | 68 (12)                         |
| Medical history         |                                   |                                    |                                      |                                             |                               |                                 |
| Diabetes mellitus       | 808 (16)                          | 0 (0)                              | 32 (9)                               | 13 (28)                                     | 275 (18)                      | 161 (28)                        |
| Hypertension            | 2021 (40)                         | 0 (0)                              | 45 (13)                              | 8 (17)                                      | 632 (41)                      | 315 (56)                        |
| Myocardial infarction   | 345 (7)                           | 0 (0)                              | 10 (3)                               | 1 (2)                                       | 445 (29)                      | 305 (54)                        |
| Atrial fibrillation     | 284 (6)                           | 0 (0)                              | 17 (5)                               | 1 (2)                                       | 462 (30)                      | 329 (58)                        |
| HF                      | 89 (2)                            | 0 (0)                              | 346 (100)                            | 47 (100)                                    | 516 (34)                      | 570 (100)                       |
| COPD or asthma          | N/A                               | N/A                                | N/A                                  | N/A                                         | 614 (40)                      | 233 (41)                        |
| Medications             |                                   |                                    |                                      |                                             |                               |                                 |
| ACE/ARB                 | 878 (17)                          | 0 (0)                              | 115 (75%)                            | 18 (51%)                                    | 456 (30)                      | 274 (49)                        |
| Beta-blocker            | 1158 (23)                         | 0 (0)                              | 138 (90%)                            | 34 (87%)                                    | 658 (43)                      | 407 (72)                        |
| Aldosterone antagonist  | 143 (3)                           | 0 (0)                              | 98 (64%)                             | 20 (57%)                                    | 124 (8)                       | 85 (15)                         |
| Loop diuretic           | 307 (6)                           | 0 (0)                              | 77 (78%)                             | 32 (97%)                                    | 561 (37)                      | 398 (70)                        |
| Plasma biomarkers       |                                   |                                    |                                      |                                             |                               |                                 |
| eGFR (CKD-EPI, mL/min/1.73 m²) | 65.9 (55.3–77.3)              | 74.1 (66.6–83.1)                   | 69.0 (50.9–89.7)                      | 46.2 (35.7–74.2)                            | 72.9 (49.1–90.9)              | 52.6 (37.3–72.9)               |
| NT-proBNP (pg/mL)       | N/A                               | N/A                                | 2581.5 (907.5–5051.5)                | 2189.0 (868.0–7102.5)                       | 815.6 (141.3–3721.0)          | 3810 (1617–8590)               |
| Bio-ADM (pg/mL)         | 14.0 (10.4–19.1)                  | 11.5 (8.8–15.0)                    | 24.9 (14.4–40.9)                     | 19.5 (11.9–30.4)                            | 28.0 (16.8–49.5)              | 42.7 (28.2–71.1)               |
| NYHA class              | I N/A                             | N/A                                | 8 (5.8)                              | -                                           | N/A                           | 86 (15.2)                       |
|                         | II 37 (27.0)                      | 1 (4.8)                            |                                      |                                             |                               | 211 (37.0)                     |
|                         | III 82 (60.0)                     | 18 (85.7)                          |                                      |                                             |                               | 111 (19.5)                     |
|                         | IV 10 (7.3)                       | 2 (9.5)                            |                                      |                                             |                               | 157 (27.5)                     |

Distributions of quantitative variables are presented as mean with standard deviation or median with interquartile range, as appropriate. For categorical variables, numbers and percentage of total are presented. For heart transplant recipients, data refer to before transplantation.

ACE/ARB, angiotensin converting enzyme/angiotensin-receptor blocker; bio-ADM, bioactive adrenomedullin; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; MPP, Malmö Preventive Project; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SaO₂, arterial oxygen saturation.
Table 2 Clinical correlates of bio-ADM in the MPP cohort

| Covariate                          | Correlation, r (P) | Univariate regression, beta (P) | Multiple regression, beta (P) |
|------------------------------------|-------------------|---------------------------------|------------------------------|
| Age                                | 0.146 (<0.0001)   | 0.158 (<0.001)                  | 0.038 (0.022)                |
| Male sexa                          | +0.204 (<0.0001)  | 0.086 (0.012)                   | 0.372 (<0.000)               |
| Body mass index                    | 0.410 (<0.0001)   | 0.462 (<0.001)                  | 0.108 (0.001)                |
| Waist, cm                          | 0.378 (<0.0001)   | 0.539 (<0.001)                  | 0.433 (<0.001)               |
| Waist hip ratio                    | 0.214 (<0.0001)   | 0.477 (<0.001)                  | −0.067 (0.065)               |
| BSA, m²                            | 0.207 (<0.0001)   | 0.441 (<0.001)                  | −0.064 (0.030)               |
| Systolic blood pressure, mmHg      | 0.106 (<0.0001)   | 0.104 (<0.001)                  | 0.020 (0.346)                |
| Diastolic blood pressure, mmHg     | 0.088 (<0.0001)   | 0.117 (<0.001)                  | −0.007 (0.731)               |
| Hypertensiona                      | +0.152 (<0.0001)  | 0.410 (<0.001)                  | 0.093 (0.003)                |
| Cholesterol, mmol/L                | −0.060 (<0.0001)  | −0.073 (<0.001)                 | ***                          |
| LDL, mmol/L                        | −0.067 (<0.0001)  | −0.071 (<0.001)                 | −0.005 (0.716)               |
| HDL, mmol/L                        | −0.182 (<0.0001)  | −0.262 (<0.001)                 | −0.025 (0.129)               |
| Triglycerides, mmol/L              | 0.257 (<0.0001)   | 0.296 (<0.001)                  | 0.137 (<0.001)               |
| Diabetesa                          | +0.490 (<0.001)   | 0.481 (<0.001)                  | 0.050 (0.310)                |
| Glucose, mmol/L                    | 0.2 (<0.0001)     | 0.220 (<0.001)                  | 0.061 (0.001)                |
| History of heart failurea          | +0.897 (<0.001)   | 0.785 (<0.001)                  | 0.163 (0.141)                |
| History of coronary eventa         | +0.307 (<0.001)   | 0.238 (<0.001)                  | −0.032 (0.567)               |
| History of strokea                 | +0.078 (0.375)    | 0.081 (0.232)                   | −0.035 (0.594)               |
| History of atrial fibrillationa     | +0.409 (<0.001)   | 0.302 (<0.001)                  | 0.035 (0.571)                |
| Current smoking                     | −0.041 (0.489)    | 0.048 (0.223)                   | 0.218 (<0.001)               |
| Log (NT-proBNP)                    | 0.189 (<0.0001)   | 0.167 (<0.001)                  | 0.154 (<0.001)               |
| eGFR                               | −0.219 (<0.0001)  | −0.211 (<0.001)                 | −0.140 (<0.001)              |

Clinical covariates of logarithm-transformed bioactive adrenomedullin (bio-ADM), based on Pearson’s correlation coefficients with corresponding P-values and beta coefficients from Tobit linear regression models with corresponding P-values in the MPP cohort (n = 5060). BSA, body surface area; LDL, low density lipoprotein; HDL, high density lipoprotein; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; eGFR, glomerular filtration rate.

For categorical variables, difference in median direction indicated by + or − is presented instead of correlation coefficients.

Discussion

We have described the population distribution of bio-ADM, the association with invasive measures of central haemodynamics before and after heart transplantation, and the diagnostic and prognostic performance in patients with dyspnoea. Our findings carry implications for the use of bio-ADM as a biomarker of congestion with potential utility to guide decongestive therapy.

Firstly, our findings add to the evidence supporting a role of bio-ADM in congestion by extension to invasive, central haemodynamic measures and establish that bio-ADM in contrast to NT-proBNP displays a stronger relation to systemic rather than pulmonary congestion. These observations were supported by a recent, smaller study of bio-ADM in relation to RHC measures in HF.19 From a mechanistic viewpoint, we note that this finding is well aligned with the view of bio-ADM as a biomarker of vascular rather than cardiac strain as for NT-proBNP. The surface area of the systemic vascular tree is substantially larger than the pulmonary counterpart, and the pulmonary circulation only contains 10% (about 500 mL) of the total blood volume. A pressure increase in the systemic veins would thus be expected to translate into a more marked bio-ADM release than in the pulmonary veins. Filling pressures represent the integrated result of cardiac systolic and diastolic function as well as blood volume and venous compliance.2 mRAP has been found to be relatively poorly correlated with blood volume in HF, likely due to

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Figure 2  Association of bio-ADM with measures of congestion and outcomes. (A, B) Scatter plots depicting the relation of bio-ADM with mean right atrial pressure (mRAP) and pulmonary arterial wedge pressure (PAWP) in patients with heart failure (HF) from the HF-RHC cohort ($n = 332$). (C, D) Receiver-operating characteristic (ROC) curves showing discrimination of elevated mRAP ($>10$ mmHg) and PAWP ($>15$ mmHg) with bio-ADM ($n = 332$) and NT-proBNP ($n = 265$). Cutoff 39 pg/mL indicated. (E) ROC curve showing discrimination of final heart failure diagnosis with NT-proBNP and bio-ADM in patients with acute dyspnoea from the ADYS cohort ($n = 1534$). (F) Kaplan–Meier curve illustrating 30 day mortality in decompensated heart failure patients ($n = 570$) with elevated bio-ADM ($>39$ pg/mL) and NT-proBNP ($>1045$ pg/mL).

(A) 

(B) 

(C) 

(D) 

(E) 

(F) 

Number at risk
- Normal bio-ADM and NT-proBNP: 130
- Elevated bio-ADM, normal NT-proBNP: 126
- Normal bio-ADM, elevated NT-proBNP: 123
- Elevated bio-ADM and NT-proBNP: 127

30-day mortality

bio-ADM (n=1504): 0.75
NT-proBNP (n=1487): 0.85

bio-ADM, area under ROC curve = 0.74
NT-proBNP, area under ROC curve = 0.68

bio-ADM, area under ROC curve = 0.70
NT-proBNP, area under ROC curve = 0.73

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the large compliance of the venous system, but it is possible that bio-ADM better represents plasma volume and venous distension. As NT-proBNP is relatively poorly correlated with blood volume, diuretic response,26 and the efficacy of SGLT2-inhibitors27 which may act at least in part through volume regulation, our findings suggest that bio-ADM may be a better marker of such processes.

Secondly, we establish reference ranges in healthy elderly subjects. Such ranges will be increasingly important as bio-ADM moves towards clinical application. We note that the upper reference threshold is well aligned with a haemodynamically inferred decision cutoff, and with mRAP kinetics. The reference range was also similar to that described in two smaller cohorts of 88 subjects (median 13.7 pg/mL)11 and 200 subjects (median 20.7 pg/mL, 99th percentile 43.0 pg/mL) referenced in several studies12,13,15,16 but not described in detail. Our study thus extends these observations to a larger cohort with similar age distribution to most HF patients. Importantly, the reference range was relatively robust across strata based on major clinical covariates. We show that measures of body size and renal function are the most important such covariates, mirroring findings for mid-regional pro-ADM.10

Finally, we applied derived reference thresholds and elevated mRAP thresholds to a mixed dyspnea cohort, and found association with adverse outcome and signs and symptoms of congestion. Although elevated bio-ADM was strongly related to HF diagnosis, the diagnostic performance was less precise than for NT-proBNP, indicating that compromised vascular integrity and strain is present also in other causes of dyspnea. Nevertheless, bio-ADM was associated with congestion measures and adverse outcome independently of NT-proBNP and could play an important role in a multimarker approach for guiding treatment and risk assessment of patients with heart failure. In the future, plasma bio-ADM may also guide therapy, as the monoclonal antibody Adrecizumab is currently being tested both in humans with heart failure and septic shock to improve vascular integrity and minimize fluid extravasation.20,21

Although information on several signs and symptoms of congestion was unavailable in our cohort, such data have been published and a literature review (Table 4) established a predominant association with clinical correlates of systemic congestion, including peripheral oedema, jugular vein distension, and hepatomegaly.

A biomarker of systemic vascular congestion may facilitate better targeting of therapy for cardiac congestion, when added to a multimodal clinical assessment strategy2 and may bring additive value to NT-proBNP that is reflecting pulmonary congestion. Whether bio-ADM adds to other systemic congestion biomarkers such as liver damage biomarkers, cholestasis biomarkers, and renal function biomarkers remains to be determined. Similarly, studies are warranted that compare bio-ADM with both ultrasound-based imaging8,26 and other promising circulating biomarkers for vascular congestion, including two vascular-derived mucins (CA125 and CD146) of which the former has also been associated with mRAP29 and the latter has been shown to be released in response to venous strain.30

A number of limitations merit consideration. Although cohorts were analysed in a blinded manner at a core laboratory, preanalytical factors are likely to influence the results with regard to comparisons across the three cohorts. Specifically, sample storage times were variable between the cohorts, samples were only obtained in the fasting state in the MPP cohort and were obtained from a central venous catheter in the HF-RHC cohort. The bio-ADM assay has shown stability across multiple freeze–thaw cycles,11 but limited data are

| Table 3 Association of bio-ADM with measures of congestion, decompensated heart failure and outcomes in dyspnea patients |
| --- |
| | Bio-ADM | NT-proBNP | Bio-ADM in NT-proBNP-adjusted | Bio-ADM decision cutoff (≥39 pg/mL) | Bio-ADM decision cutoff (≥39 pg/mL) |
| HF diagnosis (n = 570) | 2.33 (2.03–2.69) | 4.52 (3.71–5.51) | 1.60 (1.36–1.88) | 3.61 (2.82–4.63) | 1.83 (1.37–2.43) |
| Congestion measures |  |  |  |  |  |
| Chest X-ray findings: |  |  |  |  |  |
| Dilated vessels (n = 47) | 2.21 (1.55–3.16) | 5.68 (3.21–10.05) | 1.16 (0.74–1.82) | 3.73 (1.91–7.29) | 1.13 (0.50–2.54) |
| Pulmonary infiltrate (n = 155) | 1.41 (1.10–1.81) | 1.46 (1.08–1.98) | 1.26 (0.96–1.66) | 1.57 (0.99–2.48) | 1.23 (0.75–2.02) |
| Pleural effusion (n = 220) | 2.06 (1.63–2.61) | 3.10 (2.27–4.23) | 1.55 (1.20–2.00) | 3.17 (2.10–4.79) | 1.87 (1.19–2.95) |
| In-hospital diuretics (n = 417) | 2.06 (1.79–2.36) | 3.06 (2.55–3.68) | 1.57 (1.34–1.83) | 3.41 (2.65–4.39) | 2.11 (1.60–2.80) |
| Continuous positive airway pressure (n = 23) | 1.62 (1.11–2.36) | 1.91 (1.05–3.49) | 1.19 (0.73–1.94) | 2.74 (1.16–6.46) | 1.47 (0.55–3.93) |
| Hospitalization* (n = 439) | 2.11 (1.63–2.72) | 2.04 (1.49–2.79) | 1.90 (1.46–2.47) | 3.06 (2.01–4.66) | 2.50 (1.61–3.89) |
| Death at 30 days* (n = 52) | 1.75 (1.36–2.25) | 2.47 (1.55–3.93) | 1.52 (1.16–1.99) | 2.91 (1.55–5.45) | 2.24 (1.17–4.28) |
| Death at 90 days* (n = 112) | 1.61 (1.34–1.94) | 2.35 (1.70–3.25) | 1.41 (1.17–1.72) | 2.05 (1.37–3.06) | 1.61 (1.06–2.43) |

Association of bioactive adrenomedullin (bio-ADM) with heart failure (HF) diagnosis (n = 570) and measures of congestion in patients seeking an emergency department for acute dyspnea (ADYS cohort n = 1534). Associations are tested in logistic or Cox regression models per standard deviation of log-transformed bio-ADM and Amino-terminal pro-B-type natriuretic peptide (NT-proBNP), or based on a decision cutoff for bio-ADM. Odds ratios and hazard ratios (mortality) are presented, with 95% confidence intervals. All models were age- and sex-adjusted.

*Hospitalization and mortality (n = 53 deaths) was analysed in the patient subset with a HF diagnosis (n = 570).
## Table 4 Reports of prognostic impact and clinical correlates of bio-ADM in heart failure

| Reference       | Study setting                                      | Number of patients | Bio-ADM distribution (pg/mL) | Bio-ADM threshold (pg/mL) | Findings                                                                 | Prognosis                                                                 | Pulmonary                                                                 | Systemic |
|-----------------|---------------------------------------------------|--------------------|------------------------------|----------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|----------|
| Self et al.     | Acute heart failure at admission                  | 246                | 60 (46.4–92.5)               | 92 (75th percentile)       | Increased 30 day incidence of composite cardiac arrest, respiratory failure, emergency dialysis, acute coronary syndrome, hospitalization >5 days, and repeat emergency department visit or hospitalization 90 day mortality >two-fold higher in patients with high bio-ADM at 48 h | N/A                                                                       | N/A                                                                       |          |
| Tolppanen et al.| Cardiogenic shock, serially admission - 10 days later | 178                | 59.9                         | 55.7 (ROC curve)           | Higher systolic pulmonary pressure. Levels at 48–96 h related to persistently impaired cardiac and end-organ function More peripheral oedema, hepatomegaly, jugular venous distension, higher clinical congestion score More peripheral oedema, hepatomegaly, jugular venous distension; strong predictor of clinical congestion score | Higher central venous pressure                                           |                                                             |          |
| Kremer et al.   | Acute heart failure (PROTECT) at admission        | 1562               | 44.1 (25.9–82.7)             | 83 (top tertile)           | Baseline bio-ADM levels were significant predictors of the presence of residual congestion by day 7 Increased 21-month (median) all-cause mortality and HF hospitalization More orthopnoea and pulmonary rales | More orthopnoea                                                          |                                                             |          |
| Ter Maaten et al.| New-onset or worsening chronic heart failure (BIOSTAT-CHF) | 2179 + 1703        | 33.8 (22.6–53.9) + 27.3 (18.0–42.1) | 53 (top tertile); 34 (ROC curve) for congestion | More orthopnoea                                                          |                                                             |                                                             |          |
| Arrigo et al.   | Acute coronary syndrome at admission              | 927                | Mean 23.5 (SD 0.71)          | N/A                        | Higher in acute coronary syndrome complicated by acute heart failure during index hospitalization Increased 1 year mortality and rehospitalization More orthopnoea on chest X-ray |                                                             |                                                             |          |
| Molvin et al.   | Acute heart failure at admission                  | 322 + 208          | 34.6 (18.7–59.3)            | N/A                        | Increased 60 day heart failure rehospitalization (bio-ADM combined with loop diuretic use); bio-ADM strongest predictor of discharge residual congestion More orthopnoea, higher BNP |                                                             |                                                             | More peripheral oedema |
| Pandhi et al.   | Acute heart failure (PROTECT) at discharge        | 1236               | 33.7 (21.5–61.5)            | 61 (top tertile)           |                                                             |                                                             |                                                             | More peripheral oedema, jugular venous distension, higher clinical congestion score, poorer diuretic response, higher discharge loop diuretic doses |          |

Review of published studies evaluating the relation of bioactive adrenomedullin (bio-ADM) with outcomes in heart failure patients and with measures of systemic or pulmonary congestion. Findings reported as significant in the original publications were included in the table. Measures of bio-ADM distribution indicate median and interquartile range unless otherwise noted. Thresholds for elevated bio-ADM were variably derived across studies, from quantiles or from analysis of receiver-operating characteristic (ROC) curves as specified. NT-proBNP, amino-terminal pro-B-type natriuretic peptide.
available regarding the impact of fasting and sampling location. Similarly, the use of medications of potential influence on bio-ADM differed between the cohorts. In particular, substantial increases of bio-ADM have been described in patients initiating ARNi therapy, which would appear to be an important confounder, but none of the patients in this study were on ARNi therapy.

In summary, our findings support the use of bio-ADM as a biomarker for systemic venous congestion and nominates specific cutoffs informed by population distribution and hemodynamic correlations in HF.

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Conflict of interest

Janin Schulte and Oliver Hartmann are employed by SphingoTec GmbH who provide the bio-ADM assay. The rest of the authors have nothing to disclose.

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Supporting information

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

Table S1. Association of bio-ADM with hemodynamic parameters over time.

Table S2. Decision cutoffs for detection of elevated filling pressures with bio-ADM.

Table S3. Decision cutoffs for detection of decompensated heart failure in acute dyspnea patients.

Figure S1. Flowchart of exclusions from population-based cohort to achieve a reference cohort.

Figure S2. Distribution of hemodynamic measures in heart failure and after heart transplantation.

Figure S3. Correlation of hemodynamic measures and plasma biomarkers.

Figure S4. Scatter plots for bio-ADM and NT-proBNP in relation to hemodynamic measures.

Figure S5. Trajectories for bio-ADM and central hemodynamic measures after heart transplantation.

Additional information about the nature and extent of data sharing is available in the Supporting Information section.
Knots are indicated as dots on the spline and thresholds for NT-proBNP as function of mean right atrial pressure (mRAP) and pulmonary arterial wedge pressure (PAWP).

Figure S6. Restricted cubic splines describing bio-ADM and NT-proBNP as function of mean right atrial pressure (mRAP) and pulmonary arterial wedge pressure (PAWP). Knots are indicated as dots on the spline and thresholds for elevated mRAP (> 10 mmHg), PAWP (>15 mmHg) and biomarkers are indicated with dashed vertical lines.

Figure S7. Mortality at 30 days in decompensated heart failure patients across quartiles of bio-ADM.

Kaplan–Meier curve of 30-day mortality across quartiles of bioactive adrenomedullin (bio-ADM) in 570 heart failure patients from the ADYS cohort: 25th percentile (28 pg/mL, four deaths), median (43 pg/mL, four deaths), and 75th percentile (71 pg/mL, 10 deaths), with 35 deaths in the highest quartile from a total of 53 deaths.

References

1. Miller WL. Fluid volume overload and congestion in heart failure: Time to reconsider pathophysiology and how volume is assessed. Circ Heart Fail. 2016; 9: e002922.

2. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WHW, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ. The use of diuretics in heart failure with congestion - a position statement from the heart failure Association of the European Society of cardiology. Eur J Heart Fail. 2019; 21: 137–155.

3. Verbrugge FH, Guazzi M, Testani JM, Borlaug BA. Altered hemodynamics and end-organ damage in heart failure: Impact on the lung and kidney. Circulation. 2020; 142: 998–1012.

4. Harjola VP, Mullens W, Banaszewski M, Bauersachs J, Brunner-La Rocca HP, Chioucel O, Collins SP, Doehner W, Filippatos GS, Flammer AJ, Fuhrmann J, Lainscak M, Lassus J, Legrand M, Mebazaa A, Mebazaa M, Miro O, McMurray JJ, Peacock WF, Stevenson LW, Kueffer FJ, Bourge RC. Transition from chronic compensated to acute heart failure Committee of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail. 2010; 12: 423–433.

5. Gheorghide M, Pollath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Dzau RH, Foronar GC, Jaarsma T, Jondal G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pong PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Roche A, McMurray JJ, Filippatos G, European Society of C, European Society of Intensive Care M. Assessing and grading congestion in acute heart failure: A scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail. 2010; 12: 423–433.

6. Boorsma EM, Ter Maaten JM, Damman K, Dinh W, Gustafsson F, Goldsmith S, Burkhoff D, Zannad F, Udelson JE, Voors AA. Congestion in heart failure: A contemporary look at physiology, diagnosis and treatment. Nat Rev Cardiol. 2020; 17: 641–655.

7. Zile MR, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, Aranda JM Jr, Abraham WT, Smart FW, Stevenson LW, Kueffer FJ, Bourge RC. Transition from chronic compensated to acute decompensated heart failure: Pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation. 2008; 118: 1433–1441.

8. Price S, Platz E, Cullen L, Tavazzi G, Christ M, Cowie S, Maisel AS, Masip J, Miro O, McMurray JJ, Peacock WF, Martin-Sanchez FJ, Di Somma S, Bueno H, Zeymer U, Mueller C. Acute heart failure study Group of the European Society of cardiology acute cardiovascular care a. expert consensus document: Echocardiography and lung ultrasonography for the assessment and management of acute heart failure. Nat Rev Cardiol. 2017; 14: 427–440.

9. Voors AA, Kremer D, Geven C, Ter Maaten JM, Struck J, Bergmann A, Pickkers P, Metra M, Mebazaa A, Dungen HD, Butler J. Adrenomedullin in heart failure: Pathophysiology and therapeutic application. Eur J Heart Fail. 2019; 21: 163–171.

10. Smith JG, Newton-Cheh C, Heblad B, Struck J, Morgensthaler NG, Bergmann A, Wang T, Melander O. Distribution and correlates of midregional proadrenomedullin in the general population. Clin Chem. 2009; 55: 1593–1595.

11. 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.

12. Self WH, Sorrow AB, Hartmann O, Barrett TW, Ferrman GJ, Maisel AS, Struck J, Bergmann A, Collins SP. Plasma bioactive adrenomedullin as a prognostic biomarker in acute heart failure. Am J Emerg Med. 2016; 34: 257–262.

13. Tolppanen H, Rivas-Lasarte M, Lassus J, Sans-Roselló J, Hartmann O, Lindholm M, Arrigo M, Tarvasmaa T, Kober L, Thiele H, Pulkki K, Spinaj J, Parissis J, Banaszewski M, Silva-Cardoso J, Carubelli V, Sionis A, Harjola VP, Mebazaa A. Adrenomedullin: A marker of impaired hemodynamics, organ dysfunction, and poor prognosis in cardiogenic shock. Ann Intensive Care. 2017; 7: 6.

14. 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.

15. Arrigo M, Parenica J, Ganovska E, Pavlusova M, Mebazaa A. Plasma bioactive adrenomedullin is a marker of acute heart failure severity in patients with acute coronary syndrome. Int J Cardiol Heart Vasc. 2019; 22: 174–176.

16. Ter Maaten JM, Kremer D, Demissie BG, Struck J, Bergmann A, Anker SD, Ng LL, Dickstein K, Metra M, Samani NJ, Romaine SPR, Cleland J, Girerd N, Lang CC, van Veldhuisen DJ, Voors AA. Bioadrenomedullin as a marker of congestion in patients with new-onset and worsening heart failure. Eur J Heart Fail. 2019; 21: 732–743.

17. Molvin J, Juja E, Navarin S, Melander O, Zoccoli G, Hartmann O, Bergmann A, Struck J, Bachus E, Di Somma S, Magnusson M. Bioactive adrenomedullin, proenkephalin A and clinical outcomes in an acute heart failure setting. Open Heart. 2019; 6: e001048.

18. Pandhi P, Ter Maaten JM, Emmens JE, Struck J, Bergmann A, Cleland JG, Givertz MM, Metra M, O’Connor CM, Teerlink JR, Ponikowski P, Cotter G, Davison B, van Veldhuisen DJ, Voors AA. Clinical value of pre-discharge bioadrenomedullin as a marker of residual congestion and high risk of heart failure hospital readmission. Eur J Heart Fail. 2020; 22: 683–691.

19. Goetze JP, Balling I, Deis T, Struck J, Bergmann A, Gustafsson F. Bioactive adrenomedullin in plasma is associated with biventricular filling pressures in patients with advanced heart failure. Eur J Heart Fail. 2021; 23: 489–491.
20. Laterre PF, Pickkers P, Marx G, Wittebole X, Meziani F, Dugernier T, Huberland V, Schuerholz T, François B, Lascarrou JB, Beishuizen A, Oueslati H, Contou D, Hoiting O, Lacherade JC, Chousterman B, Pottecher J, Bauer M, Godet T, Karakas M, Helms J, Bergmann A, Zimmermann J, Richter K, Hartmann O, Pars M, Mebazaa A. AdrenOSS-2 study participants. Safety and tolerability of non-neutralizing adrenomedullin antibody adrecizumab (HAM8101) in septic shock patients: The AdrenOSS-2 phase 2a biomarker-guided trial. Intensive Care Med. 2021; 47: 1284–1294.

21. Karakas M, Akin I, Burdelski C, Clemmensen P, Grahn H, Jarczak D, Keßler M, Kirchhof P, Landmesser U, Lezius S, Lindner D, Mebazaa A, Nierhaus A, Ocak A, Rottbauer W, Sinning C, Skurk C, Söffker G, Westermann D, Zapf A, Zengin E, Zeller T, Kluge S. Single-dose of adrecizumab versus placebo in acute cardiogenic shock (ACCOST-HH): An investigator-initiated, randomised, double-blinded, placebo-controlled, multicentre trial. Lancet Respir Med. 2022; 10: 247–254.

22. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Nordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klerpet W, Lancellotti P, Matteucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoepfer M, Group ESCSD. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016; 37: 67–119.

23. Sokoll LJ, Baum H, Collinson PO, Gurr E, Haass M, Luthe H, Morton JJ, Nowatzke W, Zingler C. Multicenter analytical performance evaluation of the Elecsys proBNP assay. Clin Chem Lab Med. 2004; 42: 965–972.

24. Arrigo M, Truong QA, Onat D, Szymonifka J, Gayat E, Tolppanen H, Sadoune M, Demmer RT, Wong KY, Launay JM, Samuel JL, Cohen-Solal A, Januzzi JL Jr, Singh JP, Colombo PC, Mebazaa A. Soluble CD146 is a novel marker of systemic congestion in heart failure patients: An experimental mechanistic and Transcardiac clinical study. Clin Chem. 2017; 63: 386–393.

25. Arfsten H, Goliasch G, Bartko PE, Praussmuller S, Spinka G, Cho A, Novak J, Haslacher H, Strunk G, Struck J, Hußmann M, Pavo N. Increased concentrations of bioactive adrenomedullin subsequently to angiotensin-receptor/ nephrilysin-inhibitor treatment in chronic systolic heart failure. Br J Clin Pharmacol. 2021; 87: 916–924.