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Circulating adrenomedullin estimates survival and reversibility of organ failure in sepsis: the prospective observational multinational Adrenomedullin and Outcome in Sepsis and Septic Shock-1 (AdrenOSS-1) study

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Abstract

Background: Adrenomedullin (ADM) regulates vascular tone and endothelial permeability during sepsis. Levels of circulating biologically active ADM (bio-ADM) show an inverse relationship with blood pressure and a direct relationship with vasopressor requirement. In the present prospective observational multinational Adrenomedullin and Outcome in Sepsis and Septic Shock 1 (AdrenOSS-1) study, we assessed relationships between circulating bio-ADM during the initial intensive care unit (ICU) stay and short-term outcome in order to eventually design a biomarker-guided randomized controlled trial.

Methods: AdrenOSS-1 was a prospective observational multinational study. The primary outcome was 28-day mortality. Secondary outcomes included organ failure as defined by Sequential Organ Failure Assessment (SOFA) score, organ support with focus on vasopressor/inotropic use, and need for renal replacement therapy. AdrenOSS-1 included 583 patients admitted to the ICU with sepsis or septic shock.

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**Results:** Circulating bio-ADM levels were measured upon admission and at day 2. Median bio-ADM concentration upon admission was 80.5 pg/ml [IQR 41.5–148.1 pg/ml]. Initial SOFA score was 7 [IQR 5–10], and 28-day mortality was 22%. We found marked associations between bio-ADM upon admission and 28-day mortality (unadjusted standardized HR 2.3 [CI 1.9–2.9]; adjusted HR 1.6 [CI 1.1–2.5]) and between bio-ADM levels and SOFA score (p < 0.0001). Need of vasopressor/inotrope, renal replacement therapy, and positive fluid balance were more prevalent in patients with a bio-ADM > 70 pg/ml upon admission than in those with bio-ADM ≤ 70 pg/ml. In patients with bio-ADM > 70 pg/ml upon admission, decrease in bio-ADM below 70 pg/ml at day 2 was associated with recovery of organ function at day 7 and better 28-day outcome (9.5% mortality). By contrast, persistently elevated bio-ADM at day 2 was associated with prolonged organ dysfunction and high 28-day mortality (38.1% mortality, HR 4.9, 95% CI 2.5–9.8).

**Conclusions:** AdrenOSS-1 shows that early levels and rapid changes in bio-ADM estimate short-term outcome in sepsis and septic shock. These data are the backbone of the design of the biomarker-guided AdrenOSS-2 trial.

**Trial registration:** ClinicalTrials.gov, NCT02393781. Registered on March 19, 2015.

**Keywords:** Biomarker, Outcome, Sepsis-2, Sepsis-3

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**Introduction**

Adrenomedullin (ADM) is a free circulating peptide with potent vascular properties, including benefits for endothelial barriers at physiological levels. ADM has previously been described as a “double-edged sword” in sepsis [1] because high levels of ADM induce vasodilation and hypotension [2–4] on one hand while reinforcing the endothelial barrier and improving outcome on the other [5–10]. The potential of ADM as a prognostic biomarker has previously been studied in critically ill patients, often by measuring the inactive midregional pro-ADM [11, 12], or recently by direct measurement of the bioactive form of ADM (bio-ADM) [13, 14]. It has been shown repeatedly that bio-ADM greater than 70 pg/ml is associated with worse outcome [13, 14].

On the basis of previous results, we tested the hypothesis that modulating the ADM pathway in patients with high levels of circulating bio-ADM may improve short-term outcome in sepsis. Adrecizumab, a monoclonal anti-ADM antibody, has been shown to improve organ function in preclinical settings [15]. In order to design a human trial in which we would administer adrecizumab based on levels of bio-ADM, we needed to assess the relationship between initial levels of bio-ADM and short-term outcome in sepsis and in septic shock patients.

In the Adrenomedullin and Outcome in Sepsis and Septic Shock 1 (AdrenOSS-1) study, we investigated whether the initial plasma concentration of bio-ADM (on intensive care unit [ICU] admission and after 48 h) may provide insight into 28-day survival and the recovery of organ function.

**Methods**

**Study design**

AdrenOSS-1 was a European prospective observational study. Twenty-four centers in five countries (France, Belgium, The Netherlands, Italy, and Germany) contributed to the trial achievement of 583 enrolled patients. Patients were recruited from June 2015 to May 2016. The study protocol was approved by the local ethics committees and was conducted in accordance with Directive 2001/20/EC, as well as good clinical practice (International Conference on Harmonization Harmonized Tripartite Guideline version 4 of May 1, 1996, and decision of November 24, 2006) and the Declaration of Helsinki.

The study enrolled patients aged 18 years and older who were (1) admitted to the ICU for sepsis or septic shock or (2) transferred from another ICU in the state of sepsis and septic shock within less than 24 h after admission. Included patients were stratified by severe sepsis and septic shock based on definitions for sepsis and organ failure from 2001 [16]. In the present article, the term “sepsis” refers to the updated definition of Sepsis-3 [17]. Concerning septic shock, most data presented in this article are based on the former definition [16], except for the confirmatory analyses presented in the last paragraph of the “Results” section, for which the new Sepsis-3 definition of septic shock was used [17].

Exclusion criteria were pregnancy, vegetative coma, and participation in an interventional trial in the preceding month. Informed consent was obtained from all patients or their lawful representatives prior to enrollment in the study. Patients were treated according to local practice, and treatments as well as procedures were registered.

The primary endpoint was 28-day mortality. Secondary endpoints concerned organ failure (as defined by the Sequential Organ Failure Assessment [SOFA] score) and organ support, vasopressor/inotrope use, fluid balance, and use of renal replacement therapy (RRT), as well as validation of the previously identified cutoff value of 70 pg/ml [14]. The latter was identified as the optimal screening cutoff for AdrenOSS-2, an ongoing proof-of-concept and...
dose-finding phase II trial assessing adrecizumab (an antibody modulating circulating bio-ADM) in patients with early septic shock (NCT03085758). The relationship between cardiovascular SOFA subscore and bio-ADM, being a biomarker of vascular dysfunction, was evaluated.

Collection of patient data
Upon admission, demographics (age, sex), body mass index, presence of septic shock, type of ICU admission, organ dysfunction scores (SOFA, Acute Physiologic Assessment and Chronic Health Evaluation II [APACHE II]), origin of sepsis, preexisting comorbidities (i.e., treated within the last year), past medical history, laboratory values, and organ support were recorded, and blood was drawn for measurement of bio-ADM and other markers.

After patient enrollment, the following data were collected daily during the first week: SOFA score, antimicrobial therapies, fluid balance, ventilation status, Glasgow Coma Scale score, central venous pressure, need for RRT, invasive procedures for sepsis control, and vasopressor/inotrope treatment. Moreover, discharge status and mortality were recorded on day 28 after ICU admission.

Sample collection
Blood for the central laboratory was sampled within 24 h after ICU admission and on day 2 (mean 47 h, SD 9 h) after the first sample. Samples were subsequently processed and stored at −80 °C before transfer to the central laboratory for blinded bio-ADM analysis organized by the study sponsor (sphingotec GmbH, Hennigsdorf, Germany). Routine analyses (e.g., partial pressure of arterial oxygen, lactate) were performed by the local laboratories.

Bio-ADM measurement
Bio-ADM was measured using a recently developed immunoassay provided by sphingotec GmbH. For details and design principles on the assay, see publications by Marino et al. [14] and Weber et al. [18]. The analytical assay sensitivity was 2 pg/ml.

Statistical analyses
Results are presented as number and percentage, mean and SD, or median and IQR, depending on their distribution. Group comparisons for continuous variables were performed using the Kruskal-Wallis test, and appropriate post hoc tests were applied if necessary. Categorical data were compared using the chi-square test with simulated p values using 2000 replicates. Biomarker data were log-transformed if necessary. Cox proportional hazards regression was used to analyze the effect of risk factors on survival in univariable and multivariable analyses. The assumptions of proportional hazards were tested for all variables. For continuous variables, HRs were standardized to describe the HR for a biomarker change of one IQR. CIs (95% CI) for risk factors and significance levels for chi-square (Wald) test are given. The predictive value of each model was assessed by the model likelihood ratio chi-square statistic. The concordance index (C index) is given as an effect measure. It is equivalent to the concept of AUC adopted for binary outcome. For multivariable models, a bootstrap-corrected version of the C index is given. To test for added predictive value, we used the likelihood ratio chi-square test for nested models to assess whether bio-ADM adds predictive value to a clinical model or a risk score. Survival curves plotted by the Kaplan-Meier method using quartiles or predefined cut points (70 pg/ml) of bio-ADM were used for illustrative purposes. ROC curve analysis was applied for 28-day mortality to determine the optimal Youden cutoff in this cohort.

A two-sided p value of 0.05 was considered statistically significant. All analyses were performed using R version 2.5.1 (http://www.r-project.org, library Design, Hmisc, ROCR) and IBM SPSS Statistics version 22.0 software (IBM, Armonk, NY, USA).

Results
A total of 583 patients were included in the AdrenOSS-1 study. Patient characteristics, organ dysfunction scores, physiological and laboratory values, organ support upon admission, and outcome parameters are presented in Table 1. The median bio-ADM level at admission was 80.5 pg/ml [IQR 41.6–148.1] in our studied patients; 55.9% had bio-ADM level greater than 70 pg/ml at admission, and 44.1% had a bio-ADM less than 70 pg/ml. Of note, patients with septic shock had a significantly higher bio-ADM concentration at admission than patients with sepsis (114.4 [62.6–214.5] versus 57.5 pg/ml [31.2–101.5], p < 0.0001).

Bio-ADM levels and mortality
Over the 28-day follow-up period, 127 patients (22%) died: 33 with sepsis and 94 with septic shock.

In a Cox proportional hazards model adjusted for age, gender, comorbidities (cardiac and noncardiac), lactate, and diagnosis (sepsis, septic shock), bio-ADM concentration at admission was independently associated with 28-day mortality in the studied population (added chi-square 12.2, p = 0.0005; adjusted standardized HR 1.6 [95% CI 1.1–2.5], p = 0.0004) (Table 2). Noticeably, the C index for prediction of 28-day mortality for bio-ADM at admission was 0.688 (95% CI 0.642–0.733, chi-square 54.8, p < 0.0001) in the univariate Cox regression. C indexes for lactate, SOFA, and APACHE II were 0.720 (95% CI 0.672–0.768), 0.728 (95% CI 0.680–0.777), and 0.701 (95% CI 0.657–0.746), respectively (all p <
Table 1  Patient characteristics

| Patient characteristics | All | Bio-ADM < 70 pg/ml at admission | Bio-ADM > 70 pg/ml at admission | p Value* | No. |
|-------------------------|-----|---------------------------------|---------------------------------|---------|-----|
| Epidemiological data    |     |                                 |                                 |         |     |
| n                       | 583 | 257                             | 326                             |         |     |
| Bio-ADM at admission (pg/ml) | 80.5 [41.5–148.0] | 36.9 [27.1–51.0] | 136.7 [97.6–241.0] | < 0.0001 |
| Age (years)             | 66  | 64 [53–75]                      | 67 [58–76]                      | 0.0052  |     |
| Male sex (n, %)         | 364 (62.4) | 171 (66.5)                      | 193 (59.2)                      | 0.0837  |     |
| Body mass index (kg/m²) | 25.7 [22.9–30.1] | 25.0 [22.3–28.4] | 26.7 [23.2–31.6] | 0.0013  |     |
| Septic shock at admission | 293 (50.3) | 84 (32.7)                | 209 (64.1)                      | < 0.0001 |
| Type of ICU admission   |     |                                 |                                 |         |     |
| Medical                 | 473 (81.1) | 230 (89.5)              | 243 (74.5)                      | < 0.0001 |
| Surgical - emergency procedure | 93 (16) | 21 (8.2)                | 72 (22.1)                       |         |     |
| Surgical - elective procedure | 17 (2.9) | 6 (2.3)                 | 11 (3.4)                        |         |     |
| Origin of sepsis        |     |                                 |                                 | < 0.0001 |
| Lung                    | 218 (37.4) | 129 (50.2)              | 89 (27.3)                       |         |     |
| Bloodstream             | 90 (15.4) | 31 (12.1)                | 59 (18.1)                       |         |     |
| Urinary tract           | 62 (10.6) | 10 (3.9)                 | 52 (16)                         |         |     |
| Catheter                | 29 (5) | 9 (3.5)                  | 20 (6.1)                        |         |     |
| Peritonitis             | 31 (5.3) | 12 (4.7)                | 19 (5.8)                        |         |     |
| Endocarditis            | 31 (5.3) | 12 (4.7)                | 19 (5.8)                        |         |     |
| Bile duct infection     | 8 (1.4) | 2 (0.8)                 | 6 (1.8)                         |         |     |
| CNS                     | 4 (0.7) | 4 (1.6)                 | 0 (0)                           |         |     |
| Skin and soft tissue    | 10 (1.7) | 9 (3.5)                 | 1 (0.3)                         |         |     |
| Gynecologic             | 2 (0.3) | 1 (0.4)                 | 1 (0.3)                         |         |     |
| Other                   | 98 (16.8) | 38 (14.8)             | 60 (18.4)                       |         |     |
| Medical history        |     |                                 |                                 |         |     |
| Any cardiac comorbidity | 400 (68.6) | 147 (57.2)              | 253 (77.6)                      | < 0.0001 |
| Chronic heart failure   | 60 (10.3) | 19 (7.4)                | 41 (12.6)                       | 0.0544  |     |
| Hypertension            | 293 (50.3) | 105 (40.9)             | 188 (57.7)                      | < 0.0001 |
| Diabetes mellitus       | 160 (27.4) | 57 (22.2)               | 103 (31.6)                      | 0.0150  |     |
| Any noncardiac comorbidity | 414 (71) | 167 (65)              | 247 (75.8)                      | 0.0058  |     |
| Chronic renal disease   | 76 (13.0) | 19 (7.4)               | 57 (17.5)                       | 0.0004  |     |
| Active/recent malignant tumors | 124 (21.3) | 34 (13.2)             | 90 (27.6)                       | < 0.0001 |
| Smoking (active)        | 117 (20.1) | 63 (24.5)              | 54 (16.6)                       | 0.0302  |     |
| COPD                    | 89 (15.3) | 37 (14.4)              | 52 (16.0)                       | 0.6421  |     |
| Any chronic medication  | 371 (63.6) | 138 (53.7)             | 233 (71.5)                      | < 0.0001 |
| Immunosuppressive therapy | 46 (7.9) | 11 (4.3)              | 35 (10.7)                       | 0.0066  |     |
| Physiological values at admission |     |                                 |                                 |         |     |
| Temperature (°C)        | 37.2 [36.4–38.2] | 37.4 [36.6–38.2] | 37.1 [36.2–38.1] | 0.0034  |     |
| Mean blood pressure (mmHg) | 75 [64–90]  | 81 [69–95]             | 72 [60–85]                      | < 0.0001 |
| Heart rate (beats/min)  | 104 [90–119] | 100 [86–116]          | 105 [94–121]                    | 0.0013  |     |
| Central venous pressure (mmHg) | 8 [5–13]  | 8 [5–13]               | 10 [6–14]                       | 0.2419  |     |
| Glasgow Coma Scale score | 15 [14–15] | 15 [14–15]            | 15 [14–15]                      | 0.8161  |     |
| Fluid balance (ml)      | 1928 [592–3552] | 1425 [500–2699]  | 2311 [764–4202]                | < 0.0001 |
| Urine output for 24 h (ml) | 1000 [450–1900]  | 1276 [650–2050]         | 800 [300–1650]                  | < 0.0001 |
| PaO₂/FiO₂                | 228 [137–340] | 233.5 [140–360]       | 223 [137–337]                   | 0.4995  |     |
A multivariate model further demonstrated that bio-ADM had added value on top of APACHE II or SOFA score (added chi-square 24.4 [$p < 0.0001$] and 10.2 [$p = 0.0014$], respectively) (Table 2) when used as a continuous variable.

With the predefined cutoff value of 70 pg/ml, Kaplan-Meier analysis confirmed predictive value of bio-ADM for 28-day mortality in all studied patients (Additional file 1: Figure S1) and in subgroups of sepsis and septic shock (Fig. 1a and b). Patient characteristics for high and low bio-ADM levels are illustrated in Table 1, and characteristics for survivors versus nonsurvivors are provided in Additional file 2: Table S1. The optimal Youden cutoff in all patients was 101.9 pg/ml (sensitivity 67.7%, specificity 67.3%). In septic shock, the optimal Youden cutoff was 99.1 pg/ml (sensitivity 71.3%, specificity 52.3%), and in severe sepsis it was 101.9 pg/ml (sensitivity 57.6%, specificity 78.6%). This compares with a sensitivity of 77.2% and specificity of 48.9% in all patients for the predefined bio-ADM cutoff of 70 pg/ml.

We additionally assessed outcome in relation to bio-ADM changes in the initial 48 h in time-dependent

| Table 1 Patient characteristics (Continued) |
|---------------------------------------------|
| Patient characteristics | All | Bio-ADM < 70 pg/ml at admission | Bio-ADM > 70 pg/ml at admission | $p$ Value* | No. |
|--------------------------|-----|---------------------------------|---------------------------------|-----------|-----|
| Laboratory values at admission |     |                                 |                                 |           |     |
| Lactate (mmol/L)         | 1.4 [1.0–2.2] | 1.1 [0.8–1.6] | 1.8 [1.2–2.7] | < 0.0001 | n = 562 |
| Arterial pH              | 7.38 [7.3–7.44] | 7.42 [7.36–7.46] | 7.36 [7.27–7.42] | < 0.0001 |     |
| Bilirubin (µmol/L)       | 11 [6–19] | 10 [6.5–17] | 12 [6–21] | 0.1360 |     |
| Platelets (10^9/L)       | 190 [121–275] | 196 [136–279] | 181 [104–271] | 0.0583 |     |
| Creatinine (mg/dl)       | 1.4 [0.9–2.2] | 1 [0.7–1.4] | 1.8 [1.2–2.9] | < 0.0001 |     |
| BUN or urea (mg/dl)      | 61 [37–107] | 44 [28–69] | 80 [50–127] | < 0.0001 |     |
| Hematocrit (%)           | 34 [29–38] | 35 [30–38] | 34 [29–38] | 0.1010 |     |
| White blood cell count (per mm³) | 12,525 [7200–18,585] | 13,000 [8475–18,075] | 12,025 [5942–19,025] | 0.0547 |     |
| Troponin T, maximum on day 1 | 42 [18–158] | 29 [14–124] | 55 [25–176] | 0.0230 | n = 153 |
| Troponin I, maximum on day 1 | 69 [20–246] | 40 [11–228] | 99 [40–289] | 0.0049 | n = 186 |
| PCT, maximum on day 1 (ng/ml) | 11.4 [1.9–49.8] | 3.9 [0.9–19.5] | 24 [6–84] | < 0.0001 | n = 330 |
| PCT, central laboratory (ng/ml) | 10.2 [2.3–34.3] | 3.7 [0.8–13.0] | 18.2 [6.0–52.7] | < 0.0001 | n = 583 |
| NT-proBNP, maximum on day 1 | 257 [102–723] | 187 [61–388] | 473 [147–1154] | 0.0004 | n = 131 |
| BNP, maximum on day 1    | 4382 [1525–11,565] | 2170 [497–6633] | 6116 [2816–15,431] | 0.0001 | n = 117 |
| Renal replacement therapy | 49 (8.4) | 8 (3.1) | 41 (12.6) | 0.0001 |     |
| Vasopressors/inotropes at admission | 349 (59.9) | 109 (42.4) | 240 (73.6) | < 0.0001 |     |
| Organ support at admission |     |                                 |                                 |           |     |
| Mechanical ventilation   | 0.0739 |     |     |     |     |
| Invasive                 | 219 (37.6) | 85 (33.1) | 134 (41.1) |     |     |
| Noninvasive              | 131 (22.5) | 67 (26.1) | 64 (19.6) |     |     |
| None                     | 233 (40.0) | 105 (40.9) | 128 (39.3) |     |     |
| Renal replacement therapy | 49 (8.4) | 8 (3.1) | 41 (12.6) | 0.0001 |     |
| Vasopressors/inotropes at admission | 349 (59.9) | 109 (42.4) | 240 (73.6) | < 0.0001 |     |
| Organ dysfunction scores |     |                                 |                                 |           |     |
| SOFA (points)           | 7 [5–10] | 5 [3–8] | 8 [6–11] | < 0.0001 | n = 509 |
| APACHE II (points)      | 15 [11–20] | 14 [9–17] | 18 [13–22] | < 0.0001 |     |
| Length of stay (days)   |     |                                 |                                 |           |     |
| ICU                      | 5 [2–10] | 4 [2–8] | 5 [2–10] | 0.0554 |     |
| Mortality                |     |                                 |                                 |           |     |
| 28-day, deaths (%)      | 127 (21.8) | 30 (11.7) | 97 (29.8) | < 0.0001 |     |
| 90-day, deaths (%)      | 166 (28.5) | 41 (16) | 125 (38.3) | < 0.0001 |     |

Abbreviations: APACHE Acute Physiology and Chronic Health Evaluation, bio-ADM Bioactive adrenomedullin, BNP Brain-derived natriuretic peptide, BUN Blood urea nitrogen, CNS Central nervous system, COPD Chronic obstructive pulmonary disease, ICU Intensive care unit, NT-proBNP N-terminal brain natriuretic peptide, PaO₂/FiO₂ Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, PCT Procalcitonin, SOFA Sequential Organ Failure Assessment

* $p$ Value from nonparametric Kruskal-Wallis or chi-square test, respectively

* Most common comorbidities reported individually

0.0001). A multivariate model further demonstrated that bio-ADM had added value on top of APACHE II or SOFA score (added chi-square 24.4 [$p < 0.0001$] and 10.2 [$p = 0.0014$], respectively) (Table 2) when used as a continuous variable.

With the predefined cutoff value of 70 pg/ml, Kaplan-Meier analysis confirmed predictive value of bio-ADM for 28-day mortality in all studied patients (Additional file 1: Figure S1) and in subgroups of sepsis and septic shock (Fig. 1a and b). Patient characteristics for high and low bio-ADM levels are illustrated in Table 1, and characteristics for survivors versus nonsurvivors are provided in Additional file 2: Table S1. The optimal Youden cutoff in all patients was 101.9 pg/ml (sensitivity 67.7%, specificity 67.3%). In septic shock, the optimal Youden cutoff was 99.1 pg/ml (sensitivity 71.3%, specificity 52.3%), and in severe sepsis it was 101.9 pg/ml (sensitivity 57.6%, specificity 78.6%). This compares with a sensitivity of 77.2% and specificity of 48.9% in all patients for the predefined bio-ADM cutoff of 70 pg/ml.

We additionally assessed outcome in relation to bio-ADM changes in the initial 48 h in time-dependent
Cox regression. Bio-ADM trajectory over the initial 48 h after study inclusion improved prediction of 28-day survival in the overall population (added chi-square 25.8, \( p < 0.0001 \)) (Table 2; Fig. 2, Additional file 3: Figure S2) and was independent of time-dependent lactate or SOFA score evaluation (Table 2). Patients were divided into four groups based on baseline and day 2 bio-ADM concentrations and under implementation of the cutoff value of 70 pg/ml: remaining low (low-low, LL), high-to-low (HL), low-to-high (LH), and remaining high (high-high, HH). Patient characteristics of these subgroups are presented in Additional file 4: Table S2.

In patients admitted with high bio-ADM upon admission, those who decreased bio-ADM towards normal values within the first 48 h (HL group) had a similar 28-day mortality to the LL group (HL 9.5%, LL 10.5%) and a more favorable outcome than patients whose bio-ADM remained high (HH group) or became high (LH group) (28-day mortality of 38.1% and 38.2%) (Additional file 4: Table S2).

### Bio-ADM levels and organ dysfunction
Bio-ADM levels upon admission correlated with the initial SOFA score in all studied patients (\( n = 509, r = 0.49, p < 0.0001 \)) (Additional file 5: Figure S3). SOFA score was higher in patients in septic shock than in those in sepsis, and for each group in patients with high initial bio-ADM (Additional file 6: Figure S4). Figure 3a indicates that the initial level of circulating bio-ADM relates to the need for and duration of organ support in survivors (\( p < 0.0001 \)).

Concerning circulating bio-ADM levels and cardiovascular function, we found an almost linear relationship of bio-ADM and both cardiovascular SOFA subscore (\( p < 0.0001 \)) and was independent of time-dependent lactate or SOFA score evaluation (Table 2). Patients were divided into four groups based on baseline and day 2 bio-ADM concentrations and under implementation of the cutoff value of 70 pg/ml: remaining low (low-low, LL), high-to-low (HL), low-to-high (LH), and remaining high (high-high, HH). Patient characteristics of these subgroups are presented in Additional file 4: Table S2.

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### Table 2 Association between bio-ADM and 28-day mortality

| Variables                      | Chi-square | added chi-square | \( p \) Value (added value) | Std. HR bio-ADM | \( p \) Value |
|--------------------------------|------------|------------------|-----------------------------|-----------------|--------------|
| bio-ADM (univariate)           | 54.8       |                  |                             | 2.3 [1.9–2.9]   | < 0.0001     |
| Adjusted for SOFA at admission | 85.1       | 10.2             | 0.0014                      | 1.6 [1.2–2.1]   | 0.0014       |
| Adjusted for APACHE II at admission | 88.9     | 24.4             | <0.0001                     | 1.9 [1.5–2.4]   | < 0.0001     |
| Adjusted for covariates        | 132.1      | 12.2             | 0.0005                      | 1.6 [1.1–2.5]   | 0.0004       |
| bio-ADM (time-dependent Cox)   | 80.6       | 25.8             | <0.0001                     | 2.5 [2.1–3.1]   | < 0.0001     |
| Adjusted for SOFA at admission | 89.3       | 11.5             | 0.0007                      | 1.8 [1.4–2.2]   | < 0.0001     |
| Adjusted for APACHE II at admission | 108.4   | 19.5             | <0.0001                     | 2.1 [1.7–2.6]   | < 0.0001     |
| Adjusted for SOFA (t-d*)       | 101.0      | 7.9              | 0.0049                      | 1.5 [1.1–2.0]   | 0.0048       |
| Adjusted for lactate (t-d*)    | 138.0      | 35.7             | <0.0001                     | 1.9 [1.5–2.3]   | < 0.0001     |

**APACHE** Acute Physiology and Chronic Health Evaluation II, **bio-ADM** Bioactive adrenomedullin, **SOFA** Sequential Organ Failure Assessment

Results are from uni- (chi-square), multi- (added chi-square), and *time-dependent Cox regression analysis. *Time-dependent analysis includes measurements observed at baseline and day 2. \( n = 562 \) for covariates (i.e., age, gender, comorbidities [cardiac and noncardiac], diagnosis [sepsis, septic shock], lactate) model due to missing data for time-dependent lactate, and \( n = 509 \) for models including *time-dependent SOFA score.
confirmed that bio-ADM upholds a strong prognostication for organ recovery and survival in AdrenOSS-1 (both \( p < 0.0001 \)) (Additional file 11: Figure S8A and B).

**Discussion**

The AdrenOSS-1 study was a prospective multinational observational cohort study assessing the relationship between rapid changes in circulating bio-ADM levels in the first 2 days and clinical outcome in ICU patients with sepsis and septic shock. We confirmed elevated levels of bio-ADM in septic patients and the striking relationship between circulating bio-ADM at ICU admission, organ dysfunction, and death. We also demonstrated that early recovery of circulating bio-ADM levels towards normal values (i.e., <70 pg/ml) was associated with normalization of vascular function and better 28-day survival.

Our study found moderately elevated circulating levels of bio-ADM at admission in sepsis and strongly elevated bio-ADM levels in patients with septic shock, in accordance with earlier reports [13, 14]. Our study also confirmed the marked association between bio-ADM level at admission and short-term mortality as well as the prognostic cutoff value of 70 pg/ml, previously described by Marino et al. [14] and Caironi et al. [13] in both sepsis and septic shock (including the most recent definition [17]). Our study showed moderate prognostic value of bio-ADM at admission using AUC but marked prognostic value using Cox proportional hazards model adjusted for various parameters. Moreover, our study showed that prognostic value of bio-ADM at ICU admission exerts additive value (positive changes in chi-square) to various ICU severity scores. We described also the association between a bio-ADM \( \leq 70 \) pg/ml on day 2 and very low 28-day mortality, even in patients with initial high bio-ADM levels. The association of low bio-ADM by day 2 with full restoration of organ function at day 7 has been shown as well.

Concerning organ dysfunction, we found a relationship between circulating bio-ADM at ICU admission and the subsequent need for cardiovascular and/or renal support. In our studied patients, high circulating bio-ADM—known to have vasodilatory actions—might account for the deterioration of vascular tone and blood pressure, as previously described [13, 14]. In the present study, patients with high bio-ADM levels on ICU admission were more likely to need vasopressors and/or inotropes either at admission or in the following days. Moreover, they had a higher total fluid balance and higher incidence of RRT during their ICU stay. The ADM-induced vascular dysfunction may have contributed to this condition, although some data suggest that high bio-AM levels might also be protective to the kidney [19, 20]. Further studies are needed to elucidate the
exact role of bio-ADM in renal function. Of interest, the relationship between circulating bio-ADM levels and extent of organ dysfunction, present during ICU admission, was also true during the recovery phase. Indeed, bio-ADM levels decreased before the improvement of total SOFA score in our investigation. Patients with high bio-ADM levels at ICU admission who showed a decline towards normal bio-ADM values at day 2 were more likely to recover vascular function and vasopressor need by day 7. By contrast, the drop in bio-ADM from ICU admission to day 2 was associated with only limited improvement in renal function or no improvement in lung function at day 7. These observations also warrant further exploration.

Circulating bio-ADM levels were lower in AdrenOSS-1 than in the previously described ALBIOS cohort [13]. Indeed, in ALBIOS, septic patients were more severe, as suggested by greater prevalence of mechanical ventilation, length of stay, and short-term mortality. Likewise, the prevalence of septic shock was greater in ALBIOS than in AdrenOSS-1 (Additional file 12: Table S4). Of note, different definitions of septic shock in the two studies may have influenced study assessments.

Limitations included that in the present population only patients with sepsis and septic shock were studied, and results cannot be directly translated to a general ICU population. Future studies should focus on extrapolation of our results to patients with hemodynamic instability related to other disease, because as study has already been performed for cardiogenic shock [21]. Furthermore, our data suggest that ADM may be associated with myocardial function (e.g., patients with high ADM also had significantly higher circulating natriuretic

Fig. 3 Association between biologically active adrenomedullin levels upon admission and [a] length of total organ support over the first 7 days \( p < 0.0001 \), [b] length of vasopressor/inotropic support over the first 7 days \( p < 0.0001 \), [c] overall need for vasopressor support \( p < 0.0001 \), and [d] total fluid balance over the initial 48 h \( p = 0.0001 \)
peptide levels). However, data on cardiac function (e.g., cardiac output or left ventricular ejection fraction) were available in only few studied patients. Finally, we used the cut point of 70 pg/ml of circulating Bio-ADM for validation of the previously published cut point, even though the optimal Youden cut points in AdrenOSS-1 showed that 70 pg/ml with respect to a technical optimality criterion is not optimal.

Strong points of the study are the fact that it was a prospective international multicenter study with a large number of patients, with a focus on mortality and organ dysfunction. However, as is true of any observational study, only associations can be described, and cause-and-effect relationships cannot be deducted.

Conclusions
In this large prospective international cohort of critically ill patients admitted to the ICU with sepsis or septic shock, we confirmed the strict relationship between high levels of bio-ADM at ICU admission and organ dysfunction and mortality. We demonstrated that early decrease towards the normal values of circulating bio-ADM in the first days after ICU admission was associated with improvement of cardiovascular and renal function and was associated with very low 28-day mortality.

Appendix
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Additional files
Additional file 1: Figure S1. Twenty-eight-day Kaplan-Meier survival curves of low versus high bio-ADM at admission (bioADM.d0) in all patients, based on a cutoff value of 70 pg/ml. (TIF 207 kb)
Additional file 2: Table S1. Patient characteristics of survivors and nonsurvivors. (DOCX 50 kb)
Additional file 3: Figure S2. Bio-ADM levels at baseline and on day 2 in 28-day survivors and nonsurvivors. If data were missing at day 2 (e.g., owing to death or discharge; 12.7%), the last available measurement was carried forward. Horizontal lines at 70 and 130 pg/ml for better orientation; y-axis is truncated at 300 pg/ml. (TIF 206 kb)
Additional file 4: Table S2. Relationship between bio-ADM and cardiovascular SOFA subscore (r = 0.49, p < 0.0001; missing values due to missing SOFA score components). (TIF 199 kb)
Additional file 5: Figure S3. Association between the initial bio-ADM concentration and initial SOFA score (p = 0.49, n = 509, p < 0.0001; missing values due to missing SOFA score components). (TIF 217 kb)
Additional file 6: Figure S4. Association between bio-ADM concentration and initial SOFA score by sepsis and septic shock and initial bio-ADM concentration below or above 70 pg/ml (p < 0.0001 for both bio-ADM and diagnosis; p = 0.2015 for interaction; two-way analysis of variance). All data are from admission. (TIF 195 kb)
Additional file 7: Figure S5. Relationship between bio-ADM and need of vasopressor/inotropes at admission. (DOCX 23 kb)
Additional file 8: Table S3. Association between adrenomedullin and need of vasopressor/inotropes at admission. (DOCX 23 kb)
Additional file 9: Figure S6. Association between bio-ADM concentration on admission and need for renal replacement therapy on admission, later during ICU stay, or never (70.4 [36.3 – 162.6] vs. 162.6 [99.8 – 320.5] and 128.8 [76.5 – 281.0] vs. 149.0 [87.1 – 320.5] and 162.6 [99.8 – 367.5] pg/ml for patients without need for RRT, on admission, or later during ICU stay, respectively, p < 0.0001). (TIF 221 kb)
Additional file 10: Figure S7. Bio-ADM levels upon admission in 28-day survivors and time to ICU discharge (p < 0.0001); Patients with early discharge (< 2 days) are significantly different from all other groups (all p < 0.016), and late discharge (> 21 days) is significantly different from early discharge (< 2 days and 2 – 7 days, both p < 0.013). (TIF 217 kb)
Additional file 11: Figure S8. Twenty-eight-day Kaplan-Meier survival curves of low versus high bio-ADM at admission, based on a cutoff value of 70 pg/ml in patients with lactate > 2 mmol/L (p < 0.0001) (a) and SOFA score (b) for low versus high bio-ADM at admission (p < 0.0001). (TIF 229 kb)
Additional file 12: Table S4. Comparison of AdrenOSS-1 and ALBIOS. (DOCX 24 kb)
Abbreviations
ADM: Adrenomedullin; AdrenOSS: Adrenomedullin and Outcome in Sepsis and Septic Shock; APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II; bio-ADM: Biologically active adrenomedullin; BNP: Brain-derived natriuretic peptide; BUN: Blood urea nitrogen; CNS: Central nervous system; COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit; NT-proBNP: N-terminal brain natriuretic peptide; PaO2/FiO2: Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; PCT: Procalcitonin; RRT: Renal replacement therapy; SOFA: Sequential Organ Failure Assessment

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Authors’ contributions
AB, OH, PFL, AM, PS, and JS conceived of and designed the study. All collaborators acquired data (see Appendix). AB, CG, AH, AM, PFL, and JS analyzed and interpreted data. CG, AH, and AM drafted the manuscript. All authors critically revised the manuscript for important intellectual content. OH performed statistical analysis. PFL, AM, and sphingotec obtained funding. sphingotec provided administrative, technical, or material support. PFL, AM, and sphingotec supervised the study. All authors read and approved the final manuscript.

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Ethics approval and consent to participate
The present study was conducted in France, Belgium, The Netherlands, Italy, and Germany. The study protocol was approved by the local ethics committees, and the study was conducted in accordance with Directive 2001/20/EC as well as good clinical practice (International Conference on Harmonization Harmonized Tripartite Guideline version 4 of May 1, 1996, and decision of November 24, 2006) and the Declaration of Helsinki. Patients were included from June 2015 to May 2016.

Consent for publication
Not applicable.

Competing interests
AM has received speaker’s honoraria from Novartis, Orion, and Servier and fees as a member of the advisory board and/or steering committee from Cardiorentis, Adrenomed, sphingotec, Sandofi, Roche, Abbott, and Bristol–Myers Squibb. EG has received consulting fees from Adrenomed, Roche Diagnostics, and Magnusense and lecture fees from Edwards Lifesciences. AB is the managing director of sphingotec GmbH and holds shares in it. OH and JS are employees of sphingotec GmbH, the company that developed and holds patent rights in the bio-ADM assay. BF has received consulting fees from Ardis, Ferring, Arsanis, Inotrem, and Lascco. PP serves as a consultant and/or speaker for Ardis, Ferring, and Lascco. Those other authors report no conflicts of interest.

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Availability of data and materials
AM and PFL had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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