Bioactive Adrenomedullin 1-52 (bio-ADM)

A novel biomarker for dynamic monitoring of endothelial function in acute and critical care patients

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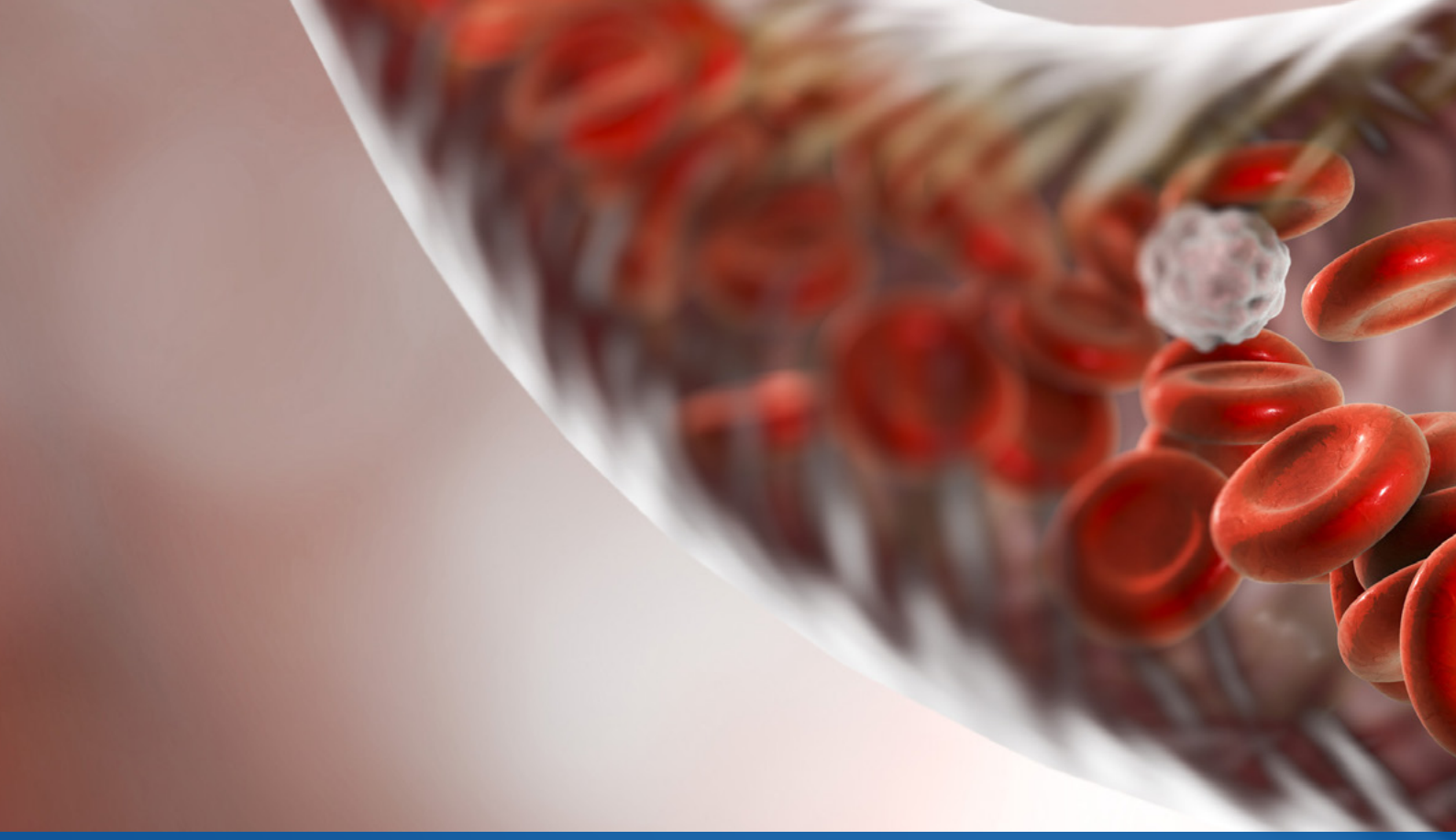
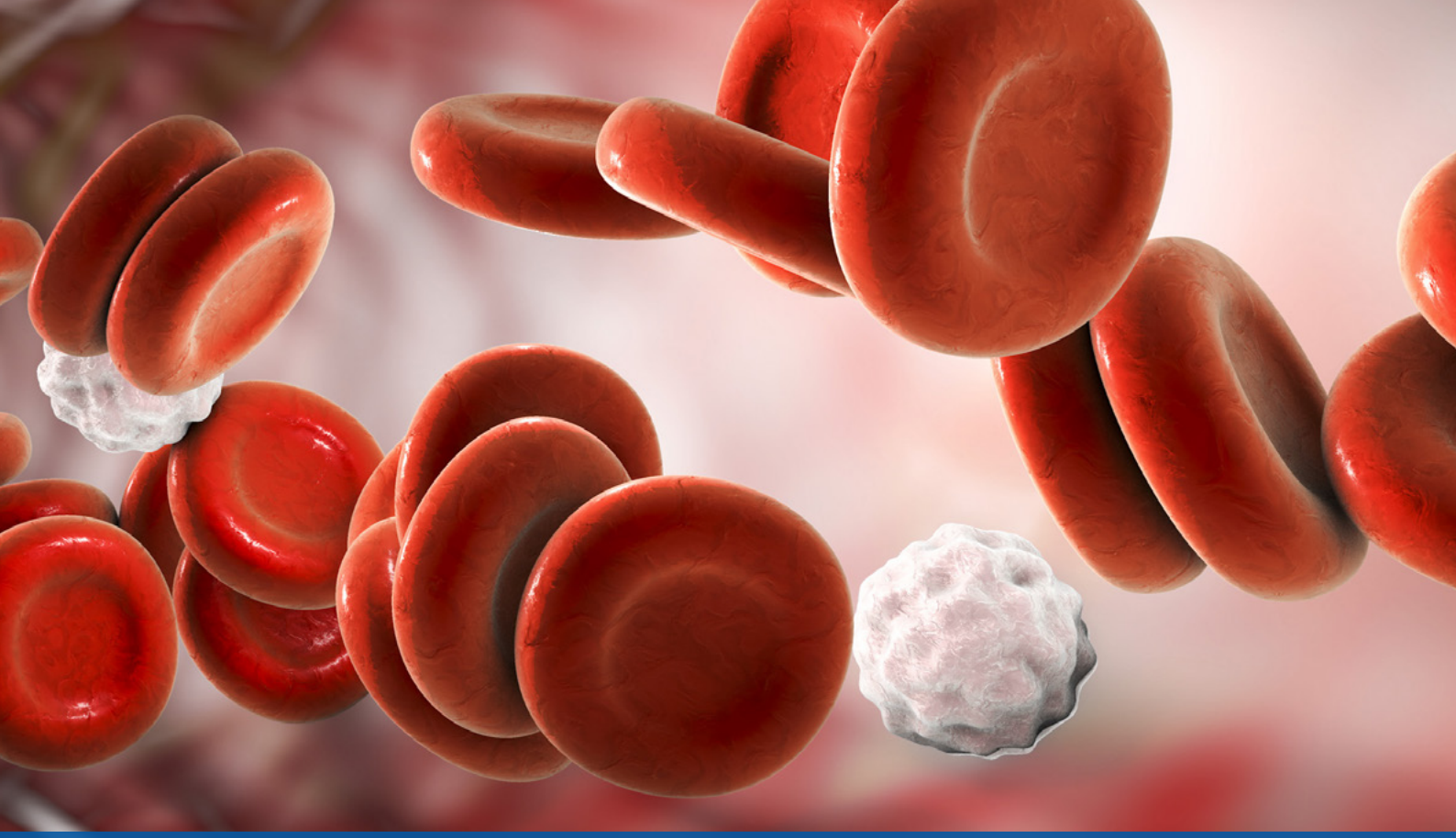




Abstract

Adrenomedullin (ADM) is a 52 amino acid peptide that acts as an endogenous guardian of endothelial integrity. ADM is produced by several body cell types, e.g., vascular smooth muscle cells (VSMC) and endothelial cells. When released into the blood circulation, ADM endorses two major functions:

1. It stabilizes the endothelial barrier through ADM receptors on endothelial cells (1).
2. It promotes vasodilation via binding to ADM receptors expressed on VSMC (1).

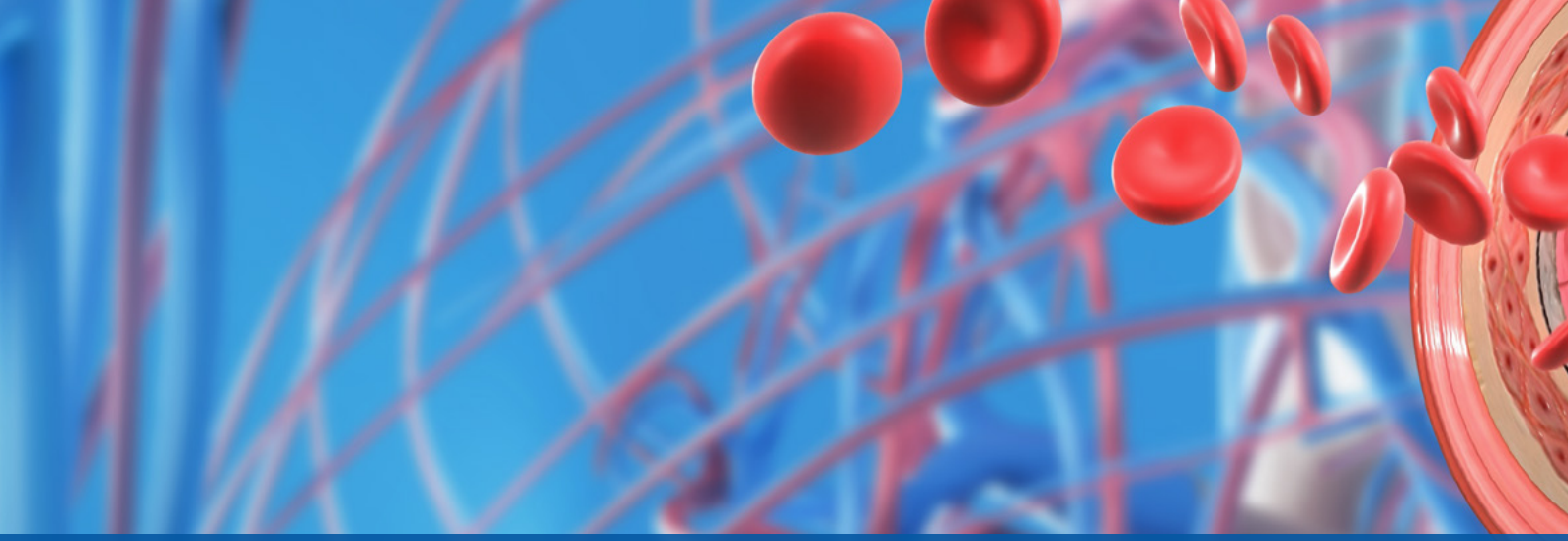
ADM and its hemodynamic effects were first described in 1993. Since then, ADM has been a molecule of interest for diagnostic and therapeutic approaches. Specifically, its modulating role in endothelial dysfunction, a hallmark of several critical care conditions such as sepsis, septic shock, or acute heart failure (AHF), has been investigated. Today there is growing evidence that measuring bioactive Adrenomedulin 1-52 (bio-ADM) provides dynamic information on endothelial dysfunction by a simple blood test.

Measuring bio-ADM gives direct insights into one of the underlying mechanisms of endothelial dysfunction, uncovering thus two unmet needs:

a) In sepsis or septic shock: bio-ADM level correlates with need, dosage, and duration of vasopressors, multiple organ failure, and poor patient outcomes. Assessment of plasma bio-ADM can aid in clinical practice to improve early risk stratification and to support patient management (2).

b) In acute decompensated heart failure: bio-ADM levels correlate with residual congestion. In clinical practice assessment of plasma bio-ADM may improve discharge decisions, the guidance of diuretic therapy, and better prediction for patient outcomes (3, 4).

By measuring bio-ADM, physicians in the emergency department (ED) or intensive care unit (ICU) can immediately assess the patient's individual risk of suffering from endothelial dysfunction, monitor therapy success, and therefore improve patient outcomes.



Introduction

Endothelial function

The endothelium – the inner cell layer of blood vessels – is of utmost importance for maintaining cardiovascular homeostasis, as it represents the primary barrier between the intravascular and interstitial space. Once disturbed (e.g., by systemic inflammatory response), endothelial dysfunction results in endothelial cell death and loss of endothelial barrier integrity. Thus, a detrimental volume redistribution among compartments causes edema and hypotension (5). At its worst, this can result in a life-threatening hypervolemic and distributive shock, leading to organ failure and death (6).

Endothelial dysfunction is relevant in several critical care indications, including sepsis and AHF (7, 8). Sepsis is associated with high mortality and long-term disability in survivors (9). AHF is a leading cause of hospitalization in patients older than 65 years, associated with high mortality and rehospitalization rates (8). Both diseases are a significant global healthcare burden with tremendous socioeconomic impact.

Sepsis

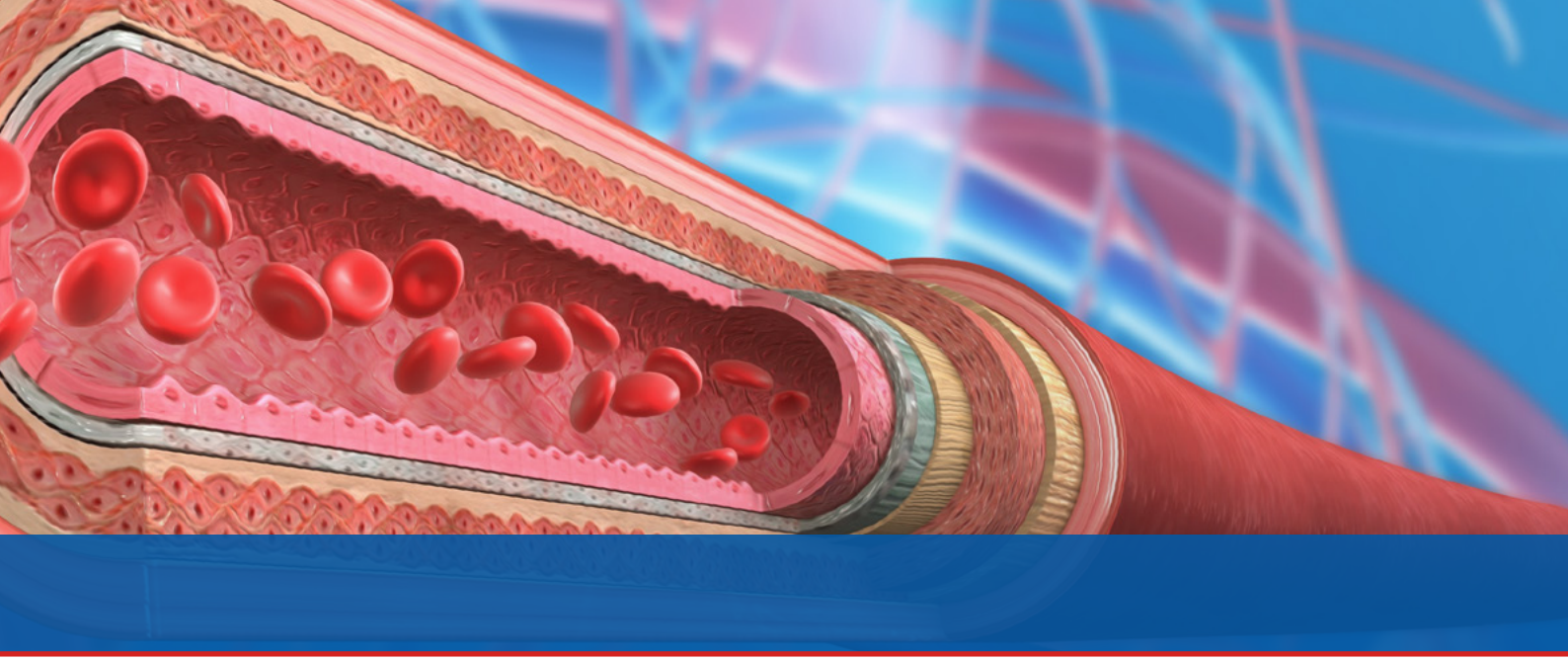
- Corresponds to **50%** of main cause of death in hospitals [10]
- A major reason for hospital re-admissions, covering **1 in 3 patients** [11]
- High healthcare cost, reaching about **24 billion dollars** [10]

Acute heart failure

- **26 Million cases** of heart failure globally [12]
- Residual **congestion** is the main cause of re-hospitalization and post-discharge mortality rates in AHF patients [13]
- **31 billion dollars** in health expenditure [12]

Maturation and measurement of bio-ADM

The gene encoding ADM is located on human chromosome 11 (14). Its messenger RNA molecule is translated into a 185 amino acid long preprohormone (pre-proADM). It is processed to the precursor peptide pro-ADM by clipping the signal sequence. Subsequently, the resulting pro-ADM is proteolytically cleaved into four fragments: proadrenomedullin N-terminal 20 peptide-glycine [PAMP-Gly], midregional(MR)-proADM, ADM-Gly, C-terminal (CT)-proADM. The biologically inactive ADM-Gly is then (partially) converted to the biologically active C-terminally amidated ADM (bio-ADM). Bio-ADM is a highly dynamic molecule , unlike MR-proADM, a biologically inactive cleavage product of ADM maturation (15).



Circulating ADM has a short half-life (around 22 min)(16), hampering its timely detection in the blood. MR-proADM has initially been introduced as a surrogate marker to overcome the problems associated with ADM measurement. Both MR-proADM and ADM are derived from the same precursor, however MR-proADM is non-functional. ADM becames biologically active through a crucial maturation step: the C-terminal amidation. The amidated ADM-variant is called bio-ADM which is stable for up to 6 hours in EDTA whole blood (at room temperature).

Bio-ADM can be detected by using specific monoclonal antibodies against the middle portion of ADM (blue “solid phase” antibody) and the amidated C-terminus (yellow “tracer” antibody (15) **(Figure 1)**.

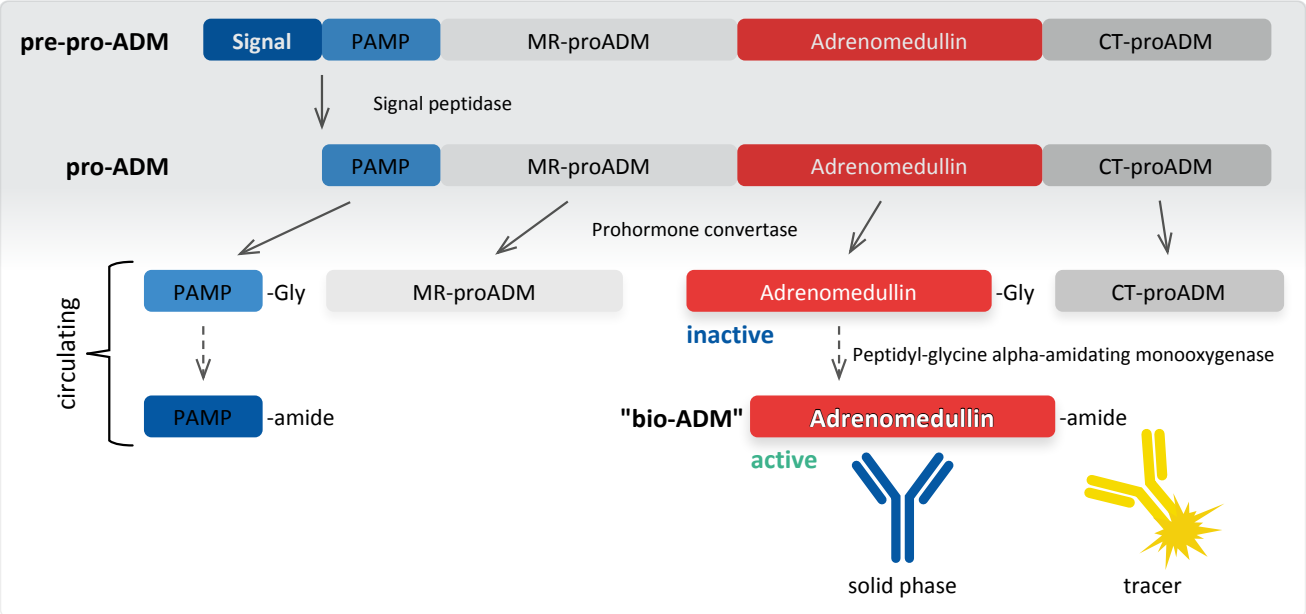


Figure 1. The scheme on the maturation and detection of bio-ADM, from the primary translational gene product pre-proADM to bio-ADM. Circulating fragments: **PAMP**: proadrenomedullin NH2-terminal 20 peptide; **MR-proADM**: midregional proadrenomedullin; **Adrenomedullin-Gly**: C-terminally glycine-extended adrenomedullin; **CT-proADM**: C-terminal proadrenomedullin, also known as adrenotensin (15).

The pathophysiological mechanism of adrenomedullin

ADM is a circulating peptide hormone (52 amino acids) belonging to the calcitonin gene-related peptide family. ADM has been identified as the guardian of the endothelial barrier in health and disease by preserving integrity through vascular tone signaling and stabilizing endothelial barrier function (17).

In the healthy state, the stabilization of the endothelial barrier and the prevention of vascular leakage happen mainly through the stabilization of cell-cell junctions – essential proteins for endothelial cells´ structural and morphological integrity. Diseases such as septic shock are often accompanied by increased endothelial permeability, resulting in the release of bio-ADM into the interstitium as well as in the intravascular space. In the interstitium bio-ADM binds to ADM receptor on VSMC, triggering vasodilation (1). This results in decreased blood pressure (hypotension), and reduced resistance of the arteries to blood flow (also known as peripheral resistance), which may lead to shock, escalating into organ failure and death (5, 17) **(Figure 2)**. Importantly, bio-ADM levels are strongly elevated under non-steady-state conditions such as septic shock to restore the endothelial integrity and homeostasis of the body(18). However, due to the loss of endothelial integrity and the free diffusion of bio-ADM out of the vessel, the vasodilatory function of bio-ADM leads to an aggravation of the clinical condition(5).

Healthy state

- Normal bio-ADM level in the intravascular space and interstitium (free diffusion).
- Plasma bio-ADM acts on endothelial cells and regulates barrier function and permeability.
- Interstitial bio-ADM acts on VSMC and regulates vasodilation.

Disease state

- High bio-ADM level indicates need for endothelial barrier support.
- Plasma bio-ADM supports endothelial barrier and counteracts vascular leakage:

- In septic shock excess interstial bio-ADM leads to excessive vasodilation and shock.
- In AHF elevated bio-ADM plasma level reflects congestion.

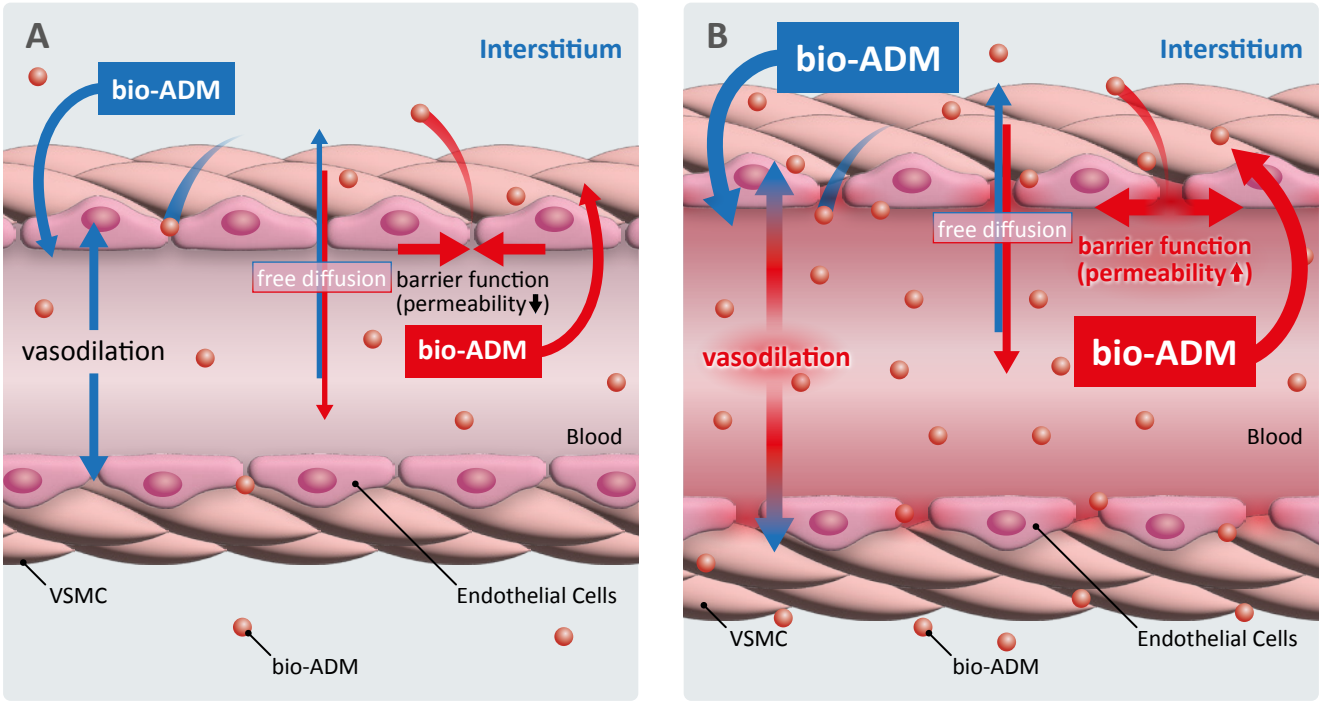


Figure 2. Bio-ADM mechanism of action in health and disease states. A. In a healthy homeostatic situation, bio-ADM can diffuse freely over the vascular barrier and exert effects on the endothelium and VSMC. **B.** Disease-induced vasodilation and impaired vascular barrier function contribute to increased circulating bio-ADM levels, but not to the extent that sufficiently counteracts impaired barrier function. Moreover, increased bio-ADM levels lead to excessive vasodilation. Modified from (17).

Scientific evidence

Currently, evaluation of vascular integrity in patients in the ICU relies on the fluid balance of the patient, measurement of mean arterial pressure (based on Sepsis-3 Guideline), and the presence of symptoms such as (pulmonary) edema. However, there is a substantial time delay between loss of vascular integrity and the onset of symptoms (19). Bio-ADM makes it possible to evaluate the patient´s condition in real-time, shedding light on endothelial funcionality, providing vital information for treatment decisions.

More than 50 publications, as well as submitted papers and ongoing projects and clinical studies, have investigated the significance of bio-ADM as a biomarker in more than 50,000 patients with different indications, allowing a clear understanding of the bio-ADM distribution and its clinical value in acute and critical care conditions.

Publications on European reference populations:

Adults: The 97.5th percentile for sphingotest® bio-ADM® in healthy subjects has been determined to be 29 pg/mL (90% CI 27 pg/mL - 38 pg/mL) (20). There is no evidence for an age-dependent influence on bio-ADM concentrations levels, however pregnancy leads to elevated bio-ADM (unpublished data).

Indication	Endpoints	Cut-off
Sepsis	• 28-, 30- or 90-day mortality (2, 21-25) • Organ support (24) • Vasopressor/inotrope use (21-25) • Positive fluid balance (22) • Sequential organ failure assessment (SOFA) score= 7 [IQR 5–10] (22) • Septic shock (25)	70 pg/mL
Heart Failure (HF)	• All-cause mortality and HF hospitalization (26) • Congestion (27)	39 pg/mL 34 pg/mL
Dyspnea in the ED	• Congestive heart failure (28) • 90-day mortality (28)	29 pg/mL

Measurement method

Microtiter plate (MTP) to assess bio-ADM at the hospital laboratory testing, using the sphingotest® bio-ADM® assay.

Results:
in 1 hour

Measuring range:
10.8 – 1.094 pg/mL

Total of samples per plate:
41 samples in double determination.

Sample volume:
100 µL EDTA plasma

Endothelial function in sepsis is lost due to the overwhelming systemic inflammatory response, leading to the activation of endothelial cells (7). A subgroup of sepsis patients develops septic shock, based on the Sepsis-3 Guidelines characterized by lactate > 2 mmol/L, vasopressor requirement and persistent hypotension, despite adequate fluid resuscitation. Thus, vasopressors are needed to maintain the mean arterial pressure ≥ 65 mmHg (29). Earlier identification of patients who will develop septic shock remains an unmet medical need.

The quick SOFA (qSOFA) score has been proposed to assess patients with sepsis in the ED. It consists of evaluating oxygen saturation, blood pressure, and consciousness. Although easy to asses, guidelines do not consider it ideal for immediate stratification of sepsis and recommend the measurement of lactate in the blood to decide whether to use antibiotics (29).
However, lactate increase during sepsis (so-called hyperlactemia) is an indicator for hypoxia but not specific marker for organ dysfunction. A more specific diagnostic tool is desired for the earlier stratification of patients presenting at the ED (18). In the case of ICU, better diagnostic could improve time to treatment and counteract mortalities rates - these are being around 35% for septic shock patients (30), increasing by 8% with every delayed hour of treatment (31).
Therefore, a biomarker that can predict shock, the need for vasopressor therapy, and monitor therapy success, adding value to qSOFA and lactate would be of high value in this context (32). Scientific evidence shows that bio-ADM can predict pathophysiological deterioration in septic or septic shock patients, as depicted in the figures below.

Scientific evidence – emergence department

Assessment of vasopressor need

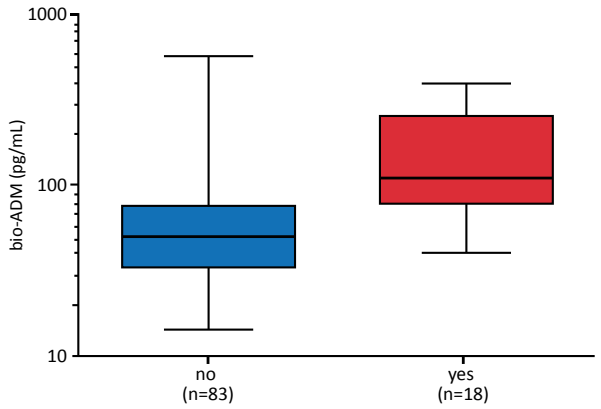


Figure 3. Bio-ADM levels at admission to the ED identify patients for need of vasopressor therapy (p<0.0001). Modified from (21).

Assessment of organ failure

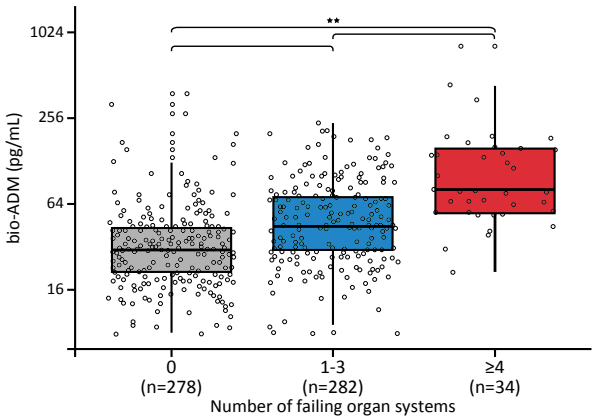


Figure 4. Bio-ADM level upon presentation to the ED significantly discriminates patients without organ failure (0), with intermediate organ failure (1-3), and severe multiple organ failure (≥4) (** : p<0.001). Modified from (33).

Assessment of disease severity

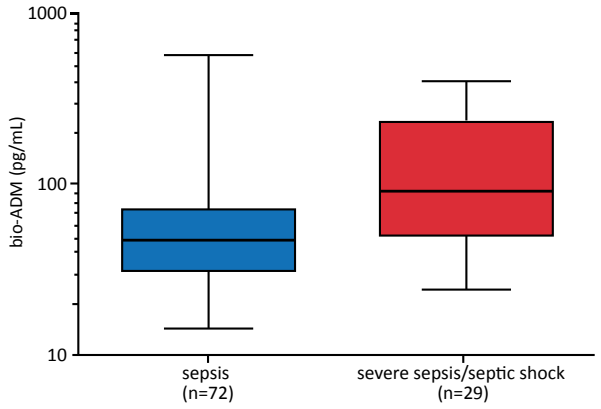


Figure 5. Bio-ADM levels increase with the disease severity, as shown for patients with sepsis and severe sepsis/septic shock on admission to ED (p<0.0001). Modified from (21).

Triage guidance

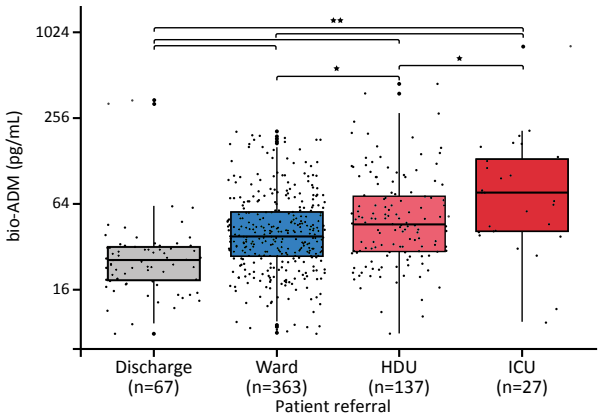


Figure 6. Bio-ADM level upon presentation to the ED is predictive for ICU admission in sepsis patients. Bio-ADM levels increased in patients admitted to the ICU [77 (42-133) pg/mL] than patients discharged [41 (28-61) pg/mL] or discharged from ED (* : p<0.05, ** : p<0.001). HDU = high dependency unit. Modified from (33).

Scientific evidence - Intensive Care Unit

Diagnosis of septic shock

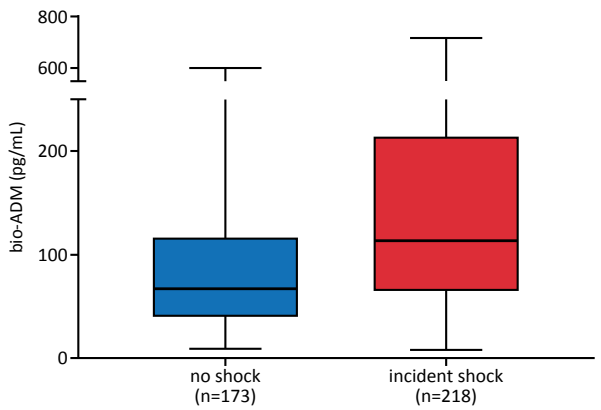


Figure 7. Plasma bio-ADM levels on day 1 after ICU admission were higher in patients with septic shock compared to patients with sepsis (p<0.0001). Modified from (2).

Prediction for vasopressor need

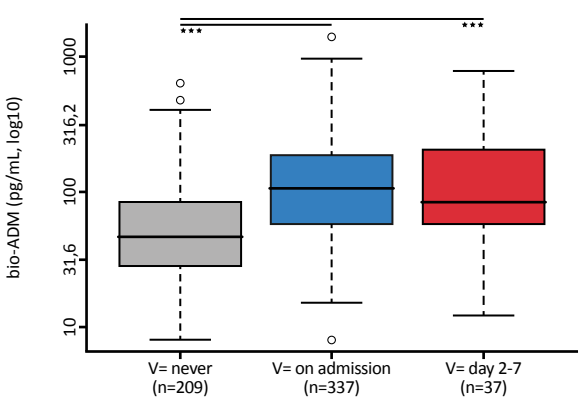


Figure 8. Bio-ADM level upon admission and the association with overall need for vasopressors. Patients with high bio-ADM at admission were in need of more vasopressors over the following 7 days. V= Vasopressors. (*** : p<0.0001). Modified from (22).

Assessment of hemodynamic support therapy

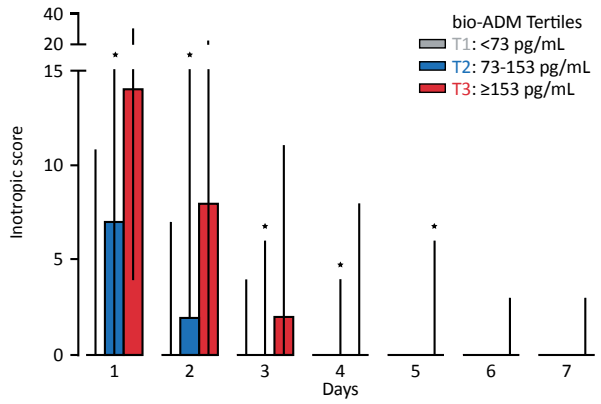


Figure 9. Inotropic score# over the first 7 days of treatment in alive sepsis patients was greater in those with higher levels of bio-ADM, indicating a need for more hemodynamic support. Conversely, patients with low inotropic score had lower level of bio-ADM at day 1 (p<0.01). Modified from (2).

Prediction of mortality risk

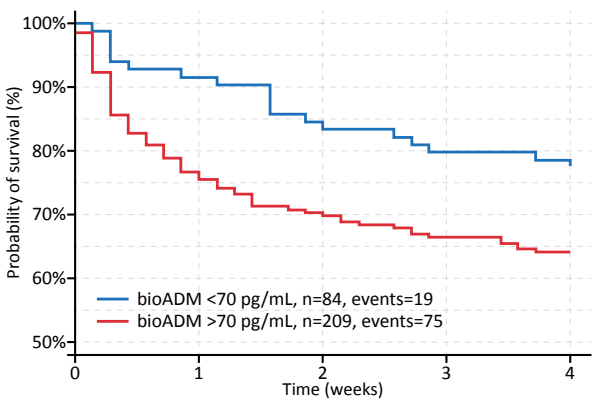
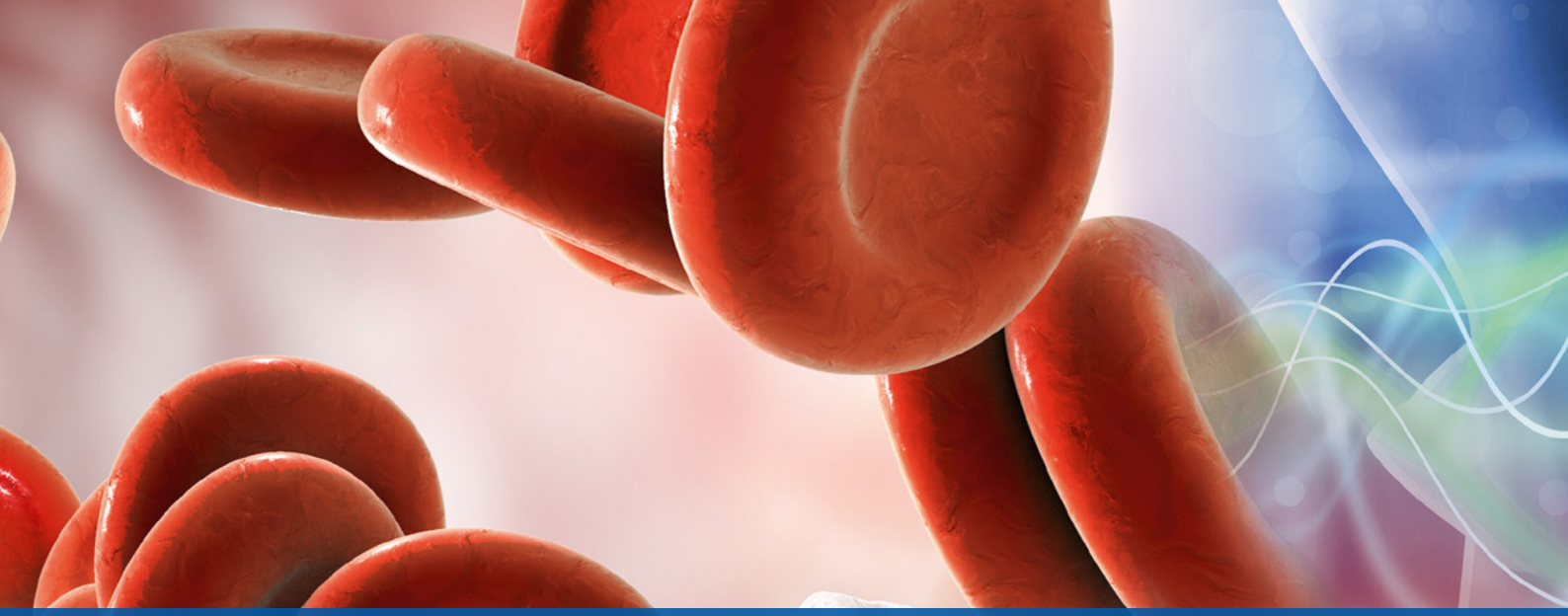


Figure 10. Kaplan-Meier survival curves of septic shock patients with low versus high bio-ADM levels on admission. Cut-off 70 pg/mL. Modified from (22).

 # Inotropic score: quantifies the degree of hemodynamic support based on the dose of various inotropes used to manage septic shock at any time.



Bio-ADM in cardiovascular disease

Cardiovascular diseases are a major health problem worldwide. Although the diagnosis of acute myocardial infarction (MI) and AHF has significantly improved over the last decades, diagnostics for residual congestion in acutely decompensated HF patients and cardiogenic shock remains underserved (34). Bio-ADM has been evaluated in specific cardiac settings to close diagnostic gaps, including cardiogenic shock, residual congestion, and complications as well as outcomes associated with cardiac surgery.

Cardiovascular diseases

Cardiogenic shock is a low-cardiac output state most frequently caused by MI, myocarditis, and acute descompensated HF (35). It is a state of hypoperfusion caused by severe cardiac dysfunction (34). Cardiogenic shock is a common cause of in-hospital death in patients with MI. There is a need for an accurate risk stratification tool that can be used to aid in treatment decision-making (35).

AHF is associated with a rapid or gradual onset of new or worsening HF signs. Clinical symptoms are shortness of breath, ankle swelling, and fatigue that may be accompanied by clinical signs such as elevated jugular venous pressure (8). It is a severe medical condition, leading patients to seek urgent medical assistance, resulting in an ED visit and unplanned hospital admission (8). The primary cause of AHF is impaired cardiac function, resulting from cardiac arrest and loss of vascular integrity, especially in the pulmonary vessels, leading to fluid overload* (or hypervolemia) and congestion[§]. Congestion often remains undiagnosed and is one of the most common causes of rehospitalization or death after hospitalization. Patients with fluid overload and congestion usually need pharmacological decongestion through the guided application of loop diuretics[#], which often provide rapid decongestion and symptomatic relief (36). So far there is no gold standard for diagnosing residual congestion, which is assessed by various non-validated clinical scores (1).

Cardiac surgery

Cardiac surgery techniques have evolved into minimally invasive procedures, and numbers of elective surgeries are rising due to increased patient age (37). Although well advanced, cardiac surgery is associated with several postoperative complications, including a 25% risk for the patients to develop a vasoplegic syndrome requiring prolonged vasopressor therapy (38). To identify organ dysfunction and the need for vasopressor therapy (39), novel diagnostics are required to stratify patients for post-surgery care.

***Fluid overload**: it is the medical condition of having too much fluid in the blood; [§]**Congestion**: excessive fluid in tissues, vessels or both; [#]**Diuretics**: medication that increase renal salt and water excretion, having therefore vasodilator properties, and helping to remove extra fluids (36)

Scientific evidence in cardiovascular disease

Identification of cardiogenic shock post TAAA surgery

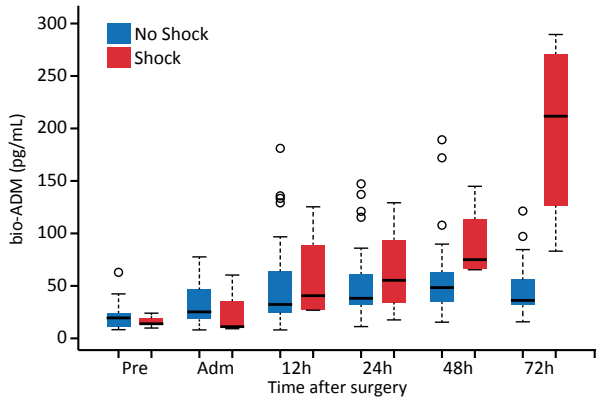


Figure 11. Higher bio-ADM levels predict cardiogenic shock after open and endovascular thoracoabdominal aortic aneurysm (TAAA) repair and increase significantly after 48h and 72h (p=0.0066 (48h), p<0.0001 (72h)). Modified from (40).

Assessment of hemodynamic support therapy after cardiac surgery

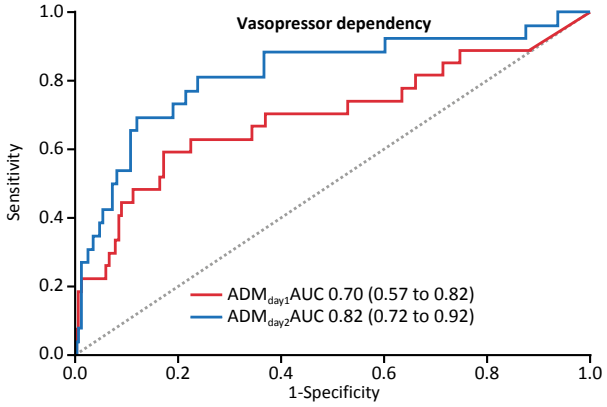


Figure 12. Receiver operating characteristic (ROC) curve of bio-ADM levels on days 1 and 2 of ICU admission after cardiac surgery. Vasopressor dependency was defined as the need for vasopressor therapy to maintain adequate blood pressure for more than 3h after admission (p=0.001 (day 1), p<0.001 (day 2)). Modified from (39).

Diagnosis and monitoring of residual congestion in AHF

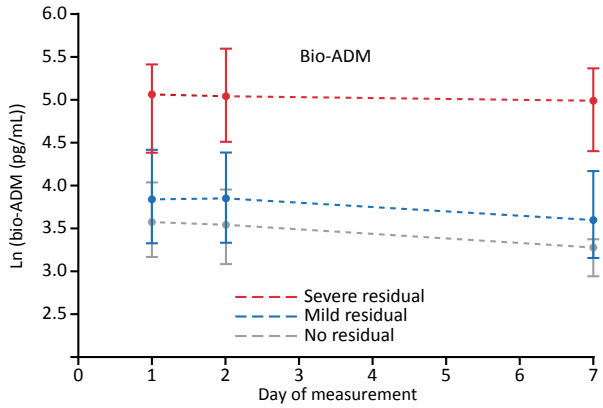


Figure 13. In AHF patients with no/mild residual congestion at day 7, bio-ADM levels had decreased between baseline and day 7. Patients with severe residual congestion on day 7 already had higher bio-ADM values at baseline. These levels remained higher up to day 7 (p<001). Modified from (3).

Guidance of loop diuretics in AHF

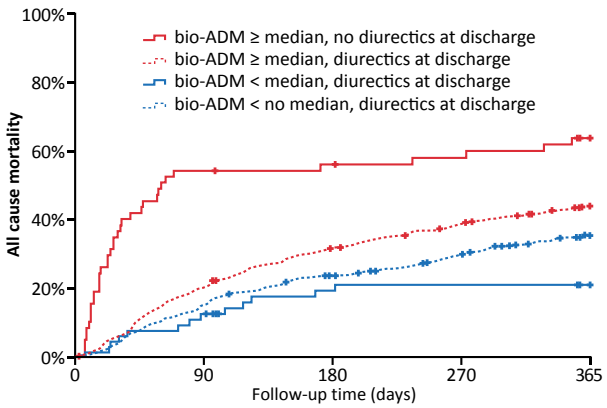


Figure 14. AHF patients with bio-ADM levels above the median have higher all-cause mortality rates compared to those with bio-ADM levels below the median at discharge. Administration of diuretics in patients with high bio-ADM levels at discharge reduces mortality rates by 40%. Risk of mortality at 90 days is halved if diuretics are administered to bio-ADM positive patients at discharge (p<0.001). bio-ADM median: 44.6 pg/mL. Modified from (4).

Overview on the main indications for bio-ADM

Scientific evidence has been compiled for bio-ADM in many critical health conditions, proving its additive value to standard clinical parameters.

Table 1: Main indications where bio-ADM showed additive value.

Indication	Scientific evidence
Sepsis and septic shock	**ICU:** Added value to lactate in the prognosis of sepsis at admission (32); bio-ADM levels at admission are associated with 30-day mortality need for organ support and sepsis identification (23, 25); bio-ADM is higher in septic shock patients than in septic patients related to 90-day mortality, multiple organ failures, and hemodynamic support therapy (fluids and vasopressors) (2). **ED:** (Serial) bio-ADM is associated with: disease severity, vasopressor requirement, 28-day mortality (21); bio-ADM at admission predicts sepsis severity, organ failure, and 30-day mortality (25).
Acute heart failure	Bio-ADM at admission and discharge allows stratification of patients who benefit from diuretics and predicts of all-cause mortality during the 365-day follow-up (4). Higher bio-ADM levels are associated with congestion, rehospitalization, and length of hospital stay (3, 27, 41, 42).
Cardiac surgery	Postoperative bio-ADM levels after 72h of surgery are associated with cardiogenic shock and death (40); bio-ADM levels predict vasopressor dependency (> 3 days), AKI, and ICU length of stay (39).
Preclinical studies and randomized controlled trials with anti-bio-ADM antibody	Preclinical studies: a non-neutralizing humanized monoclonal anti-bio-ADM antibody - Adrecizumab (INN: Enibarcimab) - restored hemodynamic parameters in an animal model (43). Clinical studies: high bio-ADM levels (>70 pg/mL) successfully guided therapeutic application of Adrecizumab in septic shock patients (44).

AKI: Acute Kidney Injury *Bio-ADM: Bioactive adrenomedullin* *ED: Emergency department* *ICU: Intensive care unit*

Summary

Bio-ADM:

- Surrogate marker to assess endothelial function and vascular integrity
- Predicts vasopressor demand, dosage and dependency in septic and cardiac surgery patients
- Identifies residual congestion in AHF patients
- Validated in over 50,000 patients

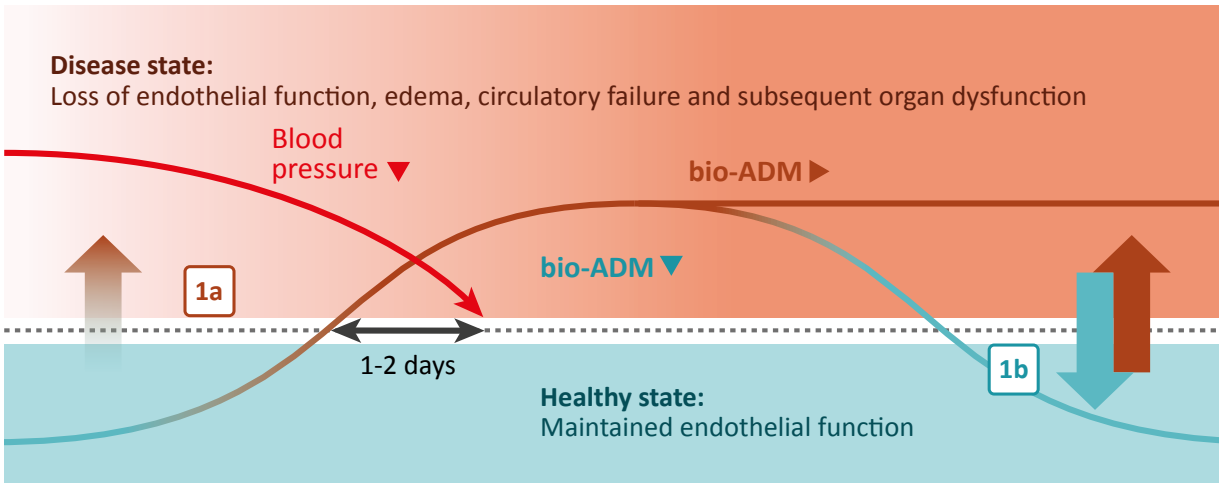


Figure 15. Bio-ADM blood levels predict the need for vasopressors due to blood pressure drop and leaky vessels leading to edema formation **(1a)**. Decreasing levels of bio-ADM reflect an improvement of endothelial function, which is closely associated with the patient's clinical condition **(1b)**.

Scientific evidence in all clinical settings already evaluated:

- AHF (3, 41, 42, 45, 46)
- AMI (47)
- Cardiogenic shock (34, 48, 49)
- Chronic HF (4, 26, 27, 42, 45, 50-56)
- Circulatory shock (57)
- Clinical therapy stratification (44, 58-60)
- COVID-19 (60, 61)
- Dyspnea (26, 28, 62)
- ICU discharge decision (63)
- Therapy stratification (64-66)
- Sepsis and septic shock (2, 21-23, 25, 32, 33, 67)
- Triaging in the ED (33)

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Abbreviations

ADM:	Adrenomedullin
Adrenomedullin-Gly:	C-terminally glycine-extended adrenomedullin
AKI:	Acute Kidney Injury
AHF:	Acute heart failure
AUC:	Area under the curve
Bio-ADM:	Bioactive adrenomedullin
COVID-19:	Coronavirus disease 2019
CT-proADM:	C-terminal pro-adrenomedullin
ED:	Emergency department
EDTA:	Ethylenediaminetetraacetic acid
HF:	Heart failure
ICU:	Intensive care unit
MI:	Myocardial infarction
MR-proADM:	Mid-regional proadrenomedullin
MTP:	Microtiter plate
PAMP:	Proadrenomedullin NH2-terminal 20 peptide
SOFA:	Sequential organ failure assessment
qSOFA:	Quick sequential organ failure assessment
ROC:	Receiver operating characteristic
VSMC:	Vascular smooth muscle cell

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