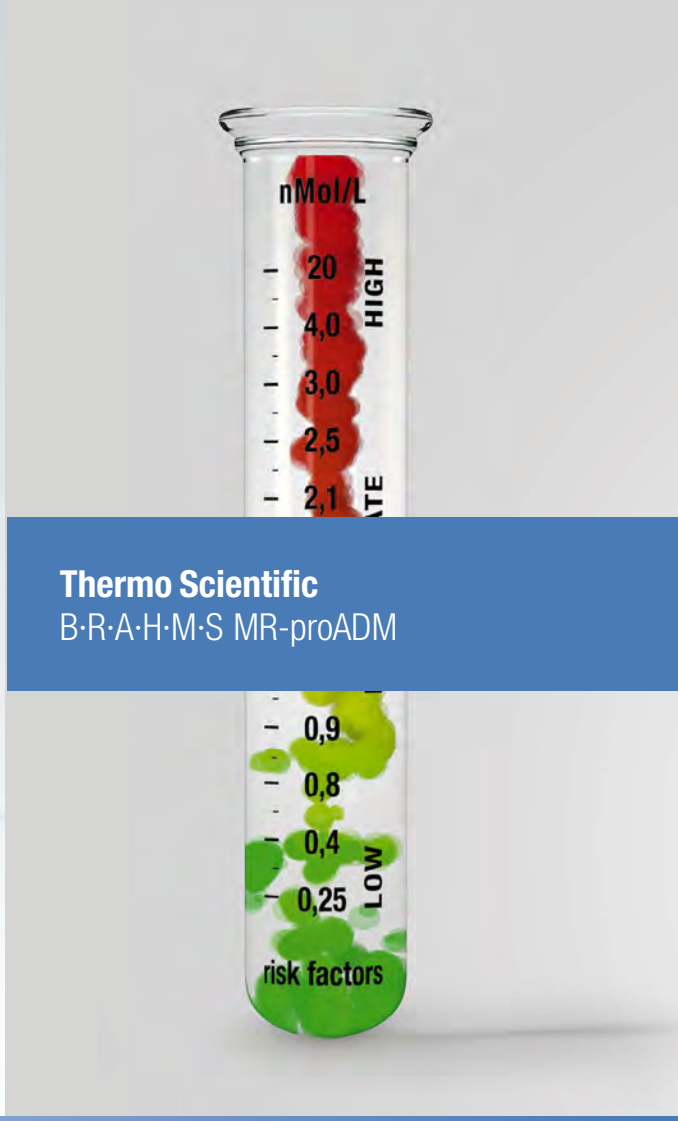


Thermo Scientific
B·R·A·H·M·S MR-proADM

MR-proADM

Optimize risk assessment, decision making and treatment processes

High accuracy in predicting short- and long-term outcomes • Established cut-offs • Improved patient classification Better alignment of clinical resources • Excellent prognosis profile in sepsis • Used in a wide range of clinical applications

Thermo SCIENTIFIC

Optimize risk assessment, decision making and treatment processes

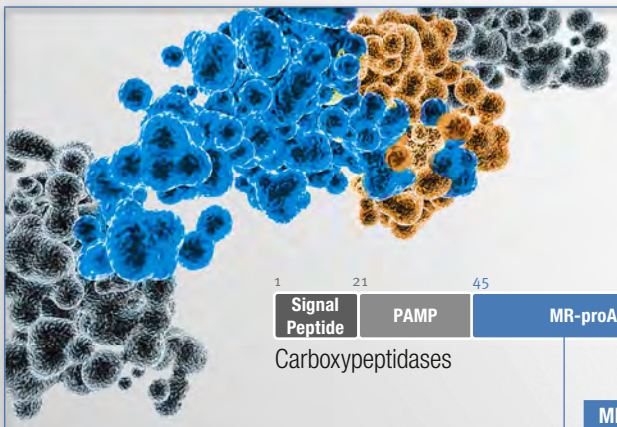
MR-proADM is a blood biomarker that provides accurate short-, mid- and long-term prognostic information and aids in the triage and multi-dimensional risk assessment of patients in the Emergency Department (ED) and Intensive Care (ICU) settings.

Adrenomedullin is the key

Adrenomedullin, a 52 amino acid peptide, is a member of the calcitonin peptide family[1] and is widely expressed in many tissues and organs. It has been shown to have a variety of physiological functions, including immune-modulating, direct bactericidal, diuretic and potent vasodilatory activity[1-5], and in healthy conditions, circulates at low picomolar concentrations[6].

In many diseased states such as hypertension[7], renal failure[7], lower respiratory diseases[8] and septic shock[9], plasma levels are significantly up-regulated in proportion to disease severity[7, 10-13]. This allows clinicians to determine the patients **most at risk of developing complications** on admission or during ED and ICU stay, in order to rapidly triage and **administer the most effective treatment**, in the shortest possible time.

The clinical and financial benefits of an early diagnosis and risk assessment to both the patient and healthcare provider, therefore, cannot be overstated.



However, reliable **measurement of ADM is challenging** due to a number of issues, such as:

- A short half life of 22 minutes[14]
- Rapid degradation by proteases[15]
- Binding to complement factor H[5]

MR-proADM provides a solution to these problems

The increased stability of its precursor molecule, MR-proADM, allows it to be reliably measured as a surrogate biomarker for the unstable ADM in a 1:1 ratio[16], thus allowing changes in biomarker concentrations to be determined.

Figure 1: preproADM molecule.

Our solution: MR-proADM
Fast, stable and independent

High correlation with increasing severity of disease[17], and accurate short- to long-term prognostic prediction capability in the ED and ICU

MR-proADM is a novel biomarker which provides more precise patient risk management and greater confidence in treatment site assignment.

Used in a variety of indications, it can enhance routine clinical investigation and treatment, and provide a viable alternative to many current risk assessment scores.

Use in the Emergency Department (ED)

Rapid triaging and risk assessment of patients on admission and throughout the ED can:

- Decrease time to treatment
- Increase out-patient numbers
- Reduce length of stay

Use in the Intensive Care Unit (ICU)

Immediate risk assessment of mortality and adverse effects in the ICU can:

- Maximize patient safety
- Guide the most appropriate treatment
- Provide an early warning of additional complications

Optimization of risk assessment and patient management using MR-proADM

- Levels are not influenced by food or water intake[18]
- No significant gender related differences[18]
- Stability of up to 72 hours in EDTA plasma at room temperature[18] and over four freeze/thaw cycles[18]
- Well documented for clinical use
- Rapidly available to aid timely clinical decision-making using the KRYPTOR™ platform*

* assay incubation time 29 mins and small sample volume (26 µL in EDTA plasma)

Mechanism of action and functions of Adrenomedullin

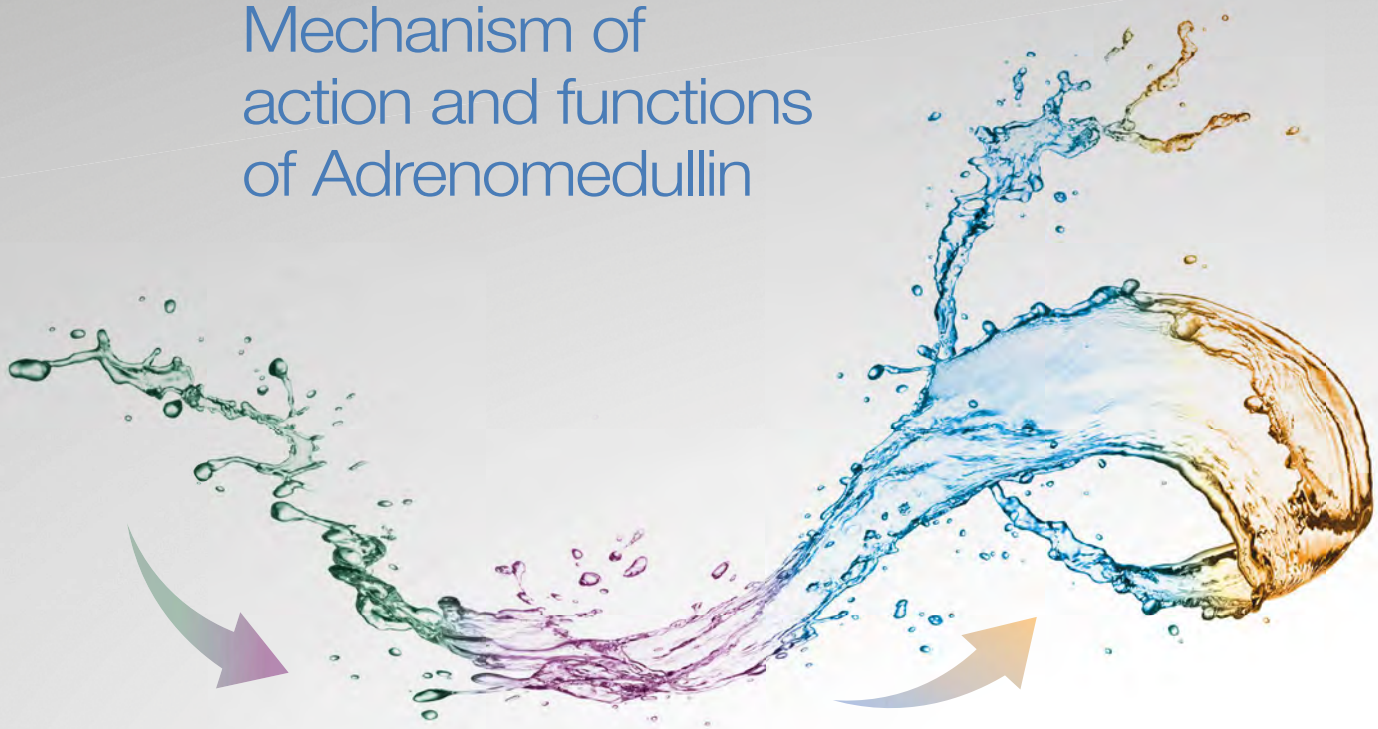


Table 1: Molecules which regulate and are regulated by ADM.

DOWN Adrenomedullin is down-regulated by	DOWN Adrenomedullin down-regulates		UP Adrenomedullin is up-regulated by		UP Adrenomedullin up-regulates
IFN-γ	TNF-α	MIP-2	LPS	Shear stress	IL-10
TGF-β	IL-6	RANTES	TNF-α	IL-1β	
	IL-1β	Serum amyloid A	IL-6	Nitric oxide	
	IL-12		Hypoxia		
	IFN-γ				

Adrenomedullin, present mainly in endothelial and vascular smooth muscle cells[19], can act as both a hormone and cytokine (often termed a "hormokine"[20]) in an autocrine and paracrine manner[21]. Its potent vasodilatory and hypotensive response is elicited through an initial increase in cyclic adenosine monophosphate levels, and a subsequent production of nitric oxide[1, 22, 23].

The importance of adrenomedullin in homeostasis is illustrated by its central role in the up- and down-regulation of cytokines and other mediators (table 1), as well as its own stimulatory and inhibitory[24, 25] effect on cytokine production. Indeed, Interleukin (IL)-1β and tumour necrosis factor (TNF) are two of the most potent stimulators for adrenomedullin production[26] and adrenomedullin itself is up-regulated by hypoxia, bacterial products and sheer stress[20].

The ubiquitous and important functional role of adrenomedullin results in its clinical use in many diverse indications (figure 2). For example, its precursor molecule, MR-proADM, has been shown to be a powerful risk assessment marker in sepsis and lower respiratory tract infections[8, 17, 27, 28], with the ability to predict 30 day mortality regardless of the underlying diagnosis[29], and in the non-specific complaints of elderly patients[30]. Its plasma concentrations have been shown to be elevated in myocardial infarction, and to correlate with the severity of acute and chronic heart failure[31-34], as well as being elevated in various types of glomerulonephritis and progressively increased in patients with chronic renal failure[35, 36].

MR-proADM: Used in a wide range of clinical applications

Cardiac Disorders

- Improved diagnostic discrimination and reclassification of patients with acute coronary syndrome
- Outperforms BNP and NT-BNP in predicting mortality in ED patients with dyspnea after 30 days

ADM levels

- ↑ Contractility
- ↑ Vasodilatation
- ↓ Blood pressure
- ↓ ANP

Kidney Disease

- Greater or comparable precision when determining risk of CKD progression compared to standard GFR measurements
- Fluctuations in creatinine levels due to livestyle, race and antibiotic use might not reflect true changes in GFR, whereas MR-proADM levels more accurately determine progression of CKD

ADM levels

- ↑ Excretion of Na+
- ↑ Urine volume
- ↑ Renal blood flow
- ↓ Synthesis of aldosterone

Lower Respiratory Tract Infections

- Optimize identification of individuals with a high risk of complications
- Accurately determine the most appropriate site of treatment and reduce overall length of stay
- Safely increase out-patient treatment through enhanced discharge management
- Accurately predict short- and long-term mortality

ADM levels

- ↓ Pulmonary hypertension
- ↓ Synthesis of ET-1 and vasoprotective NO

Non-specific complaints

- Significantly reduce evaluation and diagnostic work-up time for elderly patients
- Improve workflow in the ED through safe and rapid triage
- Enhance patient reclassification based on individual risk
- Safely increase patient discharge, reduce admissions and decrease patient time in the ED

Sepsis

- Plays a central role in the hyperdynamic and immunosuppressive phases
- Increased levels in accordance with severity of disease
- Rapid rise in concentration in response to bacterial infection
- Stratifies patients at a high risk of complications and with a poor prognosis for alternative treatment

Figure 2:
Tissue specific functions of Adrenomedullin and different indications applicable to MR-proADM.

Cut-off values:
For more accurate risk assessment and prognosis

Established cut-off values are important to help guide a clinician into making a correct assessment of risk. Healthy individuals have detectable levels of MR-proADM of approximately 0.4 nmol/L, but this value can increase significantly, depending on individual disease conditions. Cut-off values for conditions such as severe sepsis, cardiogenic shock and COPD can be found in figure 3, along with corresponding references.

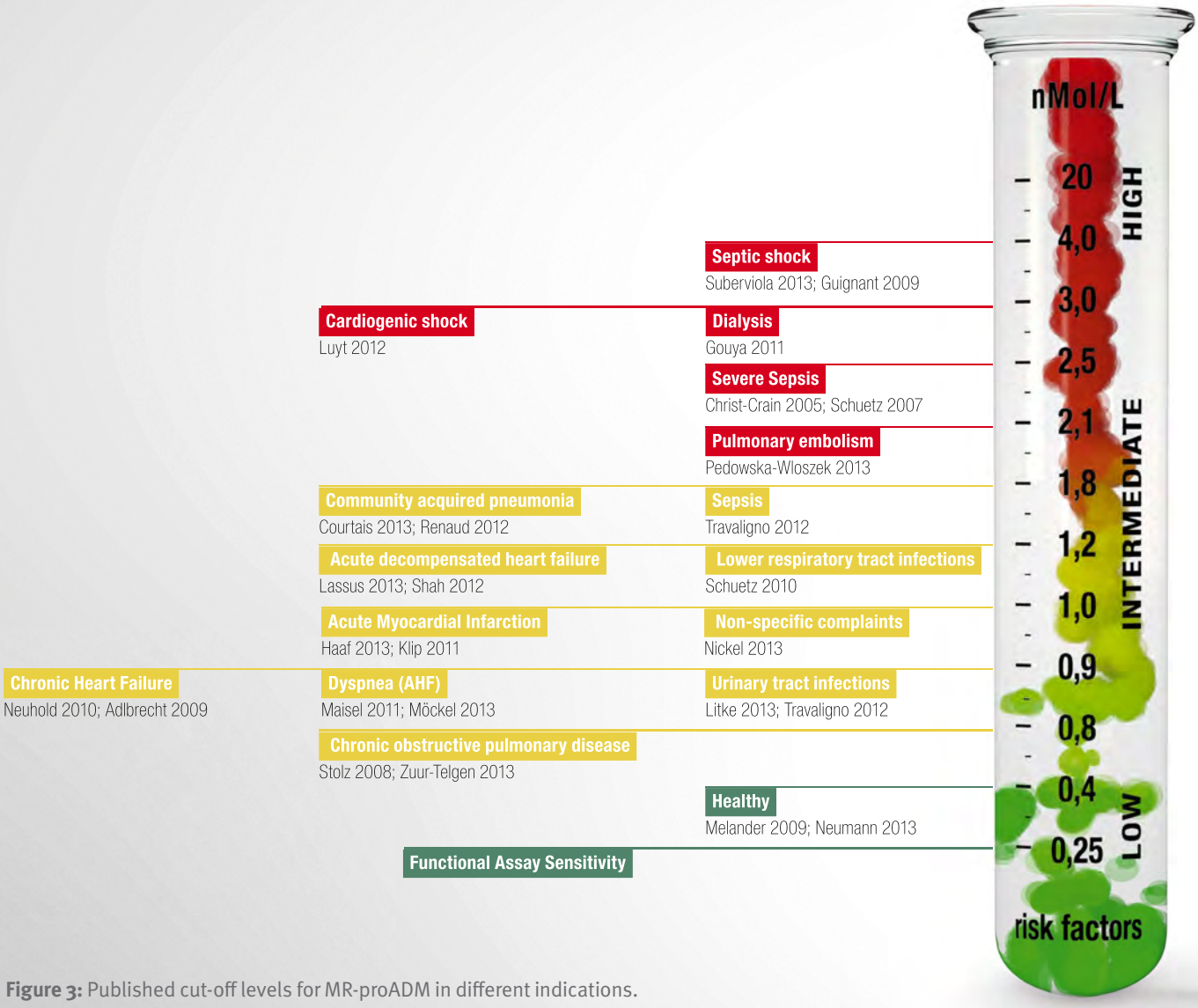


Figure 3: Published cut-off levels for MR-proADM in different indications.

Faster and more accurate patient risk stratification

The combination of established MR-proADM cut-off values with current risk assessment scores offers an easy to use algorithm for the more accurate assessment of a patient's risk of clinical complications, and a greater confidence in determining the most appropriate site of care (figure 4).

Using such an approach, **significantly more patients can be classified as having a low risk of future complications**, leading to an increase in those that can be discharged safely and treated as out-patients[37]. This consequently reduces the financial and resource consumption pressure on the healthcare provider, whilst minimizing any unnecessary clinical complications for the patient through an unwarranted hospital stay.

Furthermore, the addition of MR-proADM not only **more accurately highlights patients who should be classified as an intermediate risk**, through either a decrease or increase in risk severity; but it can also **more accurately highlight those who are at greatest risk of developing complications**, either on admission or throughout their hospital stay. Indeed, studies have shown that using MR-proADM, significant numbers of patients, formerly classified as high risk, can be treated at a lower intensity or even as out-patients[30, 37], thus freeing up precious resources in either the ICU or other high risk settings.

Accordingly, more accurate patient classification due to the addition of MR-proADM can lead to[30, 38]:

- Increased out-patient numbers
- Enhanced discharge management
- Avoiding under-treatment of patients at risk
- Decreased length of stay
- Reduced adverse complications
- Reduced costs

1. Initial Clinical Risk Assessment by ED Physician (ITT)

Combined Risk Assessment		Low Risk	Intermediate Risk	High Risk
2. MR-proADM	Low (< 0.75 nmol/L)	**Low**	**Low**	**Intermediate**
	Intermediate (≥ 0.75 and ≤ 1.5 nmol/L)	**Low**	**Intermediate**	**High**
	High (> 1.5 nmol/L)	**Intermediate**	**High**	**High**

Figure 4: Recommended algorithm for MR-proADM in combination with established clinical risk assessment scores in patients with, for example, non-specific complaints[30].

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