



Thermo Scientific
B-R-A-H-M-S Copeptin proAVP



**Early and Safe rule-out
of myocardial infarction**

Now
recommended in the
2015 ESC
guidelines

Use Copeptin to improve the management of your patients

Combining the markers Copeptin and Troponin allows a safe and rapid rule-out of myocardial infarction at presentation on admission with the first blood draw

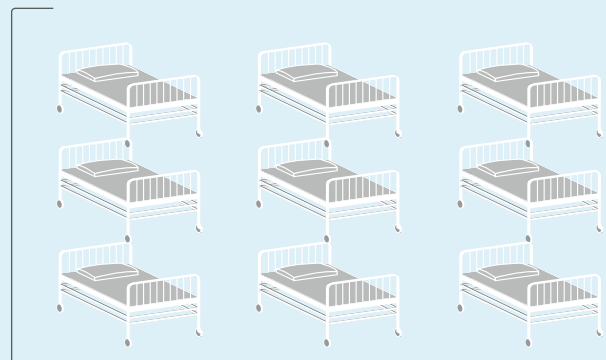
Thermo
SCIENTIFIC

Your clinical need: Safe and early rule-out of chest pain patients with a suspected Acute Coronary Syndrome

In times of overcrowded emergency departments (ED), it is of great importance to effectively allocate the available resources and improve the workflow.



only
ONE
in 10
chest pain patients
has **AMI**



While one in ten patients presents with chest pain in the ED, only about 10 % of the diagnoses in these patients actually reveal myocardial infarctions.¹ Doctors and health care professionals face the challenge of a **safe and fast rule-out** of Acute Myocardial Infarctions (AMI) on a daily basis.

Within patients presenting in the ED with a suspected Acute Coronary Syndrome (ACS), STEMI diagnosis is straightforward while NSTEMI diagnosis requires time and resource-consuming investigations that delay definitive actions. A faster decision on further intervention and adequate patient care can not only save costs and resources by optimising patient management, but also minimise waiting time and unnecessary stress for patients.^{1,2}

Our Solution: Combining Copeptin and Troponin



Combining the biomarkers Thermo Scientific™ B·R·A·H·M·S™ Copeptin proAVP and Troponin, whether conventional or high sensitivity, provides a safe and effective procedure to rule out AMI and better manage overcrowded emergency departments at the first blood sample. Various observational studies reporting negative predictive values higher than 99%^{3,4,5,6} support the sensitivity of the new strategy on a scientific basis.



A meta-analysis of 9244 patients across 14 studies confirms the improvement in sensitivity, Negative Predictive Value (NPV) and negative likelihood ratio for the combination of Copeptin and the initial Troponin in contrast to mere Troponin measurement, whether conventional or high sensitivity.^{6, 7, 8}

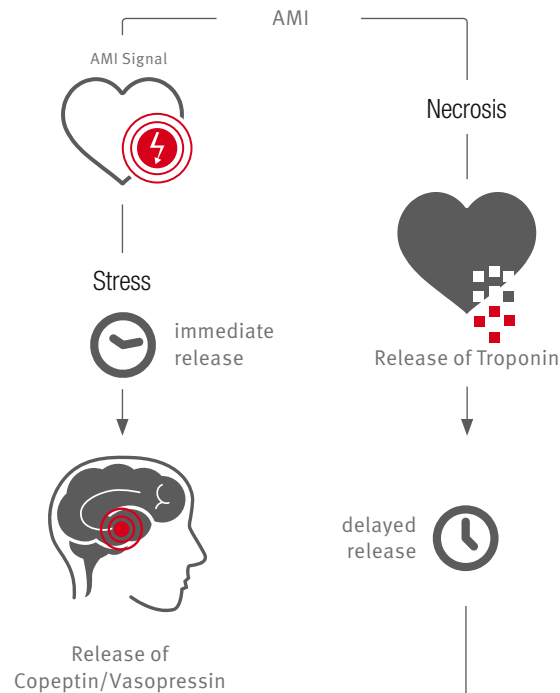
A dual marker strategy combining Copeptin and Troponin benefits from the integration of complementary information provided by pathophysiologically different processes: Copeptin for the quantification of endogenous stress and Troponin for the detection and quantification of myocardial necrosis.

Correlation of Copeptin and AMI

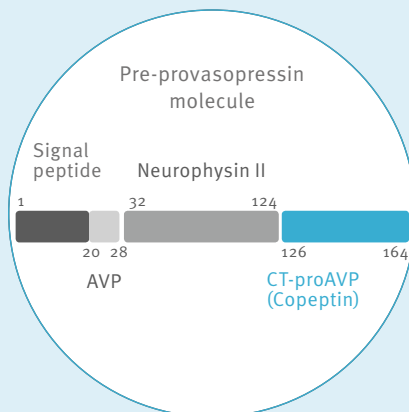
Copeptin, a 39-amino acid glycopeptide, is the C-terminal part of the prohormone of arginine vasopressin (AVP) or antidiuretic hormone (ADH).

The pre-pro-vasopressin precursor is synthesized and processed into its three components - AVP, Neurophysin II and Copeptin- within the hypothalamus; afterwards these products are transported along the neuronal axons in the granules of the posterior hypophysis (pituitary gland), where they are stored and released under appropriate stimulus.

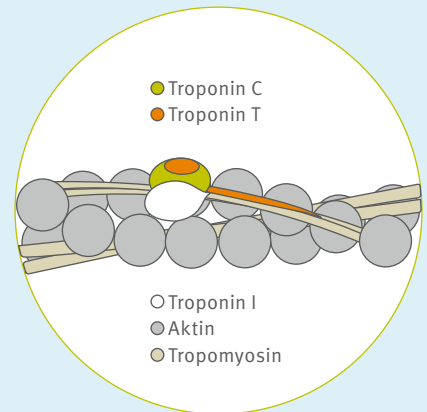
Copeptin is released together with AVP in equimolar amounts but while the measurement of the unstable AVP is prone to pre-analytical errors, Copeptin constitutes a stable surrogate marker for this key hormone in the human body.⁹

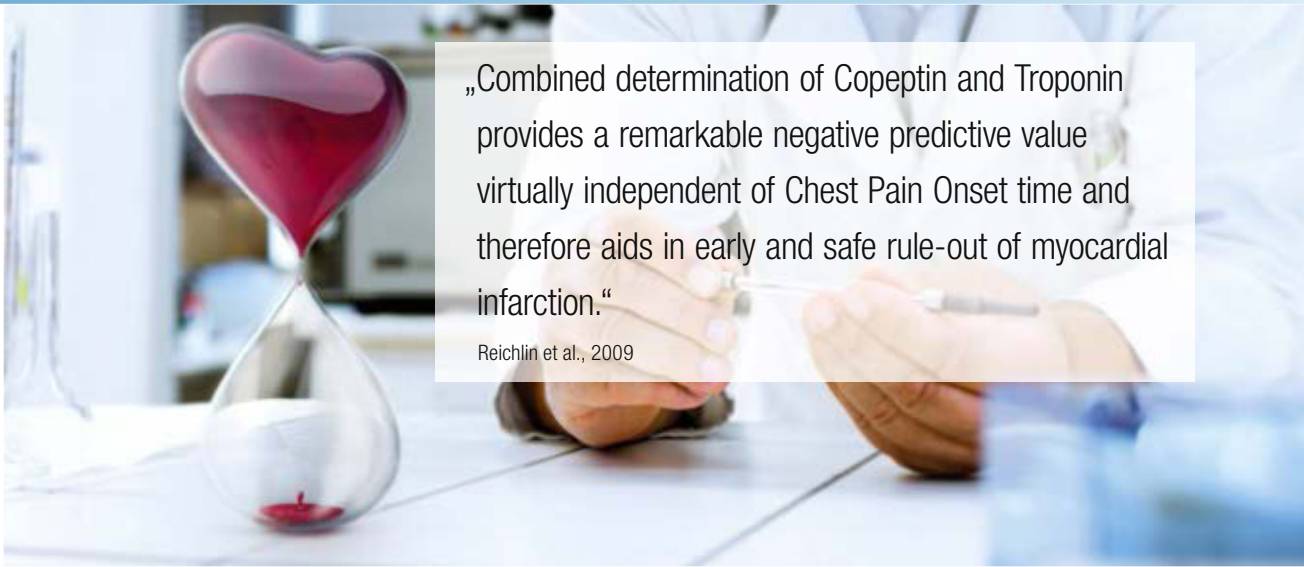


Copeptin test



Troponin test





„Combined determination of Copeptin and Troponin provides a remarkable negative predictive value virtually independent of Chest Pain Onset time and therefore aids in early and safe rule-out of myocardial infarction.“

Reichlin et al., 2009

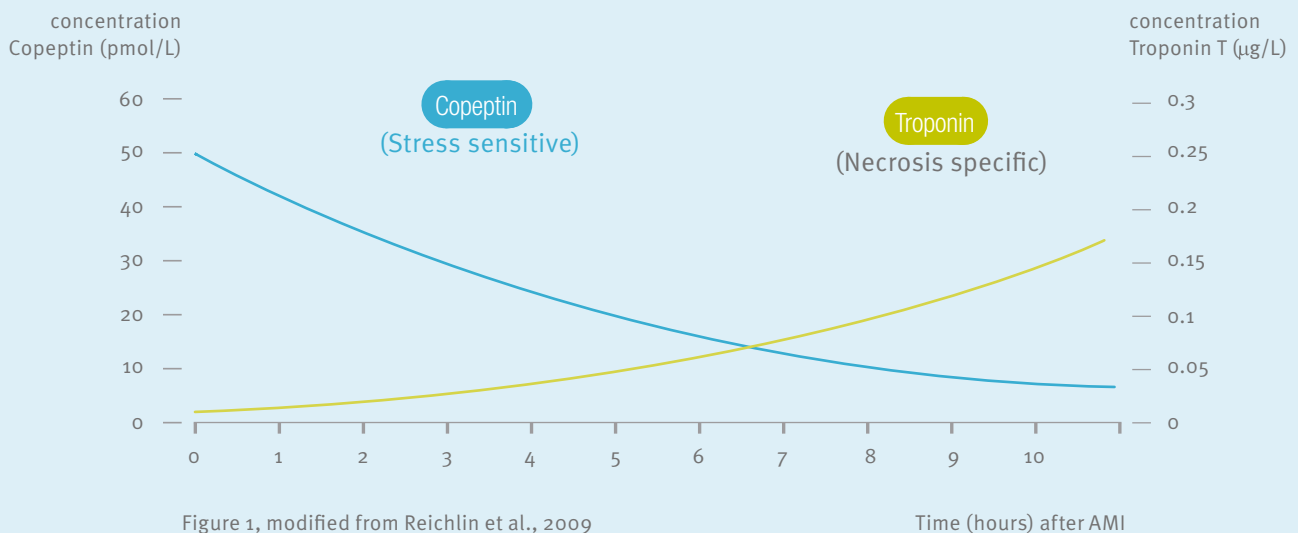
After an acute MI, the circulating Copeptin levels rapidly rise to peak values and decline over the next hours (see Figure 1). This has been also demonstrated in a study that analyzed the release kinetics of Copeptin in patients with a model of AMI.^{4,10}

The strength of a strategy combining Copeptin and Troponin can be found in the very early rule-out of

myocardial infarction with a single blood draw, since Copeptin and Troponin should cover all time frames after the acute event.

The suggested Copeptin cut-off to minimize the number of false-negative patients and obtain the highest NPV for the diagnosis of AMI is 10 pmol/L.^{10,11}

Copeptin and Troponin act complementary Sensitive and specific marking for early diagnosis of AMI



BIC-8 study

Integrating the biomarker Copeptin into standard process

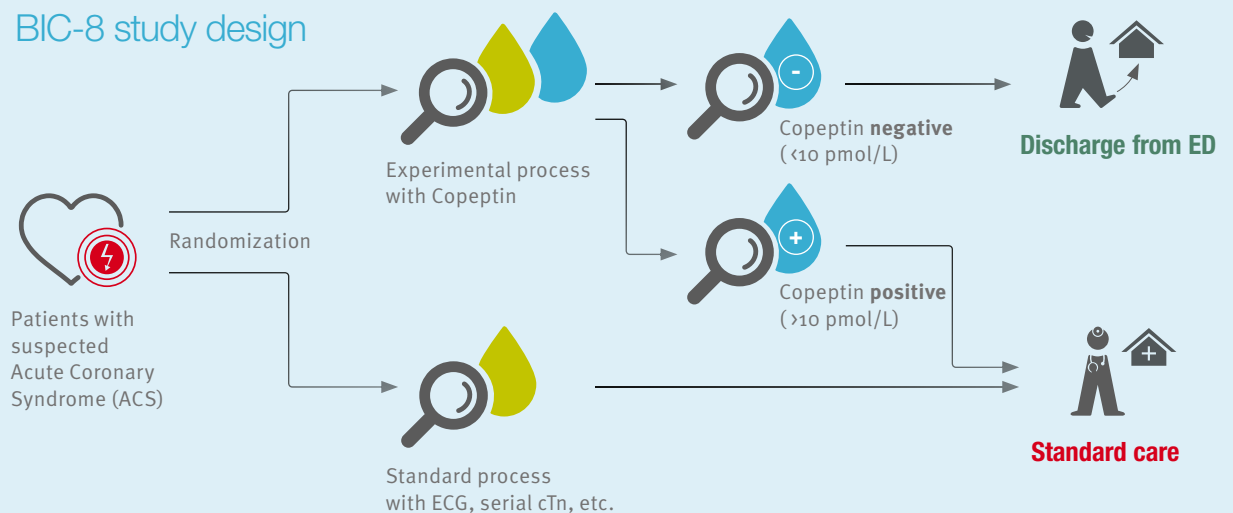
„Thanks to the Copeptin biomarker, clinics can better manage overcrowded Emergency Departments ... We have implemented a new algorithm using Copeptin and Troponin at the ED at the Charité now that our study has been published.“

Principal investigator Prof. Martin Möckel
(Department of Cardiology, Charité University Clinic, Berlin)

The Biomarkers in Cardiology (BIC)-8 study is the first interventional clinical trial in the cardiac biomarker field and it confirms the safety and efficacy of the combined use of Copeptin and Troponin in patients with ACS.¹² In this prospective multicentre study, 902 patients with negative results after Troponin testing were initially sampled. In the experimental arm (n=451), patients with a negative Copeptin

test result (less than 10 pmol/L) were eligible for discharge to ambulant care after a final clinical assessment with an outpatient visit scheduled within 72 hours, while those with a positive Copeptin test received standard treatment. Patients in the standard arm (n=451) were treated according to current guidelines; their Copeptin results were not made available to treating staff.

BIC-8 study design



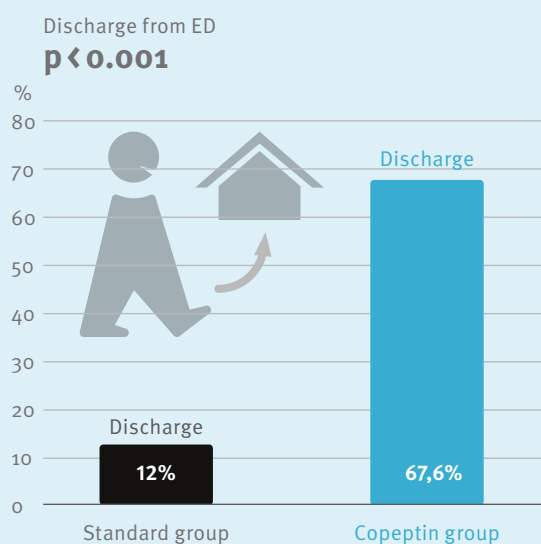
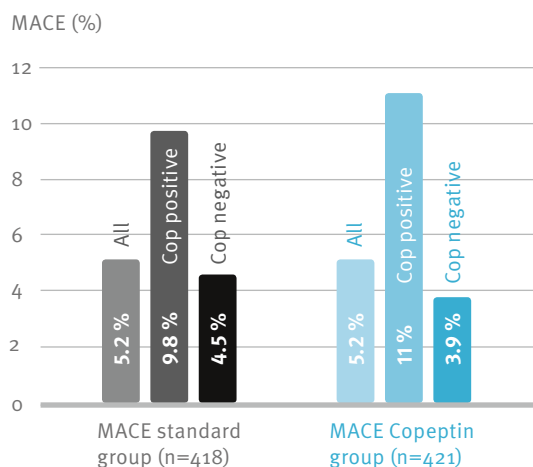
„Möckel and colleagues should be commended, as their study represents the first randomized controlled trial examining Copeptin and Troponin, an extremely important endeavour that is necessary to bridge the gap towards changing practice.”

Gandhi PU and Januzzi JL, European Heart Journal 2014¹³



In the assessment of Major Adverse Cardiac Events (MACE) within 30 days, the incidence was similar in the two groups (5.2% in the standard process vs. 5.2% in the experimental group). This noninferiority design ascertains the safety of integrating Copeptin into the process of managing patients with suspected Acute Cardiac Syndrome.

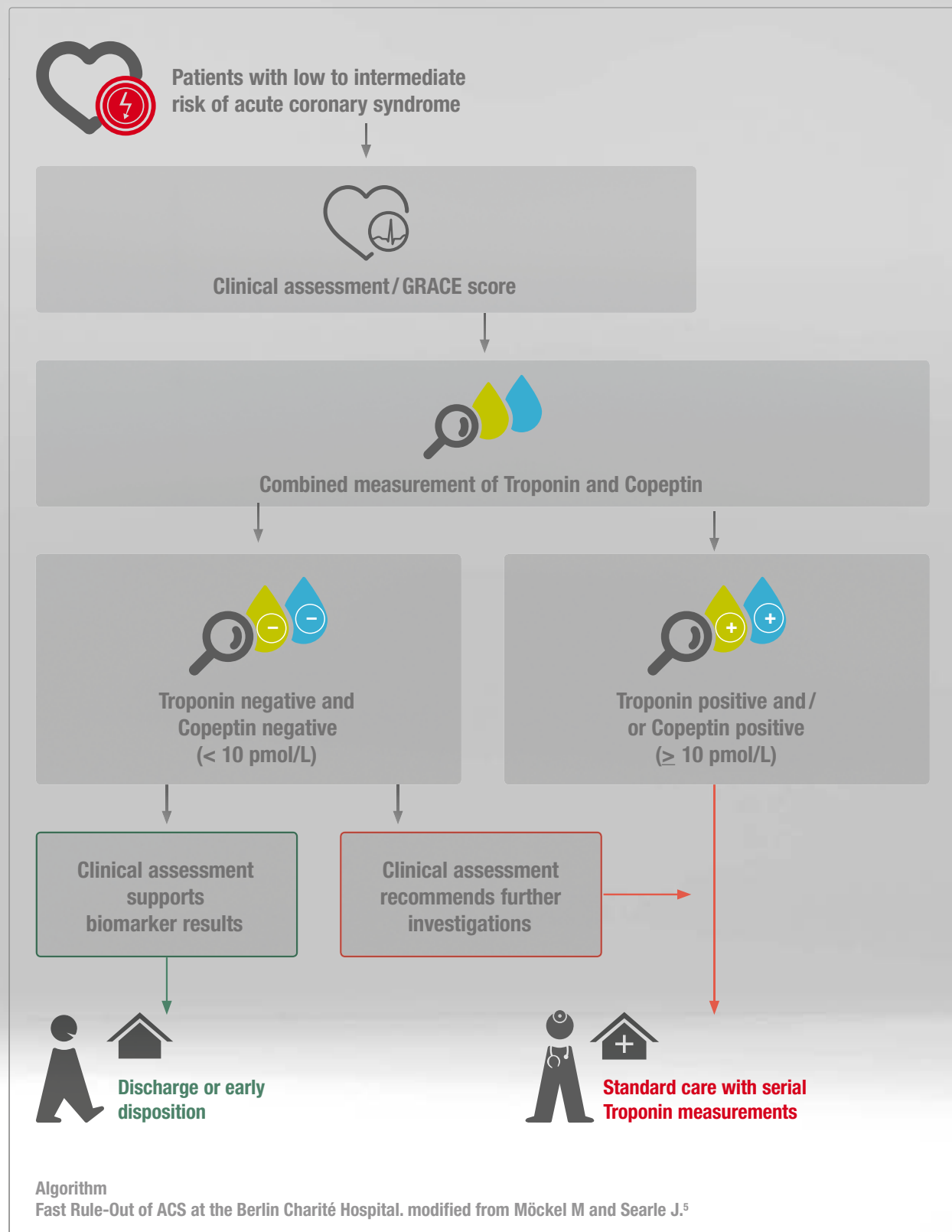
MACE proportions in the two study groups and Copeptin subgroups. Patients were randomized into Copeptin and standard group, where MACE proportions were very similar. In subgroups of Copeptin positive and Copeptin negative patients, MACE rates are higher in Copeptin positives; this suggests a prognostic value for positive Copeptin. While MACE events are lower in discharged Copeptin negative patients.



Discharge from the Emergency Department

Including Copeptin into the diagnostic process significantly improves patient management in the ED; while maintaining the same safety levels as in the standard procedure, combining Copeptin and Troponin enables higher discharges rates in the Emergency Departments (67.6% vs. 12%, $p < 0.001$).

How to use Copeptin to exclude patients from Acute Myocardial Infarction





save
at least **3**
HOURS

„The combined use of Copeptin and Troponin in patients with suspected acute coronary syndrome avoids the need for prolonged clinical monitoring and serial blood sampling in the majority of patients, with a consequent saving of resources.“

C. Domenico et al., 2013¹⁴

Save time and costs by integrating Copeptin in your standard diagnostic process

As revealed by the BIC-8 study and by other prospective studies,^{3,4,5,14} integrating Copeptin into the diagnostic process can shorten the patients' time in the emergency department by at least 3 hours. An earlier rule-out will not only improve the workflow and save costs in the health system, but also increase patient satisfaction. Considering that overcrowding in the emergency departments leads to a worse clinical outcome², the combined determination of both markers within a single blood draw can safely shorten the length of the stay in the ED and has the potential to change the clinical practice.

The favorable cost-benefit ratio for the combined assessment has recently corroborated this new procedure.¹⁴ A shorter length of stay and a more efficient use of resources for discharged patients avoids the need for prolonged clinical monitoring in low-to intermediate-risk patients with ACS. Circumventing serial ECG and Troponin tests, Copeptin simplifies the available strategy to rule-out AMI and makes it potentially more cost-effective.

Copeptin and Troponin strategy: Fast. Effective. Safe...

...Guideline Recommended

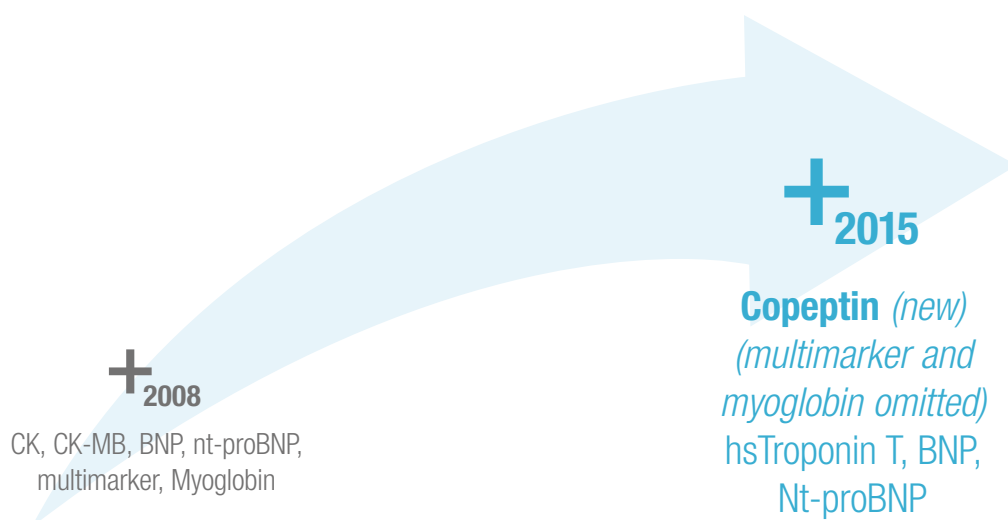


Table 1: Laboratory Value (cardiac). Modified from Post et al., 2015¹⁹

Faster Rule-Out of AMI

- Combined testing of Copeptin and Troponin allows a rapid rule-out and discharge of patients with suspected ACS from the ED.

Safe rule-out of AMI, as demonstrated in the BIC-8 interventional study

- Proved non-inferior safety compared to the conventional approach.
- The use of a single combined Copeptin and Troponin test at presentation can support a safe discharge process in low to intermediate risk patients presenting with suspected ACS.

Optimize resource allocation and processes

- Increase the patients' turnaround in the ED while reducing the need of subsequent diagnostic tests.

Optimize Patient Management in the ED

- Faster diagnosis can increase patient well-being, since unnecessary patient stress, anxiety and other risks associated with hospitalization can be avoided.

Better risk stratification

- Copeptin levels provide valuable predictive information for risk stratification and intermediate-term outcome in patients with Acute Cardiac Syndrome. In conjunction with the GRACE score, the Copeptin biomarker provides a more accurate identification of individuals at high risk.^{12, 15, 16, 17}

Copeptin in the Guidelines

- The use of Copeptin is now recommended in the 2015 ESC guidelines for the management of patients with suspected ACS and in the Criteria of the German Society of Cardiology for the establishment of chest pain units (Table 1)¹⁸



Product name	Copeptin proAVP KRYPTOR
Available on	B·R·A·H·M·S KRYPTOR compact PLUS
Assay format	Automated immunofluorescent assay (KRYPTOR)
Technology	Time Resolved Amplified Cryptate Emission (TRACE)
Direct measurement	0.7...500 pmol/L
Measuring range with automatic dilution	0.7...2000 pmol/L
Functional assay sensitivity (FAS)	<1.08 pmol/L
Detection limit	0.69 pmol/L
Incubation time	14 minutes
Sample volume	50 µL
Sample type	Serum, plasma (EDTA, heparin)
Determinations	50
Article number	857.050

References

- Möckel et al., Eur Heart J. 2015 Feb 7;36(6):369-76
- Guttmann A et al., BMJ 2011;342:d2983
- Reichlin T et al., J Am Coll Cardiol. 2009; 54(1):60-8.
- Keller T et al., J Am Coll Cardiol. 2010; 55(19):2096-2106.
- Maisel A, et al., J Am Coll Cardiol. 2013; 62(2):150-160
- Lipinski MJ., et al. Am J Cardiol 2014;113:1581e1591
- Giannitsis E et al., Clin Chem 2011;57(10):1452–1455
- Sebbane M et al., Am J Emerg Med. 2013;31(9):1302-8
- Morgenthaler NG et al., Clin Chem 2006;52:112–119
- Liebetrau C et al., Clin Chem 2013;59(3):566-569
- Möckel M et al., Curr Atheroscler Rep 2014: 16:421
- Möckel M et al., Eur Heart J 2014: DOI:10.1093/eurheartj/ehu178
- Gandhi PU et al., Eur Heart J 2014 doi:10.1093/eurheartj/ehu211
- Domenico C et al., LigandAssay 2013;18 (1):68-72
- Khan SQ et al, Circulation. 2007;115:2103-2110
- Potocki M et al., Heart 2012; 98: 558-565
- von Haehling S et al., Int J Cardiol. 2012;162(1):27-32
- Roffi et al., Eur Heart J. 2015 Aug 29; doi: <http://dx.doi.org/10.1093/eurheartj/ehv320>
- Post F. et al., Clin Res Cardiol, 2015: DOI 10.1007/s00392-015-0888-2
- Van de Werf F. and Crea F., Eur Heart J. 2015 Feb 7;36(6):342-6a
- Marston and Maisel, Expert Rev Cardiovasc Ther. 2014 Oct;12(10):1237-42.



Use Copeptin in combination with Troponin as recommended in the cardiology guidelines to:

- Early and safely rule-out AMI, as demonstrated in the BIC-8 interventional trial
- Optimize resource allocation and processes at the hospital level
- Optimize Patient Management in the ED
- Stratify risks better

thermoscientific.com

© 2015 Thermo Fisher Scientific Inc. All rights reserved.

KRYPTOR is a registered trademark of CIS bio international, licensed for use by B-R-A-H-M-S, a part of Thermo Fisher Scientific. All other trademarks are the property of Thermo Fisher Scientific and its subsidiaries. All data regarding specifications, terms and pricing correspond to the existing knowledge at the time of the printing. We are not responsible for any errors, misprints or changes. Reprint, also in parts, solely with prior written consent of B-R-A-H-M-S GmbH.

Thermo Fisher Scientific products are distributed worldwide; not all are intended uses and applications mentioned in this printing are registered in every country.

The manufacture and/or use of this product is covered by one or more of the following patents: CN200580021434, CN101600967, CN2007800452789, CN2011103593804, EP1738178, EP2089718, HK101016419, IN224950, JP4932714, JP5320294, JP5340160, MX262195, US7807397, US12447105, US8158368

Clinical Diagnostics

Thermo Fisher Scientific
B-R-A-H-M-S GmbH
Neuendorfstr. 25
16761 Hennigsdorf
Deutschland

www.thermoscientific.com/brahms
www.thermoscientific.com/copeptin

+49 (0)3302 883 0
+49 (0)3302 883 100 fax
info.brahms@thermofisher.com

Thermo
SCIENTIFIC

A Thermo Fisher Scientific Brand