

**Study details on the interventional trial BIC-8**

“Early discharge using single cardiac troponin and copeptin testing in patients with suspected acute coronary syndrome (ACS): a randomized, controlled clinical process study”

Eur Heart J. 2015 Feb 7; 36(6): 369–376.

<b>Study type</b>	Multicenter, multinational, prospective, randomized, controlled interventional		
<b>Interventional study definition</b>	Study determining interventions’ effect on patient outcomes, since patient management in the study is guided by the interventions being assessed.		
<b>Study design (figure A1)</b>	Non-inferiority safety study: Non-inferiority of Copeptin + Tn strategy vs. conventional evaluation proven if CI excluded a pre-specified >5% absolute difference in 30-day MACE rates (link to “MACE = any of death from any cause, survived sudden cardiac arrest, rehospitalization for ACS, acute unplanned PCI, CABG, documented life-threatening arrhythmias.”) favoring conventional evaluation		
<b>Rationale for non-inferiority study design</b>	Conventional patient evaluation including serial Tn testing is considered very safe.		
<b>Endpoints:</b>	Primary endpoint: 30-day MACE rate (link to “MACE = any of death from any cause, survived sudden cardiac arrest, rehospitalization for ACS, acute unplanned PCI, CABG, documented life-threatening arrhythmias.”). Secondary endpoints included ED discharge rate, hospital and ED/CPU lengths-of-stay.		
<b>Patients</b>	902 low-intermediate-risk (GRACE score $\leq 140$ ) adult patients presenting at ED or CPU with ACS signs and symptoms, but negative initial Tn and normal ECG (i.e., STEMI patients excluded)		
<b>Setting</b>	7 sites of 6 centers in Germany, Austria, Switzerland		
<b>Study arms</b>	2 arms: Copeptin arm vs. conventional evaluation arm		
<b>Copeptin arm</b>	2 arms: Copeptin arm vs. conventional evaluation arm <ul style="list-style-type: none"> <li>- Copeptin as well as Tn measured in initial blood draw</li> <li>- Treating physicians aware of Copeptin data</li> <li>- Patients with Copeptin</li> <li>- Before discharge, patients always received a final clinical assessment</li> <li>- Patients were discharged with an outpatient cardiologist appointment scheduled within 3 days</li> <li>- Patients with Copeptin <math>\geq 10</math> pmol/L underwent conventional evaluation with serial Tn testing</li> </ul>		
<b>Conventional evaluation arm</b>	<ul style="list-style-type: none"> <li>- Copeptin as well as Tn measured in initial blood draw</li> <li>- Treating physician NOT aware of Copeptin data</li> <li>- Per state-of-the-art ACS management guidelines, patients with negative initial Tn waited in ED and underwent serial Tn testing</li> </ul>		
<b>Copeptin assay</b>	Thermo Scientific B·R·A·H·M·S Copeptin us KRYPTOR		
<b>Copeptin cut-off</b>	10 pmol/L		
<b>Tn assay</b>	Tn assays used in institutional routine: <ul style="list-style-type: none"> <li>- 4 sites: high sensitivity assay</li> <li>- 2 sites: POC assay and 1 site: contemporary sensitive assay</li> </ul>		
<b>Tn cut-off</b>	Cut-offs used in institutional routine: Highly sensitive assay: 14 ng/L Contemporary sensitive assay: 2 sites, 30 ng/L; 1 site, 56 ng/L at study start, 45 ng/L later in study		
<b>30-day patient outcomes</b>	Outcome	Copeptin arm (n=451)	Conventional arm (n=451)
	Free of MACE	422	422
	MACE	23	23
	Unknown	23	23

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; CI = confidence interval; CPU = chest pain unit; ED = emergency department; IQR = interquartile range (25th– 75th percentile); MACE = major cardiovascular adverse event; POC = point-of-care; PCI = percutaneous coronary intervention; Tn = Troponin

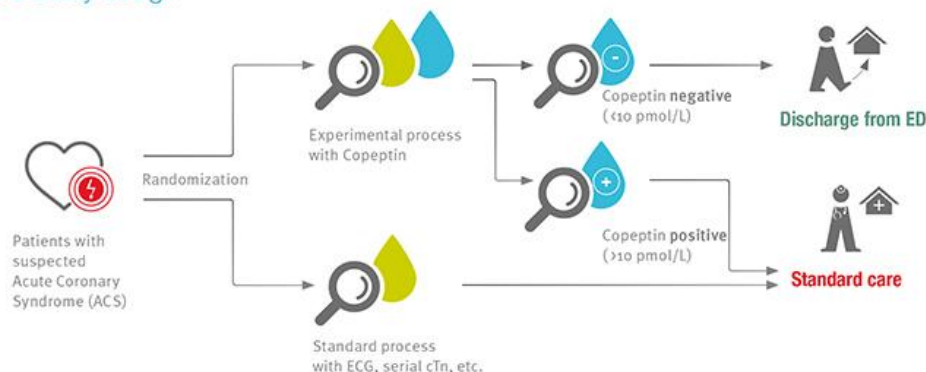
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<b>Key safety findings</b>	<p>* Copeptin arm achieved primary endpoint of non-inferior safety to that of conventional process:</p> <ul style="list-style-type: none"> <li>– 5.19% vs. 5.17% MACE rates in intention-to-treat analysis; actual 0.02%, “statistical worst-case” (i.e., according to one-sided 97.5% confidence interval of absolute difference in MACE rates in the intention-to-treat analysis) 2.94% differences favoring conventional arm</li> <li>– 3.01% vs. 5.34% MACE rates in per-protocol analysis; actual 2.33% difference favoring Copeptin arm, “statistical worst-case” (i.e., according to one-sided 97.5% confidence interval of absolute difference in MACE rates in the per-protocol analysis) 0.46% difference favoring conventional arm</li> <li>– Results confirmed by all 4 sensitivity analyses performed</li> <li>– No 30-day mortality was seen in the Copeptin arm</li> </ul>
<b>Key efficacy findings</b>	<p>Copeptin arm had significantly (P 0.001):</p> <ul style="list-style-type: none"> <li>– Higher ED discharge rate: 67.6% (305/451) vs. 12.0% (54/451)</li> <li>– Shorter median hospital length-of-stay: 4 hr vs. 7 hr</li> <li>– Shorter median ED/CPU length-of-stay: 4 hr vs. 7 hr</li> </ul>
<b>Clinical implications</b>	<p>Rapid AMI rule-out with a single Copeptin + Tn determination at presentation more often allows early discharge and decreases length-of-stay while preserving safety in low- intermediate-risk patients with symptoms suggesting AMI</p>

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**BIC-8 study design**



Biomarkers in Cardiology-8 (BIC-8) study design.

Note: adapted from Prof. Dr. Möckel, Hot Line Session IV, ESC 03.09.2013.

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