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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.

Study type	Multicenter, multinational, prospective, randomized, controlled interventional		
Interventional study definition	Study determining interventions' effect on patient outcomes, since patient management in the study is guided by the interventions being assessed.		
Study design (figure A1)	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		
Rationale for non-inferiority study design	Conventional patient evaluation including serial Tn testing is considered very safe.		
Endpoints:	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.		
Patients	902 low-intermediate-risk (GRACE score ≤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)		
Setting	7 sites of 6 centers in Germany, Austria, Switzerland		
Study arms	2 arms: Copeptin arm vs. conventional evaluation arm		
Copeptin arm	2 arms: Copeptin arm vs. conventional evaluation arm – Copeptin as well as Tn measured in initial blood draw – Treating physicians aware of Copeptin date – Patients with Copeptin – Before discharge, patients always received a final clinical assessment – Patients were discharged with an outpatient cardiologist appointment scheduled within 3 days – Patients with Copeptin ≥10 pmol/L underwent conventional evaluation with serial Tn testing		
Conventional evaluation arm	– Copeptin as well as Tn measured in initial blood draw – Treating physician NOT aware of Copeptin data – Per state-of-the-art ACS management guidelines, patients with negative initial Tn waited in ED and underwent serial Tn testing		
Copeptin assay	Thermo Scientific B·R·A·H·M·S Copeptin us KRYPTOR		
Copeptin cut-off	10 pmol/L		
Tn assay	Tn assays used in institutional routine: – 4 sites: high sensitivity assay – 2 sites: POC assay and 1 site: contemporary sensitive assay		
Tn cut-off	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		
30-day patient outcomes	Outcome Free of MACE MACE Unknown	Copeptin arm (n=451) 422 23 23	Conventional arm (n=451) 422 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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Key safety findings	* Copeptin arm achieved primary endpoint of non-inferior safety to that of conventional process: – 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 – 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 – Results confirmed by all 4 sensitivity analyses performed – No 30-day mortality was seen in the Copeptin arm
Key efficacy findings	Copeptin arm had significantly (P 0.001): – Higher ED discharge rate: 67.6% (305/451) vs. 12.0% (54/451) – Shorter median hospital length-of-stay: 4 hr vs. 7 hr – Shorter median ED/CPU length-of-stay: 4 hr vs. 7 hr
Clinical implications	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

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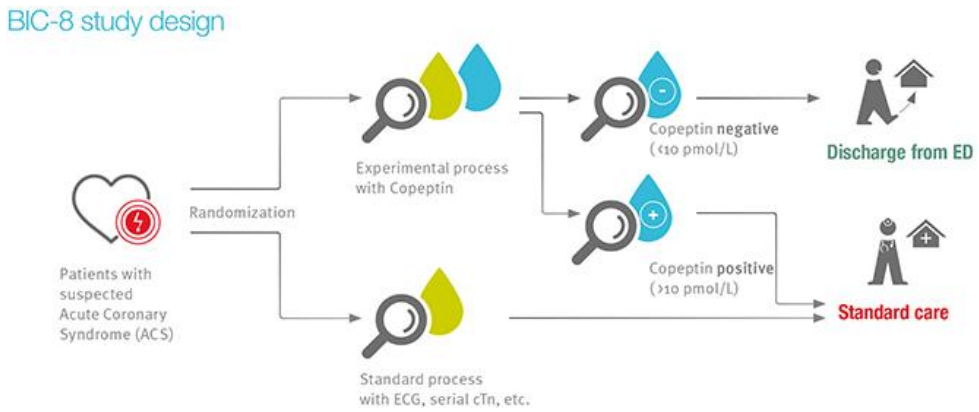

Biomarkers in Cardiology-8 (BIC-8) study design.
Note: adapted from Prof. Dr. Möckel, Hot Line Session IV, ESC 03.09.2013.

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