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

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Aims	This randomized controlled trial (RCT) evaluated whether a process with single combined testing of copeptin and troponin at admission in patients with low-to-intermediate risk and suspected acute coronary syndrome (ACS) does not lead to a higher proportion of major adverse cardiac events (MACE) than the current standard process (non-inferiority design).
Methods and results	A total of 902 patients were randomly assigned to either standard care or the copeptin group where patients with negative troponin and copeptin values at admission were eligible for discharge after final clinical assessment. The proportion of MACE (death, survived sudden cardiac death, acute myocardial infarction (AMI), re-hospitalization for ACS, acute unplanned percutaneous coronary intervention, coronary artery bypass grafting, or documented life threatening arrhythmias) was assessed after 30 days. Intention to treat analysis showed a MACE proportion of 5.17% [95% confidence intervals (CI) 3.30–7.65%; 23/445] in the standard group and 5.19% (95% CI 3.32–7.69%; 23/443) in the copeptin group. In the per protocol analysis, the MACE proportion was 5.34% (95% CI 3.38–7.97%) in the standard group, and 3.01% (95% CI 1.51–5.33%) in the copeptin group. These results were also corroborated by sensitivity analyses. In the copeptin group, discharged copeptin negative patients had an event rate of 0.6% (2/362).
Conclusion	After clinical work-up and single combined testing of troponin and copeptin to rule-out AMI, early discharge of low- to intermediate risk patients with suspected ACS seems to be safe and has the potential to shorten length of stay in the ED. However, our results need to be confirmed in larger clinical trials or registries, before a clinical directive can be propagated.
Keywords	Copeptin • Acute coronary syndrome (ACS) • Rule-out • Acute myocardial infarction (AMI) • Randomized controlled trial (RCT)

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Introduction

Rule-out of acute myocardial infarction (AMI) is a major challenge in Emergency Medicine. Around 10% of all internal medicine emergency patients present to the Emergency Department (ED) with chest pain, but only ~10% of these patients have an AMI as the underlying disease.[1] Due to the potential hazards of overseeing an evolving MI, most patients are subjected to 6–12 h observation on chest pain units (CPU) with the effect of an excellent prognosis at high costs.[2,3]

Copeptin (CT-pro-vasopressin) is a marker of acute (haemo-dynamic) stress[4] and is elevated immediately at presentation of patients with AMI.[5] A series of observational studies have shown that due to complementary pathophysiology and kinetics, copeptin in combination with conventional and high sensitivity (hs) cardiac troponin (cTn) is an excellent rule-out marker for AMI[5–11] with a high negative predictive value (NPV) of up to 99%. Some studies were not able to reproduce this high NPV[12,13] or to show an added value when copeptin was combined with hsTn.[14,15] These results could partially be influenced by late copeptin testing,[12] which impacts the ability to detect an early copeptin rise, by late patient presentation or by the selection of patient cohorts including high-risk patients. These factors would lead to a higher prevalence of positive hsTn test results at presentation, thus increasing the NPV for hsTn alone. Additionally, most studies used a copeptin assay which did not allow choosing a cut-off below 14 pmol/L.

So far, it has not been prospectively tested whether patients with negative copeptin and troponin test results can safely be discharged to outpatient care. The instant rule-out of AMI has a potentially high impact on future clinical practice, but safety of this strategy has to be assured.

We conducted a randomized controlled trial (RCT) to assess the safety of an early discharge after rule-out of AMI with a single combined testing of troponin and copeptin at presentation to the ED/CPU when compared with the current standard process with serial troponin measurements in low-to-intermediate risk patients with suspected acute coronary syndrome (ACS). The primary endpoint was the proportion of major adverse cardiac events (MACE) at 30 days, including events during the index stay. Given that the current process of evaluating patients with ACS is regarded as very safe, a non-inferiority design was chosen to test the hypothesis.

Methods

Participants

This is a multi-centre, interventional clinical process RCT. The methods are reported in full in the protocol (notfallmedizin.charite.de/forschung_lehre/nord_campi/forschung/biomarkers_in_cardiology/). Participants were recruited in the EDs and/or CPUs in five German, one Swiss, and one Austrian site from April 2011 until May 2013. Patients were eligible if they were aged ≥18 years, presented with signs and symptoms of ACS, and had a negative troponin value at presentation. Patients were excluded if they were diagnosed with ST-elevation myocardial infarction (STEMI), if hospital admission was indicated due to high risk as defined in current guidelines (continuing chest pain or recurrent episodes of chest pain under therapy, GRACE score above 140), and if hospital admission was necessary for any other reasons.

The study complies with the Declaration of Helsinki and received ethics approvals from all study sites' ethics committees. All patients provided written informed consent. The study is registered at the German Clinical Trials Register (DRKS00000276), the International Clinical Trials Registration platform of the WHO (UTN U1111-1118-1665), and at ClinicalTrials.gov (NCT0149873).

Procedures

Patients were enrolled by the treating physician and randomized using 1:1 computer-generated block randomization stratified by centre (DatInf® RandList, DatInf GmbH, Tübingen). Copeptin was measured from the same initial blood draw as the first troponin value after written informed consent and randomization.

In the standard group, patients were managed according to the current guidelines for the management of patients with suspected ACS. The copeptin values were measured but not revealed to the treating staff to assure standard care.

In the copeptin group, further patient management was dependent on the copeptin result. In case of a negative result, patients were considered low risk and could be discharged into ambulant care. Before discharge, patients had a final visit to secure their well-being. The final discharge decision was at the discretion of the attending physician who was allowed to overrule the biomarker result. All discharged patients had an outpatient cardiology appointment within a maximum of 3 days after discharge. In case of a positive copeptin result, patients were managed like the standard group.

All patients were contacted at 30 days to assess their outcome (Supplementary material online, *Figure S1*).

Outcome

Primary endpoint was the proportion of combined MACE, defined as all-cause death or survived sudden cardiac death, AMI, re-hospitalization for ACS, acute unplanned percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and documented life-threatening arrhythmias (ventricular tachycardia, ventricular fibrillation, atrio-ventricular-block III) within 30 days, including events during the index hospital stay.

Acute myocardial infarction was defined as per Universal Definition.[16] Every patient was assigned only one MACE with priority of the event that occurred first.

Secondary endpoints were proportion of coronary angiography (CA), split MACE at 30 and all MACE at 90 days, major bleeding events (as per TIMI definition), and length of stay (LOS).

All MACE and bleeding events were adjudicated by two independent Cardiologists blinded to copeptin result and group assignment.

Biomarker testing

Copeptin was measured from the routine blood sample at admission, using the Thermo Scientific B·R·A·H·M·S Copeptin ultrasensitive Kryptor assay. The assay has a detection limit of 0.9 pmol/L and a functional assay sensitivity of <2 pmol/L. A value of 10 pmol/L and above was considered positive. The cut-off was chosen with reference to Keller *et al.*[5] who determined different cut-offs in a reference population and tested the diagnostic performance of these cut-offs in an ACS population.

Troponin was tested as by routine practice at the individual sites. A conventional troponin T (TnT) POCT assay (AQT 90 -Radiometer) was used at two sites (cut-off >30 ng/L).

High-sensitive TnT (Roche) was used at four sites for all and at two sites for further serial troponin measurements (cut-off >14 ng/L). One site used troponin I (Siemens Dimension®-System) (cut-off level 56 ng/L)

until November 2012 and troponin I (Siemens Dimension Vista®-System) thereafter (cut-off level 45 ng/L).

Additional blood samples were drawn as per standard practice after 3−6 h.

Statistical analysis

All data were entered into an online electronic case report form. Statistical analyses were performed using the software packages SPSS (IBM® SPSS Statistics, Version 21) and SAS Version 9.3 (SAS® Institute Inc.).

Statistical testing of categorical variables was performed using exact binomial tests; for numerical variables, t-tests (in case of normal distribution) or Wilcoxon tests (no normal distribution) were used. For the comparison between more than two groups, Kruskall−Wallis test was used. A P-value below 0.05 was considered significant.

The study hypothesis was non-inferiority of the copeptin process against the standard process regarding the primary endpoint. The power calculation was based on an anticipated proportion of MACE within 30 days of 10%.[17−19] Confidence intervals (CI) for differences were calculated as one-sided 97.5% CI using the Wilson procedure with a correction for continuity.[20] The non-inferiority margin was set at 5%. Note: This means, that non-inferiority of the new process can be accepted if the lower bound of the one-sided 97.5% CI of MACE difference between both study groups does not exceed the 5% margin. The rationale for this margin was based on own data, previous studies, and expert consensus. The sample size calculation resulted in a required number of 446 participants per group (892 overall) with a power of 80% and a level of significance of 5%.

In the intention to treat (ITT) analysis for the primary endpoint, all patients were analysed as randomized irrespective of protocol deviations, excluding all patients with an unknown outcome.

In the per protocol (PP) analysis, all patients with protocol deviations (n = 40), over-rulers (n = 71), as well as patients with unknown outcome (n = 14) were excluded. Additionally, sensitivity analyses, assuming that all patients who were lost to follow-up (FU) (n = 14) developed either a good (no MACE) or a poor (MACE) outcome, were conducted. Patients with protocol deviations were not excluded from this sensitivity analysis and were analysed as randomized. Confidence intervals for the primary endpoint were calculated as exact binomial 95% CIs.

Results

Patient characteristics

A total of 902 patients were randomized to either the standard (n = 451) or the copeptin (n = 451) group (Figure 1). Randomisation proved successful with very similar patient characteristics, risk profile, and medical history profile in the two groups (Table 1).

Outcome

A total of 46 of all patients developed a MACE during the 30-day FU period. The absolute number of patients with MACE was equal between the two groups (n = 23 for both; Table 2, Figure 2). Intention to treat analysis showed a MACE proportion of 5.17% (95% CI 3.30−7.65%) in the standard group and 5.19% (95% CI 3.32−7.69%) in the copeptin group (Table 2). In the PP analysis, the MACE proportion was 5.34% (95% CI 3.38−7.97%) in the standard group, and 3.01% (95% CI 1.51−5.33%) in the copeptin group. In all four sensitivity

analyses, including extreme case analyses, the non-inferiority margin was not exceeded by the one-sided 97.5% CI (Figure 3).

More information on the outcome data of the compound endpoint is shown in Supplementary material online, Table S1 and Supplementary material online, Figure S2. No MIs or deaths occurred in the discharged copeptin-negative patients of the copeptin group. Detailed information on copeptin-negative patients with MACE is shown in the Supplementary material online, Table S3. Diagnoses, in-hospital course, in-hospital procedures, and length of hospital stay are shown in Supplementary material online, Table S2. Of all patients, 39.8% (359/902) were discharged from the ED. In the copeptin group, 67.6% (305/451) were discharged from the ED as opposed to 12.0% (54/451) in the standard group (P < 0.001; Table 3).

Of the copeptin-negative patients in the copeptin group, 80.7% (296/367) were discharged from the ED, as opposed to 11.6% (41/353) of copeptin negative patients in the standard group (P < 0.001; Supplementary material online, Table S2). The LOS for patients discharged after MI exclusion was analysed in all patients who were discharged the same day, or the day after presentation to the ED in order to also include patients who were admitted to the CPU for ACS evaluation. Median LOS was significantly shorter in the copeptin group (4 (IQR 2−6) h) than in the standard group (7 (IQR 4−9) h, P < 0.001).

The PCI/CA ratio was higher in the copeptin group (47.3%) when compared with the standard group (36.6%), without reaching statistical significance (P = 0.307; Table 3).

Discussion

The current study provides evidence that with appropriate clinical selection of low-to-intermediate risk patients with suspected ACS, the combination of negative troponin and negative copeptin at presentation on the basis of a thorough clinical evaluation helps identify patients who can safely be discharged into outpatient care. The MACE proportion at 30 days did not differ between the two groups confirming non-inferiority of the new process. Secondary endpoint analysis shows that the new process is effective with a reduced length of hospital stay and a higher proportion of discharges directly from the ED.

Standard process and promises of high sensitivity cardiac troponin

The standard clinical process for the acute diagnostic assessment of suspected ACS is described in current guidelines.[21] These guidelines focus on troponin measured with hs assays and on delta changes, as a number of observational studies have shown that the new assay generation might enable rule-in and rule-out of AMI earlier than conventional assays.[22−24] The exact definition of relevant troponin changes is an important and yet unsolved issue. Recent publications show conflicting delta values[25,26] and, additionally, minor delta changes may also occur in patients with AMI.[27] Additionally, hs assays identify a high number of patients with elevated troponin results without AMI, making interpretation of test results challenging. There are no interventional studies, which prospectively tested whether fast rule-out strategies with serial hsTn alone are effective and safe.
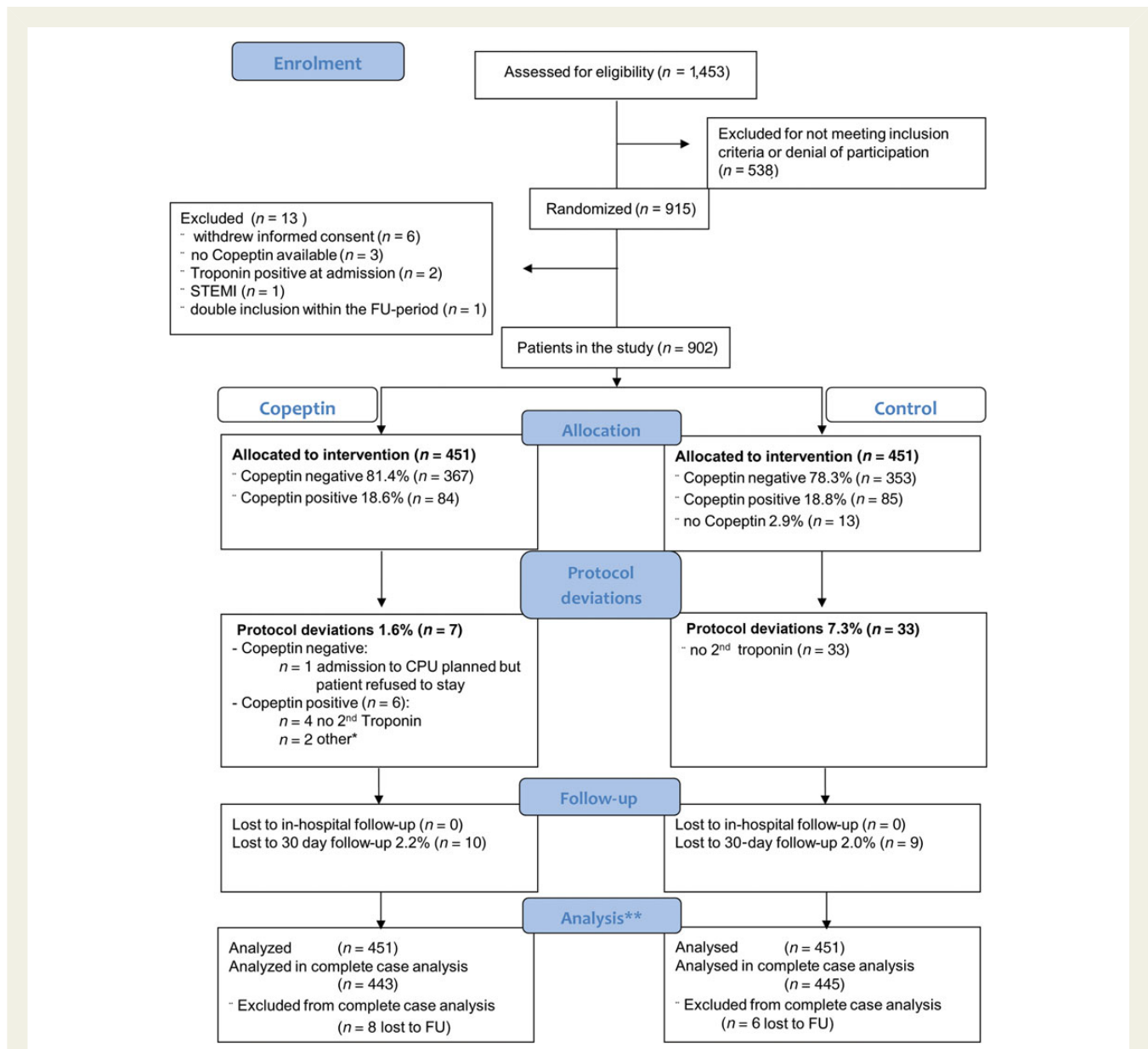
Figure 1 Consort flow diagram. A total of 13 patients were excluded from the study (6 patients withdrew, of 3 patients in the copeptin group, copeptin values were not available, 2 patients were troponin positive at admission, 1 patient had a ST-elevation myocardial infarction at admission, 1 patient had been randomized previously). In 72 copeptin-negative patients in the copeptin group, the treating physician decided that discharge was not possible, 71 of them were admitted to the chest pain units, 1 refused to be admitted. A total of 14 patients (1.6%) were lost to follow-up (FU) at 30 days and not considered in the complete case analysis, 8 in the copeptin and 6 in the standard group, the in-hospital FU was available for all patients. *n = 1 randomized 12 h after admission; n = 1 suspected aortic dissection at admission; **n = 5 patients were lost to 30d-FU but included in the complete case analysis (ITT). Of those n = 4 had an in-hospital major cardiac events (MACE), one patient did not have an initial event but his death date was identified in the German central registry.

The new process

The current process of evaluating patients with suspected ACS is regarded as safe.[21] Any new process has got to prove that patient safety is not decreased by applying the new process and that it holds advantages beyond safety.

The biomarker strategy of a combined copeptin-troponin rule-out of AMI has been analysed in a number of retrospective observational biomarker studies,[5,7,8] but this is the first interventional RCT evaluating the safety of early discharge. Clinicians may use the new strategy for a fast track which reserves space and resources for more severely ill patients. In addition, unnecessary treatment with anti-platelet and anti-thrombotic medications can be avoided, reducing the risk of bleeding complications. The shorter LOS potentially reduces risks of hospitalization, stress, and anxiety.

Table I Characteristics of all patients and in the study groups

	All patients (n = 902)	Standard group (n = 451)	Copeptin group (n = 451)
Patient characteristics			
Age (years) (mean ± SD)	54.1 ± 15.6	54.1 ± 15.1	54.1 ± 16.2
Male sex	63.2 (570)	65.4 (295)	61.0 (275)
Risk factors			
BMI	27.3 ± 4.86	27.3 ± 4.64	27.3 ± 5.1
Diabetes	13.6 (123)	14.0 (63)	13.3 (60)
Hypertension	57.5 (519)	57.0 (257)	58.1 (262)
Hyperlipidaemia	43.5 (392)	45.2 (204)	41.7 (188)
Family history of MI	25.5 (230)	22.2 (100)	28.8 (130)
Smoker	32.4 (292)	33.7 (152)	31.0 (140)
Ex-smoker	30.8 (278)	30.2 (136)	31.5 (142)
GRACE-score (mean ± SD)	80.32 ± 27.6	79.8 ± 27.6	80.9 ± 27.5
TIMI risk score (Median/IQR)	1 (0−3)	1 (0−2)	1 (0−3)
Medical history			
Known CAD	25.7 (232)	24.6 (111)	26.8 (121)
Prior MI	14.6 (132)	15.3 (69)	14.0 (63)
Prior PCI	22.2 (200)	22.1 (100)	22.2 100)
Prior CABG	5.0 (45)	3.5 (16)	6.4 (29)
Chronic heart failure	5.8 (52)	4.2 (19)	7.3 (33)
Primary valve disease	6.9 (62)	7.1 (32)	6.7 (30)
Prior valve surgery	1.2 (11)	0.9 (4)	1.6 (7)
Cardiomyopathy	2.1 (19)	1.1 (5)	3.1 (14)
Renal disease	6.2 (56)	4.9 (22)	7.5 (34)
Time since symptom onset			
0−3 h	43.2 (345)	43.8 (178)	42.6 (167)
<6 h	54.8 (437)	54.4 (221)	55.1 (216)
<12 h	64.0 (511)	62.3 (253)	65.8 (258)
Missing data	n = 104	n = 45	n = 59

Patient characteristics at admission of all patients and in the study groups as randomized. Data are shown as percent (numbers) or as stated. Abbreviations: SD, standard deviation; IQR, inter quartile ranges; BMI, body mass index.

Safety issues of the new process

Previous copeptin studies have faced criticism because the NPV is not 100% and some people may argue that it is not safe to implement a strategy which seems to 'fail' in some patients. The combined endpoint in our study was mainly driven by PCIs performed during the index hospital stay, whereas severe events like AMI and death were rare and occurred in-hospital only. Most probably, those PCIs were not triggered only by 'urgency' but also by 'occasion'.

The component 'urgent PCI' was added to the combined endpoint as we did not want to oversee PCIs after discharge which may have prevented MIs or deaths and therefore could have masked risks in the discharged group. The event rate in copeptin-negative patients discharged was in fact very low (0.6%). Life-threatening events were not detected in copeptin-negative patients.

In our study, 81.4% of patients in the copeptin group were copeptin and troponin negative. In 71 cases, the treating physician decided to overrule the negative marker result and to admit the patient to the CPU. This is an acceptable rate of overruling as the clinical responsibility needs to be in the hands of the attending physician and a 'traditional' and known process is usually favoured. Of the 14 copeptin-negative patients with MACE, 12 were not discharged despite their negative biomarker result. Of these, two patients were diagnosed with an NSTEMI during the initial hospital stay, but did not profit from a coronary intervention. The two copeptin-negative patients with MACE who were discharged had (i) an un-planned PCI and (ii) CABG surgery in the 30-day FU period. This is not surprising as copeptin is not a marker of coronary artery disease and the initial discharge was safe for both patients. Nevertheless, it should be highlighted that the patients in this study were scheduled for a cardiology outpatient visit within three working days and therefore a diagnostic workup was facilitated.

Limitations

A rapid rule-out of AMI with the combined biomarker testing from a single blood draw at admission is bound to cause concerns in some physicians who are used to 20 years of serial biomarker (troponin)

Table 2 Primary endpoint analyses

	Standard group (n = 451)	Copeptin group (n = 451)	Absolute difference in MACE proportion (97.5% one-sided CI)
MACE at 30 days			
Yes	23	23	–
No	422	422	–
Unknown	6	8	–
MACE % (95% CI): (absolute numbers)			
Intention to treat analysis	5.17 (3.30−7.65) (23/445)	5.19 (3.32−7.69) (23/443)	−0.02 (−2.94)
Per protocol analysis	5.34 (3.38−7.97) (22/412)	3.01 (1.51−5.33) (11/365)	2.33 (−0.46)
Sensitivity analyses			
Assuming poor outcome	6.43 (4.35−9.10) (29/451)	6.87 (4.72−9.61) (31/451)	−0.44 (−3.70)
Assuming good outcome	5.10 (3.26−7.55) (23/451)	5.10 (3.26−7.55) (23/451)	0.00 (−2.87)
Extreme case: favouring standard group	5.10 (3.26−7.55) (23/451)	6.87 (4.72−9.61) (31/451)	−1.77 (−4.87)
Extreme case: favouring copeptin group	6.43 (4.35−9.10) (29/451)	5.10 (3.26−7.55) (23/451)	1.33 (−1.71)

Analysis of the primary endpoint: All MACE within 30 days.
The CIs for the absolute difference between the proportions in the respective study groups did not exceed the 5% non-inferiority margin in any analysis, confirming non-inferiority of the copeptin based process as hypothesized, even if the worst case was assumed.
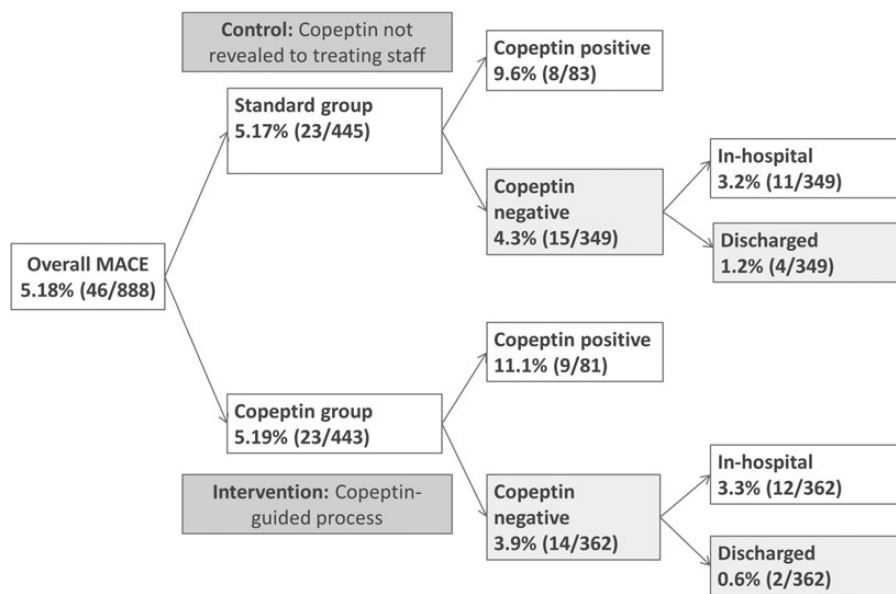

Figure 2 Major adverse cardiac events (MACE) proportions in study groups and in copeptin subgroups. Patients were randomized into copeptin and standard group, where MACE proportions were very similar. Copeptin results were only revealed to the treating staff in the copeptin group. In subgroups of copeptin-positive and copeptin-negative patients, major adverse cardiac event (MACE) rates are higher in copeptin positives. MACE proportions are lowest in discharged copeptin-negative patients.

measurements. Our study was performed in the EDs under routine conditions and by the routine ED physicians. Considering this, the number of cross-overs in our study (n = 71) should be judged as low; the majority of copeptin-negative patients were discharged early. It needs to be emphasized that any biomarker strategy must be embedded in a process of thorough physician work-up and clinical judgement.

A total number of 19 patients (2.1%, *Figure 1*) were lost to FU, which is an acceptable rate but may still have influenced the results of the trial. Notably, even the worst-case scenario sensitivity analysis, assuming a negative outcome for all patients lost to FU in the copeptin group, did not change the primary result of our study.

Due to the high number of cross-overs in the copeptin-negative study group ($n = 71$), the results of the PP analysis, which suggests superiority of the copeptin-guided process, should be interpreted with caution.
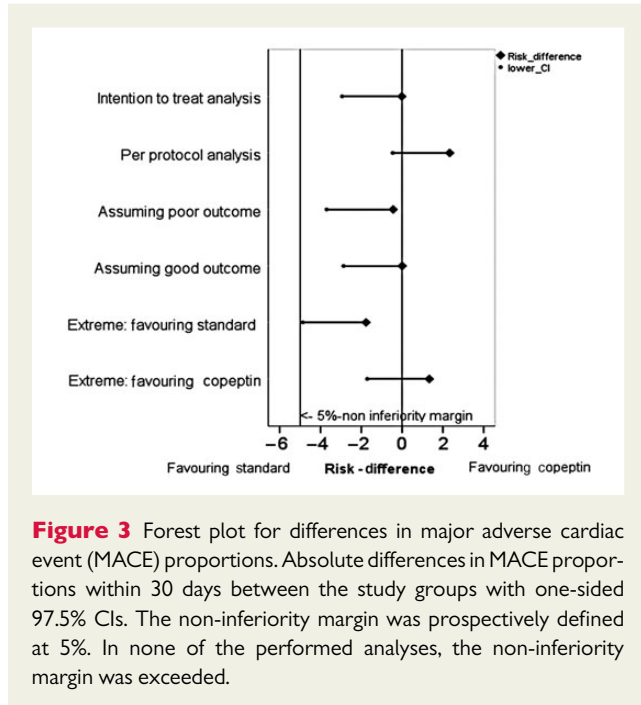

Figure 3 Forest plot for differences in major adverse cardiac event (MACE) proportions. Absolute differences in MACE proportions within 30 days between the study groups with one-sided 97.5% CIs. The non-inferiority margin was prospectively defined at 5%. In none of the performed analyses, the non-inferiority margin was exceeded.

The non-inferiority margin in this study (5%) was based on an anticipated event rate of 10%. This estimate was the result of a review of own data and historical studies.[17–19] The actually observed event rate in our study, however, was 5.2% and was thus lower than expected. This lower event rate could be explained by the fact that the availability of cardiac catheterization laboratories has increased significantly during recent years and most hospitals use invasive diagnostic strategies in chest pain patients very liberally. Thus, it would be possible that a number of patients with intermediate risk (who would have been eligible to participate) were not included because discharge was not considered.[28] The low observed event rate renders the non-inferiority margin relatively wide (relative to the event rate) and thus impacts the relevance of the statistical results which therefore need further confirmation by other clinical trials or registries before they can be regarded as clinically directive.

Conclusion

As for all new interventional strategies or therapies, it will be of major interest to evaluate the safety and effectiveness of this strategy under routine conditions and in a larger number of patients. The introduction of registries at sites who implement the new strategy will show whether the new concept is really safe or—as some fear—will be abused by busy ED physicians. The current study provides evidence that on the basis of a thorough clinical work-up and single combined testing of troponin and copeptin at presentation to rule-out AMI, early discharge of low-to-intermediate risk patients with suspected ACS seems to be safe, has the potential to shorten LOS in the ED, and may therefore benefit the patient. However, as a consequence of the relatively wide non-inferiority margin, our results need to be

Table 3 Secondary endpoints

	All patients $n =$ (902)	Standard group ($n = 451$)	Copeptin group ($n = 451$)	P-value
In-hospital course				
Discharge from ED	39.8 (359)	12.0 (54)	67.6 (305)	<0.001
Index in-hospital procedures				
CA	10.6 (96)	9.1 (41)	12.2 (55)	0.132
PCI	4.6 (41)	3.3 (15)	5.8 (26)	0.080
PCI/CA ratio (%)	42.7	36.6	47.3	0.307
CABG	0.2 (2)	–	0.4 (2)	–
LOS in % (n)				
0–1 day	85.1 (767)	84.9 (383)	85.1 (384)	1.000
2–5 days	11.3 (102)	12.4 (56)	10.2 (46)	0.344
>6 days	3.7 (33)	2.7 (12)	4.7 (21)	0.155
LOS in hours (median/IQR)				
LOS for all patients	6 (4–11)	7 (5–13)	4 (3–8)	<0.001
LOS in 0–1-day group[a]	5 (4–8)	7 (4–9)	4 (2–6)	<0.001
Major bleedings in % (n)	0.4 (4)	0.2 (1)	0.7 (3)	0.573

Secondary endpoints in all patients and in the respective study groups.
[a]The LOS for patients discharged after MI exclusion was analysed in all patients who were discharged the same day, or the day after presentation to the ED in order to include patients who were admitted to the CPU for ACS evaluation.

confirmed in larger clinical trials or registries, before a clinical directive can be propagated.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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