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Multi-Centre Registry to Monitor the Safety of Copeptin and Troponin for the Early Rule-Out of Acute Myocardial Infarction in Patients with Suspected Acute Coronary Syndrome: The Pro-Core registry

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Abstract (word count 319)

Objectives. There is sparse information on the safety of early primary discharge from the Emergency Department (ED) after rule-out of MI in suspected ACS. A dual marker strategy based on a normal cardiac troponin (Tn or hsTn) and a normal Copeptin, previously tested in a randomized trial, reduced ED stay and hospital admissions without an excess of MACE rates within 30 days compared to standard care. To confirm the randomized study results in clinical routine in patients at low-to-intermediate risk, having a broader spectrum of symptoms, across different institutional standards, and with a range of local troponin assays including hsTn, cTn, and POC Tn.

Design

Prospective, multi center European registry.

Setting

18 Emergency departments in 9 European countries (Germany, Austria, Switzerland, France, Spain, United Kingdom, Turkey, Lithuania, Hungary)

Participants

The final study cohort consisted of 2,294 patients (57.2% males, median age 57 years) with suspected acute coronary syndrome (ACS).

Interventions

This was a prospective registry. Using the new dual markers strategy, 1,477 patients were eligible for direct discharge, which was realized in 974 (42.5%) of patients.

Main outcome measures

The primary endpoint was all-cause mortality at 30 days.

Results

Compared to conventional work-up, the median length of ED stay was 60 minutes shorter (228 min vs 288 min, p<0.001) in the primary discharged group. All-cause mortality was 0.1% in this group vs 1.1% in the conventional work-up group (p<0.001). Conventional work-up instead of discharge despite negative biomarkers was observed in 503 patients (21.9%) and associated with higher prevalence of ACS (17.1% vs 0.9%, p<0.001), cardiac diagnoses (55.2% vs 23.5%, p<0.001) and risk factors (p<0.01), but with a similar all-cause mortality (0.2% vs 0.1%, p=0.64).

Conclusions. Copeptin on top of cardiac troponin supports safe discharge in patients with chest pain or other symptoms suggestive of ACS under routine conditions with the use of a broad spectrum of local standard POC, conventional and high sensitivity troponin assays.

Trial registration

ClinicalTrials.gov NCT02490969

Key words: Registry, acute coronary syndrome, myocardial infarction, Copeptin, troponin, mortality

Strengths and limitations of this study

- This is the first study of its kind to examine the clinical use of a fast rule-out and early discharge concept in suspected acute myocardial infarction using cardiac troponin and copeptin in a large European registry
- The study supports the conclusions of large observational studies and a randomized process trial regarding the safe use of the combination of cardiac troponin and copeptin in daily routine.
- The study shows the potential for more than 50% of patients presenting with acute chest pain or other symptoms suggestive of myocardial infarction to be directly discharged to outpatient workup after thorough clinical assessment and a single blood draw
- The study has been carried out in experienced centers, thus in settings with lower clinical expertise results may differ

Introduction

Chest pain accounts for approximately 8 million annual emergency department (ED) visits in the United States (1), rendering chest pain the second most common presenting symptom. In a pooled analysis on 51 observational trials, the prevalence of the final diagnosis of ACS was confirmed in a median of 14%, with a range between 5% to 42% (2).

An effective risk stratification is paramount to select the most appropriate decision for admission or direct discharge because admission of patients at low or very low risk is not safe (3,4) as it increases the risk to receive unnecessary coronary angiography, coronary interventions, multiple re-admissions (3), and eventually the risk of peri-procedural myocardial injury or type 4 MI, and procedure-related major bleedings (4). Moreover, unselected admission of chest pain patients for further work-up for the evaluation of ACS is time consuming and costly (5,6). During an interval of only 9 years (from 1999–2008), the use of advanced medical imaging for ED visits related to chest pain was found to increase dramatically by 367.6% in the CDC/NCHS, National Hospital Ambulatory Medical Care Survey (7). On the other hand, early discharge is also not without risk, as up to 2–5% of patients with ACS are reported to be inappropriately discharged from the ED every year (5,8) although the methodology to assess these numbers is limited (no complete follow up of all patients, no exact differentiation between incident and prevalent AMI and the components of ACS). Nevertheless, missed or incident AMI early after discharge is associated with a hazard ratio for death of 1.7 to 1.9% (8). Missed AMIs account for

20% of US emergency medicine related litigation dollars (9). Currently, use of high sensitivity cardiac troponins has improved the accuracy and earlier detection of an MI (10-13), and very low concentrations of hsTn have been reported to safely rule-out an MI and to be associated with rates of death or MI below 1% (14-17). Accordingly, 2015 ESC guidelines on NSTE-ACS (10) discourage routine coronary angiography in low risk patients and recommend early discharge after clinical risk stratification, and a pre- or post-discharge stress imaging test for the decision of a selective invasive strategy. Supporting evidence for early uneventful discharge of low risk patients stems mainly from observational studies (14,15,18,19) where investigators were commonly blinded to the investigational hsTn results, were unaware of retrospectively derived optimal decision cutoffs, and managed patients at their own discretion following standards of care applicable at that time. In fact, most of the patients who retrospectively fulfilled early rule-out criteria were kept in hospital and neither medical measures nor non cardiac diagnoses are reported. Only few interventional clinical trials evaluated the safety of a randomized allocation to early discharge versus conventional care in patients at low (20,21) or low-to-intermediate high risk (22). The Biomarkers-in-Cardiology 8 (BIC-8) trial (22) tested the utility of a dual biomarker strategy using normal cTn or hsTn values, i.e. below the upper limit of normal, mainly the 99th percentile, together with normal Copeptin values below the 95th percentile (<10 pmol/L) to identify candidates for direct early discharge from the ED. The findings demonstrated that this strategy reduced the length of observation time in the ED or chest pain unit and increased rates of discharge at a low risk for major adverse cardiovascular events (MACE) that was comparable or even lower in the per protocol analysis to standard of care. Compared to serial troponin-based protocols, advantages of the dual marker strategy include the ability of instant rule-out of MI without the need for additional blood draw, high sensitivities and negative predictive values (NPVs) for acute myocardial infarction (AMI) of Copeptin in combination with conventional or contemporary sensitive cTn assays (23-28), or POCT (29), particularly when hsTn or validated hsTn assays are not available, and supporting data for a safe discharge from a large, appropriately powered randomized multicenter trial (22).

The aim of the present multicenter observational trial was to confirm the safety of this strategy in routine clinical practice, across a broad spectrum of cTn assays including POCT, in an unselected population with a broader range of symptoms, and at low-to-intermediate risk presenting with suspected ACS to 18 EDs in Europe and Turkey.

Methods

The Pro-Core is a multi-center, international observational trial with 18 participating centers (figure 1S) in Europe and formally Near East (Ankara, Turkey).

Adult men and women who present to an ED or chest pain unit (CPU) with signs and symptoms suggestive of acute coronary syndrome without ST-segment elevation (NSTE-ACS) and a low-to-

intermediate risk profile, in whom an early rule-out strategy for MI was applied and who therefore underwent single combined Troponin and Copeptin testing at admission as part of standard management.

Patients were eligible if they were aged ≥18 years, presented with symptoms suggestive of ACS such as acute chest discomfort, angina pectoris, or dyspnea as leading symptoms. Patients presenting with ST-segment elevation or a final diagnosis of ST-segment elevation myocardial infarction (STEMI) were excluded from analysis (see figure 1 for patient flow).

Patients underwent clinical assessment that included medical history, physical examination, standard blood test including measurements of local (hs)-cTn, Copeptin and 12-lead ECG. Baseline information included the Killip class, and clinical information to calculate the GRACE score. Physicians had access to all clinical information including Copeptin and cTn results that were reported with local turn-around-times. Decision for primary discharge after rule-out using the dual biomarker strategy, or for disposition of patients if MI was not ruled out was left at the discretion of the attending physician. Patients were excluded if high risk features were evident (e.g. the GRACE score was above 140) and if hospital admission was obviously necessary at presentation for any reason. Final diagnosis of NSTE-ACS was performed by the ED physician applying the criteria of the 3rd universal definition of AMI (**30**). All patients were contacted at 30 days to assess all-cause and cardiac mortality. Number of patients was limited to 300 patients per participating site to limit center bias.

Biomarkers and rule-out algorithms

Copeptin and cardiac troponin were tested from fresh unfrozen blood from a single blood sample drawn at admission to the ED or CPU as part of the routine patient management.

Copeptin was measured using the automated fluoro-immunoassay B·R·A·H·M·S Copeptin proAVP KRYPTOR for the quantitative measurement of C-terminal pro-arginine-vasopressin (CT-proAVP, Copeptin) in human serum and plasma on the B·R·A·H·M·S KRYPTOR compact PLUS platform. The test has a detection limit of 0.69 pmol/L and a functional assay sensitivity (detected by inter-assay precision of 20% CV) of 1.08 pmol/L.

The recommended cut-off for the decision between a positive and a negative test is 10 pmol/L, corresponding to the 95th percentile of a healthy reference population. This cut-off was used in the randomized controlled trial by Möckel et al. (**22**), and is the recommended cut-off for the rule-out algorithms for MI.

Cardiac Troponin was measured at the individual institutions according to standard practice. An overview on local assays and cutoffs is provided as supplemental material (Table 1S). Briefly, Roche Elecsys hsTnT was used in 39%, followed by Abbott Architect hsTnI, Siemens (Vista, Loci), Beckman

Access TnI, and Radiometer (3rd gen. cTnT) in 22%, 22%, 11% and 6%, respectively. Conventional and high-sensitivity assays were permitted for the early rule-out strategy.

A patient qualified as rule-out and for early discharge if he presented with signs and symptoms suggestive of ACS, together with a low-to-intermediate risk profile defined as the absence of high risk features (e.g. a GRACE score <140), and a combined negative testing of Copeptin and troponin, defined as Copeptin below 10 pmol/L and cardiac troponin below the local AMI decision limit as recommended by the guidelines, mostly the 99th percentile value of a healthy reference population provided by the manufacturer.

Follow-Up and Clinical End Points

The primary objective was to evaluate 30-day all-cause mortality in patients in whom acute myocardial infarction was ruled-out using the early dual marker rule-out strategy and who are therefore directly discharged from the ED.

The secondary objectives were evaluated in all patients, irrespective of biomarker test results and disposition decisions. Secondary endpoints included the diagnosis of acute myocardial infarction, final hospital diagnoses, time to discharge/transfer from the ED/CPU, disposition decision (discharge or admission), length of hospital stay, ICU-treatment, performance of coronary angiography/ PCI/ CABG, performance of ECGs, stress testing, imaging, performance of cardiovascular monitoring, In-hospital all-cause mortality, 30-day all-cause mortality.

The study protocol also addressed those patients who were not primarily discharged or not admitted although criteria were fulfilled (over-rule). The reasons for over-rule or other protocol violations were registered.

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 was registered before enrollment of the first patient (ClinicalTrials.gov NCT02490969).

Statistical evaluation

Enrolment was restricted to a maximum number of 300 patients per center to ensure generality by avoiding the dominance of single centers. The total number of patients enrolled therefore depended rather on the number of participating centers than on their enrolment performance. As the primary objective of this registry was the monitoring of an already routinely applied clinical algorithm, no confirmatory study design was chosen and there was no sample size calculation performed. All data were entered into an online electronic case report form. Group comparisons for categorical variables were performed using chi-squared tests and for numerical variables using Wilcoxon rank-sum tests. A p-value below 0.05 was considered significant (no correction for multiple testing conducted).

Statistical analyses were performed using the software R Version 3.1.2 and SPSS (IBM® SPSS Statistics, Version 21).

Patient and Public Involvement

Patients or public were not involved in the development of the study protocol.

Results

A total of 2,401 consecutive patients with suspected ACS were screened from September 16th 2015 until the end of recruitment on May 23rd 2017. Of these, 107 patients were excluded from analysis due to incomplete biomarker or clinical information, withdraw of informed consent, or double entry (see patient flow diagram; Figure 1). The final study cohort consisted of 2,294 patients (57.2% males, median age 57 years) with suspected ACS. Numbers of recruited patients varied by study site but were limited per protocol to a maximum of 300 enrolments per site. The exact numbers of recruited patients is displayed in supplemental Figure 1S.

The most prevalent leading symptom at presentation (Supplemental Figure 2, Table 1) was chest pain in 70.6% (n=1619), followed by diffuse or initially mixed symptoms in 12.9% (n=297), dyspnea in 5.2% (n=119), abdominal pain in 2.9% (n=66), , focal neurology in 0.7% (n=16), headache in 0.4% (n=9), or none of the listed symptoms in 7.3% (n=168). As expected from the inclusion criteria, the study cohort represented a low-to-intermediate risk group with a median GRACE score of 89 (25th; 75th percentile: 67-114) and a Killip class of 1 in 96% of cases (n=2084). Time from onset of symptoms to presentation was below 12 hours in 50.8%. An interval of 0-3 hours, 3-6 hours and 6-12 hours was registered in 26.3% (n=558), 13.3% (n=283), and 11.2% (n=238) of patients, respectively. ECG at presentation was non-diagnostic in 87.3% of patients. Regarding initial cTn and Copeptin results, a total of 2,017 patients (87.9%) were below the diagnostic cutoff of the local cTn, and 1,615 patients (70.4%) below the cutoff for Copeptin. A total of 1477 patients (64.4%) were below the decision cutoff for both biomarkers fulfilling the criteria for early primary discharge from the ED (theoretically maximal efficiency).

Clinical pathways

974 patients (42.5%) were categorized into the primary discharge after fast rule-out pathway, and 1,320 patients into the conventional work-up pathway. Of these, 654 patients did not follow a pre-defined pathway but were either admitted although qualified for primary discharge (n=503, 21.9%), or were discharged although not ruled-out (n=151, 6.6%), see figure 2.

In the entire cohort, the overall rate of an ACS diagnosis was 12.7% (n=288), followed by non-cardiac chest pain in 28.8%, rhythm disorders in 8.7%, pulmonary disorders in 6.8%, stable CAD in 6.8%, hypertensive crisis in 6.3%, and gastrointestinal disease in 5.5%. Other cardiac diagnoses were present in 4%, and other unspecified diagnoses in 16.3% (Supplemental Figure 3S).

In the conventional care pathway, an ACS was diagnosed in 21.1% (n=279) with the majority classified as a NSTE-ACS (n=172, 61.6%). STEMI was an exceptional diagnosis in 15 patients (5.2%) since patients with STEMI were routed directly to the catheterization laboratory in most institutions and were not intended for inclusion. Only if STEMI was diagnosed later and not at admission such patients were enrolled. Other diagnosis included non-cardiac chest pain in 18.8% (n=247), rhythm disorders in 5.9% (n=133), stable CAD in 8.9% (n=117), pulmonary disease in 6.8% (n=90), hypertensive crisis in 5.9% (n=77), gastrointestinal disease in 4.7% (n=62), and other diagnoses in 14.1% (n=185).

In the primary discharge after fast rule-out pathway, only 9 patients (0.9%) were diagnosed as having an ACS, mostly unstable angina (n=4) or unclassified ACS (n=4), with only 1 case (0.1%) diagnosed as NSTEMI (NPV for MI of 99.9%). Rate of admission was only 0.1% due to a case where admission was forced by the referring primary care physician although discharge was planned.

There were two different ways how local investigators over-ruled the intended pathway. The larger group consisted of 503 patients (21.9%) who were allocated to the conventional care pathway at the discretion of the local investigator although they were categorized into the primary discharge after fast rule-out pathway. The second group consisted of 151 patients (6.6%) who were primarily discharged although they should have received conventional care). Reasons for the over-rule consisted mainly of decision of the physician to admit to hospital based on clinical judgment. Minor reasons were opposition of patients against serial blood sampling (n=2), and other unspecified reasons (n=6).

There were differences between the primary discharge after fast rule-out pathway and the over-rulers into the conventional care pathway (Table 2). Patients were older, more frequently males, had more often a history of CAD or previous MI, more risk factors including a higher prevalence of arterial hypertension, hypercholesterolemia, and diabetes mellitus. In addition, patients had more often a diagnostic ECG, and higher GRACE scores. In addition, these patients received more often an ACS diagnosis, i.e. a diagnosis of unstable angina, and spent longer times in the ED. However, and importantly, rates of all-cause mortality at 30 days were not significantly different (0.2% vs 0.1%, p=1) compared to the primary discharge after fast rule-out pathway.

Outcomes

The primary endpoint, all-cause death within 30 days among the primary discharge after fast rule-out pathway, occurred in only 1 case (0.1%). This death was not related to the biomarker algorithm: the patient was 70 years old, had a history of CAD and previous MI and presented with musculoskeletal symptoms, was primarily discharged and died 1 month later from metastatic lung cancer (table 3).

By contrast, all-cause mortality rate in the conventional care pathway was 1.1% (n=14) and thus significantly higher (p=0.011) than in the primary discharge after fast rule-out pathway (Table 3). Diagnoses in the deceased patients of the conventional care pathway included ACS (n=5), non-cardiac

chest pain (n=2), pulmonary disease (n=2), neurological disease (n=1), rhythm disorders (n=1), stable CAD (n=1), heart failure (n=1), gastrointestinal disease (n=1), and non-specified others (n=1). Patients who died were a median of 15 years older, had more often dyspnea as the leading presenting symptom, presented more frequently more than 12 hours after symptom onset, and were characterized by higher GRACE score (167 vs 90 points, p<0.001) and Killip class. In addition, non-survivors had received more extensive diagnostic workup, presented more often with a local cTn and Copeptin above cutoff, and median Copeptin values were significantly higher than among survivors (50.8 vs 7.0 pmol/L, p<0.001) underscoring the prognostic information that is provided by cTn and Copeptin independent of the underlying disease.

Regarding secondary endpoints, hospitalization rates were 0.1% in the primary discharge after fast rule-out pathway compared to 59% in the conventional care pathways (p<0.001). As expected, median lengths of stay in the ED (treatment time) were significantly shorter in the primary discharge after fast rule-out pathway vs the conventional care pathway (228 min vs 288 min, p<0.001, and rates of patients discharged within 0 to <1 hour (1.5% vs 3.6%), 1 to <2 hours (13.2% vs 13.3%), and 2 to < 3 hours (21.7% vs 16%), 3 to <6 hours (49.3% vs 37.3%) were significantly different in primary discharge after fast rule-out pathway versus conventional care pathway (p for trend < 0.001). Conversely, rates of patients with longer ED treatment times > 6 hours were significantly lower in the primary discharge after fast rule-out pathway than in the conventional care pathway out group (14.2% vs 29.8%, p<0.001).

Discussion

Information on the safety of direct discharge from an ED after rule-out of MI in patients with suspected ACS is almost exclusively restricted to findings that were generated in observational trials where attending physicians were commonly blinded to the investigational hsTn results, or to retrospectively determined optimal decision cutoffs, and where treatment decisions, based on at that time applicable standards of care, were left at the discretion of the treating physician (**16-19**,**31**).

Following the randomized BIC-8 study, which proofed safe discharge after instant rule-out of AMI by the use of troponin and Copeptin from a single blood draw (22), we could confirm in a large European registry that this is also true in clinical routine.

The superior analytical sensitivity of hsTn assays has already enabled an accurate rule-out of MI with sensitivities and NPVs of > 90% (**10**), facilitating fast rule-out based on either very low concentrations of hsTn assays obtained from a single measurement at presentation (**14,15,16-19,32**), or from serial blood draws after 1 to 3 hours (**17-19,31,33-38**) using hsTn at the 99th percentile (**10-13**), or slightly below (**18,19**) the 99th percentile of a healthy reference population. Integration of clinical judgment or

a validated clinical score such as the GRACE, TIMI, HEART, modified Goldman Score, MACS clinical decision rule, EDACS and Vancouver Chest Pain Algorithm, and North American Chest Pain Rule further improve NPV yielding NPV between 98.1-100% and 98.4-100% when cTn and hsTn assays were used, respectively (39). Although, 2015 ESC guidelines (10) discourage routine invasive strategy in low risk patients and rather recommend discharge following risk stratification, and a pre- or post-discharge stress imaging test to decide on a selective invasive strategy, evidence from randomized trials to endorse these recommendations is sparse (20,21,22). The Manchester Acute Coronary Syndrome (MACS)-Pilot study (20) enrolled 138 patients with suspected cardiac chest pain who were randomized to receive care guided by the MACS decision rule or standard care. The primary efficacy outcome was a decision to discharge within 4 hours of arrival, without missed MI and without death, AMI or coronary revascularization occurring during 30 days of follow-up. This small pilot study found a significantly higher rate of uneventful primary discharge within 4 hours (26% vs 8%, p=0.004) among those guided by the MACS rule. The HeartPathway Trial enrolled 282 patients with suspected ACS stratified into risk categories using the HEART Score (21). The study was not powered to compare event rates in randomized groups but found a decreased objective cardiac testing at 30 days by 12.1%, a reduced length of stay by 12 hours, and an increase of early discharges by 21.3%. The BIC-8 trial (22) that enrolled a total of 902 low-to-intermediate high risk patients using the GRACE score and subsequently randomized patients with normal presenting cTn and Copeptin values into an early discharge and a standard protocol group. The study demonstrated a reduction of observation time in the ED by more than 40% from a median of 7 hours to 3 hours, achieved a 5.6-fold increase in ED discharge rate from 67.7 vs 12%, and a similar 5.2% rate of 30-day major adverse cardiovascular events that were liberally defined as all-cause death, survived sudden cardiac arrest, re-hospitalization for ACS, unplanned PCI or CABG, or documented life-threatening arrhythmias in the standard and Copeptin group (22).

The present large multicenter registry was performed in patients with suspected ACS and low-to-intermediate risk to test the usefulness of a dual biomarker strategy, consisting of a normal Copeptin and cTn, to rule-out MI from a single blood draw at admission and to discharge low risk patients primarily from the ED. In order to represent clinical practice of different type of institutions, variable local practice and across the spectrum of cTn assays and grades of assays sensitivities (40,41), this observational study was conducted in 18 different institutions in Europe and Asia. Institutions included EDs in community hospitals, and CPUs in PCI centers and few University hospitals. Patients qualified for enrolment in the presence of a broader spectrum of symptoms suggestive of ACS not limited to chest pain or angina, and a broad spectrum of cTn assays and different grades of analytical sensitivities including conventional, contemporary, and hsTn assays was permitted. To reduce dominance of few high recruiting centres, enrolment rates were restricted to 300 study patients per site.

There were several key findings of this survey that support the usefulness and safety of this concept in clinical routine and outside of controlled clinical trials. First, earlier discharge from the ED in patients ruled-out at presentation using a single blood draw is feasible without any obvious safety concern. All-cause mortality rate within 30 days was 0.1% and attributed to a case with metastatic lung cancer. Second, length of stay in the ED is significantly shorter by 60 minutes allowing an earlier discharge, a finding particularly useful in congested EDs or CPUs. Thus, the present registry data confirm the findings from the randomized BIC-8 trial (22) on reduced length of stay, increased discharge rates and support the safety of a primary planned discharge from an ED after clinical risk assessment. Third, the dual marker concept is efficient as it can be applied to at least 42.5% (potentially effective in 66.4%) of patients presenting with chest pain or chest pain equivalent symptoms to an ED. Thus, efficacy of this dual marker strategy is almost comparable with the efficacy of the ESC recommended 0/1 h diagnostic algorithm that requires serial blood draws and a validated hsTn assay (currently Abbott Architect hsTnI and Roche hsTnT). While other fast rule-out algorithms based on very low hsTnI or hsTnT at the LoB or LoD may demonstrate similar diagnostic performance and safety, the numbers of patients who qualify are substantially lower (14,15,32) and these strategies have never been tested prospectively with patients being really discharged after testing.

We found a relevant number of over-rule by local ED physician leading to an admission of patients who qualified for discharge by their biomarker results (34%). Given that these patients had an uneventful clinical course (see table 2), void of primary or secondary events during follow-up, suggests an underestimated efficacy and more potential of safe discharge. Fourth, regarding the diagnostic performance for rule-out that was not in the scope of this survey, the dual marker algorithm was associated with a high negative predictive value of 99.9% for NSTEMI (1 missed NSTEMI) confirming the existing evidence on the diagnostic performance of the Copeptin/troponin dual marker strategy (22,26-28). Fifth, regarding secondary objectives, the dual marker strategy was associated with shorter stays in ED. Sixth, consistently with previous studies (26-28,42,43), elevated Copeptin levels were associated with all-cause mortality within 30 days providing confirmatory evidence that Copeptin confers prognostic information that is complementary to cTn or hsTn, in various acute cardiovascular settings including ACS (26-28,42,43), heart failure (44,45), and acute pulmonary embolism (46) but also non-cardiac disease. In addition, an elevated Copeptin should prompt a search for a variety of potentially life-threatening non-cardiac conditions including perforated stomach ulcer, pancreatitis, cholecystitis, bleedings, infections, or neurological disorders (47).

Limitations

First, we observed very low rates of all-cause mortality at 30-days, i.e. 0.1% in the primary discharge after fast rule-out pathway as compared to 1.1% in the conventional care pathway. A selection bias

towards recruitment of a non-representable low risk ACS cohort cannot be fully excluded as inclusion criteria were not limited to typical chest pain, longer pain episodes or abnormal ECG findings. However, the study population was planned to represent a real life picture of patients who present in clinical routine with various symptoms and a wide range of risk. We believe that our study cohort is also similar to other observational studies enrolling patients with suspected ACS. The overall prevalence of ACS in this registry was 12.7% and is thus very consistent with a median of 13 to 14% prevalence of ACS reported in a pooled analysis of 51 observational trials on patients with suspected ACS (**2**), In addition, the median GRACE score was 89 points (25^{th}/75^{th} perc: 67; 117) which is very similar with the mean GRACE score of 80 (SD 28 points) in the randomized intervention trial (**22**).

Second, rates of enrolment per site were heterogenous with a mix of high and low recruiting centers. However, the very low mortality rate does not allow any conclusion whether safety is influenced by center volumes or experience of physicians.

Third, currently a strategy for instant rule-out based on Copeptin and cTn is being recommended by 2015 ESC guidelines on NSTE-ACS (**10**) and an updated consensus document of the German Society of Cardiology on the use of Copeptin in CPUs (**48**) and chest pain centers (**49**). However, there is a gap between the high recommendation level endorsed by numerous clinical trials (**23-26,42,43**), editorials and state-of-the-art reviews (**38,39**), meta-analyses (**27,28**), and National practice guidelines (**10,48,49**) on the one hand and the obvious underuse in clinical practice for suspected ACS. In the elective setting, Copeptin is currently used for the diagnosis of diabetes insipidus, a non-emergent diagnosis. In emergencies requiring immediate measurement, the most probable reason for underuse is that Copeptin has to be measured on a stand-alone device which is more labor-intensive than an automated central laboratory system, which leads to the suspicion that nowadays economic features in the laboratory are hurdles for state of the art use of biomarkers. Development of a POCT system for Copeptin and implementation of Copeptin to a central laboratory platform would overcome this obstacle.

Conclusions

Copeptin on top of cardiac troponin is currently the only strategy that – based on a RCT and a large multi-centre registry - supports the safe direct discharge of patients with chest pain or chest pain equivalent symptoms suggestive of ACS under routine conditions. In this registry, investigators discharged 42.5% of patients directly after one blood draw without safety concerns. Over-rule analysis revealed potential for further 21.9% of cases. The concept appears to be robust across a spectrum of different cTn assays and assay sensitivities including the whole range of conventional, contemporary and high sensitivity cTn assays.

We believe that the present findings will have enormous implications on health care resources by shortening observation times, hospitalization rates, reducing diagnostic resources, and avoid unnecessary coronary angiographies.

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Transparency declaration

The corresponding authors (MM) author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing statement

Relevant data could be shared on reasonable request.

Conflicts of interest

EG received honoraria for lectures from Roche Diagnostics, AstraZeneca, Bayer, Daiichi-Sankyo, Lilly Eli Deutschland. He serves as a consultant for Roche Diagnostics, BRAHMS Thermo Fisher Scientific, Boehringer Ingelheim, and has received research funding from BRAHMS Thermo Fisher Scientific, Roche Diagnostics, Bayer Vital and Daiichi Sankyo;

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EG and **MM** were involved in the conception and design of the study, the acquisition, analysis and interpretation of data, drafted the manuscript, approved the final version to be published, are accountable for all aspects of the work and an d **MM** serves as guarantor for the manuscript.

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Table 1. Baseline characteristics of the patients

Variable	Category	total (n=2294)	primary discharge after fast rule out (n=974)	conventional work up (n=1320)	p-value
Age		59 (46, 72)	51 (39, 62)	65 (52, 75.25)	<0.001
Gender	Female	42.8% (981)	49.7% (484)	37.7% (497)	<0.001
Onset of symptoms before presentation	0 - 3 h	26.3% (558)	26% (228)	26.5% (330)	0.053
	3 - 6 h	13.3% (283)	11.8% (103)	14.4% (180)	
	6 - 12 h	11.2% (238)	13.1% (115)	9.9% (123)	
	> 12 h	49.2% (1043)	49.1% (430)	49.2% (613)	
Leading sympton	Chest pain	70.6% (1619)	76.9% (749)	65.9% (870)	<0.001
	Diffuse Symptoms / Initially Mixed Symptoms	12.9% (297)	9.9% (96)	15.2% (201)	
	None oft he Previous	7.3% (168)	6.6% (64)	7.9% (104)	
	Dyspnea	5.2% (119)	2.5% (24)	7.2% (95)	
	Abdominal pain	2.9% (66)	3.1% (30)	2.7% (36)	
	Focal Neurology	0.7% (16)	0.4% (4)	0.9% (12)	
	Headache	0.4% (9)	0.7% (7)	0.2% (2)	
History of CAD		29.2% (656)	16.8% (158)	38.2% (498)	<0.001
History of MI		11.7% (262)	7.3% (69)	14.8% (193)	<0.001
Risk factor: HTN		53.8% (1189)	38.3% (357)	65.1% (832)	<0.001
Risk factor: HLP		33.6% (708)	23.7% (210)	40.7% (498)	<0.001
Diabetes Mellitus		15.6% (347)	9.3% (86)	20.1% (261)	<0.001
Smoking		34.3% (633)	34.3% (264)	34.3% (369)	1.000
Positive Family History of CAD		32.4% (477)	32.3% (202)	32.5% (275)	0.956
Grace Score	<109	69.3% (1413)	86.1% (736)	57.2% (677)	<0.001
	109-140	21.9% (446)	12.7% (109)	28.5% (337)	
	≥ 140	8.8% (179)	1.2% (10)	14.3% (169)	
Killip class	I	96% (2084)	98.4% (900)	94.3% (1184)	<0.001
	II	3.2% (70)	1.6% (15)	4.4% (55)	
	III	0.7% (15)	0% (0)	1.2% (15)	
	IV	0% (1)	0% (0)	0.1% (1)	
ECG not diagnostic		87.3% (1971)	93% (892)	83% (1079)	<0.001
ST-elevation		4.2% (94)	2.6% (25)	5.4% (69)	0.002
ST-depression		7.7% (170)	3.6% (34)	10.7% (136)	<0.001
Local cTn	negative	87.9% (2017)	100% (974)	79% (1043)	<0.001
Copeptin	[pmol/l]	7.0 (3.9, 11.8)	4.9 (3.2, 7.7)	10.2 (5.3, 22.9)	<0.001
Copeptin	negative	70.4% (1615)	100% (974)	48.6% (641)	<0.001
Local troponin and copeptin	negative	64.4% (1477)	100% (974)	38.1% (503)	<0.001

Numbers are medians, interquartile ranges and p-values of Wilcoxon rank-sum test for numerical variables and, percentages, counts and p-values of chi-square test for categorical variables.

Table 2 Comparison of patient's characteristics of primary discharge versus over-rule to conventional care despite eligibility for discharge by biomarker results

Variable	Level	Total (n=1477)	Primary discharge (n=974)	Admission over-rule (n=503)	p-value
Age		59 (46, 72)	51 (39, 62)	61 (51.5, 73)	<0.001
Gender	Female	47.2% (697)	49.7% (484)	42.3% (213)	0.009
Onset of symptoms before presentation	0 - 3 h	24.5% (333)	26% (228)	21.7% (105)	0.060
	3 - 6 h	12.1% (165)	11.8% (103)	12.8% (62)	
	6 - 12 h	12.1% (164)	13.1% (115)	10.1% (49)	
	> 12 h	51.3% (698)	49.1% (430)	55.4% (268)	
Leading sympton	Chest pain	73.9% (1092)	76.9% (749)	68.2% (343)	<0.001
	Diffuse/ Initially mixed symptoms	10.9% (161)	9.9% (96)	12.9% (65)	
	Dyspnea	4.4% (64)	2.5% (24)	8.1% (40)	
	Abdominal pain	2.8% (41)	3.1% (30)	2.2% (11)	
	Focal Neurology	0.5% (7)	0.4% (4)	0.6% (3)	
	Headache	0.6% (9)	0.7% (7)	0.4% (2)	
	Other	6.9% (102)	6.6% (64)	7.6% (38)	
History of CAD		24.4% (351)	16.8% (158)	38.9% (193)	<0.001
History of MI		9.5% (136)	7.3% (69)	13.5% (67)	<0.001
Hypertension		48.7% (693)	38.3% (357)	68.2% (336)	<0.001
HLP		29.5% (401)	23.7% (210)	40.6% (191)	<0.001
Diabetes Mellitus		10.9% (155)	9.3% (86)	13.9% (69)	0.011
Smoking		34.6% (409)	34.3% (264)	35.1% (145)	0.838
Family History CAD		33.6% (322)	32.3% (202)	36% (120)	0.269
Grace Score	< 109	80.7% (1067)	86.1% (736)	70.7% (331)	<0.001
	109-140	16.8% (222)	12.7% (109)	24.1% (113)	
	≥ 140	2.6% (34)	1.2% (10)	5.1% (24)	
Killip class	I	98.4% (1378)	98.4% (900)	98.4% (478)	0.375
	II	1.6% (22)	1.6% (15)	1.4% (7)	
	III	0.1% (1)	0% (0)	0.2% (1)	
Final diagnoses	ACS total	6.5% (95)	0.9% (9)	17.1% (86)	<0.001
	unclassified ACS	1.9% (28)	0.4% (4)	4.8% (24)	
	UAP	4% (58)	0.4% (4)	10.8% (54)	
	NSTEMI	0.3% (5)	0.1% (1)	0.8% (4)	
	AMI other	0.1% (2)	0% (0)	0.4% (2)	
	STEMI	0.1% (2)	0% (0)	0.4% (2)	
Main diagnosis	Cardiac	34.4% (503)	23.5% (226)	55.2% (277)	<0.001
Mortality	30days	0.1% (2)	0.1% (1)	0.2% (1)	1

Numbers are medians, interquartile ranges and p-values of Wilcoxon rank-sum test for numerical variables and percentages, counts and p-values of chi-square test for categorical variables. CAD, coronary artery disease; HLP, hyperlipidemia; UAP, unstable angina pectoris

Table 3 All-cause death at 30 days and secondary outcomes

Variable	Categories	Total (n=2294)	Primary discharge after fast rule out (n=974)	Conventional work up (n=1320)	p-value
All-cause death	30days	0.7% (15)	0.1% (1)*	1.1% (14)	0.011
Exact length of stay in ED/CPU [hours]		4.3 (2.9, 5.9)	3.8 (2.8, 5.3)	4.8 (3.2, 6.7)	<0.001
Length of stay in ED/CPU	0 - 1 h	2.6% (53)	1.5% (13)	3.6% (40)	<0.001
	1 - 2 h	13.3% (266)	13.2% (118)	13.3% (148)	
	2 - 3 h	18.6% (372)	21.7% (194)	16% (178)	
	3 - 6 h	42.7% (855)	49.3% (440)	37.3% (415)	
	>= 6 h	22.9% (458)	14.2% (127)	29.8% (331)	
Admission	Peripheral ward	72.7% (562)	100% (1)	72.7% (561)	0.829
	IMCU	17.6% (136)	0% (0)	17.6% (136)	
	ICU	9.7% (75)	0% (0)	9.7% (75)	

Numbers are medians, interquartile ranges and p-values of Wilcoxon rank-sum test for numerical variables, percentages, counts and p-values of chi-square test for categorical variables

*70 years old male, known CAD, MI and COLD/asthma, Tn and Copeptin negative, ECG normal, diagnosis: non cardiac, atypical chest pain (musculoskeletal), death one month later from metastatic lung cancer.

Figure 1. Patient flow chart

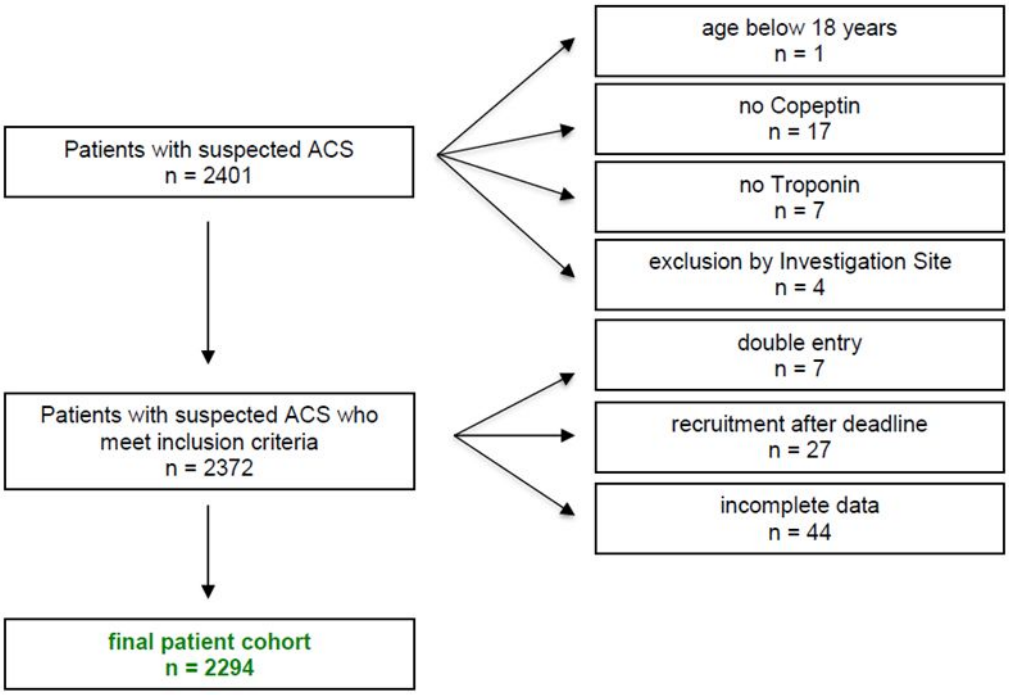
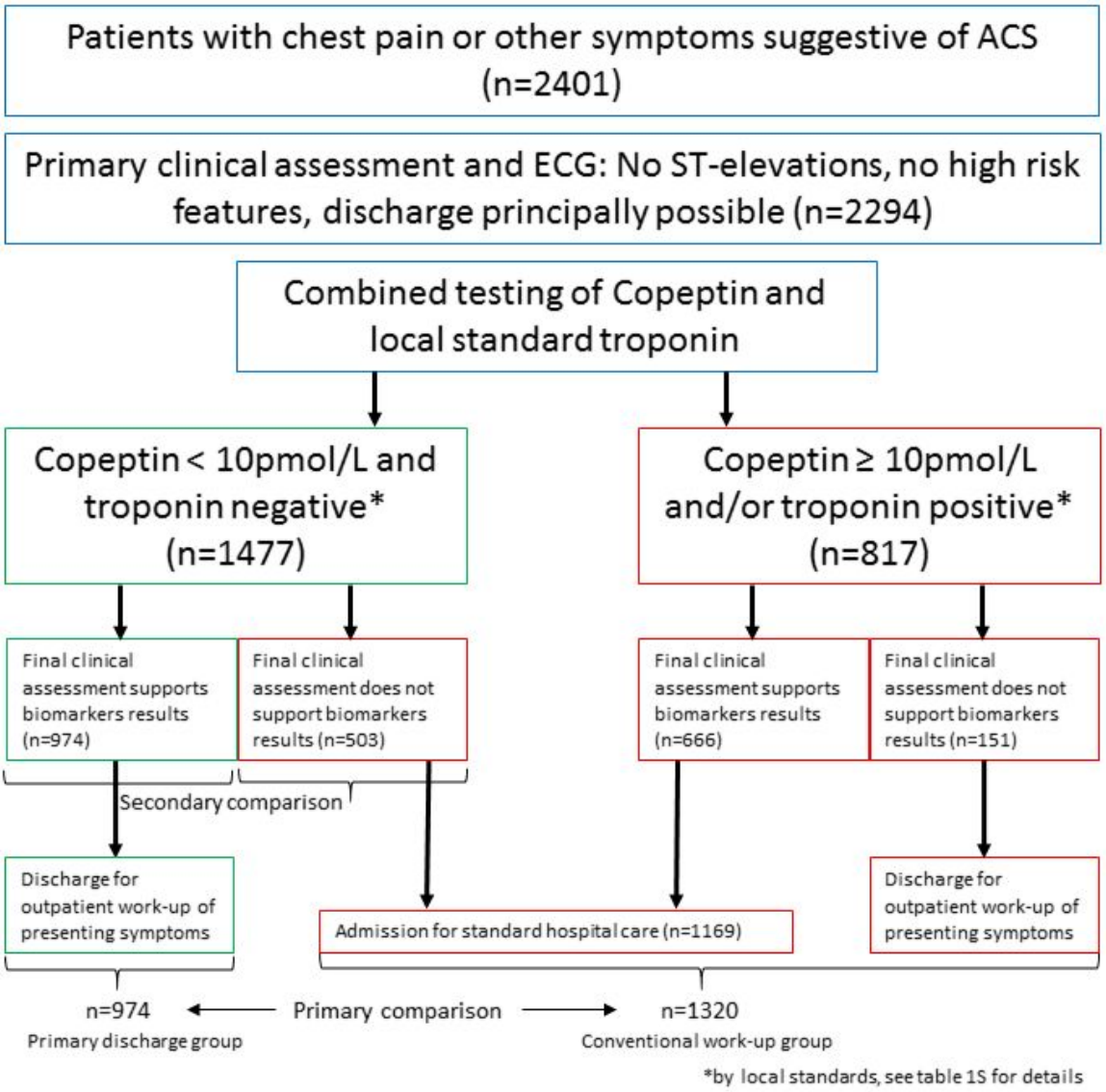


Figure 2. Algorithm for an early rule-out strategy and guidance of primary early discharge versus general hospital admission (conventional work-up)



Supplemental material

Figure 1S

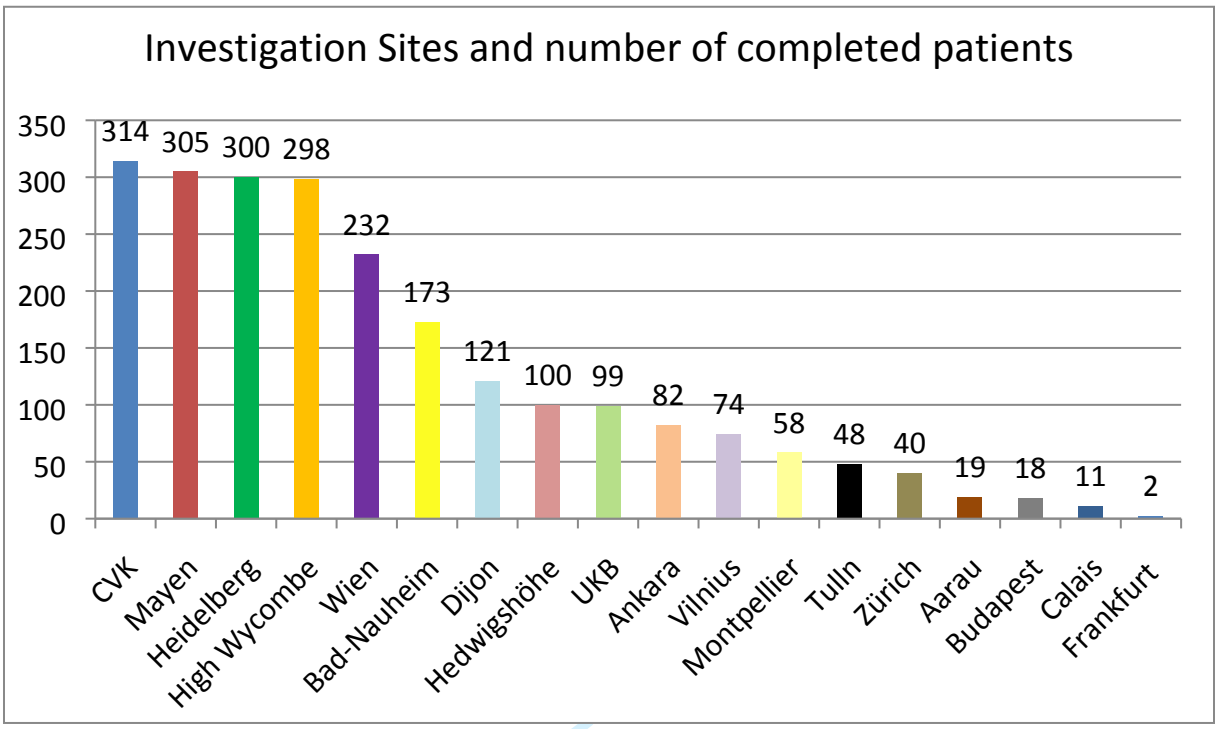


Figure 2S

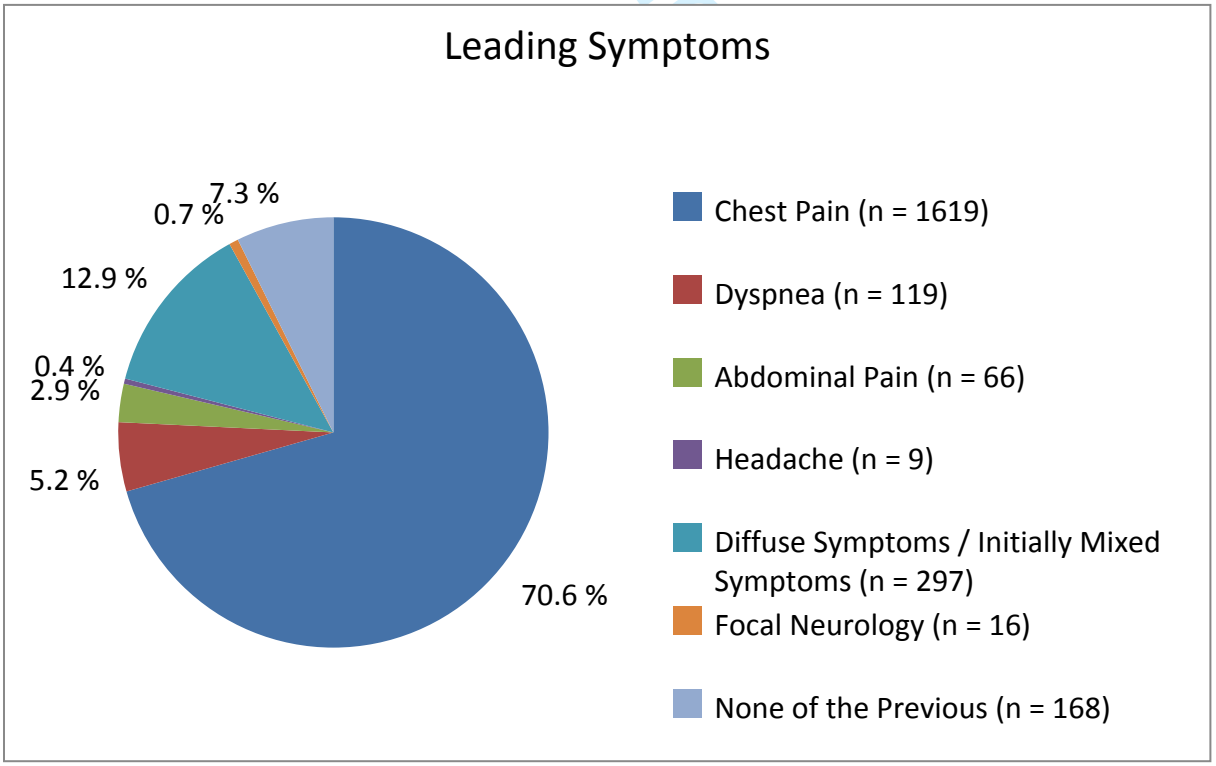


Figure 3S

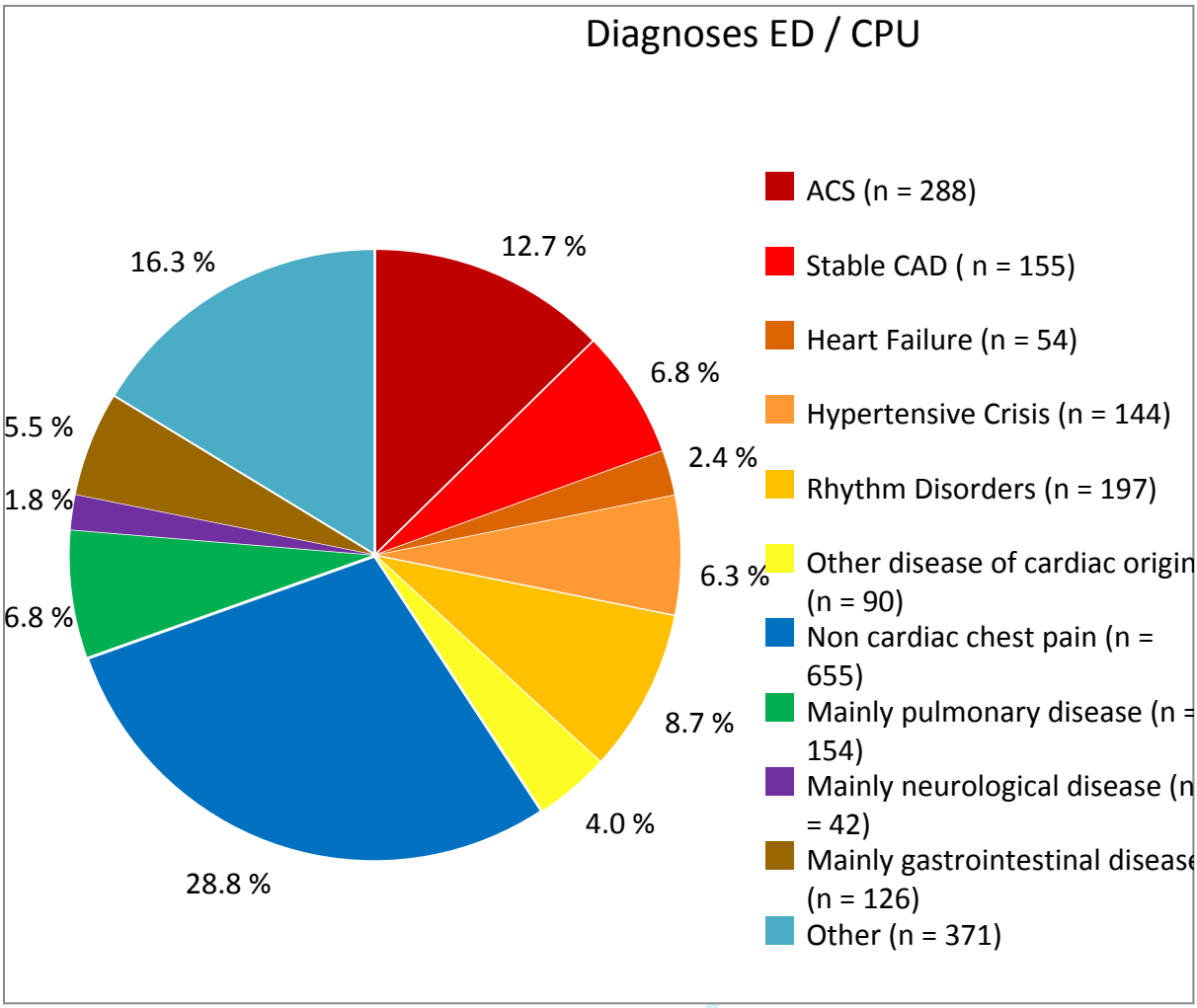


Table 1S. Local standard troponin tests and cutoffs for MI diagnosis

Center	Troponin test	MI Cut-Off
Heidelberg	Hs TnT, Elecsys, Roche Diagnostic	14 ng/l
UKB, Berlin	Hs TnT, Elecsys, Roche Diagnostic	14 ng/l
CVK, Berlin	AQT-Test POCT, Radiometer hsTnT, Elecsys, Roche Diagnostic	30 ng/l 50 ng/l
Frankfurt	Hs TnT, Elecsys, Roche Diagnostic	14 ng/l
Bad-Nauheim	Hs TnT, Elecsys, Roche Diagnostic	14 ng /l
Mayen	TnI Ortho Clinical Diagnostics and from 19.4.16 TnI, LOCI, Siemens	50 ng/l
Wien	TnI, LOCI, Siemens	45 ng/l
Calais	TnI, Access, Beckman and Coulter	30 ng/l (97.5th %le)
Vilnius	Hs TnI, Architect, Abbott	for men 34,2 ng/l for women 15,6 ng/l
Budapest	Hs TnT, Elecsys, Roche Diagnostic (Cobas e411)	14 ng/l
High Wycombe	Hs TnI, Architect, Abbott	for men 34,2 ng/l for women 15,6 ng/l
Zollichberg, Zurich	TnI-Ultra, Centaur, Siemens	40 ng/l
Aarau	TnI, LOCI, Siemens	45 ng/l
Berlin Hedwigshöhe	Hs TnI, Architect, Abbott	15 ng/l
Dijon	TnI, Vista, Siemens	100 ng/l
Ankara	TnI, Access, Beckman and Coulter	40 ng/l (99th %le)
Tulln	Hs TnT, Elecsys, Roche Diagnostic	14 ng/l
Montpellier	Hs TnT, Elecsys, Roche Diagnostic (Cobas 8000/e602 analyzer)	14 ng/l

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	24
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	21
		(b) Indicate number of participants with missing data for each variable of interest	21-23
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Multi-Centre Cross-Sectional Observational Registry to Monitor the Safety of Early Discharge after Rule-Out of Acute Myocardial Infarction by Copeptin and Troponin: The Pro-Core registry

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine, Diagnostics, Emergency medicine, Medical management
Keywords:	Registry, acute coronary syndrome, Myocardial infarction < CARDIOLOGY, Copeptin, troponin, mortality

Multi-Centre Cross-Sectional Observational Registry to Monitor the Safety of Early Discharge after Rule-Out of Acute Myocardial Infarction by Copeptin and Troponin: The Pro-Core registry

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Short title: Copeptin in ACS registry

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Abstract (294 words)

Abstract (word count 300)

Objectives. There is sparse information on the safety of early primary discharge from the Emergency Department (ED) after rule-out of MI in suspected ACS. This prospective registry aimed to confirm randomized study results in patients at low-to-intermediate risk, with a broader spectrum of symptoms, across different institutional standards, and with a range of local troponin assays including hs-cTn, cTn, and POC Tn.

Design

Prospective, multi center European registry.

Setting

18 Emergency departments in 9 European countries (Germany, Austria, Switzerland, France, Spain, United Kingdom, Turkey, Lithuania, Hungary)

Participants

The final study cohort consisted of 2,294 patients (57.2% males, median age 57 years) with suspected acute coronary syndrome (ACS).

Interventions

Using the new dual markers strategy, 1,477 patients were eligible for direct discharge, which was realized in 974 (42.5%) of patients.

Main outcome measures

The primary endpoint was all-cause mortality at 30 days.

Results

Compared to conventional work-up after dual marker measurement, the median length of ED stay was 60 minutes shorter (228min, 95%-CI: 219-239min vs. 288min, 95%-CI: 279-300min) in the primary DMS discharge group. All-cause mortality was 0.1% (95%-CI: 0%-0.6%) in the primary DMS discharge group vs. 1.1% (95%-CI: 0.6%-1.8%) in the conventional work-up group after dual marker measurement. Conventional work-up instead of discharge despite negative DMS biomarkers was observed in 503 patients (21.9%) and associated with higher prevalence of ACS (17.1% vs 0.9%, p<0.001), cardiac diagnoses (55.2% vs 23.5%, p<0.001) and risk factors (p<0.01), but with a similar all-cause mortality of 0.2% (95%-CI: 0%-1.1%) vs. primary DMS discharge (p=0.64).

Conclusions. Copeptin on top of cardiac troponin supports safe discharge in patients with chest pain or other symptoms suggestive of ACS under routine conditions with the use of a broad spectrum of local standard POC, conventional and high sensitivity troponin assays.

Trial registration

ClinicalTrials.gov NCT02490969

Key words: Registry, acute coronary syndrome, myocardial infarction, Copeptin, troponin, mortality

Strengths and limitations of this study

- This is the first large European registry demonstrating the safety of the dual marker strategy using cardiac troponin and copeptin for early discharge in patients with suspected acute coronary syndrome.
- The study supports the conclusions of a large randomized process trial regarding the safety of discharge and a reduced length of stay in ED, expanding the results to less selected patients, broader range of local cTn assays and assay generations and across different institutional standards reflecting daily routine in clinical practice.
- The study shows the potential for more than 50% of patients presenting with acute chest pain or other symptoms suggestive of myocardial infarction to be directly discharged to outpatient workup after thorough clinical assessment and a single blood draw.
- The study has been carried out in experienced centers, thus in settings with lower clinical expertise results may differ.

Introduction

Chest pain accounts for approximately 8 million annual emergency department (ED) visits in the United States (1), rendering chest pain the second most common presenting symptom. In a pooled analysis on 51 observational trials, the prevalence of the final diagnosis of ACS was confirmed in a median of 14%, with a range from 5% to 42% (2).

An effective risk stratification is paramount to select the most appropriate decision for admission or direct discharge because admission of patients at low or very low risk is not safe (3,4) as it increases the risk to receive unnecessary coronary angiography, coronary interventions, multiple re-admissions (3), and eventually the risk of peri-procedural myocardial injury or type 4 MI, and procedure-related major bleedings (4). Moreover, unselected admission of chest pain patients for further work-up for the evaluation of ACS is time consuming and costly (5,6). During an interval of only 9 years (from 1999–2008), the use of advanced medical imaging for ED visits related to chest pain was found to increase dramatically by 367.6% in the CDC/NCHS, National Hospital Ambulatory Medical Care Survey (7). On

the other hand, early discharge is also not without risk, as up to 2–5% of patients with ACS are reported to be inappropriately discharged from the ED every year (5,8) although the methodology to assess these numbers is limited (no complete follow up of all patients, no exact differentiation between incident and prevalent AMI and the components of ACS). Nevertheless, missed or incident AMI early after discharge is associated with a hazard ratio for death of 1.7 to 1.9% (8). Missed AMIs account for 20% of US emergency medicine related litigation dollars (9). Currently, use of high sensitivity cardiac troponins has improved the accuracy and earlier detection of an MI (10-13), and very low concentrations of hs-cTn have been reported to safely rule-out an MI and to be associated with rates of death or MI below 1% (14-17). Accordingly, 2015 ESC guidelines on NSTE-ACS (10) discourage routine coronary angiography in low risk patients and recommend early discharge after clinical risk stratification, and a pre- or post-discharge stress imaging test for the decision of a selective invasive strategy. Supporting evidence for early uneventful discharge of low risk patients stems mainly from observational studies (14,15,18,19) where investigators were commonly blinded to the investigational hs-cTn results, were unaware of retrospectively derived optimal decision cutoffs, and managed patients at their own discretion following standards of care applicable at that time. In fact, most of the patients who retrospectively fulfilled early rule-out criteria were kept in hospital and neither medical measures nor non cardiac diagnoses are reported. Only few interventional clinical trials evaluated the safety of a randomized allocation to early discharge versus conventional care in patients at low (20,21) or low-to-intermediate high risk (22). The Biomarkers-in-Cardiology 8 (BIC-8) trial (22) tested the utility of a dual biomarker strategy using normal cTn or hs-cTn values, i.e. below the upper limit of normal, mainly the 99th percentile, together with normal Copeptin values below the 95th percentile (<10 pmol/L) to identify candidates for direct early discharge from the ED. The findings demonstrated that this strategy reduced the length of observation time in the ED or chest pain unit and increased rates of discharge at a low risk for major adverse cardiovascular events (MACE) that was comparable or even lower in the per protocol analysis to standard of care. Compared to serial troponin-based protocols, advantages of the dual marker strategy include the ability of instant rule-out of MI without the need for additional blood draw, high sensitivities and negative predictive values (NPVs) for acute myocardial infarction (AMI) of Copeptin in combination with conventional or contemporary sensitive cTn assays (23-28), or POCT (29), particularly when hs-cTn or validated hs-cTn assays are not available, and supporting data for a safe discharge from a large, appropriately powered randomized multicenter trial (22). The value of Copeptin on top of detectable but still normal cTn or hs-cTn for rule-out of MI has been studied extensively and the DMS algorithm has been quoted as an additional option for instant rule-out in 2015 ESC guidelines (10). In contrast, there is sparse information from randomized trials on the safety of discharge (20,21) and the safety of discharge using a pre-specified algorithm has rarely been investigated in a prospective registry.

Therefore, the aim of the present multicenter observational trial was to confirm the safety of this strategy that was previously reported in a randomized interventional trial (22) in routine clinical practice, across a broad spectrum of cTn assays including POCT, in an unselected population with a broader range of symptoms, and at low-to-intermediate risk presenting with suspected ACS to 18 EDs in Europe and Turkey.

Methods

The Pro-Core is a multi-center, international observational trial with 18 participating centers (figure 1S) in Europe and formally Near East (Ankara, Turkey).

We enrolled adult men and women who present to an ED or chest pain unit (CPU) with signs and symptoms suggestive of acute coronary syndrome without ST-segment elevation (NSTE-ACS). Eligible patients qualifying for the DMS strategy were recruited consecutively but entry was restricted to patients with a low or intermediate GRACE score.

Patients were eligible if they were aged ≥18 years, presented with symptoms suggestive of ACS such as acute chest discomfort, angina pectoris, or dyspnea as leading symptoms. Patients presenting with ST-segment elevation or a final diagnosis of ST-segment elevation myocardial infarction (STEMI) were excluded from analysis (see figure 1 for patient flow).

Patients underwent clinical assessment that included medical history, physical examination, standard blood test including measurements of local (hs)-cTn, Copeptin and 12-lead ECG. Baseline information included the Killip class, and clinical information to calculate the GRACE score. Other clinical scores were not tested prospectively prohibiting any conclusion on their clinical usefulness. Physicians had access to all clinical information including Copeptin and cTn results that were reported with local turn-around-times. Decision for primary discharge after rule-out using the dual biomarker strategy, or for disposition of patients if MI was not ruled out was left at the discretion of the attending physician. Patients were excluded if high risk features were evident (e.g. the GRACE score was above 140) and if hospital admission was obviously necessary at presentation for any reason. Final diagnosis of NSTE-ACS was performed by the ED physician applying the criteria of the 3rd universal definition of AMI (**30**). Unstable angina was diagnosed in the presence of new or worsening symptoms of suspected myocardial ischemia but either normal or undetectable cTn concentrations in serial blood draws, or a cTn together with a Copeptin below the decision limit at presentation. Importantly, classification of ACS was done by the treating physician and was not subject of retrospective adjudication. All patients were contacted at 30 days to assess all-cause mortality. Number of patients was limited to 300 patients per participating site to limit center bias.

Biomarkers and rule-out algorithms

Copeptin and cardiac troponin were tested from fresh unfrozen blood from a single blood sample drawn at admission to the ED or CPU as part of the routine patient management.

Copeptin was measured using the automated fluoro-immunoassay B·R·A·H·M·S Copeptin proAVP KRYPTOR for the quantitative measurement of C-terminal pro-arginine-vasopressin (CT-proAVP, Copeptin) in human serum and plasma on the B·R·A·H·M·S KRYPTOR compact PLUS platform. The test has a detection limit of 0.69 pmol/L and a functional assay sensitivity (detected by inter-assay precision of 20% CV) of 1.08 pmol/L.

The recommended cut-off for the decision between a positive and a normal test is 10 pmol/L, corresponding to the 95th percentile of a healthy reference population. This cut-off was used in the randomized controlled trial by Möckel et al. (**22**), and is the recommended cut-off for the rule-out algorithms for MI.

Cardiac Troponin was measured at the individual institutions according to standard practice. An overview on local assays and cutoffs is provided as supplemental material (Table 1S). Briefly, Roche Elecsys hs-cTnT was used in 39%, followed by Abbott Architect hs-cTnI, Siemens (Vista, Loci), Beckman Access TnI, and Radiometer (3rd gen. cTnT) in 22%, 22%, 11% and 6%, respectively. Conventional and high-sensitivity assays were permitted for the early rule-out strategy.

A patient qualified as rule-out and for early discharge if he presented with signs and symptoms suggestive of ACS, together with a low-to-intermediate risk profile defined as the absence of high risk features (e.g. a GRACE score <140), and a combined negative testing of Copeptin and troponin, defined as Copeptin below 10 pmol/L and cardiac troponin below the local AMI decision limit as recommended by the guidelines, mostly the 99th percentile value of a healthy reference population provided by the manufacturer.

Follow-Up and Clinical End Points

The primary objective was to evaluate 30-day all-cause mortality in patients in whom acute myocardial infarction was ruled-out using the early dual marker rule-out strategy and who are therefore directly discharged from the ED. All-cause mortality was preferred over cardiovascular death because collection of information is more convenient and because the majority of eligible patients presented to the EDs with non-coronary and non-cardiac diagnoses.

The secondary objectives were evaluated in all patients, irrespective of biomarker test results and disposition. Secondary endpoints included the diagnosis of acute myocardial infarction, final hospital diagnoses, time to discharge/transfer from the ED/CPU, disposition decision (discharge or admission), length of hospital stay, ICU-treatment, performance of coronary angiography/ PCI/ CABG, performance of ECGs, stress testing, imaging, performance of cardiovascular monitoring, In-hospital all-cause mortality, 30-day all-cause mortality.

The study protocol also addressedpatients where the protocol was violated, i.e. those who were not primarily discharged or not admitted although criteria were fulfilled (over-rule). The reasons for over-rule or other protocol violations were registered.

The study complies with the Declaration of Helsinki and received the primary ethics approval from the Charité ("Ethikausschuss 1 am Campus Charité-Mitte; EA1/008/15). The positive vote was sent to all study sites. The principle investigator decided based on local and national rules, whether a separate local ethics committee submission was necessary. Additional ethics approvals were obtained from the sites listed in the supplemental table 2S. The ethics committee approved that anonymized routine data of patients were used without informed consent for this registry. The study was registered before enrollment of the first patient (ClinicalTrials.gov NCT02490969).

Statistical evaluation

Enrolment was restricted to a maximum number of 300 patients per center to ensure generality by avoiding the dominance of single centers. The total number of patients enrolled therefore depended rather on the number of participating centers than on their enrolment performance. As the primary objective of this registry was the monitoring of an already routinely applied clinical algorithm, no confirmatory study design was chosen and there was no sample size calculation performed. An exploratory analysis of the safety of DMS by local cTn assay or assay generation, or by study center was not persued as there was only 1 death precluding meaningful analysis. All data were entered into an online electronic case report form. Group comparisons for categorical variables were performed using chi-square tests and for numerical variables using Wilcoxon rank-sum tests. A p-value below 0.05 was considered significant (no correction for multiple testing conducted).95% confidence intervals were determined for binary all-cause death at 30 days by the method of Clopper and Pearson and for numeric length of stay in the ED/CPU by 2.5%- and 97.5%-quantiles estimated by bootstrapping.

Statistical analyses were performed using the software R Version 3.1.2 and SPSS (IBM® SPSS Statistics, Version 21).

Patient and Public Involvement

Patients or public were not involved in the development of the study protocol.

Results

A total of 2,401 consecutive patients with suspected ACS were screened from September 16th 2015 until the end of recruitment on May 23rd 2017. Of these, 107 patients were excluded from analysis due to incomplete biomarker or clinical information, withdraw of informed consent, or double entry (see patient flow diagram; Figure 1). The final study cohort consisted of 2,294 patients (57.2% males,

median age 57 years) with suspected ACS. Numbers of recruited patients varied by study site but were limited per protocol to a maximum of 300 enrolments per site. The exact numbers of recruited patients is displayed in supplemental Figure 1S.

The most prevalent leading symptom at presentation (Supplemental Figure 2S, Table 1) was chest pain in 70.6% (n=1619), followed by diffuse or initially mixed symptoms in 12.9% (n=297), dyspnea in 5.2% (n=119), abdominal pain in 2.9% (n=66), , focal neurology in 0.7% (n=16), headache in 0.4% (n=9), or none of the listed symptoms in 7.3% (n=168). As expected from the inclusion criteria, the study cohort represented a low-to-intermediate risk group with a median GRACE score of 89 (IQR: 67-114) and a Killip class of 1 in 96% of cases (n=2084). Time from onset of symptoms to presentation was below 12 hours in 50.8%. An interval of 0-3 hours, 3-6 hours and 6-12 hours was registered in 26.3% (n=558), 13.3% (n=283), and 11.2% (n=238) of patients, respectively. ECG at presentation was non-diagnostic in 87.3% of patients. Regarding initial cTn and Copeptin results, a total of 2,017 patients (87.9%) were below the diagnostic cutoff of the local cTn, and 1,615 patients (70.4%) below the cutoff for Copeptin. A total of 1477 patients (64.4%) were below the decision cutoff for both biomarkers fulfilling the criteria for early primary discharge from the ED (theoretically maximal efficiency).

Clinical pathways

974 patients (42.5%) were categorized into the primary discharge after fast rule-out pathway, and 1,320 patients into the conventional work-up pathway. Of these, 654 patients did not follow a pre-defined pathway but were either admitted although qualified for primary discharge (n=503, 21.9%), or were discharged although not ruled-out (n=151, 6.6%), see figure 2.

In the entire cohort, the overall rate of an ACS diagnosis was 12.7% (n=288), non-cardiac chest pain 28.8%, rhythm disorders 8.7%, pulmonary disorders 6.8%, stable CAD 6.8%, hypertensive crisis 6.3%, and gastrointestinal disease 5.5%. Other cardiac diagnoses were present in 4%, and other unspecified diagnoses in 16.3% of cases (Supplemental Figure 3S).

In the conventional care pathway, an ACS was diagnosed in 21.1% (n=279) with the majority classified as a NSTE-ACS (n=172, 61.6%). STEMI was an exceptional diagnosis in 15 patients (5.2%) since patients with STEMI were routed directly to the catheterization laboratory in most institutions and were not intended for inclusion. Only if STEMI was diagnosed later and not at admission such patients were enrolled. Other diagnoses included non-cardiac chest pain in 18.8% (n=247), rhythm disorders in 5.9% (n=133), stable CAD in 8.9% (n=117), pulmonary disease in 6.8% (n=90), hypertensive crisis in 5.9% (n=77), gastrointestinal disease in 4.7% (n=62), and other diagnoses in 14.1% (n=185).

In the primary discharge after fast rule-out pathway, only 9 patients (0.9%) were diagnosed as having an ACS, mostly unstable angina (n=4) or unclassified ACS (n=4), with only 1 case (0.1%) diagnosed as

NSTEMI (NPV for MI of 99.9%). Rate of admission was only 0.1% due to a case where admission was forced by the referring primary care physician although discharge was planned.

There were two different ways how local investigators over-ruled the intended pathway. The larger group consisted of 503 patients (21.9%) who were allocated to the conventional care pathway at the discretion of the local investigator although they were categorized into the primary discharge after fast rule-out pathway. The second group consisted of 151 patients (6.6%) who were primarily discharged although they should have received conventional care. Reasons for the over-rule consisted mainly of decisions of the physician to admit to hospital based on clinical judgment. Minor reasons were opposition of patients against serial blood sampling (n=2), and other unspecified reasons (n=6).

There were differences between the primary discharge after fast rule-out pathway and the over-rulers into the conventional care pathway (Table 2). Patients were older, more frequently males, had more often a history of CAD or previous MI, more risk factors including a higher prevalence of arterial hypertension, hypercholesterolemia, and diabetes mellitus. In addition, patients had more often a diagnostic ECG, and higher GRACE scores. In addition, these patients received more often an ACS diagnosis, i.e. a diagnosis of unstable angina, and spent longer times in the ED. However, and importantly, rates of all-cause mortality at 30 days were not significantly different (0.2% vs 0.1%, p=1) compared to the primary discharge after fast rule-out pathway.

Outcomes

The primary endpoint, all-cause death within 30 days among the primary discharge after fast rule-out pathway, occurred in only 1 case of 974 patients (0.1%, 95%-CI: 0%-0.6%). This death was not related to the biomarker algorithm: the patient was 70 years old, had a history of CAD and previous MI and presented with musculoskeletal symptoms, was primarily discharged and died 1 month later from metastatic lung cancer (table 3).

By contrast, all-cause mortality rate in the conventional care pathway was 1.1% (14 of 1320 patients, 95%-CI: 0.6%-1.8%) and thus significantly higher (p=0.011) than in the primary discharge after fast rule-out pathway (Table 3). Diagnoses in the deceased patients of the conventional care pathway included ACS (n=5), non-cardiac chest pain (n=2), pulmonary disease (n=2), neurological disease (n=1), rhythm disorders (n=1), stable CAD (n=1), heart failure (n=1), gastrointestinal disease (n=1), and non-specified others (n=1). Patients who died were a median of 15 years older, had more often dyspnea as the leading presenting symptom, presented more frequently more than 12 hours after symptom onset, and were characterized by higher GRACE score (167 vs 90 points, p<0.001) and Killip class. In addition, non-survivors had received more extensive diagnostic workup, presented more often with a local cTn and Copeptin above cutoff, and median Copeptin values were significantly higher than among

survivors (50.8 vs 7.0 pmol/L, p<0.001) underscoring the prognostic information that is provided by cTn and Copeptin independent of the underlying disease.

Regarding secondary endpoints, hospitalization rates were 0.1% in the primary discharge after fast rule-out pathway compared to 59% in the conventional care pathways (p<0.001). As expected, median lengths of stay in the ED (treatment time) were significantly shorter in the primary discharge after fast rule-out pathway vs the conventional care pathway (228 min vs 288 min, p<0.001, and rates of patients discharged within 0 to <1 hour (1.5% vs 3.6%), 1 to <2 hours (13.2% vs 13.3%), and 2 to < 3 hours (21.7% vs 16%), 3 to <6 hours (49.3% vs 37.3%) were significantly different in primary discharge after fast rule-out pathway versus conventional care pathway (p for trend < 0.001). Conversely, rates of patients with longer ED treatment times > 6 hours were significantly lower in the primary discharge after fast rule-out pathway than in the conventional care pathway out group (14.2% vs 29.8%, p<0.001).

Discussion

Information on the safety of direct discharge from an ED after rule-out of MI in patients with suspected ACS is almost exclusively restricted to findings that were generated in observational trials where attending physicians were commonly blinded to the investigational hs-cTn results, or to retrospectively determined optimal decision cutoffs. Treatment decisions based on at that time applicable standards of care and were left at the discretion of the treating physician (**16-19**,**31**).

Following the randomized BIC-8 study, which proofed safe discharge after instant rule-out of AMI by the use of troponin and Copeptin from a single blood draw (22), we could confirm in a large European registry that this is also true in clinical routine.

The superior analytical sensitivity of hs-cTn assays has already enabled an accurate rule-out of MI with sensitivities and NPVs of > 90% (**10**), facilitating fast rule-out based on either very low concentrations of hs-cTn assays obtained from a single measurement at presentation (**14,15,16-19,32**), or from serial blood draws after 1 to 3 hours (**17-19,31,33-38**) using hs-cTn at the 99th percentile (**10-13**), or slightly below (**18,19**) the 99th percentile of a healthy reference population. Integration of clinical judgment or a validated clinical score such as the GRACE, TIMI, HEART, modified Goldman Score, MACS clinical decision rule, EDACS and Vancouver Chest Pain Algorithm, and North American Chest Pain Rule further improve NPV yielding NPV between 98.1-100% and 98.4-100% when cTn and hs-cTn assays were used, respectively (**39**). Although, 2015 ESC guidelines (**10**) discourage routine invasive strategy in low risk patients and rather recommend discharge following risk stratification, and a pre- or post-discharge stress imaging test to decide on a selective invasive strategy, evidence from randomized trials to endorse these recommendations is sparse (**20,21,22**). The Manchester Acute Coronary Syndrome

(MACS)-Pilot study (20) enrolled 138 patients with suspected cardiac chest pain who were randomized to receive care guided by the MACS decision rule or standard care. The primary efficacy outcome was a decision to discharge within 4 hours of arrival, without missed MI and without death, AMI or coronary revascularization occurring during 30 days of follow-up. This small pilot study found a significantly higher rate of uneventful primary discharge within 4 hours (26% vs 8%, p=0.004) among those guided by the MACS rule. The HeartPathway Trial enrolled 282 patients with suspected ACS stratified into risk categories using the HEART Score (21). The study was not powered to compare event rates in randomized groups but found a decreased objective cardiac testing at 30 days by 12.1%, a reduced length of stay by 12 hours, and an increase of early discharges by 21.3%. The BIC-8 trial (22) that enrolled a total of 902 low-to-intermediate high risk patients using the GRACE score and subsequently randomized patients with normal presenting cTn and Copeptin values into an early discharge and a standard protocol group. The study demonstrated a reduction of observation time in the ED by more than 40% from a median of 7 hours to 3 hours, achieved a 5.6-fold increase in ED discharge rate from 67.7 vs 12%, and a similar 5.2% rate of 30-day major adverse cardiovascular events that were liberally defined as all-cause death, survived sudden cardiac arrest, re-hospitalization for ACS, unplanned PCI or CABG, or documented life-threatening arrhythmias in the standard and Copeptin group (22).

The present large multicenter registry was performed in patients with suspected ACS and low-to-intermediate risk to test the usefulness of a dual biomarker strategy, consisting of a normal Copeptin and cTn, to rule-out MI from a single blood draw at admission and to discharge low risk patients primarily from the ED. In order to represent clinical practice of different type of institutions, variable local practice and across the spectrum of cTn assays and grades of assays sensitivities (40,41), this observational study was conducted in 18 different institutions in Europe and Asia. Institutions included EDs in community hospitals, and CPUs in PCI centers and few University hospitals. Patients qualified for enrolment in the presence of a broader spectrum of symptoms suggestive of ACS not limited to chest pain or angina, and a broad spectrum of cTn assays and different grades of analytical sensitivities including conventional, contemporary, and hs-cTn assays was permitted. To reduce dominance of few high recruiting centres, enrolment rates were restricted to 300 study patients per site.

There were several key findings of this survey that support the usefulness and safety of this concept in clinical routine and outside of controlled clinical trials. First, earlier discharge from the ED in patients ruled-out at presentation using a single blood draw is feasible without any obvious safety concern. All-cause mortality rate within 30 days was 0.1% and attributed to a case with metastatic lung cancer. Second, length of stay in the ED is significantly shorter by 60 minutes allowing an earlier discharge, a finding particularly useful in congested EDs or CPUs. Thus, the present registry data confirm the findings from the randomized BIC-8 trial (22) on reduced length of stay, increased discharge rates and support the safety of a primary planned discharge from an ED after clinical risk assessment. Third, the

dual marker concept is efficient as it can be applied to at least 42.5% (potentially effective in 66.4%) of patients presenting with chest pain or chest pain equivalent symptoms to an ED. Thus, efficacy of this dual marker strategy is almost comparable with the efficacy of the ESC recommended 0/1 h diagnostic algorithm that requires serial blood draws and a validated hs-cTn assay (currently Abbott Architect hs-cTnI and Roche hs-cTnT). While other fast rule-out algorithms based on very low hs-cTnI or hs-cTnT at the LoB or LoD may demonstrate similar diagnostic performance and safety, the numbers of patients who qualify are substantially lower (**14,15,32**) and these strategies have never been tested prospectively with patients being really discharged after testing.

We found a relevant number of over-rule by local ED physician leading to an admission of patients who qualified for discharge by their biomarker results (34%). Given that these patients had an uneventful clinical course (see table 2), void of primary or secondary events during follow-up, suggests an underestimated efficacy and more potential of safe discharge. Fourth, regarding the diagnostic performance for rule-out that was not in the scope of this survey, the dual marker algorithm was associated with a high negative predictive value of 99.9% for NSTEMI (1 missed NSTEMI) confirming the existing evidence on the diagnostic performance of the Copeptin/troponin dual marker strategy (**22,26-28**). Fifth, regarding secondary objectives, the dual marker strategy was associated with shorter stays in ED. Sixth, consistently with previous studies (**26-28**,**42,43**), elevated Copeptin levels were associated with all-cause mortality within 30 days providing confirmatory evidence that Copeptin confers prognostic information that is complementary to cTn or hs-cTn, in various acute cardiovascular settings including ACS (**26-28,42,43**), heart failure (**44,45**), and acute pulmonary embolism (**46**) but also non-cardiac disease. In addition, an elevated Copeptin should prompt a search for a variety of potentially life-threatening non-cardiac conditions including perforated stomach ulcer, pancreatitis, cholecystitis, bleedings, infections, or neurological disorders (**47**).

Limitations

First, we observed very low rates of all-cause mortality at 30-days, i.e. 0.1% (95%-CI: 0%-0.6%) in the primary discharge after fast rule-out pathway as compared to 1.1% (95%-CI: 0.6%-1.8%) in the conventional care pathway. Low event rates may be explained by restriction of the DMS algorithm to patients at low or intermediate risk based on the GRACE score. Therefore, our findings cannot be extrapolated to settings where risk stratification after rule-out is based on other clinical scores or on clinical judgement. Moreover, a selection bias towards recruitment of a non-representable low risk ACS cohort cannot be fully excluded as inclusion criteria were not limited to typical chest pain, longer pain episodes or abnormal ECG findings. However, the study population was planned to represent a real life picture of patients who present in clinical routine with various symptoms and a wide range of risk. Copeptin concentration return to normal within few hours reducing the diagnostic performance

of the DMS algorithm to early presenters. As a tribute to the consecutive enrolment of patients, we were not able to enrich the study population by patients presenting within 6 hours from onset of symptoms (49.2% of the entire study cohort reported onset of symptoms more than 12 hours before presentation). Therefore, scrutiny is advised regarding the interpretation of the DMS result in patients presenting very late or who cannot state a precise onset of symptoms. We believe that our study cohort is also similar to other observational studies enrolling patients with suspected ACS. The overall prevalence of ACS in this registry was 12.7% and is thus very consistent with a median of 13 to 14% prevalence of ACS reported in a pooled analysis of 51 observational trials on patients with suspected ACS (**2**). In addition, the median GRACE score was 89 points (IQR: 67-114) which is very similar with the mean GRACE score of 80 (SD 28 points) in the randomized intervention trial (**22**).

Second, rates of enrolment per site were heterogenous with a mix of high and low recruiting centers. However, the very low mortality rate does not allow any exploratory analyses on the safety of discharge by center volumes,experience of physicians, local cTn assay or assay generation.

Third, currently a strategy for instant rule-out based on Copeptin and cTn is being recommended by 2015 ESC guidelines on NSTE-ACS (**10**) and an updated consensus document of the German Society of Cardiology on the use of Copeptin in CPUs (**48**) and chest pain centers (**49**). However, there is a gap between the high recommendation level endorsed by numerous clinical trials (**23-26,42,43**), editorials and state-of-the-art reviews (**38,39**), meta-analyses (**27,28**), and National practice guidelines (**10,48,49**) on the one hand and the obvious underuse in clinical practice for suspected ACS. In the elective setting, Copeptin is currently used for the diagnosis of diabetes insipidus, a non-emergent diagnosis. In emergencies requiring immediate measurement, the most probable reason for underuse is that Copeptin has to be measured on a stand-alone device that is more labor-intensive than an automated central laboratory system, which leads to the suspicion that nowadays economic features in the laboratory are hurdles for state of the art use of biomarkers. Development of a POCT system for Copeptin and implementation of Copeptin to a central laboratory platform would overcome this obstacle. In this registry, however, Copeptin was measured on a Kryptor platform with a measuring time of 14 minutes and immediate reporting of the result to the ED physician. Accordingly, most of the time delays between diagnosis and the disproportionally longer stay in ED are regarded to be related to other time consuming processes including diagnostic work-up for differential diagnoses and drafting of the discharge report, particularly in the presence of crowding in the ED.

Conclusions

Copeptin on top of cardiac troponin is currently the only strategy that – based on a RCT and a large multi-centre registry - supports the safe direct discharge of patients with chest pain or chest pain equivalent symptoms suggestive of ACS under routine conditions. There are only few randomized trials

that provide evidence for a safe discharge after rule-out in low risk patients. The present registry confirms findings from the randomized BIC-8 trial in an independent real world registry. The efficacy of the DMS in terms of patients potentially qualifying is at least 42.5% or potentially considerably higher.

We believe that the present findings will have enormous implications on health care resources by shortening observation times, hospitalization rates, reducing diagnostic resources, and avoid unnecessary coronary angiographies.

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Transparency declaration

The corresponding authors (MM) author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing statement

Relevant data could be shared on reasonable request.

Conflicts of interest

EG received honoraria for lectures from Roche Diagnostics, AstraZeneca, Bayer, Daiichi-Sankyo, Lilly Eli Deutschland. He serves as a consultant for Roche Diagnostics, BRAHMS Thermo Fisher Scientific, Boehringer Ingelheim, and has received research funding from BRAHMS Thermo Fisher Scientific, Roche Diagnostics, Bayer Vital and Daiichi Sankyo;

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EG and **MM** were involved in the conception and design of the study, the acquisition, analysis and interpretation of data, drafted the manuscript, approved the final version to be published, are accountable for all aspects of the work and an d **MM** serves as guarantor for the manuscript.

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Table 1. Baseline characteristics of the patients

Variable	Category	total (n=2294)	primary discharge after fast rule out (n=974)	conventional work up (n=1320)	p-value
Age		59 (46, 72)	51 (39, 62)	65 (52, 75.25)	<0.001
Gender	Female	42.8% (981)	49.7% (484)	37.7% (497)	<0.001
Onset of symptoms before presentation	0 - 3 h	26.3% (558)	26% (228)	26.5% (330)	0.053
	3 - 6 h	13.3% (283)	11.8% (103)	14.4% (180)	
	6 - 12 h	11.2% (238)	13.1% (115)	9.9% (123)	
	> 12 h	49.2% (1043)	49.1% (430)	49.2% (613)	
Leading sympton	Chest pain	70.6% (1619)	76.9% (749)	65.9% (870)	<0.001
	Diffuse Symptoms / Initially Mixed Symptoms	12.9% (297)	9.9% (96)	15.2% (201)	
	None oft he Previous	7.3% (168)	6.6% (64)	7.9% (104)	
	Dyspnea	5.2% (119)	2.5% (24)	7.2% (95)	
	Abdominal pain	2.9% (66)	3.1% (30)	2.7% (36)	
	Focal Neurology	0.7% (16)	0.4% (4)	0.9% (12)	
	Headache	0.4% (9)	0.7% (7)	0.2% (2)	
History of CAD		29.2% (656)	16.8% (158)	38.2% (498)	<0.001
History of MI		11.7% (262)	7.3% (69)	14.8% (193)	<0.001
Risk factor: HTN		53.8% (1189)	38.3% (357)	65.1% (832)	<0.001
Risk factor: HLP		33.6% (708)	23.7% (210)	40.7% (498)	<0.001
Diabetes Mellitus		15.6% (347)	9.3% (86)	20.1% (261)	<0.001
Smoking		34.3% (633)	34.3% (264)	34.3% (369)	1.000
Positive Family History of CAD		32.4% (477)	32.3% (202)	32.5% (275)	0.956
Grace Score	<109	69.3% (1413)	86.1% (736)	57.2% (677)	<0.001
	109-140	21.9% (446)	12.7% (109)	28.5% (337)	
	> 140	8.8% (179)	1.2% (10)	14.3% (169)	
Killip class	I	96% (2084)	98.4% (900)	94.3% (1184)	<0.001
	II	3.2% (70)	1.6% (15)	4.4% (55)	
	III	0.7% (15)	0% (0)	1.2% (15)	
	IV	0% (1)	0% (0)	0.1% (1)	
ECG not diagnostic		87.3% (1971)	93% (892)	83% (1079)	<0.001
ST-elevation		4.2% (94)	2.6% (25)	5.4% (69)	0.002
ST-depression		7.7% (170)	3.6% (34)	10.7% (136)	<0.001
Local cTn	negative	87.9% (2017)	100% (974)	79% (1043)	<0.001
Copeptin	[pmol/l]	7.0 (3.9, 11.8)	4.9 (3.2, 7.7)	10.2 (5.3, 22.9)	<0.001
Copeptin	negative	70.4% (1615)	100% (974)	48.6% (641)	<0.001
Local troponin and copeptin	negative	64.4% (1477)	100% (974)	38.1% (503)	<0.001

Numbers are medians, interquartile ranges and p-values of Wilcoxon rank-sum test for numerical variables and, percentages, counts and p-values of chi-square test for categorical variables.

Table 2 Comparison of patient's characteristics of primary discharge versus over-rule to conventional care despite eligibility for discharge by biomarker results

Variable	Level	Total (n=1477)	Primary discharge (n=974)	Admission over-rule (n=503)	p-value
Age		59 (46, 72)	51 (39, 62)	61 (51.5, 73)	<0.001
Gender	Female	47.2% (697)	49.7% (484)	42.3% (213)	0.009
Onset of symptoms before presentation	0 - 3 h	24.5% (333)	26% (228)	21.7% (105)	0.060
	3 - 6 h	12.1% (165)	11.8% (103)	12.8% (62)	
	6 - 12 h	12.1% (164)	13.1% (115)	10.1% (49)	
	> 12 h	51.3% (698)	49.1% (430)	55.4% (268)	
Leading sympton	Chest pain	73.9% (1092)	76.9% (749)	68.2% (343)	<0.001
	Diffuse/ Initially mixed symptoms	10.9% (161)	9.9% (96)	12.9% (65)	
	Dyspnea	4.4% (64)	2.5% (24)	8.1% (40)	
	Abdominal pain	2.8% (41)	3.1% (30)	2.2% (11)	
	Focal Neurology	0.5% (7)	0.4% (4)	0.6% (3)	
	Headache	0.6% (9)	0.7% (7)	0.4% (2)	
	Other	6.9% (102)	6.6% (64)	7.6% (38)	
History of CAD		24.4% (351)	16.8% (158)	38.9% (193)	<0.001
History of MI		9.5% (136)	7.3% (69)	13.5% (67)	<0.001
Hypertension		48.7% (693)	38.3% (357)	68.2% (336)	<0.001
HLP		29.5% (401)	23.7% (210)	40.6% (191)	<0.001
Diabetes Mellitus		10.9% (155)	9.3% (86)	13.9% (69)	0.011
Smoking		34.6% (409)	34.3% (264)	35.1% (145)	0.838
Family History CAD		33.6% (322)	32.3% (202)	36% (120)	0.269
Grace Score	< 109	80.7% (1067)	86.1% (736)	70.7% (331)	<0.001
	109-140	16.8% (222)	12.7% (109)	24.1% (113)	
	≥ 140	2.6% (34)	1.2% (10)	5.1% (24)	
Killip class	I	98.4% (1378)	98.4% (900)	98.4% (478)	0.375
	II	1.6% (22)	1.6% (15)	1.4% (7)	
	III	0.1% (1)	0% (0)	0.2% (1)	
Final diagnoses	ACS total	6.5% (95)	0.9% (9)	17.1% (86)	<0.001
	unclassified ACS	1.9% (28)	0.4% (4)	4.8% (24)	
	UAP	4% (58)	0.4% (4)	10.8% (54)	
	NSTEMI	0.3% (5)	0.1% (1)	0.8% (4)	
	AMI other	0.1% (2)	0% (0)	0.4% (2)	
	STEMI	0.1% (2)	0% (0)	0.4% (2)	
Main diagnosis	Cardiac	34.4% (503)	23.5% (226)	55.2% (277)	<0.001
Mortality	30days	0.1% (2)	0.1% (1)	0.2% (1)	1

Numbers are medians, interquartile ranges and p-values of Wilcoxon rank-sum test for numerical variables and percentages, counts and p-values of chi-square test for categorical variables. CAD, coronary artery disease; HLP, hyperlipidemia; UAP, unstable angina pectoris

Table 3 All-cause death at 30 days and secondary outcomes

Variable	Categories	Total (2294 patients)	Primary discharge after fast rule out (974 patients)	Conventional work up (1320 patients)
All-cause death	30days	0.7% (0.4%-1.1%) n=15	0.1% (0%-0.6%), n=1*	1.1% (0.6%-1.8%) n=14
Exact length of stay in ED/CPU [hours]		4.3 (4.1-4.5)	3.8 (3.6-4.0)	4.8 (4.7-5.0)
Length of stay in ED/CPU	0 - 1 h	2.6% (n=53)	1.5% (n=13)	3.6% (n=40)
	1 - 2 h	13.3% (n=266)	13.2% (n=118)	13.3% (n=148)
	2 - 3 h	18.6% (n=372)	21.7% (n=194)	16% (n=178)
	3 - 6 h	42.7% (n=855)	49.3% (n=440)	37.3% (n=415)
	>= 6 h	22.9% (n=458)	14.2% (n=127)	29.8% (n=331)
Admission	Peripheral ward	72.7% (n=562)	100% (n=1)	72.7% (n=561)
	IMCU	17.6% (n=136)	0% (n=0)	17.6% (n=136)
	ICU	9.7% (n=75)	0% (n=0)	9.7% (n=75)

Percentages and counts (denoted by "n=") for categorical variables and medians for the numeric variable "Exact length of stay in ED/CPU"; 95% confidence intervals added in brackets for all-cause death and Exact length of stay in ED/CPU.

*70 years old male, known CAD, MI and COLD/asthma, Tn and Copeptin negative, ECG normal, diagnosis: non cardiac, atypical chest pain (musculoskeletal), death one month later from metastatic lung cancer.

Figure legends

Figure 1. Patient flow chart

Figure 2. Algorithm for an early rule-out strategy and guidance of primary early discharge versus general hospital admission (conventional work-up)

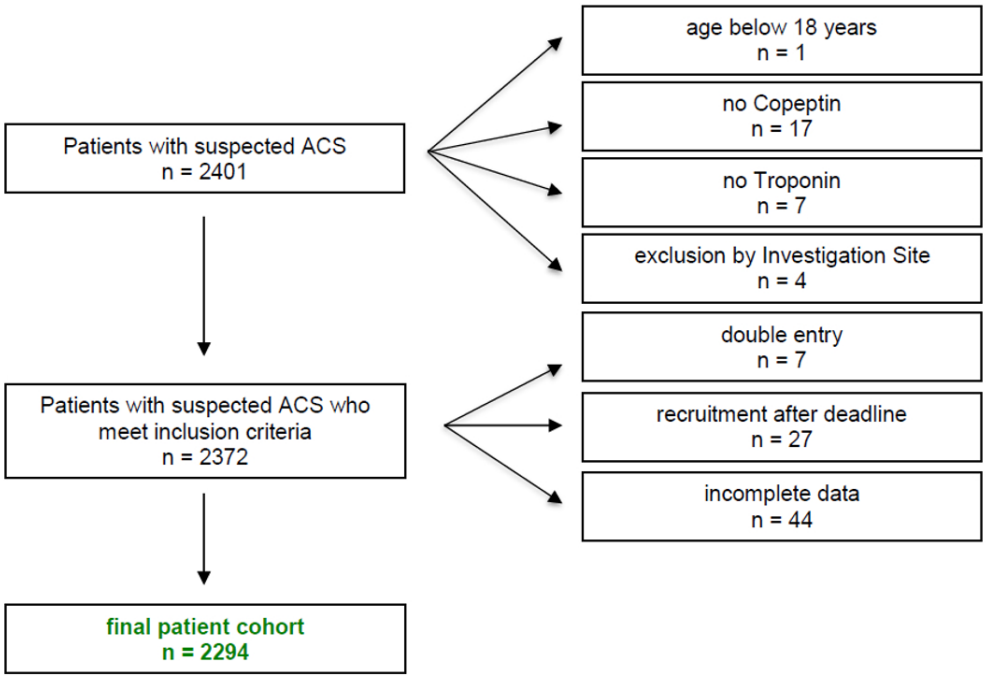
Supplemental material

Figure legends

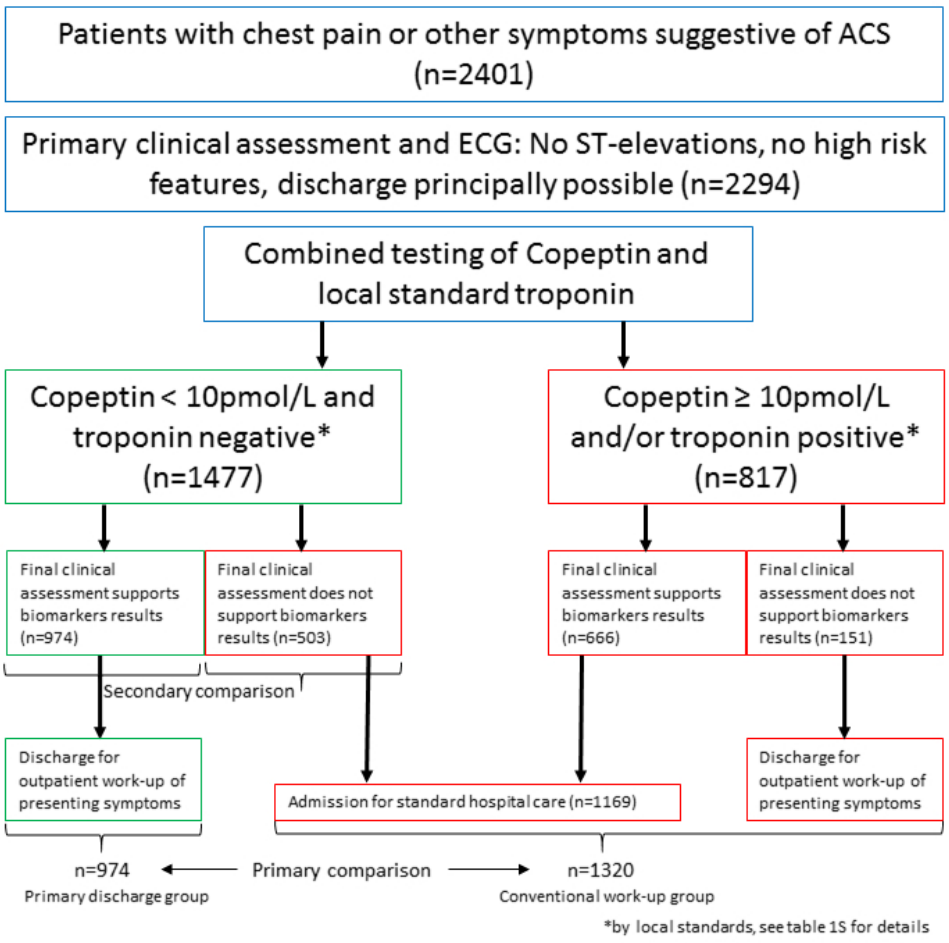
Figure 1S. Investigation sites and number of completed patients. CVK, Charité Virchow-Klinikum; UKB, Unfallkrankenhaus Berlin.

Figure 2S. Distribution of leading symptoms

Figure 3S. Distribution of diagnoses in the Emergency Department (ED) and/or the Chest Pain Unit (CPU)



Patient flow chart



Algorithm for an early rule-out strategy and guidance of primary early discharge versus general hospital admission (conventional work-up)

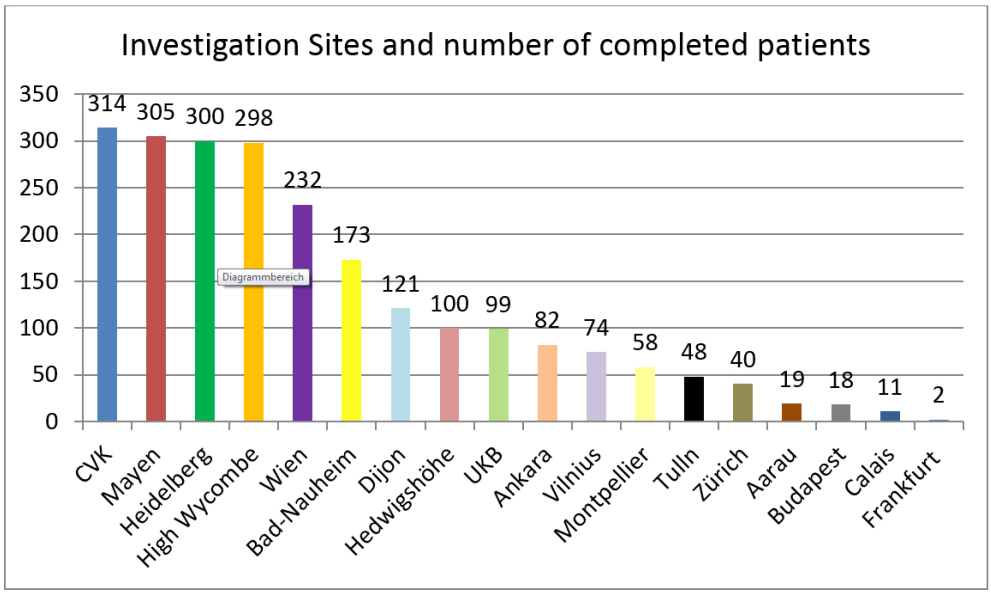
Table 1S. Local standard troponin tests and cutoffs for MI diagnosis

Center	Troponin test	MI Cut-Off
Heidelberg	Hs TnT, Elecsys, Roche Diagnostic	14 ng/l
UKB, Berlin	Hs TnT, Elecsys, Roche Diagnostic	14 ng/l
CVK, Berlin	AQT-Test POCT, Radiometer hsTnT, Elecsys, Roche Diagnostic	30 ng/l 50 ng/l
Frankfurt	Hs TnT, Elecsys, Roche Diagnostic	14 ng/l
Bad-Nauheim	Hs TnT, Elecsys, Roche Diagnostic	14 ng /l
Mayen	TnI Ortho Clinical Diagnostics and from 19.4.16 TnI, LOCI, Siemens	50 ng/l
Wien	TnI, LOCI, Siemens	45 ng/l
Calais	TnI, Access, Beckman and Coulter	30 ng/l (97.5th %le)
Vilnius	Hs TnI, Architect, Abbott	for men 34,2 ng/l for women 15,6 ng/l
Budapest	Hs TnT, Elecsys, Roche Diagnostic (Cobas e411)	14 ng/l
High Wycombe	Hs TnI, Architect, Abbott	for men 34,2 ng/l for women 15,6 ng/l
Zollichberg, Zurich	TnI-Ultra, Centaur, Siemens	40 ng/l
Aarau	TnI, LOCI, Siemens	45 ng/l
Berlin Hedwigshöhe	Hs TnI, Architect, Abbott	15 ng/l
Dijon	TnI, Vista, Siemens	100 ng/l
Ankara	TnI, Access, Beckman and Coulter	40 ng/l (99th %le)
Tulln	Hs TnT, Elecsys, Roche Diagnostic	14 ng/l
Montpellier	Hs TnT, Elecsys, Roche Diagnostic (Cobas 8000/e602 analyzer)	14 ng/l

Summary of ethics approval

- The principle ethics vote is from the principal investigator site, Charité (Berlin). Reference number EA1/00815, on the 05.06.2015
- Some German participant centres (Mayen, Hedwigshohe, UKB) accepted the ethics approval from the principal investigator site (Charité, Berlin).
  All the local ethics committee were informed accordingly.
- Bad Nauheim: The ACS Registry was approved by the ethical board of the Justus-Liebig-University Giessen (FF 17/2011)
- Frankfurt: The ProCore Registry was approved by the ethical board of the Goethe-University Frankfurt (318/15)
- Heidelberg: The ProCore Registry was approved by the ethical board of the Medizinische Fakultät Heidelberg (S-382/2015)
- The principle Austrian ethics vote is from the Vienna university hospital (Reference number EK-15-198-1015 on the 28th of October 2016)
- The hospital of Tulln accepted the Austrian ethics vote from Vienna.
- The principle Swiss ethics vote is from the Zollikerberg (Zurich) hospital (reference number BASEC 2016-00401 on the 13.03.2016)
- The Aarau hospital accepted the Swiss ethics vote from Zurich on the 14.12.2016
- High Wycombe hospital ethics vote approved the study with the following REC reference number: 16/SC/0198, IRAS project ID:193406
- The Ankara university hospital accepted the ethics vote from the principal investigator site, Charité (Berlin)
- The Budapest university hospital accepted the ethics vote from the principal investigator site, Charité (Berlin)
- The Vilnius University hospital accepted the ethics vote from the principal investigator site, Charité (Berlin)
- The French participants centres (Calais, Montpellier, Dijon) were using the dual marker strategy in routine; the local ethics committee was informed and accepted the data anonymisation of the electronic case report form.

Figure 1S


Investigation Sites and number of completed patients
350
300
250
200
150
100
50
0
314
305
300
298
232
173
121
100
99
82
74
58
48
40
19
18
11
2
Diagrammbereich
CVK
Mayen
Heidelberg
High Wycombe
Wien
Bad-Nauheim
Dijon
Hedwigshöhe
UKB
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Vilnius
Montpellier
Tulln
Zürich
Aarau
Budapest
Calais
Frankfurt

Figure 2S

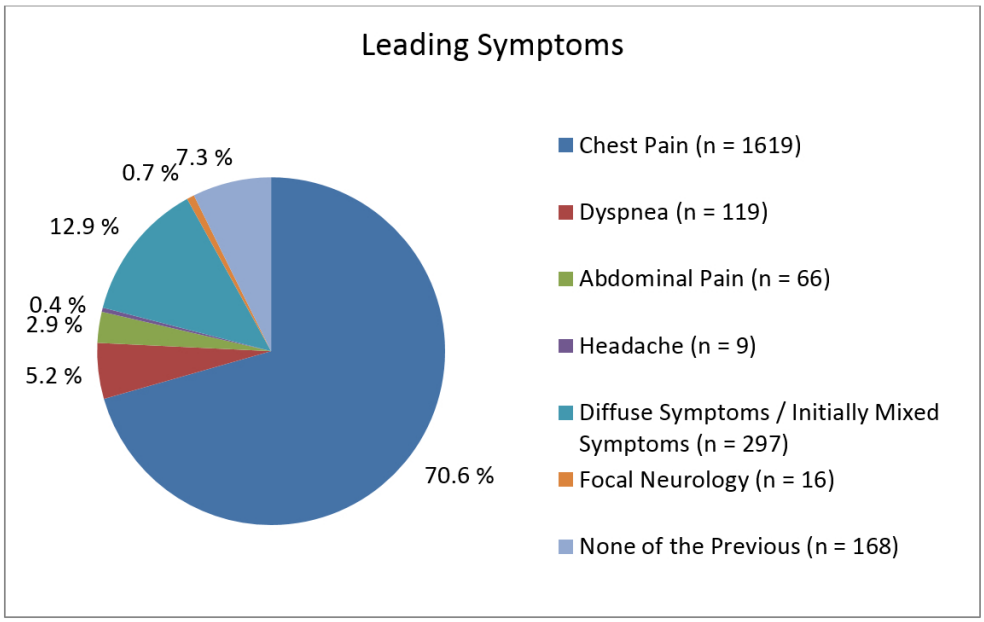
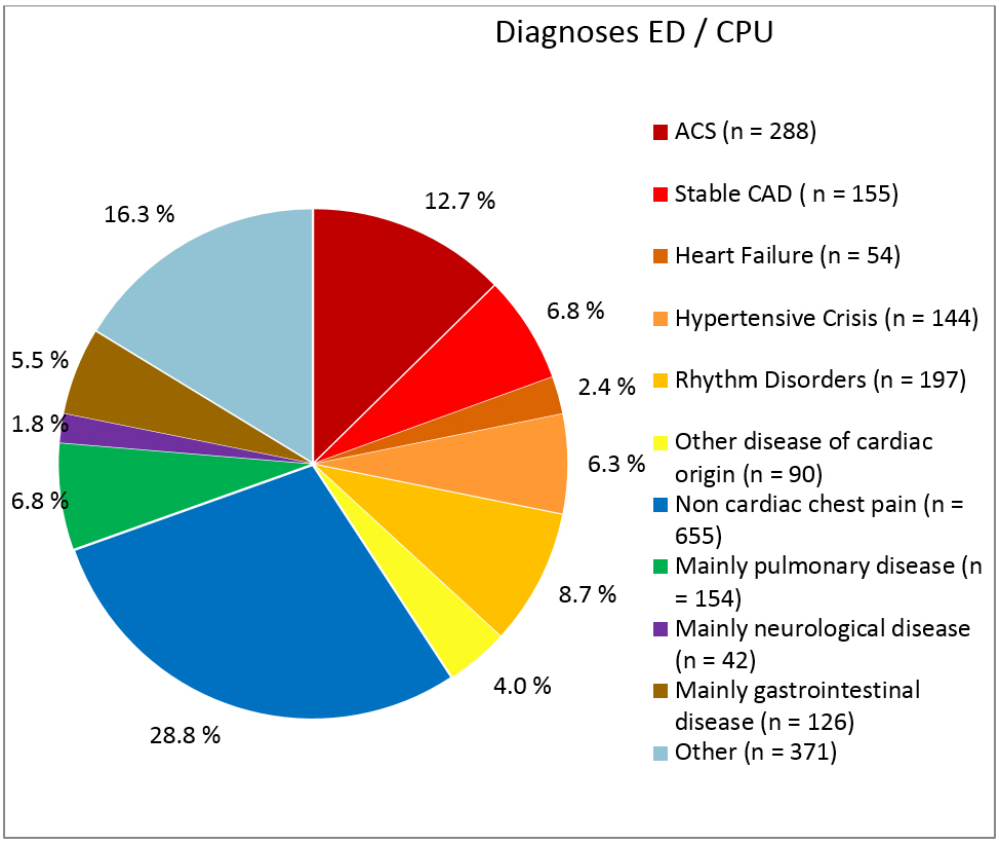

Leading Symptoms
Chest Pain (n = 1619)
Dyspnea (n = 119)
Abdominal Pain (n = 66)
Headache (n = 9)
Diffuse Symptoms / Initially Mixed Symptoms (n = 297)
Focal Neurology (n = 16)
None of the Previous (n = 168)
70.6 %
5.2 %
2.9 %
0.4 %
12.9 %
0.7 %
7.3 %

Figure 3S


Diagnoses ED / CPU
ACS (n = 288)
Stable CAD (n = 155)
Heart Failure (n = 54)
Hypertensive Crisis (n = 144)
Rhythm Disorders (n = 197)
Other disease of cardiac origin (n = 90)
Non cardiac chest pain (n = 655)
Mainly pulmonary disease (n = 154)
Mainly neurological disease (n = 42)
Mainly gastrointestinal disease (n = 126)
Other (n = 371)
12.7 %
6.8 %
2.4 %
6.3 %
8.7 %
4.0 %
28.8 %
6.8 %
1.8 %
5.5 %
16.3 %

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Fig.1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	24
		(b) Indicate number of participants with missing data for each variable of interest	24-26
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	26

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14-15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Multi-Centre Cross-Sectional Observational Registry to Monitor the Safety of Early Discharge after Rule-Out of Acute Myocardial Infarction by Copeptin and Troponin: The Pro-Core registry

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Multi-Centre Cross-Sectional Observational Registry to Monitor the Safety of Early Discharge after Rule-Out of Acute Myocardial Infarction by Copeptin and Troponin: The Pro-Core registry

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Short title: Copeptin in ACS registry

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Abstract (294 words)

Abstract (word count 300)

Objectives. There is sparse information on the safety of early primary discharge from the Emergency Department (ED) after rule-out of MI in suspected ACS. This prospective registry aimed to confirm randomized study results in patients at low-to-intermediate risk, with a broader spectrum of symptoms, across different institutional standards, and with a range of local troponin assays including hs-cTn, cTn, and POC Tn.

Design

Prospective, multi center European registry.

Setting

18 Emergency departments in 9 European countries (Germany, Austria, Switzerland, France, Spain, United Kingdom, Turkey, Lithuania, Hungary)

Participants

The final study cohort consisted of 2,294 patients (57.2% males, median age 57 years) with suspected acute coronary syndrome (ACS).

Interventions

Using the new dual markers strategy, 1,477 patients were eligible for direct discharge, which was realized in 974 (42.5%) of patients.

Main outcome measures

The primary endpoint was all-cause mortality at 30 days.

Results

Compared to conventional work-up after dual marker measurement, the median length of ED stay was 60 minutes shorter (228min, 95%-CI: 219-239min vs. 288min, 95%-CI: 279-300min) in the primary DMS discharge group. All-cause mortality was 0.1% (95%-CI: 0%-0.6%) in the primary DMS discharge group vs. 1.1% (95%-CI: 0.6%-1.8%) in the conventional work-up group after dual marker measurement. Conventional work-up instead of discharge despite negative DMS biomarkers was observed in 503 patients (21.9%) and associated with higher prevalence of ACS (17.1% vs 0.9%, p<0.001), cardiac diagnoses (55.2% vs 23.5%, p<0.001) and risk factors (p<0.01), but with a similar all-cause mortality of 0.2% (95%-CI: 0%-1.1%) vs. primary DMS discharge (p=0.64).

Conclusions. Copeptin on top of cardiac troponin supports safe discharge in patients with chest pain or other symptoms suggestive of ACS under routine conditions with the use of a broad spectrum of local standard POC, conventional and high sensitivity troponin assays.

Trial registration

ClinicalTrials.gov NCT02490969

Key words: Registry, acute coronary syndrome, myocardial infarction, Copeptin, troponin, mortality

Strengths and limitations of this study

- This is the first large European registry demonstrating the safety of the dual marker strategy using cardiac troponin and copeptin for early discharge in patients with suspected acute coronary syndrome.
- The study recruited less selected patients, a broader range of local cTn assays and assay generations and across different institutional standards than former studies and thus reflects daily routine in clinical practice.
- The study has been carried out in experienced centers, thus in settings with lower clinical expertise results may differ.
- The very low mortality rate does not allow any exploratory analyses on the safety of discharge by center volumes, experience of physicians, local cTn assay or assay generation.

Introduction

Chest pain accounts for approximately 8 million annual emergency department (ED) visits in the United States(1), rendering chest pain the second most common presenting symptom. In a pooled analysis on 51 observational trials, the prevalence of the final diagnosis of ACS was confirmed in a median of 14%, with a range from 5% to 42%(2).

An effective risk stratification is paramount to select the most appropriate decision for admission or direct discharge because admission of patients at low or very low risk is not safe(3, 4) as it increases the risk to receive unnecessary coronary angiography, coronary interventions, multiple re-admissions (3), and eventually the risk of peri-procedural myocardial injury or type 4 MI, and procedure-related major bleedings(4). Moreover, unselected admission of chest pain patients for further work-up for the evaluation of ACS is time consuming and costly(5, 6). During an interval of only 9 years (from 1999–2008), the use of advanced medical imaging for ED visits related to chest pain was found to increase dramatically by 367.6% in the CDC/NCHS, National Hospital Ambulatory Medical Care Survey(7). On the other hand, early discharge is also not without risk, as up to 2–5% of patients with ACS are reported

to be inappropriately discharged from the ED every year(5, 8) although the methodology to assess these numbers is limited (no complete follow up of all patients, no exact differentiation between incident and prevalent AMI and the components of ACS). Nevertheless, missed or incident AMI early after discharge is associated with a hazard ratio for death of 1.7 to 1.9%(8). Missed AMIs account for 20% of US emergency medicine related litigation dollars(9). Currently, use of high sensitivity cardiac troponins has improved the accuracy and earlier detection of an MI(10-13), and very low concentrations of hs-cTn have been reported to safely rule-out an MI and to be associated with rates of death or MI below 1%(14-17). Accordingly, 2015 ESC guidelines on NSTE-ACS(10) discourage routine coronary angiography in low risk patients and recommend early discharge after clinical risk stratification, and a pre- or post-discharge stress imaging test for the decision of a selective invasive strategy. Supporting evidence for early uneventful discharge of low risk patients stems mainly from observational studies(14, 15, 18, 19) where investigators were commonly blinded to the investigational hs-cTn results, were unaware of retrospectively derived optimal decision cutoffs, and managed patients at their own discretion following standards of care applicable at that time. In fact, most of the patients who retrospectively fulfilled early rule-out criteria were kept in hospital and neither medical measures nor non cardiac diagnoses are reported. Only few interventional clinical trials evaluated the safety of a randomized allocation to early discharge versus conventional care in patients at low(20, 21) or low-to-intermediate high risk(22). The Biomarkers-in-Cardiology 8 (BIC-8) trial(22) tested the utility of a dual biomarker strategy using normal cTn or hs-cTn values, i.e. below the upper limit of normal, mainly the 99th percentile, together with normal Copeptin values below the 95th percentile (<10 pmol/L) to identify candidates for direct early discharge from the ED. The findings demonstrated that this strategy reduced the length of observation time in the ED or chest pain unit and increased rates of discharge at a low risk for major adverse cardiovascular events (MACE) that was comparable or even lower in the per protocol analysis to standard of care. Compared to serial troponin-based protocols, advantages of the dual marker strategy include the ability of instant rule-out of MI without the need for additional blood draw, high sensitivities and negative predictive values (NPVs) for acute myocardial infarction (AMI) of Copeptin in combination with conventional or contemporary sensitive cTn assays (23-28), or POCT(29), particularly when hs-cTn or validated hs-cTn assays are not available, and supporting data for a safe discharge from a large, appropriately powered randomized multicenter trial (22). The value of Copeptin on top of detectable but still normal cTn or hs-cTn for rule-out of MI has been studied extensively and the DMS algorithm has been quoted as an additional option for instant rule-out in 2015 ESC guidelines(10). In contrast, there is sparse information from randomized trials on the safety of discharge(20, 21) and the safety of discharge using a pre-specified algorithm has rarely been investigated in a prospective registry.

Therefore, the aim of the present multicenter observational trial was to confirm the safety of this strategy that was previously reported in a randomized interventional trial(22) in routine clinical practice, across a broad spectrum of cTn assays including POCT, in an unselected population with a broader range of symptoms, and at low-to-intermediate risk presenting with suspected ACS to 18 EDs in Europe and Turkey.

Methods

The Pro-Core is a multi-center, international observational trial with 18 participating centers (figure 1S) in Europe and formally Near East (Ankara, Turkey).

We enrolled adult men and women who present to an ED or chest pain unit (CPU) with signs and symptoms suggestive of acute coronary syndrome without ST-segment elevation (NSTE-ACS). Eligible patients qualifying for the DMS strategy were recruited consecutively but entry was restricted to patients with a low or intermediate GRACE score.

Patients were eligible if they were aged ≥18 years, presented with symptoms suggestive of ACS such as acute chest discomfort, angina pectoris, or dyspnea as leading symptoms. Patients presenting with ST-segment elevation or a final diagnosis of ST-segment elevation myocardial infarction (STEMI) were excluded from analysis (see figure 1 for patient flow).

Patients underwent clinical assessment that included medical history, physical examination, standard blood test including measurements of local (hs)-cTn, Copeptin and 12-lead ECG. Baseline information included the Killip class, and clinical information to calculate the GRACE score. Other clinical scores were not tested prospectively prohibiting any conclusion on their clinical usefulness. Physicians had access to all clinical information including Copeptin and cTn results that were reported with local turn-around-times. Decision for primary discharge after rule-out using the dual biomarker strategy, or for disposition of patients if MI was not ruled out was left at the discretion of the attending physician. Patients were excluded if high risk features were evident (e.g. the GRACE score was above 140) and if hospital admission was obviously necessary at presentation for any reason. Final diagnosis of NSTE-ACS was performed by the ED physician applying the criteria of the 3rd universal definition of AMI(30). Unstable angina was diagnosed in the presence of new or worsening symptoms of suspected myocardial ischemia but either normal or undetectable cTn concentrations in serial blood draws, or a cTn together with a Copeptin below the decision limit at presentation. Importantly, classification of ACS was done by the treating physician and was not subject of retrospective adjudication. All patients were contacted at 30 days to assess all-cause mortality. Number of patients was limited to 300 patients per participating site to limit center bias.

Biomarkers and rule-out algorithms

Copeptin and cardiac troponin were tested from fresh unfrozen blood from a single blood sample drawn at admission to the ED or CPU as part of the routine patient management.

Copeptin was measured using the automated fluoro-immunoassay B·R·A·H·M·S Copeptin proAVP KRYPTOR for the quantitative measurement of C-terminal pro-arginine-vasopressin (CT-proAVP, Copeptin) in human serum and plasma on the B·R·A·H·M·S KRYPTOR compact PLUS platform. The test has a detection limit of 0.69 pmol/L and a functional assay sensitivity (detected by inter-assay precision of 20% CV) of 1.08 pmol/L.

The recommended cut-off for the decision between a positive and a normal test is 10 pmol/L, corresponding to the 95th percentile of a healthy reference population. This cut-off was used in the randomized controlled trial by Möckel et al.(22), and is the recommended cut-off for the rule-out algorithms for MI.

Cardiac Troponin was measured at the individual institutions according to standard practice. An overview on local assays and cutoffs is provided as supplemental material (Table 1S). Briefly, Roche Elecsys hs-cTnT was used in 39%, followed by Abbott Architect hs-cTnI, Siemens (Vista, Loci), Beckman Access TnI, and Radiometer (3rd gen. cTnT) in 22%, 22%, 11% and 6%, respectively. Conventional and high-sensitivity assays were permitted for the early rule-out strategy.

A patient qualified as rule-out and for early discharge if he presented with signs and symptoms suggestive of ACS, together with a low-to-intermediate risk profile defined as the absence of high risk features (e.g. a GRACE score <140), and a combined negative testing of Copeptin and troponin, defined as Copeptin below 10 pmol/L and cardiac troponin below the local AMI decision limit as recommended by the guidelines, mostly the 99th percentile value of a healthy reference population provided by the manufacturer.

Follow-Up and Clinical End Points

The primary objective was to evaluate 30-day all-cause mortality in patients in whom acute myocardial infarction was ruled-out using the early dual marker rule-out strategy and who are therefore directly discharged from the ED. All-cause mortality was preferred over cardiovascular death because collection of information is more convenient and because the majority of eligible patients presented to the EDs with non-coronary and non-cardiac diagnoses.

The secondary objectives were evaluated in all patients, irrespective of biomarker test results and disposition. Secondary endpoints included the diagnosis of acute myocardial infarction, final hospital diagnoses, time to discharge/transfer from the ED/CPU, disposition decision (discharge or admission), length of hospital stay, ICU-treatment, performance of coronary angiography/ PCI/ CABG, performance

of ECGs, stress testing, imaging, performance of cardiovascular monitoring, In-hospital all-cause mortality, 30-day all-cause mortality.

The study protocol also addressed patients where the protocol was violated, i.e. those who were not primarily discharged or not admitted although criteria were fulfilled (over-rule). The reasons for over-rule or other protocol violations were registered.

The study complies with the Declaration of Helsinki and received the primary ethics approval from the Charité ("Ethikausschuss 1 am Campus Charité-Mitte; EA1/008/15). The positive vote was sent to all study sites. The principle investigator decided based on local and national rules, whether a separate local ethics committee submission was necessary. Additional ethics approvals were obtained from the sites listed in the supplemental table 2S. The ethics committee approved that anonymized routine data of patients were used without informed consent for this registry. The study was registered before enrollment of the first patient (ClinicalTrials.gov NCT02490969).

Statistical evaluation

Enrolment was restricted to a maximum number of 300 patients per center to ensure generality by avoiding the dominance of single centers. The total number of patients enrolled therefore depended rather on the number of participating centers than on their enrolment performance. As the primary objective of this registry was the monitoring of an already routinely applied clinical algorithm, no confirmatory study design was chosen and there was no sample size calculation performed. An exploratory analysis of the safety of DMS by local cTn assay or assay generation, or by study center was not done as there was only 1 death precluding meaningful analysis. All data were entered into an online electronic case report form. Group comparisons for categorical variables were performed using chi-square tests and for numerical variables using Wilcoxon rank-sum tests. A p-value below 0.05 was considered significant (no correction for multiple testing conducted).95% confidence intervals were determined for binary all-cause death at 30 days by the method of Clopper and Pearson and for numeric length of stay in the ED/CPU by 2.5%- and 97.5%-quantiles estimated by bootstrapping.

Statistical analyses were performed using the software R Version 3.1.2 and SPSS (IBM® SPSS Statistics, Version 21).

Patient and Public Involvement

Patients or public were not involved in the development of the study protocol.

Results

A total of 2,401 consecutive patients with suspected ACS were screened from September 16th 2015 until the end of recruitment on May 23rd 2017. Of these, 107 patients were excluded from analysis due

to incomplete biomarker or clinical information, withdraw of informed consent, or double entry (see patient flow diagram; Figure 1). The final study cohort consisted of 2,294 patients (57.2% males, median age 57 years) with suspected ACS. Numbers of recruited patients varied by study site but were limited per protocol to a maximum of 300 enrolments per site. The exact numbers of recruited patients are displayed in supplemental Figure 1S.

The most prevalent leading symptom at presentation (Supplemental Figure 2S, Table 1) was chest pain in 70.6% (n=1619), followed by diffuse or initially mixed symptoms in 12.9% (n=297), dyspnea in 5.2% (n=119), abdominal pain in 2.9% (n=66), focal neurology in 0.7% (n=16), headache in 0.4% (n=9), or none of the listed symptoms in 7.3% (n=168). As expected from the inclusion criteria, the study cohort represented a low-to-intermediate risk group with a median GRACE score of 89 (IQR: 67-114) and a Killip class of 1 in 96% of cases (n=2084). Time from onset of symptoms to presentation was below 12 hours in 50.8%. An interval of 0-3 hours, 3-6 hours and 6-12 hours was registered in 26.3% (n=558), 13.3% (n=283), and 11.2% (n=238) of patients, respectively. ECG at presentation was non-diagnostic in 87.3% of patients. Regarding initial cTn and Copeptin results, a total of 2,017 patients (87.9%) were below the diagnostic cutoff of the local cTn, and 1,615 patients (70.4%) below the cutoff for Copeptin. A total of 1477 patients (64.4%) were below the decision cutoff for both biomarkers fulfilling the criteria for early primary discharge from the ED (theoretically maximal efficiency).

Clinical pathways

974 patients (42.5%) were categorized into the primary discharge after fast rule-out pathway, and 1,320 patients into the conventional work-up pathway. Of these, 654 patients did not follow a pre-defined pathway but were either admitted although qualified for primary discharge (n=503, 21.9%), or were discharged although not ruled-out (n=151, 6.6%), see figure 2.

In the entire cohort, the overall rate of an ACS diagnosis was 12.7% (n=288), non-cardiac chest pain 28.8%, rhythm disorders 8.7%, pulmonary disorders 6.8%, stable CAD 6.8%, hypertensive crisis 6.3%, and gastrointestinal disease 5.5%. Other cardiac diagnoses were present in 4%, and other unspecified diagnoses in 16.3% of cases (Supplemental Figure 3S).

In the conventional care pathway, an ACS was diagnosed in 21.1% (n=279) with the majority classified as a NSTE-ACS (n=172, 61.6%). STEMI was an exceptional diagnosis in 15 patients (5.2%) since patients with STEMI were routed directly to the catheterization laboratory in most institutions and were not intended for inclusion. Only if STEMI was diagnosed later and not at admission such patients were enrolled. Other diagnoses included non-cardiac chest pain in 18.8% (n=247), rhythm disorders in 5.9% (n=133), stable CAD in 8.9% (n=117), pulmonary disease in 6.8% (n=90), hypertensive crisis in 5.9% (n=77), gastrointestinal disease in 4.7% (n=62), and other diagnoses in 14.1% (n=185).

In the primary discharge after fast rule-out pathway, only 9 patients (0.9%) were diagnosed as having an ACS, mostly unstable angina (n=4) or unclassified ACS (n=4), with only 1 case (0.1%) diagnosed as NSTEMI (NPV for MI of 99.9%). Rate of admission was only 0.1% due to a case where admission was forced by the referring primary care physician although discharge was planned.

There were two different ways how local investigators over-ruled the intended pathway. The larger group consisted of 503 patients (21.9%) who were allocated to the conventional care pathway at the discretion of the local investigator although they were categorized into the primary discharge after fast rule-out pathway. The second group consisted of 151 patients (6.6%) who were primarily discharged although they should have received conventional care. Reasons for the over-rule consisted mainly of decisions of the physician to admit to hospital based on clinical judgment. Minor reasons were opposition of patients against serial blood sampling (n=2), and other unspecified reasons (n=6).

There were differences between the primary discharge after fast rule-out pathway and the over-rulers into the conventional care pathway (Table 2). Patients were older, more frequently males, had more often a history of CAD or previous MI, more risk factors including a higher prevalence of arterial hypertension, hypercholesterolemia, and diabetes mellitus. In addition, patients had more often a diagnostic ECG, and higher GRACE scores. In addition, these patients received more often an ACS diagnosis, i.e. a diagnosis of unstable angina, and spent longer times in the ED. However, and importantly, rates of all-cause mortality at 30 days were not significantly different (0.2% vs 0.1%, p=1) compared to the primary discharge after fast rule-out pathway.

Outcomes

The primary endpoint, all-cause death within 30 days among the primary discharge after fast rule-out pathway, occurred in only 1 case of 974 patients (0.1%, 95%-CI: 0%-0.6%). This death was not related to the biomarker algorithm: the patient was 70 years old, had a history of CAD and previous MI and presented with musculoskeletal symptoms, was primarily discharged and died 1 month later from metastatic lung cancer (table 3).

By contrast, all-cause mortality rate in the conventional care pathway was 1.1% (14 of 1320 patients, 95%-CI: 0.6%-1.8%) and thus significantly higher (p=0.011) than in the primary discharge after fast rule-out pathway (Table 3). Diagnoses in the deceased patients of the conventional care pathway included ACS (n=5), non-cardiac chest pain (n=2), pulmonary disease (n=2), neurological disease (n=1), rhythm disorders (n=1), stable CAD (n=1), heart failure (n=1), gastrointestinal disease (n=1), and non-specified others (n=1). Patients who died were a median of 15 years older, had more often dyspnea as the leading presenting symptom, presented more frequently more than 12 hours after symptom onset, and were characterized by higher GRACE score (167 vs 90 points, p<0.001) and Killip class. In addition, non-survivors had received more extensive diagnostic workup, presented more often with a local cTn

and Copeptin above cutoff, and median Copeptin values were significantly higher than among survivors (50.8 vs 7.0 pmol/L, p<0.001) underscoring the prognostic information that is provided by cTn and Copeptin independent of the underlying disease.

Regarding secondary endpoints, hospitalization rates were 0.1% in the primary discharge after fast rule-out pathway compared to 59% in the conventional care pathways (p<0.001). As expected, median lengths of stay in the ED (treatment time) were significantly shorter in the primary discharge after fast rule-out pathway vs the conventional care pathway (228 min vs 288 min, p<0.001, and rates of patients discharged within 0 to <1 hour (1.5% vs 3.6%), 1 to <2 hours (13.2% vs 13.3%), and 2 to < 3 hours (21.7% vs 16%), 3 to <6 hours (49.3% vs 37.3%) were significantly different in primary discharge after fast rule-out pathway versus conventional care pathway (p for trend < 0.001). Conversely, rates of patients with longer ED treatment times > 6 hours were significantly lower in the primary discharge after fast rule-out pathway than in the conventional care pathway out group (14.2% vs 29.8%, p<0.001).

Discussion

Information on the safety of direct discharge from an ED after rule-out of MI in patients with suspected ACS is almost exclusively restricted to findings that were generated in observational trials where attending physicians were commonly blinded to the investigational hs-cTn results, or to retrospectively determined optimal decision cutoffs. Treatment decisions based on at that time applicable standards of care and were left at the discretion of the treating physician(16-19, 31).

Following the randomized BIC-8 study, which proofed safe discharge after instant rule-out of AMI by the use of troponin and Copeptin from a single blood draw(22) and also showed cost-effectiveness in a health economic sub-study(32), we could confirm in a large European registry that this is also true in clinical routine.

The superior analytical sensitivity of hs-cTn assays has already enabled an accurate rule-out of MI with sensitivities and NPVs of > 90%(10), facilitating fast rule-out based on either very low concentrations of hs-cTn assays obtained from a single measurement at presentation(14-19, 33), or from serial blood draws after 1 to 3 hours(17-19, 31, 34-39) using hs-cTn at the 99th percentile(10-13), or slightly below (18, 19) the 99th percentile of a healthy reference population. Integration of clinical judgment or a validated clinical score such as the GRACE, TIMI, HEART, modified Goldman Score, MACS clinical decision rule, EDACS and Vancouver Chest Pain Algorithm, and North American Chest Pain Rule further improve NPV yielding NPV between 98.1-100% and 98.4-100% when cTn and hs-cTn assays were used, respectively(40). Although, 2015 ESC guidelines(10) discourage routine invasive strategy in low risk patients and rather recommend discharge following risk stratification, and a pre- or post-discharge

stress imaging test to decide on a selective invasive strategy, evidence from randomized trials to endorse these recommendations is sparse(20-22). The Manchester Acute Coronary Syndrome (MACS)-Pilot study(20) enrolled 138 patients with suspected cardiac chest pain who were randomized to receive care guided by the MACS decision rule or standard care. The primary efficacy outcome was a decision to discharge within 4 hours of arrival, without missed MI and without death, AMI or coronary revascularization occurring during 30 days of follow-up. This small pilot study found a significantly higher rate of uneventful primary discharge within 4 hours (26% vs 8%, p=0.004) among those guided by the MACS rule. The HeartPathway Trial enrolled 282 patients with suspected ACS stratified into risk categories using the HEART Score(21). The study was not powered to compare event rates in randomized groups but found a decreased objective cardiac testing at 30 days by 12.1%, a reduced length of stay by 12 hours, and an increase of early discharges by 21.3%. The BIC-8 trial(22) that enrolled a total of 902 low-to-intermediate high risk patients using the GRACE score and subsequently randomized patients with normal presenting cTn and Copeptin values into an early discharge and a standard protocol group. The study demonstrated a reduction of observation time in the ED by more than 40% from a median of 7 hours to 3 hours, achieved a 5.6-fold increase in ED discharge rate from 67.7 vs 12%, and a similar 5.2% rate of 30-day major adverse cardiovascular events that were liberally defined as all-cause death, survived sudden cardiac arrest, re-hospitalization for ACS, unplanned PCI or CABG, or documented life-threatening arrhythmias in the standard and Copeptin group(22).

The present large multicenter registry was performed in patients with suspected ACS and low-to-intermediate risk to test the usefulness of a dual biomarker strategy, consisting of a normal Copeptin and cTn, to rule-out MI from a single blood draw at admission and to discharge low risk patients primarily from the ED. In order to represent clinical practice of different type of institutions, variable local practice and across the spectrum of cTn assays and grades of assays sensitivities(41, 42), this observational study was conducted in 18 different institutions in Europe and Asia. Institutions included EDs in community hospitals, and CPUs in PCI centers and few University hospitals. Patients qualified for enrolment in the presence of a broader spectrum of symptoms suggestive of ACS not limited to chest pain or angina, and a broad spectrum of cTn assays and different grades of analytical sensitivities including conventional, contemporary, and hs-cTn assays was permitted. To reduce dominance of few high recruiting centres, enrolment rates were restricted to 300 study patients per site.

There were several key findings of this survey that support the usefulness and safety of this concept in clinical routine and outside of controlled clinical trials. First, earlier discharge from the ED in patients ruled-out at presentation using a single blood draw is feasible without any obvious safety concern. All-cause mortality rate within 30 days was 0.1% and attributed to a case with metastatic lung cancer. Second, length of stay in the ED is significantly shorter by 60 minutes allowing an earlier discharge, a finding particularly useful in congested EDs or CPUs. Thus, the present registry data confirm the

findings from the randomized BIC-8 trial(22) on reduced length of stay, increased discharge rates and support the safety of a primary planned discharge from an ED after clinical risk assessment. Third, the dual marker concept is efficient as it can be applied to at least 42.5% (potentially effective in 66.4%) of patients presenting with chest pain or chest pain equivalent symptoms to an ED. Thus, efficacy of this dual marker strategy is almost comparable with the efficacy of the ESC recommended 0/1 h diagnostic algorithm that requires serial blood draws and a validated hs-cTn assay (currently Abbott Architect hs-cTnI and Roche hs-cTnT). While other fast rule-out algorithms based on very low hs-cTnI or hs-cTnT at the LoB or LoD may demonstrate similar diagnostic performance and safety, the numbers of patients who qualify are substantially lower(14, 15, 33) and these strategies have never been tested prospectively with patients being really discharged after testing.

We found a relevant number of over-rule by local ED physician leading to an admission of patients who qualified for discharge by their biomarker results (34%). Given that these patients had an uneventful clinical course (see table 2), void of primary or secondary events during follow-up, suggests an underestimated efficacy and more potential of safe discharge. Fourth, regarding the diagnostic performance for rule-out that was not in the scope of this survey, the dual marker algorithm was associated with a high negative predictive value of 99.9% for NSTEMI (1 missed NSTEMI) confirming the existing evidence on the diagnostic performance of the Copeptin/troponin dual marker strategy (22, 26-28). Fifth, regarding secondary objectives, the dual marker strategy was associated with shorter stays in ED. Sixth, consistently with previous studies(26-28, 43, 44), elevated Copeptin levels were associated with all-cause mortality within 30 days providing confirmatory evidence that Copeptin confers prognostic information that is complementary to cTn or hs-cTn, in various acute cardiovascular settings including ACS(26-28, 43, 44), heart failure(45, 46), and acute pulmonary embolism(47) but also non-cardiac disease. In addition, an elevated Copeptin should prompt a search for a variety of potentially life-threatening non-cardiac conditions including perforated stomach ulcer, pancreatitis, cholecystitis, bleedings, infections, or neurological disorders(48).

Limitations

First, we observed very low rates of all-cause mortality at 30-days, i.e. 0.1% (95%-CI: 0%-0.6%) in the primary discharge after fast rule-out pathway as compared to 1.1% (95%-CI: 0.6%-1.8%) in the conventional care pathway. Low event rates may be explained by restriction of the DMS algorithm to patients at low or intermediate risk based on the GRACE score. Therefore, our findings cannot be extrapolated to settings where risk stratification after rule-out is based on other clinical scores or on clinical judgement. Moreover, a selection bias towards recruitment of a non-representable low risk ACS cohort cannot be fully excluded as inclusion criteria were not limited to typical chest pain, longer pain episodes or abnormal ECG findings. However, the study population was planned to represent a

real life picture of patients who present in clinical routine with various symptoms and a wide range of risk. Copeptin concentration return to normal within few hours reducing the diagnostic performance of the DMS algorithm to early presenters. As a tribute to the consecutive enrolment of patients, we were not able to enrich the study population by patients presenting within 6 hours from onset of symptoms (49.2% of the entire study cohort reported onset of symptoms more than 12 hours before presentation). Therefore, scrutiny is advised regarding the interpretation of the DMS result in patients presenting very late or who cannot state a precise onset of symptoms. We believe that our study cohort is also similar to other observational studies enrolling patients with suspected ACS. The overall prevalence of ACS in this registry was 12.7% and is thus very consistent with a median of 13 to 14% prevalence of ACS reported in a pooled analysis of 51 observational trials on patients with suspected ACS (**2**). In addition, the median GRACE score was 89 points (IQR: 67-114) which is very similar with the mean GRACE score of 80 (SD 28 points) in the randomized intervention trial(22).

Second, rates of enrolment per site were heterogenous with a mix of high and low recruiting centers. However, the very low mortality rate does not allow any exploratory analyses on the safety of discharge by center volumes, experience of physicians, local cTn assay or assay generation.

Third, currently a strategy for instant rule-out based on Copeptin and cTn is being recommended by 2015 ESC guidelines on NSTE-ACS(10) and an updated consensus document of the German Society of Cardiology on the use of Copeptin in CPUs(49) and chest pain centers(50). However, there is a gap between the high recommendation level endorsed by numerous clinical trials (23-26, 43, 44), editorials and state-of-the-art reviews(38, 40), meta-analyses(27, 28), and National practice guidelines (10, 49, 50) on the one hand and the obvious underuse in clinical practice for suspected ACS. In the elective setting, Copeptin is currently used for the diagnosis of diabetes insipidus, a non-emergent diagnosis. In emergencies requiring immediate measurement, the most probable reason for underuse is that Copeptin has to be measured on a stand-alone device that is more labor-intensive than an automated central laboratory system, which leads to the suspicion that nowadays economic features in the laboratory are hurdles for state of the art use of biomarkers. Development of a POCT system for Copeptin and implementation of Copeptin to a central laboratory platform would overcome this obstacle. In this registry, however, Copeptin was measured on a Kryptor platform with a measuring time of 14 minutes and immediate reporting of the result to the ED physician. Accordingly, most of the time delays between diagnosis and the disproportionally longer stay in ED are regarded to be related to other time consuming processes including diagnostic work-up for differential diagnoses and drafting of the discharge report, particularly in the presence of crowding in the ED.

Conclusions

Copeptin on top of cardiac troponin is currently the only strategy that – based on a RCT and a large multi-centre registry - supports the safe direct discharge of patients with chest pain or chest pain equivalent symptoms suggestive of ACS under routine conditions. There are only few randomized trials that provide evidence for a safe discharge after rule-out in low risk patients. The present registry confirms findings from the randomized BIC-8 trial in an independent real world registry. The efficacy of the DMS in terms of patients potentially qualifying is at least 42.5% or potentially considerably higher.

We believe that the present findings have potential impact on health care resources by shortening observation times, hospitalization rates, reducing diagnostic resources, and avoid unnecessary coronary angiographies should barriers to adoption be overcome.

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Transparency declaration

The corresponding authors (MM) author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing statement

Relevant data could be shared on reasonable request. The corresponding authors will accept requests via Email.

Conflicts of interest

EG received honoraria for lectures from Roche Diagnostics, AstraZeneca, Bayer, Daiichi-Sankyo, Lilly Eli Deutschland. He serves as a consultant for Roche Diagnostics, BRAHMS Thermo Fisher Scientific, Boehringer Ingelheim, and has received research funding from BRAHMS Thermo Fisher Scientific, Roche Diagnostics, Bayer Vital and Daiichi Sankyo;

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EG and **MM** were involved in the conception and design of the study, the acquisition, analysis and interpretation of data, drafted the manuscript, approved the final version to be published, are accountable for all aspects of the work and an d **MM** serves as guarantor for the manuscript.

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Table 1. Baseline characteristics of the patients

Variable	Category	total (n=2294)	primary discharge after fast rule out (n=974)	conventional work up (n=1320)	p-value
Age		59 (46, 72)	51 (39, 62)	65 (52, 75.25)	<0.001
Gender	Female	42.8% (981)	49.7% (484)	37.7% (497)	<0.001
Onset of symptoms before presentation	0 - 3 h	26.3% (558)	26% (228)	26.5% (330)	0.053
	3 - 6 h	13.3% (283)	11.8% (103)	14.4% (180)	
	6 - 12 h	11.2% (238)	13.1% (115)	9.9% (123)	
	> 12 h	49.2% (1043)	49.1% (430)	49.2% (613)	
Leading sympton	Chest pain	70.6% (1619)	76.9% (749)	65.9% (870)	<0.001
	Diffuse Symptoms / Initially Mixed Symptoms	12.9% (297)	9.9% (96)	15.2% (201)	
	None oft he Previous	7.3% (168)	6.6% (64)	7.9% (104)	
	Dyspnea	5.2% (119)	2.5% (24)	7.2% (95)	
	Abdominal pain	2.9% (66)	3.1% (30)	2.7% (36)	
	Focal Neurology	0.7% (16)	0.4% (4)	0.9% (12)	
	Headache	0.4% (9)	0.7% (7)	0.2% (2)	
History of CAD		29.2% (656)	16.8% (158)	38.2% (498)	<0.001
History of MI		11.7% (262)	7.3% (69)	14.8% (193)	<0.001
Risk factor: HTN		53.8% (1189)	38.3% (357)	65.1% (832)	<0.001
Risk factor: HLP		33.6% (708)	23.7% (210)	40.7% (498)	<0.001
Diabetes Mellitus		15.6% (347)	9.3% (86)	20.1% (261)	<0.001
Smoking		34.3% (633)	34.3% (264)	34.3% (369)	1.000
Positive Family History of CAD		32.4% (477)	32.3% (202)	32.5% (275)	0.956
Grace Score	<109	69.3% (1413)	86.1% (736)	57.2% (677)	<0.001
	109-140	21.9% (446)	12.7% (109)	28.5% (337)	
	> 140	8.8% (179)	1.2% (10)	14.3% (169)	
Killip class	I	96% (2084)	98.4% (900)	94.3% (1184)	<0.001
	II	3.2% (70)	1.6% (15)	4.4% (55)	
	III	0.7% (15)	0% (0)	1.2% (15)	
	IV	0% (1)	0% (0)	0.1% (1)	
ECG not diagnostic		87.3% (1971)	93% (892)	83% (1079)	<0.001
ST-elevation		4.2% (94)	2.6% (25)	5.4% (69)	0.002
ST-depression		7.7% (170)	3.6% (34)	10.7% (136)	<0.001
Local cTn	negative	87.9% (2017)	100% (974)	79% (1043)	<0.001
Copeptin	[pmol/l]	7.0 (3.9, 11.8)	4.9 (3.2, 7.7)	10.2 (5.3, 22.9)	<0.001
Copeptin	negative	70.4% (1615)	100% (974)	48.6% (641)	<0.001
Local troponin and copeptin	negative	64.4% (1477)	100% (974)	38.1% (503)	<0.001

Numbers are medians, interquartile ranges and p-values of Wilcoxon rank-sum test for numerical variables and, percentages, counts and p-values of chi-square test for categorical variables.

Table 2. Comparison of patient's characteristics of primary discharge versus over-rule to conventional care despite eligibility for discharge by biomarker results

Variable	Level	Total (n=1477)	Primary discharge (n=974)	Admission over-rule (n=503)	p-value
Age		59 (46, 72)	51 (39, 62)	61 (51.5, 73)	<0.001
Gender	Female	47.2% (697)	49.7% (484)	42.3% (213)	0.009
Onset of symptoms before presentation	0 - 3 h	24.5% (333)	26% (228)	21.7% (105)	0.060
	3 - 6 h	12.1% (165)	11.8% (103)	12.8% (62)	
	6 - 12 h	12.1% (164)	13.1% (115)	10.1% (49)	
	> 12 h	51.3% (698)	49.1% (430)	55.4% (268)	
Leading sympton	Chest pain	73.9% (1092)	76.9% (749)	68.2% (343)	<0.001
	Diffuse/ Initially mixed symptoms	10.9% (161)	9.9% (96)	12.9% (65)	
	Dyspnea	4.4% (64)	2.5% (24)	8.1% (40)	
	Abdominal pain	2.8% (41)	3.1% (30)	2.2% (11)	
	Focal Neurology	0.5% (7)	0.4% (4)	0.6% (3)	
	Headache	0.6% (9)	0.7% (7)	0.4% (2)	
	Other	6.9% (102)	6.6% (64)	7.6% (38)	
History of CAD		24.4% (351)	16.8% (158)	38.9% (193)	<0.001
History of MI		9.5% (136)	7.3% (69)	13.5% (67)	<0.001
Hypertension		48.7% (693)	38.3% (357)	68.2% (336)	<0.001
HLP		29.5% (401)	23.7% (210)	40.6% (191)	<0.001
Diabetes Mellitus		10.9% (155)	9.3% (86)	13.9% (69)	0.011
Smoking		34.6% (409)	34.3% (264)	35.1% (145)	0.838
Family History CAD		33.6% (322)	32.3% (202)	36% (120)	0.269
Grace Score	< 109	80.7% (1067)	86.1% (736)	70.7% (331)	<0.001
	109-140	16.8% (222)	12.7% (109)	24.1% (113)	
	≥ 140	2.6% (34)	1.2% (10)	5.1% (24)	
Killip class	I	98.4% (1378)	98.4% (900)	98.4% (478)	0.375
	II	1.6% (22)	1.6% (15)	1.4% (7)	
	III	0.1% (1)	0% (0)	0.2% (1)	
Final diagnoses	ACS total	6.5% (95)	0.9% (9)	17.1% (86)	<0.001
	unclassified ACS	1.9% (28)	0.4% (4)	4.8% (24)	
	UAP	4% (58)	0.4% (4)	10.8% (54)	
	NSTEMI	0.3% (5)	0.1% (1)	0.8% (4)	
	AMI other	0.1% (2)	0% (0)	0.4% (2)	
	STEMI	0.1% (2)	0% (0)	0.4% (2)	
Main diagnosis	Cardiac	34.4% (503)	23.5% (226)	55.2% (277)	<0.001
Mortality	30days	0.1% (2)	0.1% (1)	0.2% (1)	1

Numbers are medians, interquartile ranges and p-values of Wilcoxon rank-sum test for numerical variables and percentages, counts and p-values of chi-square test for categorical variables. CAD, coronary artery disease; HLP, hyperlipidemia; UAP, unstable angina pectoris

Table 3. All-cause death at 30 days and secondary outcomes

Variable	Categories	Total (2294 patients)	Primary discharge after fast rule out (974 patients)	Conventional work up (1320 patients)
All-cause death	30days	0.7% (0.4%-1.1%) n=15	0.1% (0%-0.6%), n=1*	1.1% (0.6%-1.8%) n=14
Exact length of stay in ED/CPU [hours]		4.3 (4.1-4.5)	3.8 (3.6-4.0)	4.8 (4.7-5.0)
Length of stay in ED/CPU	0 - 1 h	2.6% (n=53)	1.5% (n=13)	3.6% (n=40)
	1 - 2 h	13.3% (n=266)	13.2% (n=118)	13.3% (n=148)
	2 - 3 h	18.6% (n=372)	21.7% (n=194)	16% (n=178)
	3 - 6 h	42.7% (n=855)	49.3% (n=440)	37.3% (n=415)
	>= 6 h	22.9% (n=458)	14.2% (n=127)	29.8% (n=331)
Admission	Peripheral ward	72.7% (n=562)	100% (n=1)	72.7% (n=561)
	IMCU	17.6% (n=136)	0% (n=0)	17.6% (n=136)
	ICU	9.7% (n=75)	0% (n=0)	9.7% (n=75)

Percentages and counts (denoted by "n=") for categorical variables and medians for the numeric variable "Exact length of stay in ED/CPU"; 95% confidence intervals added in brackets for all-cause death and Exact length of stay in ED/CPU.

*70 years old male, known CAD, MI and COLD/asthma, Tn and Copeptin negative, ECG normal, diagnosis: non cardiac, atypical chest pain (musculoskeletal), death one month later from metastatic lung cancer.

Figure legends

Figure 1. Patient flow chart

Figure 2. Algorithm for an early rule-out strategy and guidance of primary early discharge versus general hospital admission (conventional work-up)

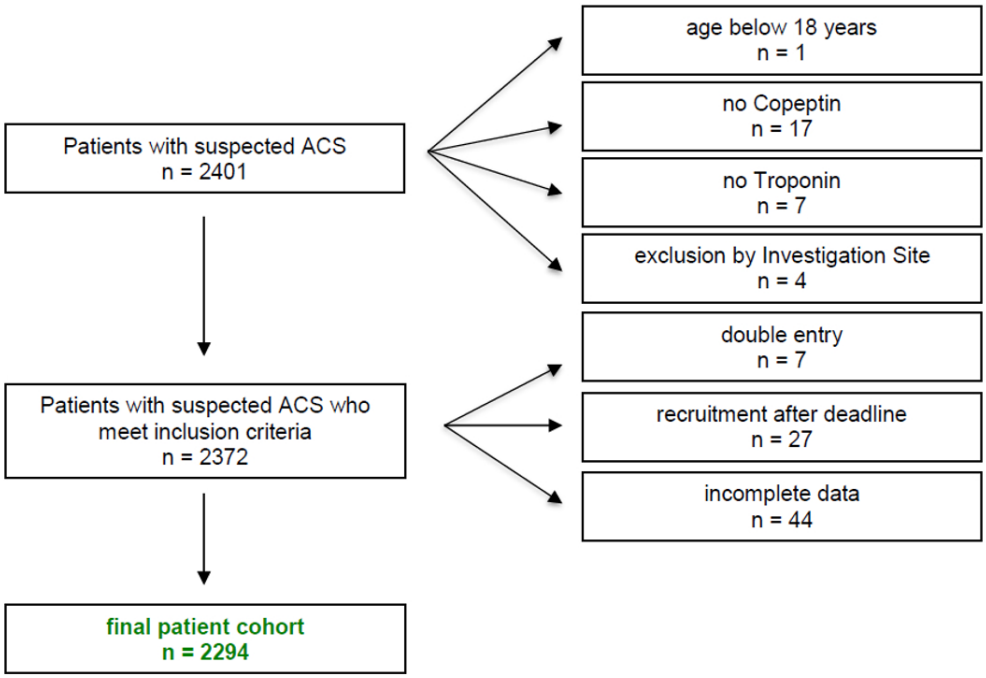
Supplemental material

Figure legends

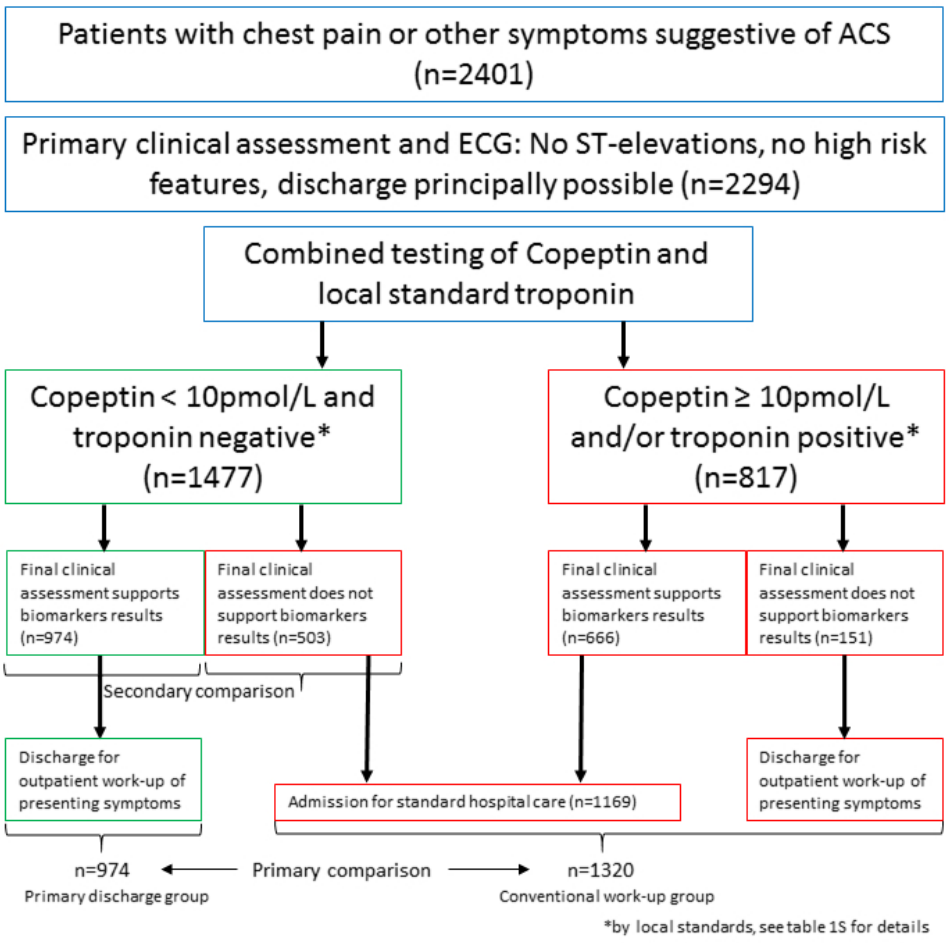
Figure 1S. Investigation sites and number of completed patients. CVK, Charité Virchow-Klinikum; UKB, Unfallkrankenhaus Berlin.

Figure 2S. Distribution of leading symptoms

Figure 3S. Distribution of diagnoses in the Emergency Department (ED) and/or the Chest Pain Unit (CPU)



Patient flow chart



Algorithm for an early rule-out strategy and guidance of primary early discharge versus general hospital admission (conventional work-up)

Table 1S. Local standard troponin tests and cutoffs for MI diagnosis

Center	Troponin test	MI Cut-Off
Heidelberg	Hs TnT, Elecsys, Roche Diagnostic	14 ng/l
UKB, Berlin	Hs TnT, Elecsys, Roche Diagnostic	14 ng/l
CVK, Berlin	AQT-Test POCT, Radiometer hsTnT, Elecsys, Roche Diagnostic	30 ng/l 50 ng/l
Frankfurt	Hs TnT, Elecsys, Roche Diagnostic	14 ng/l
Bad-Nauheim	Hs TnT, Elecsys, Roche Diagnostic	14 ng /l
Mayen	TnI Ortho Clinical Diagnostics and from 19.4.16 TnI, LOCI, Siemens	50 ng/l
Wien	TnI, LOCI, Siemens	45 ng/l
Calais	TnI, Access, Beckman and Coulter	30 ng/l (97.5th %le)
Vilnius	Hs TnI, Architect, Abbott	for men 34,2 ng/l for women 15,6 ng/l
Budapest	Hs TnT, Elecsys, Roche Diagnostic (Cobas e411)	14 ng/l
High Wycombe	Hs TnI, Architect, Abbott	for men 34,2 ng/l for women 15,6 ng/l
Zollichberg, Zurich	TnI-Ultra, Centaur, Siemens	40 ng/l
Aarau	TnI, LOCI, Siemens	45 ng/l
Berlin Hedwigshöhe	Hs TnI, Architect, Abbott	15 ng/l
Dijon	TnI, Vista, Siemens	100 ng/l
Ankara	TnI, Access, Beckman and Coulter	40 ng/l (99th %le)
Tulln	Hs TnT, Elecsys, Roche Diagnostic	14 ng/l
Montpellier	Hs TnT, Elecsys, Roche Diagnostic (Cobas 8000/e602 analyzer)	14 ng/l

Summary of ethics approval

- The principle ethics vote is from the principal investigator site, Charité (Berlin). Reference number EA1/00815, on the 05.06.2015
- Some German participant centres (Mayen, Hedwigshohe, UKB) accepted the ethics approval from the principal investigator site (Charité, Berlin).
  All the local ethics committee were informed accordingly.
- Bad Nauheim: The ACS Registry was approved by the ethical board of the Justus-Liebig-University Giessen (FF 17/2011)
- Frankfurt: The ProCore Registry was approved by the ethical board of the Goethe-University Frankfurt (318/15)
- Heidelberg: The ProCore Registry was approved by the ethical board of the Medizinische Fakultät Heidelberg (S-382/2015)
- The principle Austrian ethics vote is from the Vienna university hospital (Reference number EK-15-198-1015 on the 28th of October 2016)
- The hospital of Tulln accepted the Austrian ethics vote from Vienna.
- The principle Swiss ethics vote is from the Zollikerberg (Zurich) hospital (reference number BASEC 2016-00401 on the 13.03.2016)
- The Aarau hospital accepted the Swiss ethics vote from Zurich on the 14.12.2016
- High Wycombe hospital ethics vote approved the study with the following REC reference number: 16/SC/0198, IRAS project ID:193406
- The Ankara university hospital accepted the ethics vote from the principal investigator site, Charité (Berlin)
- The Budapest university hospital accepted the ethics vote from the principal investigator site, Charité (Berlin)
- The Vilnius University hospital accepted the ethics vote from the principal investigator site, Charité (Berlin)
- The French participants centres (Calais, Montpellier, Dijon) were using the dual marker strategy in routine; the local ethics committee was informed and accepted the data anonymisation of the electronic case report form.

Figure 1S

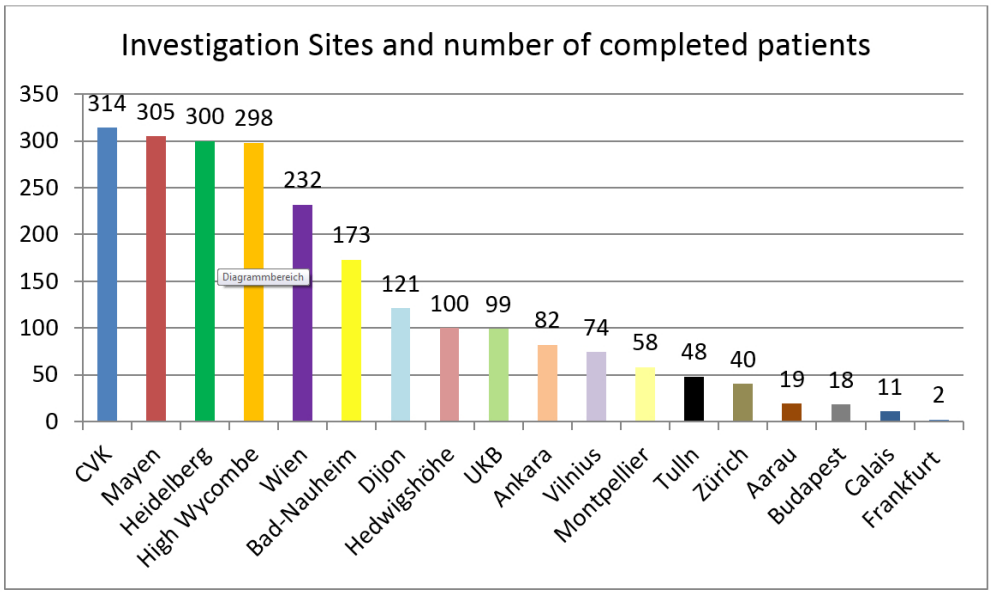

Investigation Sites and number of completed patients
350
300
250
200
150
100
50
0
314
305
300
298
232
173
121
100
99
82
74
58
48
40
19
18
11
2
Diagrammbereich
CVK
Mayen
Heidelberg
High Wycombe
Wien
Bad-Nauheim
Dijon
Hedwigshöhe
UKB
Ankara
Vilnius
Montpellier
Tulln
Zürich
Aarau
Budapest
Calais
Frankfurt

Figure 2S

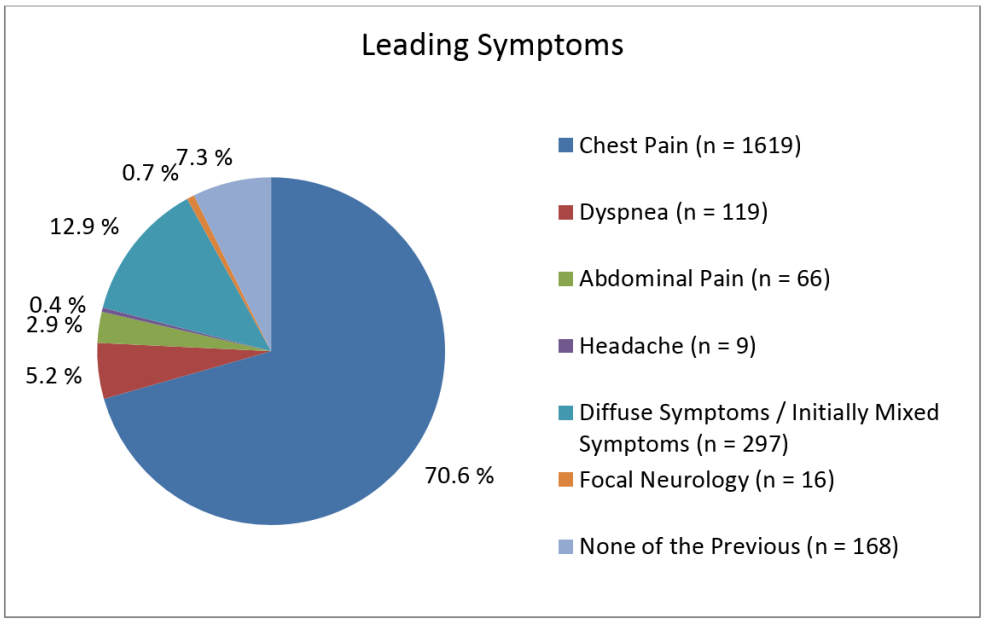
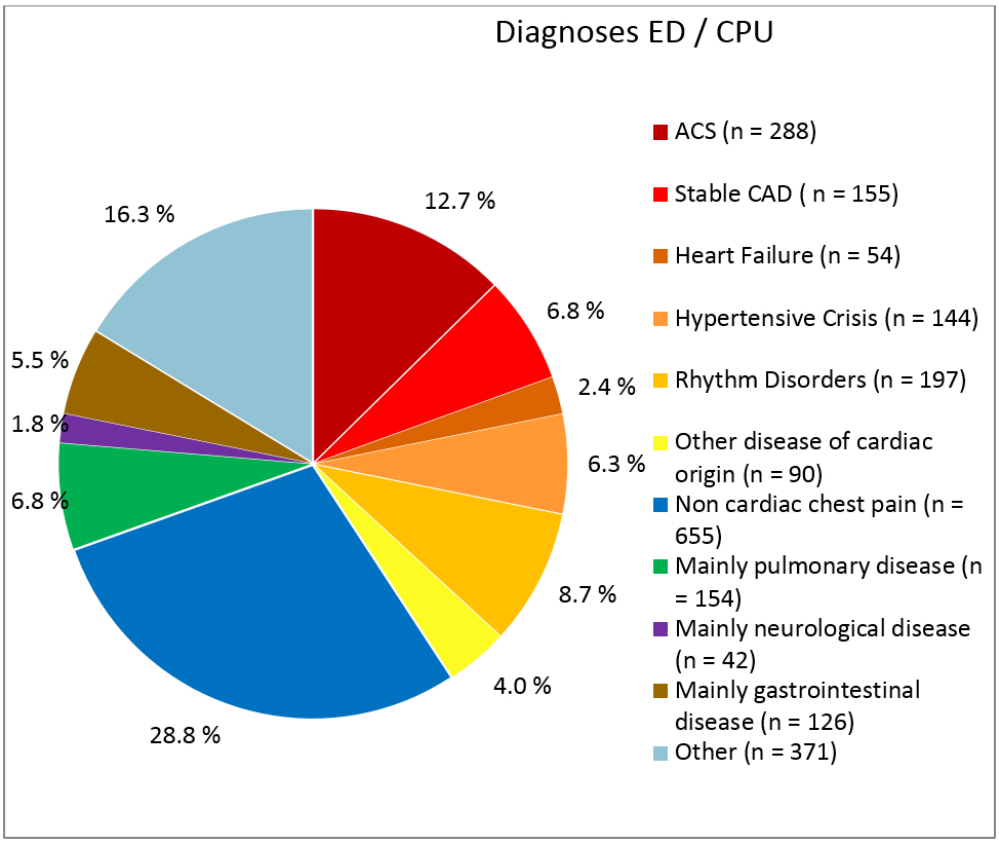

Leading Symptoms
Chest Pain (n = 1619)
Dyspnea (n = 119)
Abdominal Pain (n = 66)
Headache (n = 9)
Diffuse Symptoms / Initially Mixed Symptoms (n = 297)
Focal Neurology (n = 16)
None of the Previous (n = 168)
70.6 %
5.2 %
2.9 %
0.4 %
12.9 %
0.7 %
7.3 %

Figure 3S


Diagnoses ED / CPU
12.7 %
6.8 %
2.4 %
6.3 %
8.7 %
4.0 %
28.8 %
6.8 %
1.8 %
5.5 %
16.3 %
ACS (n = 288)
Stable CAD (n = 155)
Heart Failure (n = 54)
Hypertensive Crisis (n = 144)
Rhythm Disorders (n = 197)
Other disease of cardiac origin (n = 90)
Non cardiac chest pain (n = 655)
Mainly pulmonary disease (n = 154)
Mainly neurological disease (n = 42)
Mainly gastrointestinal disease (n = 126)
Other (n = 371)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Fig.1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	24
		(b) Indicate number of participants with missing data for each variable of interest	24-26
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	26

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14-15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.