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Combined testing of copeptin and high-sensitivity cardiac troponin T at presentation in comparison to other algorithms for rapid rule-out of acute myocardial infarction

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ABSTRACT

Background: We aimed to directly compare the diagnostic and prognostic performance of a dual maker strategy (DMS) with combined testing of copeptin and high-sensitivity (hs) cardiac troponin T (cTnT) at time of presentation with other algorithms for rapid rule-out of acute myocardial infarction (AMI).

Methods: 922 patients presenting to the emergency department with suspected AMI and available baseline copeptin measurements qualified for the present TRAPID-AMI substudy. Diagnostic measures using the DMS (copeptin <10, <14 or < 20 pmol/L and hs-cTnT≤14 ng/L), the 1 h-algorithm (hs-cTnT<12 ng/L and change <3 ng/L at 1 h), as well as the hs-cTnT limit-of-blank (LoB, <3 ng/L) and -detection (LoD, <5 ng/L) were compared. Outcomes were assessed as combined end-points of death and myocardial re-infarction.

Results: True-negative rule-out using the DMS could be achieved in 50.9%–62.3% of all patients compared to 35.0%, 45.3% and 64.5% using LoB, LoD or the 1 h-algorithm, respectively. The DMS showed NPVs of 98.1%–98.3% compared to 99.2% for the 1 h-algorithm, 99.4% for the LoB and 99.3% for the LoD. Sensitivities were 93.5%–94.8%, as well as 96.8%, 98.7% and 98.1%, respectively. Addition of clinical low-risk criteria such as a HEART-score ≤ 3 to the DMS resulted in NPVs and sensitivities of 100% with a true-negative rule-out to 33.8%–41.6%. Rates of the combined end-point of death/MI within 30 days ranged between 0.2% and 0.3% for all fast-rule-out protocols.

Conclusion: Depending on the applied copeptin cut-off and addition of clinical low-risk criteria, the DMS might be an alternative to the hs-cTn-only-based algorithms for rapid AMI rule-out with comparable diagnostic measures and outcomes.

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1. Introduction

With the introduction of high-sensitivity (hs) cardiac troponin (cTn) assays and the increased accuracy to diagnose acute myocardial infarction (AMI) at time of presentation or within the first hours of presentation, various biomarker algorithms have been proposed for an accelerated rule-in and rule-out of AMI. We recently evaluated the 1 h-algorithm in the TRAPID-AMI trial [1], which allowed for an accurate rule-in and a safe rule-out of AMI within 1 h with a negative predictive value (NPV) above 99% in several large multi-center trials [1,2]. Moreover, an increasing number of studies has recently shown that the limit-of-detection (LoD) or the limit-of-blank (LoB) of hs-cTn can be used for rapid AMI rule-out [3–8]. In addition, the current ESC guidelines for non-ST-elevation (NSTE) - acute coronary syndrome (ACS) recommend a combination of the 1 h-algorithm with the LoD for rapid rule-out when hs-cTn assays are available [9]. As an alternative, the ESC guidelines also recommend application of a dual marker strategy (DMS) combining low levels of copeptin with normal levels of contemporary cTn at time of presentation [9]. Copeptin is the C-terminal part of the arginine vasopressin prohormone (CT-proAVP) and has been described as a marker of endogenous stress with high blood levels shortly after a severe event, thus offering complementary release kinetics in combination to cTn, which is measurable in blood with a certain delay when using contemporary cTn assays [10–12]. Thus, while copeptin seems to be most beneficial in the combination with contemporary cTn, the advantage of the complementary release kinetics of copeptin to cTn in the presence of current hs-assays, which may allow early detection of cTn blood level changes, has yet to be investigated [13]. Recent studies question the incremental overall diagnostic value of copeptin beyond hs-cTn, nonetheless, there is evidence that early rule-out may be facilitated by the combination of copeptin and hs-cTn [10]. Möckel et al. also showed that early discharge of patients with suspected ACS seems to be safe based on copeptin and cTn testing at time of presentation [14]. However, no study has yet directly compared the DMS combining copeptin and hs-cTnT with the 1 h-algorithm and the LoD/LoB-rule-out protocols, which are applicable in the presence of hs-cTn assays. The aim of this sub-analysis of the TRAPID-AMI study is thus to evaluate the diagnostic and prognostic performance of the DMS with hs-cTnT and copeptin using different cut-offs in direct comparison to the other fast AMI rule-out algorithms.

2. Materials and methods

2.1. Study population

Patients presenting to the ED with acute chest pain symptoms suggestive of AMI with an onset or peak within 6 h were recruited as part of the prospective international multicenter TRAPID-AMI (High sensitivity cardiac Troponin T assay for RAPID rule-out of Acute Myocardial Infarction) study as previously described [1,15]. In total, 922 patients among the 1282 patients of the main trial could be included for further analysis. Patients qualified for the current sub-analysis, when baseline copeptin measurements were available. 2 of 12 participating sites did not give consent for storage of blood samples and thus these patients (n = 212) were excluded. In addition, patients had to be excluded for insufficient blood volumes for copeptin measurements (n = 113) (Suppl. Fig. 1).

Adjudication criteria have been described earlier [1,15]. In brief, AMI was diagnosed according to the universal MI definition when an elevated cTn level above the 99th percentile cut-off value was present together with a significant kinetic change of cTn and clinical signs or symptoms of myocardial ischemia [16]. To provide the best possible cTn-based diagnosis independent from hs-cTnT values, the most sensitive cTnI-assay available at the time of the adjudication (cTnI Ultra, Siemens Healthcare) was used for determination of AMI. Final adjudicated diagnosis was made by two independent cardiologists, with discrepancies solved by discussion with a third cardiologist [1]. Timing and selection of diagnostic or therapeutic procedures were left at the discretion of the attending physician. Follow-up of patients following hospital discharge was performed after 30 days, 3 months and 12 months by telephone calls or in written form. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all patients.

2.2. Laboratory analysis

Blood samples were collected in EDTA-plasma tubes at presentation and according to pre-defined time intervals up to 4–14 h after presentation [1]. Following centrifugation, samples were frozen at −80 °C until further measurement in a blinded fashion. Baseline samples and 1 h samples were available in all patients of the main trial for measurements of Elecsys® Troponin T high sensitive (Roche Diagnostics) using the Elecsys® 2010 Immunoassay Analyzer (Roche Diagnostics) and cTnI Ultra (Siemens Healthcare) using the ADVIA Centaur immunoassay system (Siemens Healthcare) in a core laboratory. Limit of detection, 10% coefficient of variation (CV) and 99th percentile cut-off values have been found to be 5 ng/L, 13 ng/L and 14 ng/L for the hs-cTnT assay [17,18] and 6 ng/L, 30 ng/L and 40 ng/L for the cTnI Ultra assay [19,20]. In addition, the 922 patients which qualified for the present sub-analysis had available baseline samples for re-measurement of copeptin with the copeptin proAVP assay on the KRYPTOR compact plus (BRAHMS Thermo Scientific) in a second central laboratory (Wels, Austria). The copeptin proAVP assay has been assigned a detection limit of 0.69 pmol/L and a precision of 20% CV at 1.08 pmol/L [21]. In a population-based study, 95th, 97.5th and 99th percentile values for copeptin were reported as 9.8 pmol/L, 13 pmol/L and 18.9 pmol/L [11].

2.3. Outcome measures

Early rule-out was performed using the DMS with copeptin and hs-cTnT at time of presentation. In accordance to previous investigated cut-offs and approx. corresponding to population-based reference values [10–12,14,22], we applied copeptin cut-offs of <10 pmol/L, <14 pmol/L and <20 pmol/L. For hs-cTnT, the 99th percentile value of ≤14 ng/L was used. The DMS was compared to other established rule-out protocols using hs-cTnT assays including hs-cTnT ≤14 ng/L alone (99th percentile), <3 ng/L (LoB) or <5 ng/L (LoD) at presentation, hs-cTnT<12 ng/L and absolute delta change <3 ng/L at 1 h (1 h-algorithm) as well as hs-cTnT <5 ng/L and chest pain onset >3 h OR hs-cTnT <12 ng/L and absolute delta change <3 ng/L at 1 h as recently proposed by the ESC NSTE-ACS guidelines (ESC algorithm) [9]. The primary outcome measure was the NPV for early AMI rule-out. Secondary outcome measures were assessment of sensitivities of AMI at the index event as well as rates of the combined end-point of all-cause death and myocardial re-infarction within 30 days, 3 months and 12 months.

Impact of clinical criteria on diagnostic and prognostic outcomes for the DMS with hs-cTnT was assessed using ACS risk scores such as the GRACE- and HEART-score or ECG findings. The GRACE- and HEART-scores were calculated in the modified versions as previously described [23–25]. The absence of ECG ischemia was defined as evaluable ECGs with absence of ST-segment elevation or depression, T-wave changes, left bundle branch block, q-waves and ventricular paced rhythm.

2.4. Statistical methods

Continuous parameters were given as means (±standard deviation) for normally distributed data or as median with interquartile range for non-normal data. The Mann-Whitney *U* test or the Student's *t*-test was used to compare continuous variables, whereas a Chi-square test was applied for categorical parameters. Rule-out for AMI diagnosis was assessed by calculation of NPVs (with 95% confidence intervals) using specific hs-cTnT and copeptin cut-offs and compared to different rule-out strategies. Other diagnostic measures for predefined cut-offs included sensitivities, specificities and positive predictive values (PPVs), whereas overall diagnostic performance was assessed by areas-under-the-curves (AUC).

All hypothesis testing was two-tailed and P-values <0.05 were considered statistically significant. All statistical analyses were performed using MedCalc 15.6 (MedCalc Software), SPSS 22.0 (IBM) and R 3.2 (The R Foundation for Statistical Computing).

3. Results

3.1. Baseline characteristics

AMI was the final adjudicated diagnosis in 154 (16.7%) patients. Suppl. Table 1 displays baseline characteristics of the entire cohort and stratified according to the different fast-rule-out algorithms.

3.2. Diagnostic performance of the DMS using hs-cTnT and copeptin

Overall diagnostic performance for AMI diagnosis as measured by AUC was 0.93 (95% CI 0.91–0.95) for the combination of copeptin and hs-cTnT compared to 0.92 (0.90–0.94) for hs-cTnT alone (p = NS). Using specific cut-offs for AMI rule-out, the DMS enabled a true-negative rule-out in 469 patients (50.9%) for a copeptin cut-off <10 pmol/L, 530 (57.5%) for <14 pmol/L and 574 (62.3%) for <20 pmol/L. NPVs were 98.3%, 98.1% and 98.3% with sensitivities of 94.8%, 93.5% and 93.5%, respectively. Detailed diagnostic measures of the DMS using hs-cTnT<14 ng/L in combination with different copeptin cut-offs can be found in Table 1. Diagnostic results with exclusion of patients with STEMI (n = 16) are shown in Suppl. Table 2. NPVs and sensitivities for the DMS stratified for age, gender and symptom onset are displayed in Suppl. Table 3.

Table 1
Diagnostic performance of the dual marker strategy using copeptin and hs-cTnT compared to other AMI rule-out protocols.

	NPV [%] (95%CI)	Sensitivity [%] (95%CI)	PPV [%] (95%CI)	Specificity [%] (95%CI)	Rule-out[i] [%]
hs-cTnT ≤ 14 ng/L	97.4	89.0	50.6	82.6	68.8
(99th perc.)	(95.9–98.5)	(82.9–93.4)	(44.4–56.7)	(79.7–85.2)	(65.7–71.7)
hs-cTnT & Copeptin < 10[a]	98.3	94.8	32.8	61.1	50.9
	(96.7–99.3)	(90.0–97.7)	(28.5–37.4)	(57.5–64.5)	(47.6–54.1)
+ No ECG ischemia[f]	98.9	97.3	27.0	48.5	40.5
	(97.2–99.7)	(93.2–99.3)	(23.2–31.0)	(44.8–52.1)	(37.3–43.8)
+ GRACE[g] Score < 109	98.8	97.2	25.5	45.5	38.2
	(97.1–99.7)	(93.0–99.2)	(21.9–29.4)	(41.9–49.2)	(35.0–41.5)
+ GRACE[g] Score < 140	98.6	95.8	30.5	58.2	48.8
	(97.1–99.5)	(91.2–98.5)	(26.3–35.0)	(54.6–61.7)	(45.5–52.2)
+ HEART[h]-Score ≤ 3	100.0 (98.8–100)	100.0	24.6	40.3	33.7
		(97.5–100)	(21.2–28.3)	(36.8–44.0)	(30.6–37.0)
hs-cTnT & Copeptin < 14[b]	98.1	93.5	37.7	69.0	57.5
	(96.6–99.1)	(88.4–96.8)	(32.8–42.8)	(65.6–72.3)	(54.2–60.7)
+ No ECG ischemia[f]	99.0	97.3	29.3	54.1	45.2
	(97.5–99.7)	(93.2–99.3)	(25.3–33.6)	(50.4–57.7)	(41.9–48.5)
+ GRACE[g] Score < 109	99.0	97.2	27.7	51.4	43.1
	(97.4–99.7)	(93.0–99.2)	(23.9–31.8)	(47.8–55.0)	(39.9–46.4)
+ GRACE[g] Score < 140	98.6	95.1	34.4	65.2	54.7
	(97.1–99.4)	(90.2–98.0)	(29.8–39.3)	(61.7–68.7)	(51.4–58.0)
+ HEART-Score[h] ≤ 3	100.0	100.0	26.5	45.9	38.4
	(98.9–100)	(97.5–100)	(22.8–30.4)	(42.2–49.5)	(35.2–41.7)
hs-cTnT & Copeptin < 20[c]	98.3	93.5	42.6	74.7	62.3
	(96.9–99.2)	(88.4–96.8)	(37.3–48.1)	(71.5–77.8)	(59.0–65.4)
+ No ECG ischemia[f]	99.1	97.3	31.4	58.3	48.8
	(97.7–99.8)	(93.2–99.3)	(27.1–35.8)	(54.7–61.9)	(45.5–52.1)
+ GRACE[g] Score < 109	99.0	97.2	29.4	55.1	46.3
	(97.6–99.7)	(93.0–99.2)	(25.3–33.7)	(51.5–58.7)	(43.0–49.6)
+ GRACE[g] Score < 140	98.4	93.8	41.4	74.6	62.6
	(97.0–99.3)	(88.5–97.1)	(36.0–47.0)	(71.3–77.6)	(59.3–65.8)
+ HEART-Score[h] ≤ 3	100.0	100.0	27.9	49.7	41.6
	(99.0–100)	(97.5–100)	(24.1–32.0)	(46.0–53.3)	(38.3–44.9)
hs-cTnT < 3 ng/L (LoB)	99.4	98.7	25.5	42.1	35.0
	(97.8–99.9)	(95.4–99.8)	(22.0–29.2)	(38.5–45.6)	(32.0–38.2)
+ HEART-Score[h] ≤ 3	100.0	100.0	23.0	32.4	27.0
	(98.5–100)	(97.6–100	(19.8–26.4)	(29.1–35.9)	(24.1–30.0)
hs-cTnT < 5 ng/L (LoD)	99.3	98.1	30.1	54.4	45.3
	(97.9–99.9)	(94.4–99.6)	(26.1–34.4)	(50.8–58.0)	(42.1–48.6)
+ HEART-Score[h] ≤ 3	100.0	100.0	25.8	41.7	34.7
	(98.8–100)	(97.6–100)	(22.4–29.6)	(38.2–45.3)	(31.6–37.9)
1 h-algorithm[d]	99.2	96.8	46.3	77.5	64.5
	(98.1–99.7)	(92.6–98.9)	(40.7–51.9)	(74.4–80.4)	(61.3–67.6)
+ HEART-Score[h] ≤ 3	99.7	99.3	30.3	53.2	44.1
	(98.6–100)	(96.4–100)	(26.3–34.6)	(49.5–56.8)	(40.8–47.4)
ESC algorithm[e]	99.5	98.7	31.5	52.6	43.1
	(98,0–99.9)	(95.4–99.8)	(27.4–35.9)	(48.8–56.4)	(39.7–46.5)

ECG; electrocardiogram; hs, high-sensitivity; cTn; cardiac troponin; LoB, limit of blank; LoD, limit of detection; ESC: European Society of Cardiology.
[a] Dual marker strategy for rule-out using copeptin <10 pmol/L and hs-cTnT ≤14 ng/L.
[b] Dual marker strategy for rule-out using copeptin <14 pmol/L and hs-cTnT ≤14 ng/L.
[c] Dual marker strategy for rule-out using copeptin <20 pmol/L and hs-cTnT ≤14 ng/L.
[d] hs-cTnT <12 ng/L and absolute delta change <3 ng/L at 1 h.
[e] hs-cTnT <5 ng/L and chest pain onset >3 h OR hs-cTnT <12 ng/L and absolute delta change <3 ng/L at 1 h.
[f] Evaluable ECG and absence of ST-segment elevation or depression, T-wave changes, left bundle branch block, q-waves and ventricular paced rhythm.
[g] Modified GRACE 2.0 with substitution of diuretic usage for Killip class.
[h] Modified HEART-score according to McCord et al. (24).
[i] True-negative rule-out rate.

3.3. Diagnostic performance of the other rule-out algorithms compared to the DMS

Compared to the true-negative rule-out rate for the DMS ranging from 50.9% to 62.3%, the other tested rule-out algorithms reached values of 68.8% for the general hs-cTnT 99th percentile, 64.5% for the 1 h-algorithm, 43.1% for the ESC algorithm as well as 45.3% and 35.0% for the LoD/LoB, respectively.

Using the general hs-cTnT 99th percentile at presentation revealed NPVs and sensitivities of 97.4% and 89.0% whereas the remaining algorithms (1 h-algorithm, ESC algorithm, LoD, LoB) all had NPVs of ≥99%. Sensitivities were >98% for LoD and LoB as well as 96.8% for the 1 h-algorithm and 98.7% for the ESC algorithm. Fig. 1 displays NPVs, sensitivities and true-negative rule-out rates for the DMS compared to other hs-cTnT fast-rule-out algorithms. The total number of patients assigned to either rule-out or non-rule-out depending on the algorithm is shown in Suppl. Fig. 3.

3.4. Addition of clinical criteria to the DMS and other rule-out algorithms

Using the DMS in combination with absence of ischemia on ECG or GRACE<109 resulted in NPVs of 98.9%–99.1% and sensitivities of 97.2%–97.3%, however, true-negative rule-out rates were reduced to 38.2%–48.8% depending on the copeptin cut-off (Table 1, Fig. 2). Implementation of a HEART-score ≤ 3 to the DMS reached NPVs and sensitivities of 100% for all three copeptin cut-offs with true-negative rule-out

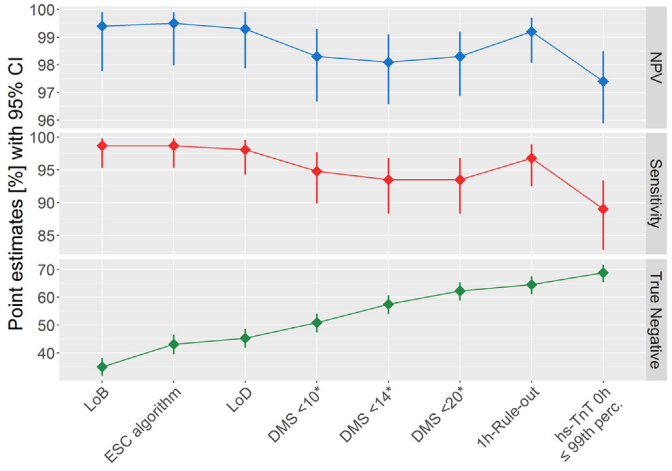

Fig. 1. Diagnostic measures for the DMS with *copeptin cut-offs of <10, <14 or < 20 pmol/L compared to other hs-cTnT fast-rule-out algorithms.

rates up to 41.6% (DMS with copeptin cut-off <20 pmol/L) (Fig. 2). In comparison, combination of a HEART-score ≤ 3 with the LoB or LoD also resulted in 100% NPV and sensitivity, while true-negative rule-out rates were 27.0% and 34.7%, respectively (Table 1). The NPV of the 1 h-algorithm with addition of the HEART-score was 99.2% compared to 99.7% without, however, the true-negative rule-out rate was considerably reduced (64.5% vs. 44.1%).

3.5. Prognostic outcomes in ruled-out patients

Rates of the combined end-point of death/MI within 30 days ranged between 0.2% and 0.3% for all fast-rule-out protocols. In patients with GRACE-score < 109 and HEART-score ≤ 3, the DMS rule-out resulted in an event rate of 0% for death/MI at 30 days and at 3 months (Table 2). Detailed outcomes for all tested rule-out algorithms after 30 days, 3 and 12 months are displayed in Table 2. Event rates with exclusion of STEMI (n = 16) are shown in Suppl. Table 4.

4. Discussion

In the present TRAPID-AMI sub-study in patients presenting with symptoms suggestive of AMI, we assessed the diagnostic and prognostic performance of the DMS with combined testing of copeptin and hs-cTnT at time of presentation in comparison to other established fast-rule-out algorithms.

This is the first study with direct comparison of the DMS using a hs-cTn assay to other guideline-recommended fast AMI rule-out protocols. Thus, our study provides novel insights regarding the relative merits of the DMS in comparison to other rule-out strategies.

We found the following results: First, depending on the copeptin cut-off, the DMS allows for a rapid rule-out at presentation in up to 62.3% of patients with symptoms suggestive of AMI. Second, NPVs of 98.1–98.3% without clinical criteria and 100% in combination with clinical low-risk criteria such as a HEART-score ≤ 3 could be achieved by the DMS, while sensitivities of 94.8% and 100%, respectively, were reached. Third, the NPV was maintained when increasing the copeptin cut-offs from 10 to 20 pmol/L and further resulted in improvement of specificity. Fourth, patients who qualified for rule-out by the DMS had an excellent prognosis in short- and long-term follow-up indicating the potential not only for an immediate but also of a safe rule-out. Finally, the DMS and the other recommended hs-cTnT fast-rule-out algorithms provided a comparable diagnostic and prognostic performance in terms of true-negative rule-out rate, sensitivity, NPV and outcome rates in short- and long-term follow-up.

4.1. Incremental value of copeptin

Several studies have been focused on the incremental value of copeptin to cTn in recent years. Due to the advantage of the complementary release kinetics, the addition of copeptin to contemporary cTn was found to significantly improve diagnostic performance and facilitate early rule-out with very high NPVs [11,12,26,27]. Thus, the diagnostic benefit of using copeptin in combination with contemporary cTn has been generally regarded as considerable [13]. However, the combination with sensitive or hs-cTn assays may provide only limited diagnostic added value based on overall diagnostic performance mainly driven by a loss of specificity. In our study, diagnostic performance was not significantly improved by the addition of copeptin to hs-cTnT (0.93 vs. 0.92). This is in line with findings from two recent meta-analyses, which observed pooled AUC values of 0.92 for hs-cTn alone and 0.91 for the combination with copeptin [10,28]. On the contrary, when copeptin was used with specific cut-offs and in combination with hs-cTnT, pooled NPVs and sensitivities improved from 96% to 98% and 88% to 96%, respectively. Similarly, we found high NPVs between 98.1% and 98.3% and sensitivities of 93.5% to 94.8% for the DMS. True-negative rule-out was feasible in up to 62.3% of all patients depending on the copeptin cut-off. Notably, copeptin cut-offs of 10, 14 or 20 pmol/L revealed no difference in regard to NPVs and sensitivities,

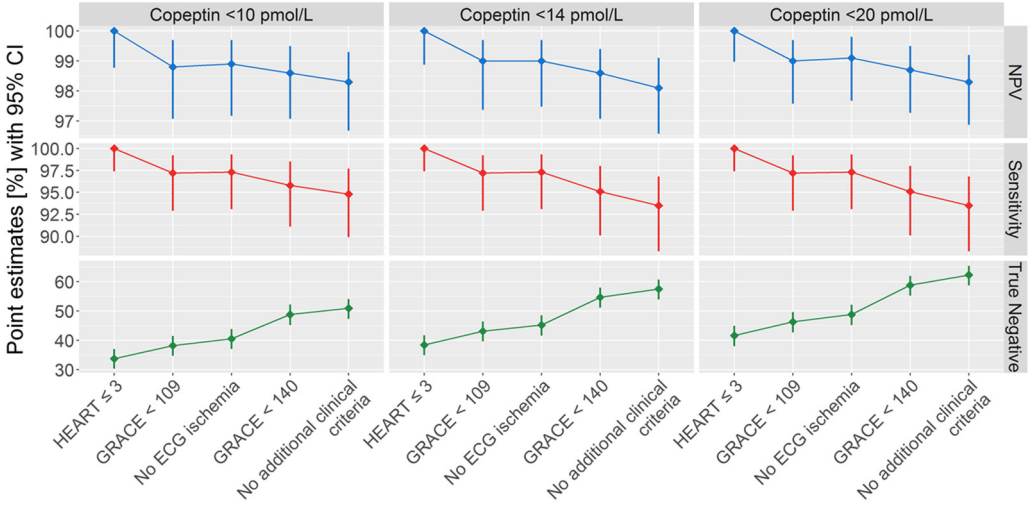

Fig. 2. NPVs, sensitivities and true-negative rule-out rates for the DMS without and with addition of clinical criteria.

Table 2
Short and long-term risk of death and MI in patients ruled-out.

	Death/MI 30 days		Death/MI 3 months		Death/MI 12 months	
	[%] (95% CI)	[No.]	[%] (95% CI)	[No.]	[%] (95% CI)	[No.]
hs-cTnT ≤ 14 ng/L (99^{th} perc.)	0.3 (0.0–1.1)	2/643	0.5 (0.1–1.4)	3/640	1.6 (0.8–2.9)	10/629
hs-cTnT & Copeptin < 10[a]	0.2 (0.0–1.2)	1/473	0.2 (0.0–1.2)	1/471	1.1 (0.4–2.5)	5/462
+ No ECG ischemia[f]	0.3 (0.1–1.5)	1/365	0.3 (0.0–1.5)	1/363	1.1 (0.3–2.9)	4/355
+ GRACE[g] Score < 109	0.0 (0.0–1.1)	0/342	0.0 (0.0–1.1)	0/340	0.6 (0.1–2.2)	2/333
+ GRACE[g] Score < 140	0.2 (0.0–1.3)	1/439	0.2 (0.0–1.3)	1/437	0.9 (0.3–2.4)	4/428
+ HEART-Score[h] ≤ 3	0.0 (0.0–1.2)	0/295	0.0 (0.0–1.3)	0/293	0.7 (0.1–2.5)	2/287
hs-cTnT & Copeptin < 14[b]	0.2 (0.1–1.0)	1/535	0.2 (0.1–1.0)	1/533	1.1 (0.4–2.5)	7/524
+ No ECG ischemia[f]	0.2 (0.0–1.4)	1/407	0.2 (0.1–1.4)	1/405	1.0 (0.3–2.6)	4/397
+ GRACE[g] Score < 109	0.0 (0.0–1.0)	0/385	0.0 (0.0–1.0)	0/383	0.5 (0.1–1.9)	2/376
+ GRACE[g] Score < 140	0.2 (0.1–1.1)	1/492	0.2 (0.1–1.1)	1/490	0.8 (0.2–2.1)	4/481
+ HEART-Score[h] ≤ 3	0.0 (0.0–1.1)	0/336	0.0 (0.0–1.1)	0/334	0.6 (0.1–2.2)	2/328
hs-cTnT & Copeptin < 20[c]	0.2 (0.0–1.0)	1/577	0.2 (0.0–1.0)	1/575	1.1 (0.4–2.3)	7/566
+ No ECG ischemia[f]	0.2 (0.0–1.3)	1/437	0.2 (0.0–1.3)	1/435	0.9 (0.3–2.4)	4/427
+ GRACE[g] Score < 109	0.0 (0.0–0.9)	0/411	0.0 (0.0–0.9)	0/409	0.5 (0.1–1.8)	2/402
+ GRACE[g] Score < 140	0.2 (0.0–1.1)	1/526	0.2 (0.0–1.1)	1/524	0.8 (0.2–2.0)	4/515
+ HEART-Score[h] ≤ 3	0.0 (0.0–1.0)	0/362	0.0 (0.0–1.0)	0/360	0.6 (0.1–2.0)	2/354
hs-cTnT < 3 ng/L (LoB)	0.3 (0.0–1.7)	1/323	0.6 (0.1–2.2)	2/321	1.0 (0.2–2.8)	3/314
+ HEART-Score[h] ≤ 3	0.0 (0.0–1.5)	0/244	0.4 (0.0–2.3)	1/242	0.4 (0.0–2.3)	1/237
hs-cTnT < 5 ng/L (LoD)	0.2 (0.0–1.3)	1/418	0.5 (0.1–1.7)	2/415	1.0 (0.3–2.5)	4/406
+ HEART-Score[h] ≤ 3	0.0 (0.0–1.2)	0/311	0.3 (0.0–1.8)	1/309	0.7 (0.1–2.4)	2/303
1 h-algorithm[d]	0.2 (0.0–0.9)	1/593	0.3 (0.0–1.2)	2/590	1.4 (0.6–2.7)	8/580
+ HEART-Score[h] ≤ 3	0.0 (0.0–0.9)	0/391	0.3 (0.0–1.4)	1/389	1.0 (0.3–2.7)	4/382
ESC algorithm[e]	0.3 (0.0–1.5)	1/364	0.6 (0.1–2.0)	2/362	1.7 (0.6–3.6)	6/355

ECG; electrocardiogram; hs, high-sensitivity; cTn; cardiac troponin; LoB, limit of blank; LoD, limit of detection; ESC, European Society of Cardiology.
[a] Dual marker strategy for rule-out using copeptin <10 pmol/L and hs-cTnT ≤14 ng/L.
[b] Dual marker strategy for rule-out using copeptin <14 pmol/L and hs-cTnT ≤14 ng/L.
[c] Dual marker strategy for rule-out using copeptin <20 pmol/L and hs-cTnT ≤14 ng/L.
[d] hs-cTnT <12 ng/L and absolute delta change <3 ng/L at 1 h.
[e] hs-cTnT <5 ng/L and chest pain onset >3 h OR hs-cTnT <12 ng/L and absolute delta change <3 ng/L at 1 h.
[f] Evaluable ECG and absence of ST-segment elevation or depression, T-wave changes, left bundle branch block, q-waves and ventricular paced rhythm.
[g] Modified GRACE 2.0 with substitution of diuretic usage for Killip class.
[h] Modified HEART-score according to McCord et al. (24).

indicating that also patients with slightly higher copeptin values than suggested in the NSTE-ACS guidelines may qualify for immediate rule-out when a hs-cTn assay is used [9]. Addition of clinical low-risk criteria further increased NPVs up to 100%, however, at the expense of reducing the number of true-negative rule-out to a still acceptable number of 41.6% when using the higher copeptin cut-off <20 pmol/L. The DMS, similar to the other recommended fast rule-out algorithms, has the potential to facilitate work-up in the ED by preventing patients from unnecessary diagnostic and therapeutic procedures without posing a risk at the expense of patient's safety, since the 1- and 3-month death/MI rates were found to be very low (0.0% to 0.2%). In a recent randomized interventional biomarker trial, Möckel et al. confirmed the safety of an early discharge after AMI rule-out using the DMS in low-to intermediate risk patients with suspected ACS [14]. In conjunction with our current findings, the rapid rule-out of AMI currently seems to be the most promising setting for copeptin in acute cardiovascular care with the potential to facilitate ACS management in the ED [13].

4.2. Comparison to other rule-out algorithms

In recent years, several fast-rule-out strategies have emerged and were evaluated in numerous studies. To date, only few studies have directly compared the different hs-cTn fast rule-out strategies [29,30] and none has evaluated the DMS in this setting. The concept of undetectable hs-cTnT (either LoD or LoB) has been evaluated in conjunction with or without ECG changes and resulted in NPVs and sensitivities >99% for

AMI rule-out [5,6,31]. However, the percentage of patients that could be ruled-out for AMI in a recent prospective validation study using this concept ranged between only 4.8% and 20.7% [5]. The lowest true-negative rule-out rate in our study with the DMS of 33.7% was observed using a copeptin cut-offs <10 pmol/L in combination with a HEART-score ≤ 3 resulting in NPVs and sensitivities of 100%. When comparing an algorithm with a rule-out rate in the same range, the LoB without clinical criteria showed slightly lower NPV of 99.4% and sensitivity of 98.7% at a rule-out rate of 35.0%. Conversely, when applying clinical criteria such as a HEART-score ≤ 3 to the LoB or LoD, NPVs and sensitivities also reached 100%, however, rule-out rates were only 27.0% and 34.7% for the LoB/LoD, respectively, compared to 33.7% to 41.6% using the DMS with different copeptin cut-offs and a HEART-score ≤ 3.

The use of a single or dual marker strategy at presentation obviates the need for serial blood draws and may reduce waiting times in the ED thus saving diagnostic and therapeutic resources in the presence of ED crowding. These algorithms are focused on rule-out, but provide only limited information on the rule-in in case of oppositional results. In order to promote both strategies, Reichlin et al. introduced the concept of the 1 h-algorithm, which was optimized to assign the majority of patients to a definite rule-in or rule-out strategy within a maximum of 1 h [32]. Two subsequent multi-center validation cohorts confirmed the initial results with NPVs and sensitivities >99%, but also 30-day mortality rates of 0.0% and 0.1%, respectively, indicating that the 1 h-rule-out strategy may be reliable and safe [1,2].

Within our current analysis the highest true-negative rule-out rate for the DMS of 62.3% was observed using a copeptin cut-off <20 pmol/L, which was in the range of the rule-out rates achieved by the 1 h-algorithm (64.5%). Concerning NPVs, values for the DMS with a copeptin cut-off <20 pmol/L were slightly lower compared to the 1 h-algorithm (98.3% vs. 99.2%). However, considering the need for serial sampling at 1 h and thus additional delay with the 1 h-algorithm as well as the fact, that the same single patient with an outcome event after a 30-day follow-up was overseen by both algorithms, the clinical risk/benefit ratio seems to be equally distributed between the DMS and the 1 h-algorithm.

Apart from the complementary clinical characteristics, the DMS showed in a randomized-controlled trial that effective and safe discharge is feasible [14]. Recently, the findings were confirmed in clinical routine use as part of a prospective European registry (ProCore) on 2294 patients presenting with symptoms suggestive of ACS to the ED [33]. Moreover, the DMS with immediate rule-out and flexibility to adapt the strategy depending on the clinical situation (e.g. higher copeptin cut-offs without clinical criteria for higher true-negative rule-out rates and lower copeptin cut-offs with addition of clinical risk score for more precise rule-out) may have apparent logistic advantages, especially in the presence of ED crowding, in which a second blood draw after 1 h and prolonged monitoring may be an additional obstacle for the patient and the ED staff. Importantly, reducing time to discharge based on the DMS compared to serial cTn sampling may save diagnostic, therapeutic as well as personnel resources and lead to cost reductions as recently observed by Reinhold et al. in the randomized BIC-8 trial [34].

4.3. Limitations

There are several limitations which have to be considered: First, the inconvenience of measurement of a second marker on an additional analyzer and thus potential necessity of two different diagnostic platforms may be a major limitation in the current use in clinical routine. Moreover, the utility of the DMS depends on a short time span between blood draw and the availability of the results, which seems challenging in current practice. However, there are ongoing efforts to overcome these impediments by development of automated cTn and copeptin measurement platforms and point-of-care copeptin assays [13,35]. Second, the potential benefits of the DMS for rule-out are encountered by the low PPVs for AMI rule-in in case of elevated copeptin and normal hs-cTn levels at presentation leading to clinical situations in which EDs stays are prolonged rather than shortened. On the other hand, use of higher copeptin cut-off such as 20 pmol/L bears the potential to miss AMI patients and thus requires further clinical validation before any final recommendation for clinical use of this higher copeptin cut-off can be given. Third, addition of clinical criteria increase NPV and sensitivity, but may add to the complexity of the DMS and further reduce efficiency for rule-out. However, to account for false-negative rule-out, consideration of clinical criteria including symptom characteristics, ECG changes, risk scores etc. is crucial when rapid rule-out algorithms are applied and not restricted to the DMS [9].

Finally, it remains unclear, whether the DMS but also the other rule-out strategy may translate into time and cost saving in the real-life setting. Although initial studies are promising [34,36], randomized controlled trials in an interventional setting with a larger number of patients and health economic studies are necessary to clarify all these important issues.

5. Conclusions

The DMS allowed for a true-negative rule-out in up to 62.3% of chest pain patients and obviates the need for serial sampling, albeit, at the cost of a slightly lower NPV, sensitivity and rule-out rate compared to the 1 h-algorithm. Conversely, addition of clinical criteria such as the HEART-score to the DMS and the LoD/LoB reached NPVs and sensitivities of 100%, however, true-negative rule-out rates were considerably higher for the DMS alone. Comparison of outcomes further revealed rates for short- and long-term follow-up in the same range for all tested rule-out algorithms. Our results support that the combination of copeptin and hs-cTnT might be an alternative to the hs-cTnT-only-based fast-rule-out algorithms. In addition, the DMS might provide incremental clinical value of either preventing serial sampling (vs. 1 h-algorithm and the ESC algorithm) or resulting in higher rule-out rates at a comparable diagnostic and prognostic performance (vs. LoB/LoD). However, further proof of the added clinical value of copeptin on rapid AMI rule-out may depend on future health economic analyses in a randomized, interventional setting.

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Potential conflicts of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.084.

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