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Evaluation of a new ultra-sensitivity troponin I assay in patients with suspected myocardial infarction☆

Johannes Tobias Neumann [a,b,*], Nils Arne Sörensen [a,b], Nicole Rübsamen [a], Francisco Ojeda [a], Alina Schock [a], Parisa Seddighizadeh [a], Tanja Zeller [a,b], Dirk Westermann [a,b], Stefan Blankenberg [a,b]

[a] University Heart Center Hamburg, Hamburg, Germany
[b] German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Hamburg, Germany

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ABSTRACT

Aims: Troponin is the gold-standard for diagnostic evaluation of patients with suspected myocardial infarction (MI). We aimed to evaluate the diagnostic and prognostic performance of a new ultra-sensitivity troponin I (us-TnI) assay in patients with suspected MI.

Methods and results: 1534 patients with suspected MI were included. Us-TnI measurements were performed directly on admission and after one hour. One-year rates of mortality and incident MI were assessed. For diagnostic evaluation the negative and positive predictive value (NPV/PPV) using admission us-TnI concentrations and 0/1h delta were calculated. For rule-out an NPV > 99.5% (100% for single-admission-value) and for rule-in a PPV > 80% was targeted. Internal derivation/validation was used. In the derivation dataset 155/767 (20.2%) patients were diagnosed with having non-ST-elevation MI (NSTEMI). For rule-out of NSTEMI an us-TnI < 1 ng/L directly on admission resulted in an NPV of 100.0% (CI 98.2–100.0). Using serial sampling an admission us-TnI < 2 ng/L and a 0/1h delta < 1 ng/L resulted in an NPV of 99.7% (CI 98.4–100.0) and ruled-out NSTEMI in 46.8% of all patients. The respective one-year rate of death or MI was 0.6%. For rule-in of NSTEMI an us-TnI ≥ 25 ng/L on admission or a 0/1h delta ≥ 6 ng/L resulted in a PPV of 81.3% (CI 73.7–87.5) and ruled-in NSTEMI in 18.5% of all patients. The one-year event rate was 12.7%. Results were similar in 767 patients from the validation cohort.

Conclusion: Application of an us-TnI assay allows the accurate triage of a large proportion of patients with suspected MI using a 0/1h algorithm.

Trial registration: www.clinicaltrials.gov (NCT02355457)

1. Introduction

Patients with suspected myocardial infarction (MI) frequently presenting to the emergency department (ED) require rapid and accurate diagnostic evaluation [1]. Besides ECG and clinical symptoms, serial measurement of cardiac troponin constitutes a cornerstone in the diagnostic evaluation of patients with suspected MI [2]. Using newer, high-sensitivity troponin (hs-Tn) assays, the detection of low troponin concentrations of less <10 ng/L became possible. This improved sensitivity stimulated the development of faster diagnostic algorithms and shortened the time until decision-making. These algorithms are based on low hs-Tn concentrations and their dynamic changes after 1 or 3 h [2–4]. More recently, even a low single admission hs-Tn concentration has been reported to safely rule-out acute non-ST-elevation MI (NSTEMI) [5–7].

A newly developed ultra-sensitivity troponin I (us-TnI) assay enables the accurate detection of even lower troponin concentrations of less <0.1 ng/L using a micro particle immunoassay and singlemolecule counting technology in the Clarity System [8]. Troponin concentrations measured using an earlier version of this assay have been reported to predict coronary artery disease (CAD) in patients with angina pectoris and furthermore predict outcome in the general population [9–12]. However, the diagnostic performance using this ultra-sensitivity assay in patients with suspected MI is unknown. Therefore, we aimed to derive and validate a diagnostic 0/1h algorithm to safely rule-out or rule-in NSTEMI and to evaluate its association with one-year outcome.

2. Methods

2.1. Study population

For the present analyses patients from the Biomarkers in Acute Cardiac Care (BACC) study population were selected. This study has been published before [4,5]. Briefly,

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: University Heart Center Hamburg, Department of General and Interventional Cardiology, Martinistr. 52, 20246 Hamburg, Germany.
E-mail address: j.neumann@uke.de (J.T. Neumann).

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patients with symptoms suggestive of MI presenting to the ED of the University Heart Center Hamburg were included. All patients were above 18 years old and provided written informed consent. Patients with ST-elevation MI were excluded. In total 1534 patients were available for analyses. A temporal split-sample approach was used to divide the sample into a derivation dataset (admission date ≤04.08.2014, $N = 767$) and a validation dataset (admission date >04.08.2014, N = 767). The BACC study was approved by the local Ethics Committee and registered at www.clinicaltrials.gov (NCT02355457). The study design complied with the Declaration of Helsinki. The STARD checklist is provided in Table S1.

2.2. Study-specific design and adjudication of final diagnosis

Patients with suspected MI were evaluated according to the current ESC guidelines, which included ECG, serial sampling of hs-TnT (Roche Elecsys) at admission and after 3 h, echocardiography and further imaging, when required [13,14]. In addition to collection of blood samples for routine clinical use blood samples were also collected for biobanking directly at admission and after 1 h. Samples were stored at −80 °C under standardized conditions. Afterwards, decision on admission or discharge was made by the treating physician as part of clinical routine.

The final index diagnosis of each patient was adjudicated at least 30 days after the initial presentation. During the adjudication process two physicians independently reviewed the case using all available clinical and imaging results, ECG and standard laboratory testing, including hs-TnT. Based on these parameters, the final diagnosis of NSTEMI was adjudicated according to the Third Universal Definition of MI [15]. For diagnosing NSTEMI evidence of myocardial necrosis and a clinical setting of myocardial ischemia were required. Myocardial necrosis was defined by a hs-TnT concentration above the 99th percentile in combination with a significant change within 3 h [16]. In cases of disagreement, a third physician reviewed the case.

2.3. Investigational troponin I measurements

Independently from clinical routine, us-TnI was measured in stored blood samples collected directly at admission and after one hour using the Singulex Clarity® cTnI assay. The manufacturer reports a limit of detection of 0.08 ng/L and a coefficient of variation (CV) < 10% at a concentration of 0.53 ng/L [8]. The 99th percentile has been described at <8.67 ng/L [8].

Additionally, hs-TnI was measured using the Architect immunoassay (Abbott Diagnostics, ARCHITECT i1000SR) at admission and after one hour. This assay had a limit of detection at a concentration of 1.9 ng/L and a 10% coefficient of variation at a concentration of 5.2 ng/L [17]. In the general population the 99th percentile has been reported at 27 ng/L [18].

2.4. Statistical analysis

Continuous variables were described as quartiles; categorical variables as absolute numbers and percentages. The Wilcoxon rank-sum (for continuous variables) or the χ^2 (for categorical variables) test were employed for between-group comparisons.

2.5. Diagnostic evaluation

The diagnostic performance was evaluated in the derivation dataset by calculation of the area under the curve (AUC), negative predictive value (NPV), sensitivity, positive predictive value (PPV) and specificity using admission us-TnI concentrations (cutoff C1) and the absolute 0/1h Δ delta (cutoff C2). In addition, the efficacy (determined by the proportion of patients classified into one group) was calculated. For rule-out of NSTEMI two strategies were evaluated: (i) a single admission rule-out using us-TnI 0h < C1 and (ii) a 0/1h algorithm using (us-TnI 0h < C1 AND us-TnI Δ 0/1h < C2). For rule-in of NSTEMI (us-TnI 0h ≥ C3 OR us-TnI Δ 0/1h ≥ C4) was used. An NPV of 100.0% (single admission rule-out) or 99.5% (0/1h algorithm) for rule-out and a PPV above 80% for rule-in was targeted. The selected algorithm was then applied to the validation population. Fisher's exact test was used to test for differences between NPV and PPV in the derivation dataset versus in the validation dataset. Finally, the derived algorithm was applied in the overall dataset and compared to the performance of the established ESC 0/1h hs-TnI-based algorithm.

2.6. Prognostic evaluation

All patients were followed for up to one year to assess mortality and incident MI (all MI events after the index event). Patients were contacted by phone/mail, contacting the general practitioner or review of the medical records. In cases without direct contact, the local register of death was contacted and all cases of death were assessed. All incident MIs were again adjudicated based on the third universal definition of MI. Using the above described algorithm, the one-year rate of death or incident MI was calculated using the Kaplan-Meier method.

3. Results

3.1. Study population

Overall, 1534 patients were available for analyses. Among 767 patients from the derivation population, 155 (20.2%) were diagnosed as having NSTEMI (Table 1). These patients were significantly older and had a higher cardiovascular risk profile compared to non-MI patients. 205 (29.1%) of all patients were early-presenters with a symptom onset of less than 3 h. Baseline characteristics and the percentage of NSTEMI diagnosis (16.9%) were similar in the validation population.

3.2. Us-TnI measurements

99% of all patients had detectable us-TnI concentrations at admission. The median us-TnI concentration measured directly at admission was 2.1 ng/L and did not change after 1 h in the derivation population (Table 1). In patients diagnosed with NSTEMI the median admission us-TnI was 28.6 ng/L (interquartile range (IQR) 8.5–256.7) and increased to 53.8 ng/L (IQR 14.4–396.4) after 1 h (Fig. 1).

3.3. Diagnostic evaluation

The AUC of us-TnI measured directly at admission was 0.92 (95% Confidence interval (CI) 0.90–0.94) and increased to 0.95 (CI 0.93–0.97) after one hour, while the AUC of hs-TnT increased from 0.89 (CI 0.86–0.92; p-value for comparison to us-TnI = 0.002) to 0.93

Table 1
Baseline characteristics of the derivation and validation dataset.

	Derivation				Validation			
	All (N = 767)	NSTEMI ($N = 155$)	Non-MI ($N = 612$)	p-Value	All (N = 767)	NSTEMI ($N = 130$)	Non-MI ($N = 637$)	p-Value
Age (years)	64.0 (52.0, 74.0)	69.0 (60.0, 77.8)	63.0 (50.0, 73.0)	<0.001	65.0 (51.0, 75.0)	71.0 (59.9, 76.0)	63.0 (50.0, 75.0)	<0.001
Sex (male) (%)	490 (63.9)	105 (67.7)	385 (62.9)	0.31	481 (62.7)	83 (63.8)	398 (62.5)	0.85
Hypertension (%)	525 (68.9)	126 (81.8)	399 (65.6)	<0.001	502 (65.4)	99 (76.2)	403 (63.3)	0.0066
Dyslipidemia (%)	325 (42.4)	84 (54.2)	241 (39.4)	0.0012	228 (29.7)	53 (40.8)	175 (27.5)	0.0035
Diabetes (%)	113 (14.8)	33 (21.4)	80 (13.2)	0.015	89 (11.8)	20 (15.4)	69 (11.0)	0.21
Current smoker (%)	169 (22.0)	36 (23.2)	133 (21.7)	0.77	190 (25.0)	37 (28.7)	153 (24.3)	0.35
Former smoker (%)	265 (34.6)	54 (34.8)	211 (34.5)	1.00	137 (18.1)	31 (24.0)	106 (16.8)	0.070
History of CAD (%)	271 (35.3)	76 (49.0)	195 (31.9)	<0.001	259 (33.8)	53 (40.8)	206 (32.3)	0.080
History of MI (%)	122 (15.9)	39 (25.3)	83 (13.6)	<0.001	130 (16.9)	26 (20.0)	104 (16.3)	0.37
Symptom onset < 3h (%)	205 (29.1)	48 (32.9)	157 (28.1)	0.30	238 (32.8)	40 (32.0)	198 (32.9)	0.92
BMI (kg/m^2)	26.0 (23.4, 29.4)	26.3 (23.5, 29.8)	25.9 (23.3, 29.3)	0.50	26.3 (23.7, 30.0)	26.5 (23.8, 29.7)	26.3 (23.7, 30.0)	0.82
Creatinine (mg/dL)	1.0 (0.8, 1.2)	1.1 (0.8, 1.2)	0.9 (0.8, 1.1)	0.0012	1.0 (0.8, 1.2)	1.1 (1.0, 1.3)	1.0 (0.8, 1.1)	<0.001
us-TnI 0h (ng/L)	2.1 (0.9, 6.5)	28.6 (8.5, 256.7)	1.5 (0.8, 3.0)	<0.001	2.0 (0.8, 6.5)	61.5 (9.1, 370.3)	1.5 (0.7, 3.9)	<0.001
us-TnI 1h (ng/L)	2.1 (1.0, 8.0)	53.8 (14.4, 369.4)	1.6 (0.8, 3.3)	<0.001	2.1 (0.8, 7.2)	127.5 (19.3, 453.9)	1.6 (0.7, 3.6)	<0.001
us-TnI Δ 0/1h (ng/L)	0.5 (0.1, 1.9)	18.0 (4.4, 83.3)	0.3 (0.1, 0.8)	<0.001	0.4 (0.1, 1.6)	27.8 (7.1, 101.9)	0.3 (0.1, 0.7)	<0.001

Abbreviations: CAD = coronary artery disease; MI = myocardial infarction; BMI = body mass index; us-TnI = ultra-sensitivity troponin I; h = hour; NSTEMI = non-ST-elevation myocardial infarction. p-Value provided for comparison of NSTEMI vs non-MI patients.

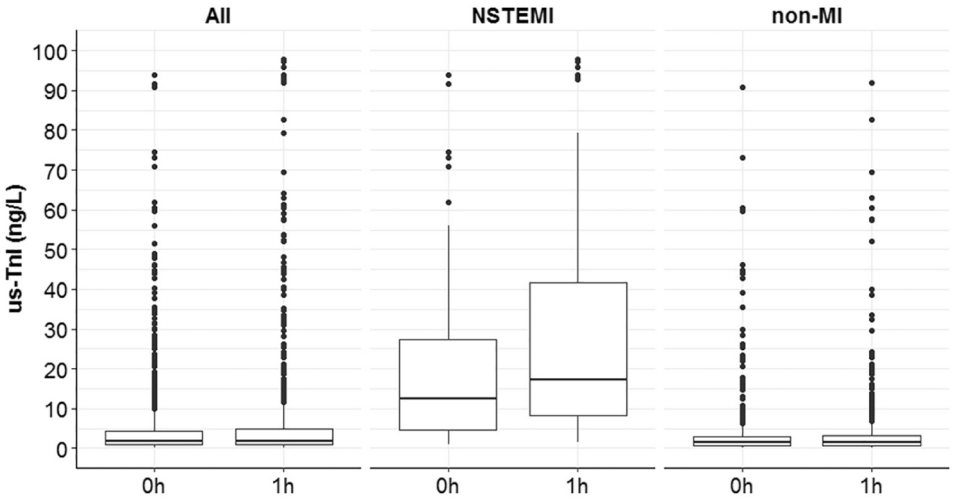

Fig. 1. Boxplot showing the us-TnI concentrations in the overall population, patients diagnosed with NSTEMI and non-MI patients directly at admission and after 1 h. AbbreviationsMI = myocardial infarction; us-TnI = ultra-sensitivity troponin I; h = hour; NSTEMI = non-ST-elevation myocardial infarction.

(CI 0.91–0.95; *p*-value for comparison to us-TnI = 0.027) (Fig. 2). For rule-out of NSTEMI various cutoff combinations, reflecting a wide diagnostic range, were evaluated (Table S2). Targeting strategy (i) using a single admission us-TnI concentration, the NPV of 100% (95% Confidence interval (CI) 98.2–100.0) was reached at an us-TnI concentration of <1 ng/L (Table 2). The sensitivity for this cutoff was 100% (95% CI 97.6–100.0) and the efficacy (the proportion of patients classified as rule-out) was 26.2% (95% CI 23.1–29.5). Using serial sampling after one hour, the targeted NPV of 99.5% was reached using an admission us-TnI < 2 ng/L and a 0/1h delta <1 ng/L. This approach resulted in an NPV of 99.7% (95% CI 98.4–100.0) and ruled-out NSTEMI in 46.8% (95% CI 43.1–50.5) of all patients.

For rule-in of NSTEMI various cutoff combinations, reflecting a wide diagnostic range, were evaluated (Table S3). The targeted PPV of 80% was reached using an us-TnI ≥ 25 ng/L on admission or a 0/1h delta ≥6 ng/L (Table 2). This approach resulted in a PPV of 81.3% (95% CI 73.7–87.5) and ruled-in NSTEMI in 18.5% (95% CI 15.7–21.5) of all patients.

The diagnostic results were similar in 767 patients from the validation population. The NPV for the single admission us-TnI of <1 ng/L was 99.6% (95% CI 97.6–100.0, not significantly different from the NPV in the derivation dataset, $p > 0.99$) and 99.7% (95% CI 98.4–100.0, not significantly different from the NPV in the derivation dataset, $p > 0.99$) using an admission us-TnI < 2 ng/L and a 0/1h delta <1 ng/L. The PPV for an us-TnI ≥ 25 ng/L on admission or a 0/1h delta ≥6 ng/L was 77.7% (95% CI 69.6–84.5, not significantly different from the PPV in the derivation dataset, $p = 0.54$) in the validation population.

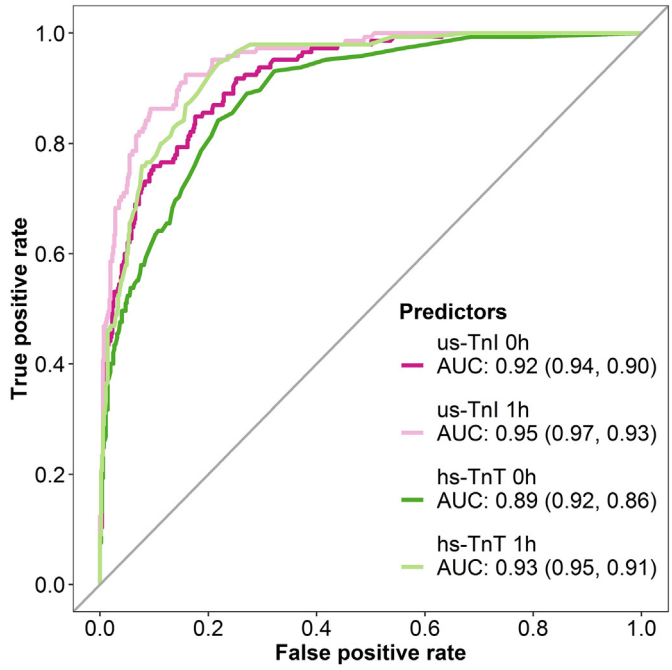

Fig. 2. Area under the curve for diagnosis of NSTEMI using 0/1h hs-TnT and us-TnI. Abbreviations: AUC = area under the curve; us-TnI = ultra-sensitivity troponin I; h = hour; NSTEMI = non-ST-elevation myocardial infarction.

3.4. Comparison to ESC 0/1h hs-TnI algorithm

The derived us-TnI algorithm and the established ESC 0/1h hs-TnI algorithm were finally applied in the overall dataset (Fig. 3). Here, the us-TnI algorithm resulted in an NPV of 99.6% (95% CI 98.8–99.9) and ruled-out NSTEMI in 47.3% (95% CI 44.8–49.9), while the PPV was 79.5% (95% CI 74.2–84.1) and 17.8% (95% CI 15.9–19.8) were ruled-in. The ESC 0/1h hs-TnI-based algorithm resulted in an NPV of 99.3% (95% CI 98.2–99.8) and ruled-out NSTEMI in 37.2% (95% CI 34.7–39.6), while the PPV was 67.8% (95% CI 62.6–72.7) and 22.5% (95% CI 20.4–24.7) were ruled-in. The rate of patients triaged to the observe-zone was similar using both algorithms (35.1% vs. 38.1%).

3.5. Prognostic evaluation

The median (25th percentile, 75th percentile) follow-up time for the combined endpoint of death or incident MI was 636 (610, 665) days in the overall population. In 91.8% of the study population direct contact was available and only 3 individuals were lost to follow-up. The overall rate of death or MI was 6.1% after one year (88 events). Patients classified as rule-out according to the developed us-TnI algorithm had a 1-year rate of death or MI of 1.0% (95% CI 0.3–1.7), while patients classified as rule-in had a 1-year rate of death or MI of 12.7% (95% CI 7.6–15.4) (Fig. S1 and Fig. 3). Those patients remaining in the observe-zone (neither fulfilling the criteria for rule-out or rule-in), had a 1-year rate of death or MI of 10.0% (95% CI 7.3–12.6). The event rates for the rule-out and rule-in populations were similar, when the ESC 0/1h hs-TnI algorithm was applied, while the event rate in the observe-zone was lower.

Table 2
Diagnostic performance A) for rule-out and B) for rule-in of NSTEMI in the derivation and validation dataset.

A		Rule-out: us-TnI 0h < C1 AND us-TnI Δ 0/1h < C2				Classification of patients			
C1: us-TnI 0h cut-off (ng/L)	C2: us-TnI Δ 0/1h cut-off (ng/L)	NPV (95% CI)	Sensitivity (95% CI)	Ruled-out % (95% CI)	1-year rate of death/MI (95% CI)	FN	TN	TP	FP
Derivation									
1	–	100.0 (98.2–100.0)	100.0 (97.6–100.0)	26.2 (23.1–29.5)	0.5 (0–1.5)	0	201	155	411
2	1	99.7 (98.4–100.0)	99.3 (96.2–100.0)	46.8 (43.1–50.5)	0.6 (0–1.4)	1	338	144	241
Validation									
1	–	99.6 (97.6–100.0)	99.2 (95.8–100.0)	30.2 (27.0–33.6)	0.9 (0–2.1)	1	231	129	406
2	1	99.7 (98.4–100.0)	99.2 (95.6–100.0)	47.9 (44.2–51.6)	1.2 (0–2.4)	1	351	124	259
B		Rule-in: us-TnI 0h ≥ C1 OR us-TnI Δ 0/1h ≥ C2				Classification of patients			
C3: us-TnI 0h cut-off (ng/L)	C4: us-TnI Δ 0/1h cut-off (ng/L)	PPV (95% CI)	Specificity (95% CI)	Ruled-in % (95% CI)	1-year rate of death/MI (95% CI)	FN	TN	TP	FP
Derivation									
25	6	81.3 (73.7–87.5)	95.7 (93.7–97.2)	18.5 (15.7–21.5)	12.7 (6.9–18.1)	36	554	109	25
Validation									
25	6	77.7 (69.6–84.5)	95.2 (93.2–96.8)	17.7 (15.0–20.6)	9.9 (4.4–15.2)	24	581	101	29

Abbreviations: C = cutoff; NPV = negative predictive value; PPV = positive predictive value; FN = false negative; TN = true negative; TP = true positive; FP = false positive; NSTEMI = non-ST-elevation myocardial infarction; MI = myocardial infarction; h = hour.

4. Discussion

The application of a newly developed ultra-sensitivity troponin assay enables the accurate triage of a large proportion of patients with suspected MI using a 0/1h algorithm. We applied this troponin assay in a large population of patients with suspected MI, derived and validated a 0/1h algorithm providing high negative and positive predictive values. Furthermore, this developed algorithm was associated with cardiovascular outcome after one year.

Due to an increasing number of patients presenting to the EDs with suspected MI, there is a need for fast and precise rule-out strategies to enable rapid decision-making. This need is addressed by recently suggested 0/1h algorithms, or even single-troponin rule-out strategies directly at admission. Those novel strategies are already incorporated in current ESC guidelines [5–7,14]. As an example the ESC 0/1h algorithm based on hs-TnI recommends an admission cutoff concentration of <2 ng/L or an admission concentration of <5 ng/L combined with a 0/1h delta of <2 ng/L. Therefore, this "rapid-decision" concept requires the application of troponin assays with a high sensitivity and a low limit of detection. Each different hs-Tn assay requires distinct cut-off concentrations, which need to be generated and validated in cohorts to enable application by clinicians in the daily routine. This is an inherent problem and makes no single concentration usable in all hs-Tn assays. Therefore, we utilized the BACC study to generate these values with the investigated new ultra-sensitivity troponin assay. It is characterized by the lowest limit of detection of any commercially available troponin assay so far. Earlier studies using this assay reported a predictive value for CAD, but diagnostic studies in patients with suspected MI are lacking.

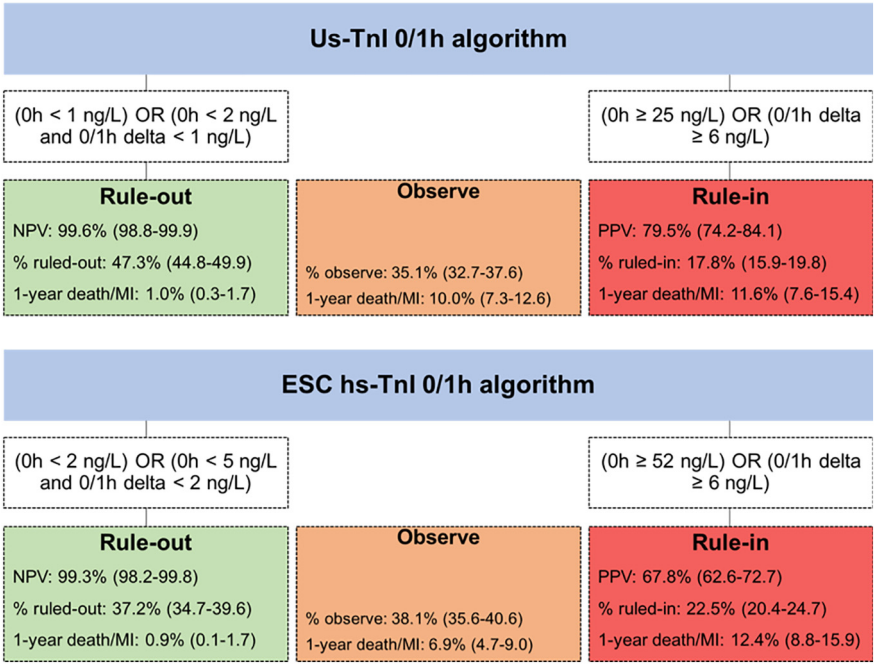

Fig. 3. Central Illustration: Diagnostic performance of the newly developed us-TnI 0/1h and the established ESC hs-TnI 0/1h algorithm[14] in the overall study population. Abbreviations: NPV = negative predictive value; PPV = positive predictive value; MI = myocardial infarction; h = hour. ESC 0/1h algorithm based on hs-TnI (Abbott Architect) measurements.

Therefore, our study addresses a clinical need and our findings have several implications. First, the proposed algorithm enables an effective rule-out of MI with a high NPV. The algorithm is based on a very low admission concentration of <1 ng/L or the combination of an admission concentration < 2 ng/L and a 0/1h delta of <1 ng/L. This approach allows direct rule-out of MI after only one single us-TnI measurement in more than one fourth of all patients. After serial sampling the proportion of patients is substantially increased to nearly 50% of all patients. Second, this algorithm allows for early rule-in of MI with a high PPV. The combination of a single admission concentration ≥ 25 ng/L or a 0/1h delta of ≥6 ng/L triaged nearly one fifth of all patients to the rule-in group. Third, the developed algorithm provides similar safety and efficacy, when compared to an established and guideline-based 0/1h hs-TnI algorithm. Furthermore, these results are in line with earlier publications on early diagnostic strategies [4,7,19].

Besides the acute triage of patients with suspected MI, troponin is also important as a prognostic marker for longer term outcome [20]. While the additional diagnostic value of even more sensitivity might be limited in times of high-sensitivity assays, it could be of interest for risk prediction. The prognostic effect of us-TnI was confirmed in our present study, as the one-year event rate of death or MI ranged between 1% for the rule-out population and 12% for the rule-in population. Importantly, those individuals classified as "observe-zone" had a high event rate, which was similar to the rule-in population. In the future, troponin concentrations could also be used for risk prediction in a setting apart from acute cardiac care. Earlier studies reported a high prognostic value of troponin in individuals from the general population and here, very low concentrations measured by an ultra-sensitivity assay might provide additional value, when compared to less sensitive troponin assays [10,21,22].

Our study has several strength and limitations. A major strength is, that all patients were prospectively enrolled, and the final diagnosis was adjudicated according to Universal Definition blinded by two physicians. Furthermore, our manuscript presents the first developed and validated algorithm for using us-TnI. However, the BACC study population is based on a single center experience and for the present analyses a split dataset was used for derivation and validation, whereas external validation of this algorithm is needed. This is also important, as MI prevalence might vary among different populations, which incluences NPV and PPV. A second limitation is the measurement in batched samples, which have been stored at −80 °C before, as this might impact on long-term stability. However, earlier studies provided evidence for a high stability even after long-term storage [17,23]. Finally, our results are limited to this investigated troponin assay and cannot be transferred to other assays.

In conclusion, we derived and validated a 0/1h algorithm using an ultra-sensitivity troponin I assay with low cutoff concentrations. This concept allows accurate and fast triage of a large proportion of patients presenting with suspected MI.

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Disclosures

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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.2018.12.001.

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