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Immediate Rule-Out of Acute Myocardial Infarction Using Electrocardiogram and Baseline High-Sensitivity Troponin I

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AIMS: Serial measurements of high-sensitivity troponin are used to rule out acute myocardial infarction (AMI) with an assay specific cutoff at the 99th percentile. Here, we evaluated the performance of a single admission troponin with a lower cutoff combined with a low risk electrocardiogram (ECG) to rule out AMI.

METHODS: Troponin I measured with a high-sensitivity assay (hs-TnI) was determined at admission in 1040 patients presenting with suspected AMI (BACC study). To rule out AMI we calculated the negative predictive value (NPV) utilizing the optimal hs-TnI cutoff combined with a low risk ECG. The results were validated in 3566 patients with suspected AMI [2-h Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker (ADAPT) studies]. Patients were followed for 6 or 12 months.

RESULTS: 184 of all patients were diagnosed with AMI. An hs-TnI cutoff of 3 ng/L resulted in a NPV of 99.3% (CI 97.3–100.0), ruling out 35% of all non-AMI patients. Adding the information of a low risk ECG resulted in a 100% (CI 97.5–100.0) NPV (28% ruled out). The 2 validation cohorts replicated the high NPV of this approach. The follow-up mortality in the ruled out population was low (0 deaths in BACC and Stenocardia, 1 death in ADAPT).

CONCLUSIONS: A single hs-TnI measurement on admission combined with a low risk ECG appears to rule out AMI safely without need for serial troponin testing.
Trial Registration: www.clinicaltrials.gov (NCT02355457).

Cardiac troponin is an established biomarker to differentiate between acute myocardial infarction (AMI)[9] and non-AMI patients *(1, 2)*. Owing to limited resources in the emergency department (ED) there is a clinical need to rapidly and safely rule out AMI. The recent 2015 European Society of Cardiology (ESC) guidelines recommend a serial troponin measurement after 3 h with a high-sensitivity troponin assay to rule out non–ST-elevation AMI, when the concentration is below the 99th percentile *(3)*. Using substantially lower troponin cutoff concentrations, a rapid 1-h rule-out algorithm was shown to be safely applicable in patients with suspected AMI utilizing high-sensitivity troponin assays *(4–8)*. This approach is recommended in the ESC-2015 guideline as an alternative strategy *(3)*.

Even faster rule-out concepts using a single baseline troponin measurement have also been investigated *(9–11)*. Retrospective registry work suggested that undetect-

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[9] Nonstandard abbreviations: AMI, acute myocardial infarction; ED, emergency department; ESC, European Society of Cardiology; hs-TnT, high-sensitivity troponin T; NPV, negative predictive value; hs-TnI, high-sensitivity troponin I; ECG, electrocardiogram; BACC, Biomarkers in Acute Cardiac Care; STEMI, ST-elevation MI; LoD, limit of detection; PCI, percutaneous coronary intervention; ADAPT, 2-h Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker; CNCCP, cardiac non-coronary chest pain; NCCP, non-cardiac chest pain; UAP, unstable angina pectoris; CAD, coronary artery disease.

able concentrations of troponin T as measured with a high-sensitivity troponin T (hs-TnT)<5 ng/L resulted in a high negative predictive value (NPV) for AMI *(12)*. This concept rules out a small percentage of all admitted patients by application of hs-TnT. Another study suggested using a single baseline hs–troponin I (hs-TnI) measurement with a cutoff at 5 ng/L in 6304 patients, which resulted in a 99.6% NPV with 61% of all patients without AMI being ruled out *(13)*. It remains unclear, whether the adoption of one baseline single high-sensitivity troponin determination allows for safe rule-out across a variety of suspected AMI populations that may include various pretest probabilities.

Here, we aimed to evaluate the diagnostic performance of a single baseline hs-TnI measurement in combination with a low risk electrocardiogram (ECG) in emergency patients with different pretest probabilities for AMI.

Methods

BACC STUDY POPULATION

The Biomarkers in Acute Cardiac Care (BACC) study has been described previously *(4)*. Briefly, we included 1040 patients presenting to the ED and chest pain unit of the University Heart Center Hamburg with suspected AMI. All patients were enrolled between July 2013 and December 2014. The inclusion criteria were a suspected AMI, age above 18 and the ability to provide written informed consent. We excluded all patients with ST-elevation MI (STEMI) (n = 57) from further analyses. The BACC study was registered at www.clinicaltrials.gov (NCT02355457), complied with the Declaration of Helsinki and was approved by the local Ethics Committee.

THE STANDARD DIAGNOSTIC APPROACH AND AMI ADJUDICATION

The standard diagnostic approach in all individuals was, according to the ESC-2015 guideline, a blood sample directly at admission and after 3 h *(3)*. Troponin was routinely measured using the TnT assay (Elecsys® troponin T high sensitive) by Roche Diagnostics. A standard ECG was collected on admission by trained medical staff. The final diagnosis was adjudicated based on all available clinical and imaging results, ECG, standard laboratory testing, including hs-TnT. The final diagnosis of all patients was made by 2 cardiologists independently. In cases of disagreement (n = 132), a third cardiologists review was obtained. Type 1 and 2 AMIs were classified according to the third universal definition of myocardial infarction *(14)*.

STUDY SPECIFIC MEASUREMENTS

Independently of the diagnosis, TnI was measured using an hs-TnI immunoassay (Abbott Diagnostics, ARCHITECT i1000SR). The test specific limit of detection (LoD) was 1.9 ng/L (range 0–50 000 ng/L), with a 10% CV at a concentration of 5.2 ng/L. The intraassay and interassay CVs of this assay were 4.26% and 6.29% *(15)*. The 99th percentile concentration was 27 ng/L in the general population *(16)*.

To reflect usual standard of care, the ECG was interpreted acutely by the emergency physician who based the diagnosis of ischemia on the universal definition of AMI *(14)*: ST-depression (≥0.05 mV) or T-wave inversion (≥0.1mV) in 2 contiguous leads, or ST-elevation (≥0.1 mV or ≥0.2 mV in V2/3). Furthermore, heart rhythm, atrio-ventricular and bundle branch blocks were recorded. All ECGs were reinterpreted by a cardiologist. In cases of disagreement a second cardiologist was consulted. The ECG was deemed as low risk, when a normal sinus rhythm without signs of ischemia, atrial or ventricular arrhythmia, tachycardia, atrio-ventricular, or bundle branch block was documented. Previous ECGs were not available for the adjudication.

The clinical parameters and cardiovascular risk factors are reported in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol63/issue1.

FOLLOW-UP

The follow-up was performed 6 and 12 months after admission, with a follow-up response rate of 99.8% after 12 months. All patients were followed by contacting the general practitioner, medical record, or by questionnaire via mail or phone. In cases without follow-up information, the local register of death was contacted and all cases of death were assessed. All-cause mortality, any incident AMI or any percutaneous coronary intervention (PCI) after discharge, and cardiac rehospitalization (any rehospitalization for a cardiac reason, including AMI or revascularization) were registered.

EVALUATION OF DIFFERENT ADMISSION TnI BASED RULE-OUT ALGORITHMS

We aimed to derive an optimal rule-out algorithm based on admission hs-TnI and ECG. We defined optimal as the algorithm that could rule out the maximum number of individuals at admission with maximum safety (NPV = 100%). Therefore, we evaluated the diagnostic performance: (*a*) at hs-cTnI cutoff concentrations of 1.9 (LoD), 2, 3, 4, 5, 5.2, 6, 7, 8, 9, 10, and 27 (99th percentile) ng/L to rule out AMI; (*b*) at these thresholds combined with ECG results classified as low risk.

VALIDATION COHORTS

The baseline rule-out algorithm of the BACC study was validated in 2 independent studies of patients with acute

Table 1. Baseline characteristics.[a]

	All (n = 1,040)	Non-AMI (n = 799)	AMI (n = 184)	*P* value
Age, years	65.0 (52.0, 75.0)	64.0 (51.0, 74.0)	70.0 (60.4, 77.0)	<0.001
Male, %	673 (64.7)	506 (63.3)	124 (67.4)	n.s.[b]
BMI, kg/m^2	26.0 (23.5, 29.4)	26.0 (23.4, 29.4)	26.2 (23.7, 29.7)	n.s.
Hypertension, %	719 (69.6)	539 (68.0)	146 (79.8)	<0.0.01
Hyperlipoproteinemia, %	456 (43.8)	333 (41.7)	103 (56.0)	<0.001
Diabetes, %	150 (14.5)	102 (12.8)	39 (21.3)	<0.01
Current smoker, %	241 (23.2)	172 (21.5)	41 (22.3)	n.s.
History of AMI, %	162 (15.6)	115 (14.4)	41 (22.4)	<0.01
History of CAD, %	349 (33.6)	260 (32.5)	80 (43.5)	<0.01
Atrial fibrillation, %	222 (21.3)	177 (22.2)	42 (22.8)	n.s.
Reduced EF <35%, %	150 (14.4)	104 (13.0)	40 (21.7)	<0.01
CRP, mg/L	4.9 (4.9, 7.1)	4.9 (4.9, 7.0)	4.9 (4.9, 9.3)	n.s.
Creatinine, mg/dL[c]	1.0 (0.8, 1.2)	1.0 (0.8, 1.1)	1.1 (0.8, 1.3)	<0.001
Time from admission to first hs-TnI, min	22.0 (14.0, 37.0)	23.0 (15.0, 38.0)	20.0 (13.0, 33.0)	<0.05

[a] Continuous variables are described by its quartiles [i.e. median (25th percentile; 75th percentile)] and binary ones by its absolute and relative frequencies in parentheses.
[b] n.s., not significant; BMI, body mass index; EF, ejection fraction; CRP, C-reactive protein.
[c] To convert mg/dL to mmol/L for creatinine multiply by 76.26.

onset of chest pain. The first cohort was the Stenocardia study, which has been described previously *(2)*. Briefly, this study included 1818 patients with acute chest pain presenting to 3 German EDs (Mainz, Koblenz, Hamburg) between 2007 and 2008. The second cohort was the 2-h Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker (ADAPT) study, which included 1748 patients with suspected AMI presenting to the EDs in Brisbane, Australia and Christchurch, New Zealand *(17)*. The methodology, follow-up and adjudication of outcomes have been previously reported in detail *(17)*. The hs-TnI assay used in both studies was the same as described above.

STATISTICS

Continuous variables are described by their median and interquartile range, and categorical variables as absolute and relative frequencies. Different binary diagnostic algorithms for the diagnosis of AMI (all excluding STEMI) or Type 1 AMI were considered. The diagnoses contrasted were all non-STEMI AMIs (or Type 1 AMI) vs non-AMI, defined as cardiac noncoronary chest pain (CNCCP), noncardiac chest pain (NCCP), or unstable angina pectoris (UAP). For the binary tests sensitivity, specificity, and predictive values were calculated, together with 95% CIs. Survival probabilities were estimated via the Kaplan–Meier estimator. All analyses were performed using R 3.2.2 (R Foundation for Statistical Computing).

Results

BASELINE CHARACTERISTICS

The baseline characteristics of the derivation population have been described previously *(4)*. Of 1040 patients with suspected myocardial injury 184 were diagnosed with AMI (17.7%, Table 1). 114 patients were classified as Type 1 AMI and 70 patients as Type 2 AMI. The mean age was 65 and 64.7% were male. Hypertension was prevalent in 69.6% and diabetes in 14.5% of all patients. A history of AMI was known in 15.6%.

RULE-OUT RESULTS USING DIFFERENT BASELINE TnI CONCENTRATIONS

The median time from presentation (first registration in the ED) to the first hs-TnI measurement was 22 min (25th and 75th percentile 14; 37) in the overall population. Optimal safety performance (NPV = 100%) was not possible at any cutoff using hs-TnI alone. The application of the lowest possible cutoff of 1.9 ng/L (the LoD) resulted in a 99.5% NPV (95% CI 97.2–100.0) with 1 false negative patient (Table 2). At this threshold, 25.4% of all non-AMI patients could be considered for early discharge. With increasing hs-TnI concentrations the NPV decreased. Using the recently proposed 5 ng/L cutoff *(13)*, the NPV was 97.4% (CI 95.5–98.7) and the assay-specific 99th percentile of 27 ng/L provided a NPV of 91.3% (CI 89.1–93.1) with 69 patients being characterized as false negative. The re-

Table 2. Rule-out results using different baseline troponin I concentrations without ECG information.[a]

	AMI				Type 1 AMI			
≤ Cutoff, ng/L	NPV	Sensitivity	FN[b] + TN	% of all Non-AMI	NPV	Sensitivity	FN + TN	% of all Non-AMI
1.9, LoD	99.5 (97.2–100.0)	99.4 (96.9–100.0)	1 + 198 = 199	25.4	99.5 (97.2–100.0)	99.1 (95.1–100.0)	1 + 198 = 199	25.4
2	99.5 (97.3–100.0)	99.4 (96.9–100.0)	1 + 206 = 207	26.4	99.5 (97.3–100.0)	99.1 (95.1–100.0)	1 + 206 = 207	26.4
3	99.3 (97.4–99.9)	98.9 (96.0–99.9)	2 + 276 = 278	35.4	99.3 (97.4–99.9)	98.2 (93.7–99.8)	2 + 276 = 278	35.4
4	98.3 (96.4–99.4)	96.6 (92.8–98.8)	6 + 352 = 358	45.2	98.9 (97.1–99.7)	96.4 (91.1–99.0)	4 + 352 = 356	45.2
5	97.4 (95.5–98.7)	93.9 (89.3–96.9)	11 + 419 = 430	53.8	98.8 (97.3–99.6)	95.5 (89.9–98.5)	5 + 419 = 424	53.8
5.2, 10% CV	97.3 (95.3–98.6)	93.3 (88.6–96.5)	12 + 430 = 442	55.2	98.9 (97.3–99.6)	95.5 (89.9–98.5)	5 + 430 = 435	55.2
6	97.1 (95.2–98.4)	92.2 (87.2–95.7)	14 + 475 = 489	61.0	98.5 (97.0–99.4)	93.8 (87.5–97.5)	7 + 475 = 482	61.0
7	96.2 (94.2–97.6)	88.3 (82.6–92.6)	21 + 526 = 547	67.5	98.3 (96.8–99.2)	92.0 (85.3–96.3)	9 + 526 = 535	67.5
8	96.3 (94.4–97.6)	87.7 (82.0–92.1)	22 + 566 = 588	72.7	98.4 (97.0–99.3)	92.0 (85.3–96.3)	9 + 566 = 575	72.7
9	95.6 (93.7–97.1)	84.9 (78.8–89.8)	27 + 586 = 613	75.2	98.2 (96.7–99.1)	90.2 (83.1–95.0)	11 + 586 = 597	75.2
10	94.9 (92.9–96.4)	81.6 (75.1–87.0)	33 + 610 = 643	78.3	97.8 (96.3–98.8)	87.5 (79.9–93.0)	14 + 610 = 624	78.3
27, 99th Pctl.	91.3 (89.1–93.1)	61.5 (53.9–68.6)	69 + 720 = 789	92.4	95.7 (94.0–97.1)	71.4 (62.1–79.6)	32 + 720 = 752	92.4

[a] CIs are 95%.
[b] FN, false negative; TN, true negative; pctl, percentile.

sults were similar, when only patients with Type 1 AMI were addressed.

The combination of hs-TnI below a cutoff with a low risk ECG could result in maximum safety (NPV = 100%, Table 3). When combined with a finding of low risk ECG, a cutoff of 3 ng/L was the highest, to give 100% NPV (CI 96.7–100.0). There were no false negative patients at this cutoff and 218 (28.4% of all non-AMI) patients were immediately ruled out.

For a cutoff of 3 ng/L with low risk ECG we performed subgroup analyses according to duration of preceding symptoms onset (*a*) <1 h or (*b*) 1–3 h before hospital admission), or (*c*) longer duration until first troponin measurement (see online Supplementary Table 1). The above-described results were confirmed in all subgroups irrespective of the confounding subgroup variables.

FOLLOW-UP EVENTS

The follow-up mortality in the overall population was 3.0% and 5.1% after 6 and 12 months, respectively. No deaths occurred during follow-up in the rule-out population when using a single hs-TnI measurement with a 3 ng/L cutoff concentration and a low risk ECG (Table 4, Fig. 1). The 12-month mortality rate was 1.1% (3 deaths), when only the 3 ng/L hs-TnI cutoff was used. There was 1 observed AMI in the follow-up period in individuals ruled out by the hs-TnI cutoff of 3 ng/L alone, but none after addition of a low risk ECG as a rule-out criterion. The event rates for PCI, or cardiac rehospitalizations were similar between both groups.

Individuals who did not meet the criteria for a baseline rule-out and had a final diagnosis of non-AMI showed a mortality rate of 5.8% after 12 months. In those without baseline rule-out who had a final diagnosis of AMI (Type 1 and 2) an overall mortality rate of 10.2% was observed. Clinical events (AMI, PCI, cardiac rehospitalization) occurred more frequently in these nonrule-out groups. (Table 4)

VALIDATION OF THE ALGORITHM

The application of a 3 ng/L cutoff concentration with or without a low risk ECG in the Stenocardia cohort provided similar results. 283 of 1818 (15.6%) patients were diagnosed with AMI (see online Supplementary Table 2). The NPV was 100% (CI 97.9–100.0) for hs-TnI concentrations below or equal to 3 ng/L, which resulted in 24.1% of all non-AMI patients ruled out (Table 5). Additional application of a low risk ECG reduced the percentage ruled out to 6.7%. In the 6 months follow-up period zero deaths or AMI were seen in patients ruled out either by hs-TnI alone or by hs-TnI combined with low risk ECG. Using hs-TnI only resulted in 10 events of death, AMI, PCI, or cardiac rehospitalization during follow-up; additional use of the ECG reduced the number of events to 6.

In the ADAPT study 249 of 1748 (14.2%) patients presented with a AMI (see online Supplementary Table 3). Here, a single baseline measurement of hs-TnI had a NPV of 99.8% (99.1–100.0), with no change after additional use of the ECG. This approach translated to 43% (single hs-TnI only) and 30% (single hs-TnI and ECG criteria included) of all non-AMI patients being ruled out. Using the hs-TnI 3 ng/L cutoff for the 1-year follow-up of ruled out patients, 1 patient died of a noncardiovascular cause, 9 patients experienced an AMI, urgent revascularization, or death. Application of a low risk ECG resulted in 1 death (noncardiovascular cause) and 5 patients with AMI, urgent revascularization, or death.

Discussion

The salient finding of this study is that application of a 3 ng/L hs-TnI cutoff incorporating a negative ECG yields a 100% NPV for ruling out myocardial infarction with 0% follow-up mortality in patients presenting with chest pain at the ED. This was validated in 2 further independent cohorts including patients with different pretest probabilities of suspected AMI.

SINGLE BASELINE TROPONIN MEASUREMENT TO RULE OUT AMI

Several earlier studies investigated the application of a baseline troponin measurement to rule out AMI in patients with recent onset of chest pain. A recently published study by Carlton et al. investigated the performance of a very low hs-TnI cutoff concentration below the LOD (1.2 ng/L) to exclude AMI in patients with suspected AMI and low risk ECG *(18)*. This multicenter study reported a NPV of 99.5% for this approach, which resulted in immediate rule-out in 19% of all patients. Shah et al. documented in the large High-STEACS cohort of patients with suspected AMI, that a baseline hs-TnI concentration below 5 ng/L resulted in a 99.6% NPV to rule out AMI. By comparison in the present BACC cohort, the NPV for this cutoff was lower at only 97.4% NPV. This translated into 11 patients who would have been incorrectly labeled as false negative for AMI. This difference might be explained partially by the duration from initial admission to the first troponin blood sample. Because troponin concentrations increase within hours after myocardial injury, the time from initial symptom onset until troponin sampling is highly important for the analyses. In the High-STEACS population the vast majority had a symptom onset more than 2 h before admission to the ED and the first troponin sample was 54 min after the admission resulting in a net delay of approximately 3 h. Interestingly, in the group of patients with chest pain onset <2 h before admission, the NPV de-

Table 3. Rule-out of AMI using hsTnI and ECG information.[a]

	AMI				Type 1 AMI			
≤Cutoff, ng/L	NPV	Sensitivity	FN[b] + TN	% of all Non-AMI	NPV	Sensitivity	FN + TN	% of all Non-AMI
1.9, LoD	100.0 (96.5–100.0)	100.0 (96.9–100.0)	0 + 158 = 158	20.6	100.0 (96.5–100.0)	100.0 (95.1–100.0)	0 + 158 = 158	20.6
2	100.0 (96.7–100.0)	100.0 (96.9–100.0)	0 + 165 = 165	21.5	100.0 (96.7–100.0)	100.0 (95.1–100.0)	0 + 165 = 165	21.5
3	100.0 (97.5–100.0)	100.0 (96.9–100.0)	0 + 218 = 218	28.4	100.0 (97.5–100.0)	100.0 (95.1–100.0)	0 + 218 = 218	28.4
4	99.3 (97.4–99.9)	98.9 (96.0–99.9)	2 + 274 = 276	35.7	99.6 (98.0–100.0)	99.1 (95.1–100.0)	1 + 274 = 275	35.7
5	98.5 (96.5–99.5)	97.2 (93.5–99.1)	5 + 321 = 326	41.9	99.7 (98.3–100.0)	99.1 (95.1–100.0)	1 + 321 = 322	41.9
5.2, 10% CV	98.5 (96.5–99.5)	97.2 (93.5–99.1)	5 + 327 = 332	42.6	99.7 (98.3–100.0)	99.1 (95.1–100.0)	1 + 327 = 328	42.6
6	98.4 (96.4–99.4)	96.6 (92.7–98.7)	6 + 358 = 364	46.7	99.4 (98.0–99.9)	98.2 (93.6–99.8)	2 + 358 = 360	46.7
7	98.0 (96.1–99.1)	95.5 (91.2–98.0)	8 + 388 = 396	50.6	99.2 (97.8–99.8)	97.3 (92.3–99.4)	3 + 388 = 391	50.6
8	98.1 (96.3–99.2)	95.5 (91.2–98.0)	8 + 413 = 421	53.8	99.3 (97.9–99.9)	97.3 (92.3–99.4)	3 + 413 = 416	53.8
9	97.4 (95.5–98.7)	93.8 (89.1–96.8)	11 + 420 = 431	54.8	98.8 (97.3–99.6)	95.5 (89.8–98.5)	5 + 420 = 425	54.8
10	96.8 (94.8–98.3)	92.0 (87.0–95.6)	14 + 430 = 444	56.1	98.4 (96.7–99.4)	93.7 (87.4–97.4)	7 + 430 = 437	56.1
27, 99th Pctl.	95.1 (92.8–96.8)	86.4 (80.4–91.1)	24 + 464 = 488	60.5	97.7 (95.9–98.8)	90.1 (83.0–94.9)	11 + 464 = 475	60.5

[a] CIs are 95%.
[b] FN, false negative; TN, true negative; pctl, percentile.

Table 4. 1-year follow-up results of the BACC cohort.

	TnI 0 h ≤ 3 ng/L	TnI 0 h ≤ 3 ng/L + low risk ECG	TnI 0 h > 3 ng/L or no low risk ECG + final diagnosis of non-AMI	T,I 0 h > 3 ng/L or no low risk ECG + final diagnosis of AMI (type 1 and type 2)
Death, % events[a]	3 out of 277, 1.08%	0 out of 217, 0%	32 out of 549, 5.83%	18 out of 176, 10.23%
Incident AMI, % events	1 out of 277, 0.36%	0 out of 217, 0%	3 out of 549, 0.56%	3 out of 176, 1.82%
PCI, % events	7 out of 277, 2.54%	4 out of 217, 1.84%	16 out of 549, 2.97%	9 out of 176, 5.31%
Cardiac rehospitalization, % events	35 out of 277, 12.69%	23 out of 217, 10.60%	109 out of 549, 20.34%	42 out of 175, 25.19%

[a] The 1-year % of events is estimated via the Kaplan–Meier estimator.

clined to values similar to those we documented in our cohort. This makes timing of chest pain onset a crucial further question. To address that, we measured the time from admission to first troponin measurement in our study. This period was short at 22 min (median). To further investigate this, we performed subgroup analyses for individuals with early symptom onset and longer duration until first troponin sample. Here we observed stable results among all subgroups with our low cutoff concentration. Therefore, this cutoff of 3 ng/L might increase clinical safety for ruled out patients that are sent home directly after the first troponin results become available. The clinical safety of an immediate rule-out is further represented by the follow-up mortality.

Importantly, compared to our study most other studies used less sensitive troponin assays *(11)*. These studies could show high NPVs of up to 100% and ruled out around 25% of the population. In a large register of 14638 individuals Bandstein et al. investigated the clinical safety of a single hs-TnT measurement *(12)*. Patients with an hs-TnT below 5 ng/L (which is the LoD of this specific assay) had a low follow-up rate of AMI or death. Importantly the time from first symptom onset until first troponin sample was only given for the subgroup of pa-

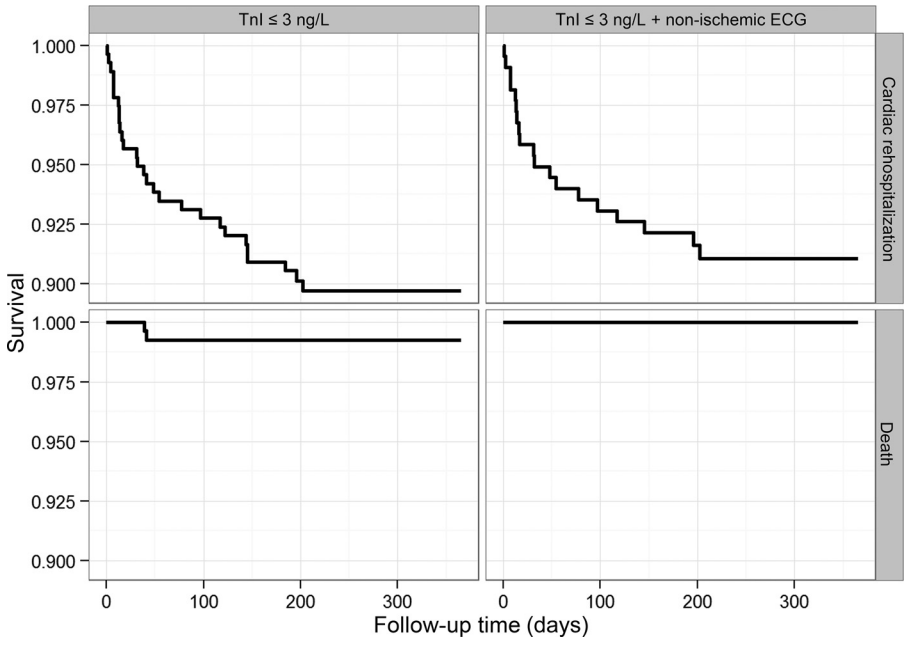

Fig. 1. Outcome in the BACC study.

Displayed are the 1-year Kaplan–Meier curves for cardiac rehospitalization and overall death for a baseline hs-TnI concentration below 3 ng/L and additional combination with a low risk ECG.

Table 5. Rule-out results in the 2 validation cohorts.

	TnI 0 h ≤ 3 ng/L	TnI 0 h ≤ 3 ng/L + low risk ECG
Stenocardia Study		
NPV	100.0 (97.9–100.0)	100.0 (97.9–100.0)
% of all non-AMI	24.1%	6.7%
Total n	1598	1585
Outcome 6 months		
Death, n	0	0
AMI, PCI, rehospitalization, death, n	10	6
ADAPT Study		
NPV	99.8 (99.1–100.0)	9 9.8 (98.8–100.0)
% of all non-AMI	42.9%	30.1%
Total n	1751	1751
Outcome 12 months		
Death, n	1	1
AMI, revascularization, death, n	9	5

tients with hs-TnT below 5 ng/L and a low risk ECG that had AMI within 30 days. 73% of those patients had an early symptom onset and had the first hs-TnT measurement within 2 h after first symptoms. Those individuals would have been missed using a single hs-TnT approach, owing to lower troponin concentrations. Applying a more sensitive hs-TnI assay, much lower troponin concentrations can be detected. This validates our approach utilizing an hs-TnI for acute cardiovascular diagnosis.

FOLLOW-UP OF CHEST PAIN PATIENTS

In the overall study population the total mortality was 3.0% after 6 months and 5.3% after 12 months. To place these results into context, the 6 months mortality rate of the GRACE registry was 4.8% *(19)*. This difference might be explained partly by the strict inclusion criteria of the GRACE registry, in which patients had ECG changes, increased biomarker concentrations, or known coronary artery disease (CAD). GRACE represents a subgroup of patients with a higher rate of cardiovascular events in the future. Among those individuals ruled out with a low risk ECG and an hs-TnI below 3 ng/L the mortality rate was zero in the BACC and Stenocardia cohort, whereas 1 patient died of a noncardiovascular reason in the ADAPT study. Furthermore the incidence of revascularization and rehospitalization was lower when the ECG was included, as compared to hs-TnI alone. Overall these results strengthen the safety of the suggested rule-out algorithm and suggest that an immediate rule-out concept is clinically feasible.

VALIDATION COHORTS

Two independent cohorts utilizing the same hs-TnI assay validated the results of the BACC cohort and showed a NPV of 100% (Stenocardia) and 99.8% (ADAPT) for an hs-TnI below 3 ng/L combined with a low risk ECG. Overall, the algorithm was tested in 4606 individuals, which increases the impact of our findings. Importantly, it was tested in different geographical areas. Moreover, we applied it to 3 cohorts with different pretest probabilities for myocardial ischemia, given the slightly different design and work flow of the specific cohort studies. Therefore, the percentages of patients without AMI ruled out by this specific algorithm differ between 7% and 30% in the various cohorts. Nevertheless, the algorithm was safe in all cohorts, which allows a wide application of this concept.

STRENGTHS AND LIMITATIONS

The current analyses capitalize on a large sample set of 4606 individuals from different areas. The initial diagnoses in this study were based on a different troponin assay in study populations that most likely had different pretest probabilities. Homogeneous application of a high-sensitivity assay allowed a very low TnI cutoff application, which realistically opens the avenue for baseline rule-out strategies. Such strategies are particularly important in ambulatory settings or crowded general emergency rooms. Several limitations of this study merit consideration. Importantly, all results were specific for the applied troponin assay and cannot be generalized to other assays. Although this study was performed prospectively, it was not randomized to the clinical gold standard. Therefore, a prospective, controlled and randomized trial is important and should be conducted to prove the safety of this rapid rule-out approach. The study results were validated in 2 external cohorts, which did not use high sensitivity-troponin for adjudication of the final diagno-

sis. This could influence the results of the validation, because fewer non-ST-elevation AMIs might have been detected. A limitation regarding the ECG is that the interpretation was not done blinded from other clinical parameters. Finally, only a limited percentage of patients, varying between 7% and 30% according to the pretest probability, can be ruled out by using the baseline concept. Serial measurements are mandatory to rule out individuals with higher baseline troponin concentrations but without a rising pattern.

Conclusion

A single hs-TnI measurement below a cutoff value of 3 ng/L combined with a low risk ECG may allow for safe immediate discharge in low risk patients presenting at the ED with suspicion of AMI. All other patients require serial troponin testing and further clinical evaluation.

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