Supplement

Two-Hour Algorithm for Early Diagnosis of Acute Myocardial Infarction Using A High-sensitivity Cardiac Troponin I Assay

Supplemental Methods

Derivation Cohort (APACE)

Patient Population

Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective international multicenter study with 12 centers in 5 European countries (Switzerland, Spain, Italy, Poland, Czech Republic) designed to contribute to improving the management of patients with MI. (ClinicalTrials.gov registry, number NCT00470587).(1)(2)(3)(4)(5) Adult patients presenting to the emergency department (ED) with symptoms suggestive of AMI (such as acute chest discomfort and angina pectoris) with an onset or peak within the last 12 hours were recruited. Enrollment was independent from renal function at presentation, while patients with terminal renal failure on chronic dialysis were excluded. 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.

Routine Clinical Assessment

All patients underwent a clinical assessment that included standardized and detailed medical history including assessment of 34 predefined chest pain characteristics, vital signs, physical examination, 12-lead ECG, continuous ECG rhythm monitoring, pulse oximetry, standard blood test, and chest radiography if indicated. Concentrations of

cardiac troponins (cTn) including high-sensitivity cTn (hs-cTn) in some centers were measured at presentation and serially thereafter as long as clinically indicated. Treatment of patients was left to discretion of the attending physician. Clinical suspicion for acute coronary syndrome (ACS) as the cause of the presenting symptom was quantified 90 min after presentation by the treating emergency department (ED) physician using a visual analog scale (VAS). At this time point, the ED physician had completed his/her clinical assessment, including patient history, chest pain characteristics, and detailed physical examination including vital signs, and reviewed the ECG and the first local cTn measurement. We considered a concentration of ≥ 80% as high pretest probability for ACS.(6)

Reference Standard: Adjudicated Final Diagnosis

AMI was defined and cTn concentrations interpreted as recommended in current guidelines.(7)(8–10) In brief, AMI was diagnosed when there was evidence of myocardial necrosis with a significant rise and/or fall in a clinical setting consistent with myocardial ischemia. Patients with AMI were further subdivided into type 1 AMI (primary coronary events) and type 2 AMI (ischemia due to increased demand or decreased supply, for example tachyarrhythmia or hypertensive crisis).(8,11)

The adjudication of final diagnoses was performed centrally in the core lab (University Hospital Basel) for all patients incorporating concentrations of hs-cTnT (primary analysis). More specifically, two independent cardiologists not directly involved in patient care reviewed all available medical records (including patient history, physical examination, results of laboratory testing including hs-cTnT concentrations, radiologic testing, ECG, echocardiography, cardiac exercise test, lesion severity and morphology in coronary angiography, discharge summary)

pertaining to the patient from the time of ED presentation to 90-day follow-up. In general, serial sampling was performed until at least 3-6h after presentation to the ED or onset of chest pain. In situations of diagnostic disagreement, cases were reviewed and adjudicated in conjunction with a third cardiologist. While discharge diagnoses often were correct and in agreement with the final adjudicated diagnosis, there were also cases where the discharge diagnosis needed to be revised, most often because more information became available from medical testing during early follow-up, and more rarely, because the discharge diagnosis was not in agreement with the Universal Definition of AMI.

The 99th percentile (hs-cTnT: 14ng/L) was used as cut-off for myocardial necrosis. Absolute cTn changes were used to determine significant changes based on the diagnostic superiority of absolute over relative changes.(12–17) Based on studies of the biological variation of cTn.(18,19) as well as on data from previous chest pain cohort studies,(12,20) a significant absolute change was defined as a rise or fall of at least 10ng/L within six hours, or, in an assumption of linearity, as an absolute change of 6ng/L within three hours. Predefined alternative diagnoses included “unstable angina” (UA), “Cardiac symptoms of origin other than coronary artery disease” and “non-cardiac chest pain”.

Clinical Care: The (hs)-cTn assays and cut-off concentrations used for local clinical care

Routine clinical care comprised five different cTn assays at the different hospitals throughout the whole recruitment period. The cTn assays used clinically in most of the participating institutions changed during the study from a conventional cTn assay to the hs-cTnT assay. In order to take advantage of the higher sensitivity and higher overall diagnostic accuracy offered by the hs-cTnT assay (primary analysis), patients

were adjudicated using the hs-cTnT concentrations obtained from study specific blood samples in addition to the clinically used (hs)-cTn concentrations.

The following conventional cTn assays were used: For the Roche cTnT 4th generation assay, the 10% CV concentration is 0.035µg/L. The laboratories of the participating sites reported only two decimals; therefore 0.04µg/L was used as a cut-off for myocardial necrosis. In order to fulfil the criteria of a significant change (30% of 99th percentile or 10% CV concentration), a patient would e.g. need to have a concentration of <0.01µg/L at presentation and 0.04µg/L at 6h. A patient would also qualify if the first concentration is 0.02µg/L and the second 0.04µg/L. A patient would not fulfil the criteria if the first concentration is 0.03µg/L and the second is 0.04µg/L. If the first concentration is 0.04µg/L, the second concentration needs to be at least 0.06µg/L.

For the Abbott Axsym cTnI ADV, the 10% CV concentration is 0.16µg/L. A patient having 0.16µg/L at presentation would meet the criteria for significant change if the second was ≥0.21µg/L. A patient having <0.12µg/L at presentation (limit of detection) would qualify if the second is >0.16µg/L.

For the Beckmann Coulter Accu cTnI, the 10% CV concentration is 0.06µg/L. A patient having 0.06µg/L at presentation would qualify if the second is ≥0.08µg/L. A patient having 0.05µg/l at presentation would qualify if the second is 0.07µg/L, but not 0.06µg/L. A patient having undetectable cTnI (cTnI <0.01µg/L) at presentation would qualify if the second is ≥0.06µg/L.

For the Siemens Dimension Vista s-cTnI, the 10% CV concentration is 40ng/L. The limit of detection is 15ng/L and the 99th percentile is 45ng/L. An absolute change of 20ng/L or more within 3-6h was considered significant.

For Elecsys hs-cTnT measured clinically, the same change criteria were applied as for hs-cTnT measured from the study blood samples.

Follow-up

Patients were contacted 3, 12 and 24 months after discharge by telephone calls or in written form. Information regarding death during follow up was furthermore obtained from the patient's hospital notes, the family physician's records and the national registry on mortality.

Validation Cohort (ADAPT and IMPACT)

Patient Population

Accelerated Diagnostic Protocol to Assess patients with chest Pain symptoms using contemporary Troponins as the only biomarker (ADAPT) was a multicenter, diagnostic study enrolling patients between November 2007 and February 2011 in two study centers in Australia and New Zealand.(21) The current study only uses data from the Australian site. The Improved Assessment of Chest pain trial (IMPACT) was a single center intervention study enrolling patients in the same Australian site between February 2011 and March 2014.(22) Criteria for enrollment were the same for ADAPT and IMPACT and included ≥18 years of age, with at least 5 minutes of symptoms where the attending physician planned to perform serial s-cTnI tests. The American Heart Association case definitions for possible cardiac symptoms were used (i.e., acute chest, epigastric, neck, jaw, or arm pain; or discomfort or pressure without an apparent non cardiac source).(23) Patients were excluded for any of the following: a clear cause other than acute coronary syndrome for the symptoms at presentation (e.g., examination findings of pneumonia), inability to provide informed consent, staff considered recruitment to be inappropriate (e.g., receiving palliative treatment), transfer from another hospital, pregnancy, previous enrollment, or inability to be contacted after discharge. Patients with STEMI on presentation were also

removed from the current analysis. Perceived high risk was not used as an exclusion criterion. The studies were carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees.

Routine Clinical Assessment

All patients underwent a clinical assessment that included standardized and detailed medical history including vital signs, physical examination, 12-lead ECG, continuous ECG rhythm monitoring, pulse oximetry, standard blood test, and chest radiography if indicated. Concentrations of s-cTnI were measured at presentation and serially thereafter as long as clinically indicated.

Reference Standard: Adjudicated Final Diagnosis

In the ADAPT and IMPACT cohorts, 30-day outcomes and final diagnoses were adjudicated independently by local cardiologists using predefined standardized reporting guidelines according to the current universal definition of myocardial infarction. Cardiologists had knowledge of the clinical record, ECG, s-cTnI results and objective testing from standard care. A second cardiologist conducted a blind review of all acute coronary syndrome (ACS) cases and 10% of non-ACS cases. In cases of disagreement, endpoints were agreed by consensus. Consensus was achieved for all endpoints. Late samples were available for adjudication of final diagnosis in all patients of the validation cohort, which means that serial sampling was performed until at least 6h after presentation to the ED in all patients. For ADAPT, adjudication of final diagnosis included s-cTnI measurements from blood samples obtained at presentation and 6 to 12h thereafter. For IMPACT, adjudication included s-cTnI

measurements from blood samples obtained at presentation and at least 2 h thereafter.

The Beckman Coulter 2nd generation AccuTnI assay (Beckman Coulter, Chaska, MN) was used at the Australian site. This assay has a LoD of 10 ng/L, a 99th percentile of 40ng/L and a 10% CV of 60ng/L. The 99th percentile (40ng/L) was used as cut-off for myocardial necrosis. A delta of ≥20% was used to detect a rising or falling pattern and at least one value above the 99th percentile was necessary to qualify for AMI diagnosis.

Follow-up and clinical endpoints

Patients were contacted at 6 weeks and 12 months by telephone calls or in written form. 6 weeks follow-up was conducted for all patients, while 12 months follow-up information was only available where the patient provided consent to further contact. Information regarding death at twelve months was furthermore obtained from the patient's hospital notes, the family physician's records and the national registry on mortality. The primary prognostic endpoint was 30 days all-cause mortality.

Derivation and validation of the hs-cTnI-Access 0/2h-algorithm

The 0/2h-algorithm incorporates hs-cTnI concentration concentrations at presentation and absolute hs-cTnI- changes within 2h as well as time since chest pain onset in order to reflect the concept of the current hs-cTn 0/1h-algorithms suggested by the ESC. The rule-out criteria for hs-cTnI are defined as an undetectable (very low) concentration at presentation or a low baseline hs-cTnI concentration together with no relevant absolute change within the first 2 hours Rule-in is defined by a high baseline hs-cTnI

concentration or a relevant absolute change in hs-cTnI within the first 2 hours. The remaining patients were triaged towards the observe zone The hs-cTnI-Access 0/2h-algorithm was developed in the derivation cohort (APACE) in selected patients with available hs-cTnI-Access measurements at baseline and after 2h. The 0/2h-algorithm incorporates hs-cTnI-Access concentrations at presentation and absolute hs-cTnI-Access changes within 2h. (**Supplemental Figure 2**). Selection of these parameters was based on the very high diagnostic accuracy of the combination of blood concentrations at presentation with absolute changes for rule-out and rule-in of AMI.(12,24–31) Derived thresholds for rule-out were selected to allow for a minimal sensitivity and negative predictive value (NPV) of 99.5% and sensitivity of 99.0%. Derived thresholds for rule-in were obtained based on a classification and regression tree (CART) analysis targeting a minimal positive predictive value (PPV) of 70%.(32) Nodes in the CART tree were constrained to have a minimal number of cases of 20 in parent and child nodes. If a predefined target performance was missed in the derivation sample using the CART-derived thresholds, thresholds were changed stepwise until the predefined performance was fulfilled. The algorithm developed in the derivation sample was tested for its diagnostic accuracy in an independent validation sample consisting of the remaining subjects. The decision values derived in the derivation sample were rounded to give whole values in ng/L. The whole algorithm developed in the derivation cohort was then tested for diagnostic accuracy in the validation cohort (ADAPT and IMPACT).

Direct comparison of the hs-cTnI-Access 0/2h-algorithm with the 0/2h-algorithms using hs-cTnT-Elecsys and hs-cTnI-Architect

The diagnostic performance of the hs-cTnI-Access 0/2h-algorithm in both cohorts was directly compared to the performances of the hs-cTnT-Elecsys 0/2h-algorithm and the

hs-cTnI-Architect 0/2h-algorithm in all patients of the validation cohort, who also had a full set of hs-cTnT-Elecsys and hs-cTnI-Architect measurements at 0h and 2h.

Follow-up

The co-primary prognostic endpoints were overall survival after 30 days and 2 years in the derivation cohort and 30 days and 1 year in the validation cohort.

Statistical analysis

Continuous variables are described as mean ± SD or median with interquartile range (IQR), categorical variables by numbers and percentages. Differences in baseline characteristics between patients with and without AMI as well as between patients in the derivation and validation cohort were assessed using the Mann-Whitney U test for continuous variables and the Pearson Chi-square test for categorical variables.

For the assessment of the diagnostic performance of the hs-cTnI-Access 0/2h-algorithm in the derivation and validation cohort, safety was assessed as the NPV and the sensitivity for AMI in the rule-out group, accuracy of the rule-in strategy as the PPV and specificity for AMI in the rule-in group while efficacy was quantified as the percentage of patients triaged towards rule-out or rule-in for AMI within 2h.

Survival during 30 days and 365/720 days of follow-up according to the classification provided by the hs-cTnI-Access 0/2h-algorithm was plotted in Kaplan-Meier curves and the log-rank test was used to assess differences in survival between groups. Bootstrapping has been used to calculate confidence intervals.

All hypothesis testing was two-tailed and *P*-values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (SPSS Inc), MedCalc 17.6 (MedCalc Software) and Stata 14 (StataCorp).

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Online Tables and Figures

Supplemental Table 1: Study specific characteristics in both cohorts

	Derivation cohort (APACE)	Validation cohort (ADAPT and IMPACT)
Study design and study population		
Study design	prospective observational study	prospective observational study (ADAPT) Intervention study (IMPACT)
Study centers	12 centers in 5 European countries (Switzerland, Spain, Italy, Poland, Czech Republic)	1 center in Australia
Inclusion criteria	patients presenting with symptoms suggestive of AMI to an ED, age ≥18years	patients presenting with symptoms suggestive of AMI to an ED, age ≥18years
Informed Consent	Obtained in the emergency department	Obtained in the emergency department or during hospitalization
Chest pain onset	onset or peak within last 12h before presentation	onset or peak within last 12h before presentation
Exclusion criteria	Patients with terminal renal failure on chronic dialysis, no informed consent obtained	Patients with a clear cause other than acute coronary syndrome at presentation, palliative treatment at presentation, pregnant women, transfer from another hospital no informed consent obtained
All 3 studies 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.		
Routine clinical assessment	medical history, 34 predefined chest pain characteristics, vital signs, physical examination, 12-lead ECG, continuous ECG rhythm monitoring, pulse oximetry, standard blood tests, chest radiography	medical history, vital signs, physical examination, 12-lead ECG, continuous ECG rhythm monitoring, pulse oximetry, standard blood tests, chest radiography
Routine treatment of patients	at discretion of the attending physician	at discretion of the attending physician
Investigational troponin assays	hs-cTnT Elecsys, hs-cTnI Architect and Hs-cTnI Access	hs-cTnT Elecsys, hs-cTnI Architect and Hs-cTnI Access

Blood sampling	obtained in plasma or EDTA tubes, centrifugated and frozen at -80°C until assayed in a blinded fashion in a dedicated core laboratory.	obtained in plasma or EDTA tubes, centrifugated and frozen at -80°C until assayed in a blinded fashion in a dedicated core laboratory.
Time points of measurement	at presentation and after 1h, 2h, 3h and 6h	at presentation and after 2h and 6h to 12h for ADAPT at presentation and after 2h for low to intermediate risk patients and 6 to 12h for high risk patients in IMPACT
Number of patients with measured hs-cTnT/I (for APACE) and s-cTnI (for ADAPT and Impact) concentration for adjudication	0h: 1131/1131 patients (100%) 1h: 1091/1131 patients (96.5%) 2h: 1129/1131 patients (99.8%) 3-6h: 442/1131 patients (39.1%) Clinically used assays: 0-2h 1115/1132 (98.6%) 3-6h 567/1131 (50.1%)	0h: 1277/1280 (99.8%) 2h: 1275/1280 (99.6%) 6h: 687/1280 (53.7%)
central adjudication of final diagnoses		
Troponin assays used for central adjudication of final diagnoses	hs-cTnT Elecsys Roche Assay, and hs-cTnI Architect Abbott Assay measured at presentation and after 1h to 6h PLUS the clinically used (hs)-cTnT/I assay (hs-cTnT, or s-cTnI-Vista, or cTnI-Axsym, or cTnT) measured at presentation and serially thereafter	cTnI Beckman Coulter 2nd generation AccuTnI assay measured at presentation and after 6h to 12h
Troponin criteria used for central adjudication to qualify for AMI	at least one value above the 99th percentile together with a significant rise and/or fall defined as a rise or fall of at least 10ng/L within six hours, or of 6ng/L within three hours	at least one value above the 99th percentile together with a significant rise and/or fall defined as a relative change of at least 20%
Number of patients who are lost for follow-up	2/1131 patients (0.2%)	No patients were lost to follow-up. However, one-year follow-up only occurred for the 1056/1280 of patients who consented to be contacted at 1 year.

Table Legend: AMI: acute myocardial infarction, ED: emergency department, ECG: electrocardiography, (hs)-cTn: high sensitivitiy-cardiac troponin

LBBB: left bundle branch block, * = detailed description of investigational assays in the main manuscript

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	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	4
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	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5-6, supplement
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5-6, supplement
	9	Whether participants formed a consecutive, random or convenience series	5-6, supplement
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	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	5-8
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	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	5-8
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Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	supplement
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	21a	Distribution of severity of disease in those with the target condition	9-11
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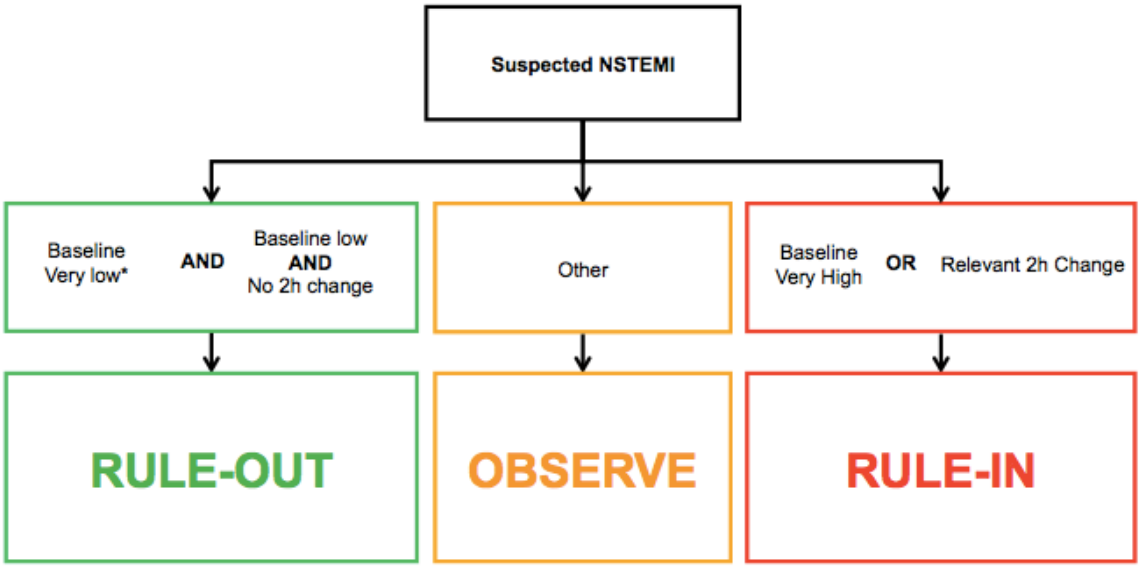
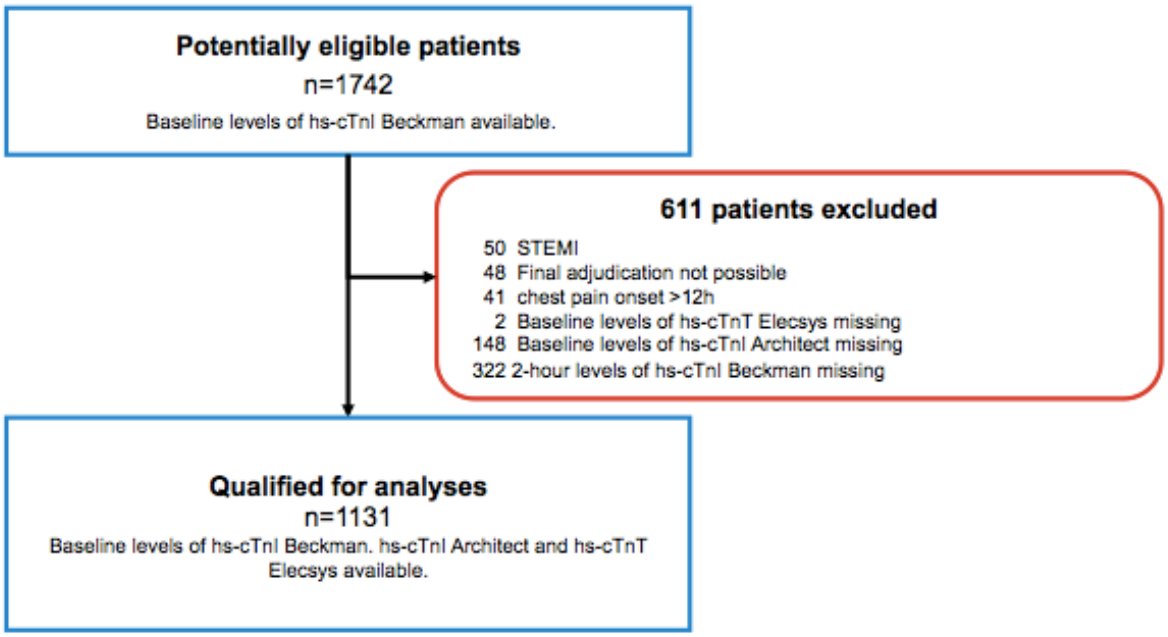
Supplemental Table 2 **STARD Checklist for Studies of Diagnostic Accuracy**



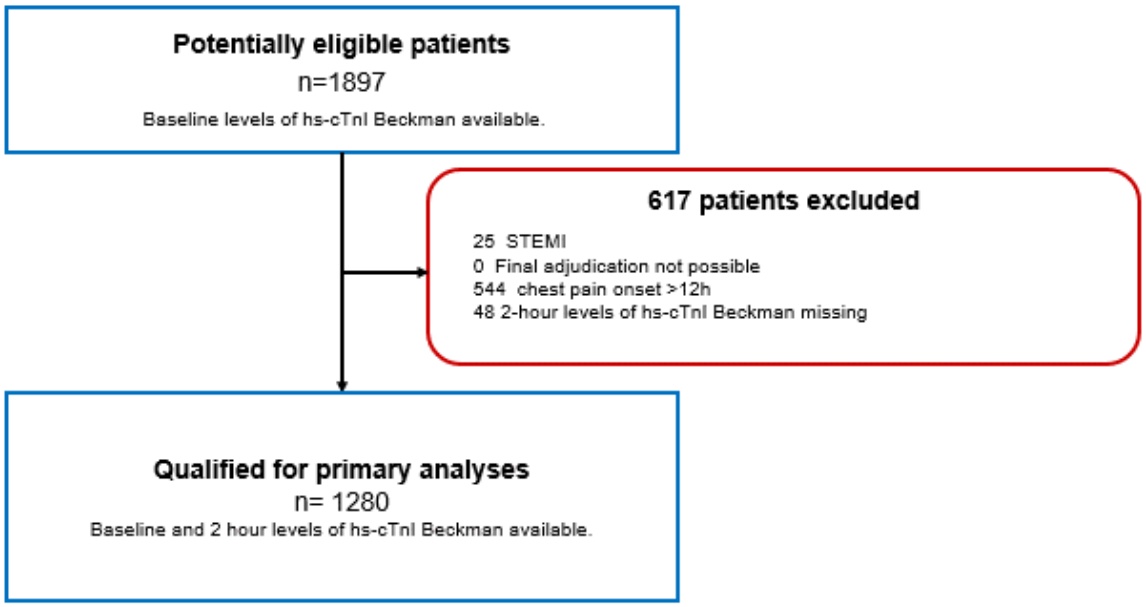
Supplemental Figure 1 **Concept of the hs-cTnI-Access 0/2h-algorithm**

The official concept of the hs-cTn 0/2h-algorithm. Patients are triaged towards rule-out, observe, and rule-in. *if chest pain onset >3h



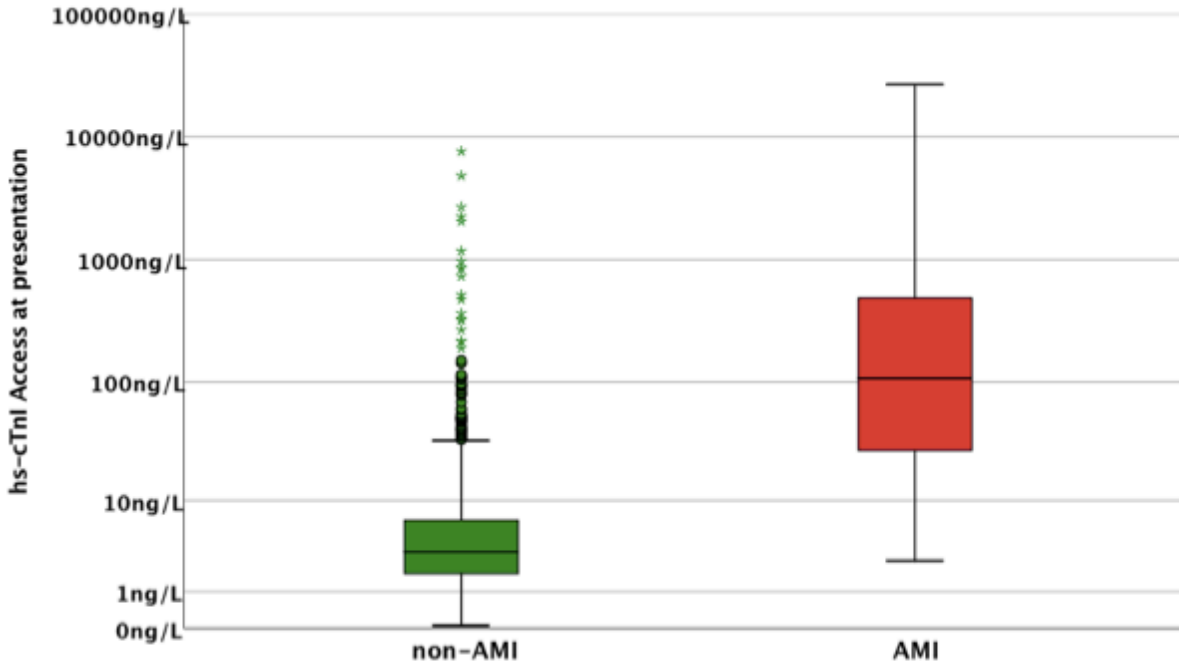
Supplemental Figure 2A **Patient flow of enrolled patients in the derivation cohort**

Hs-cTnI denotes high-sensitivity cardiac troponin I; hs-cTnT denotes high-sensitivity cardiac troponin T; STEMI denotes ST-elevation myocardial infarction.



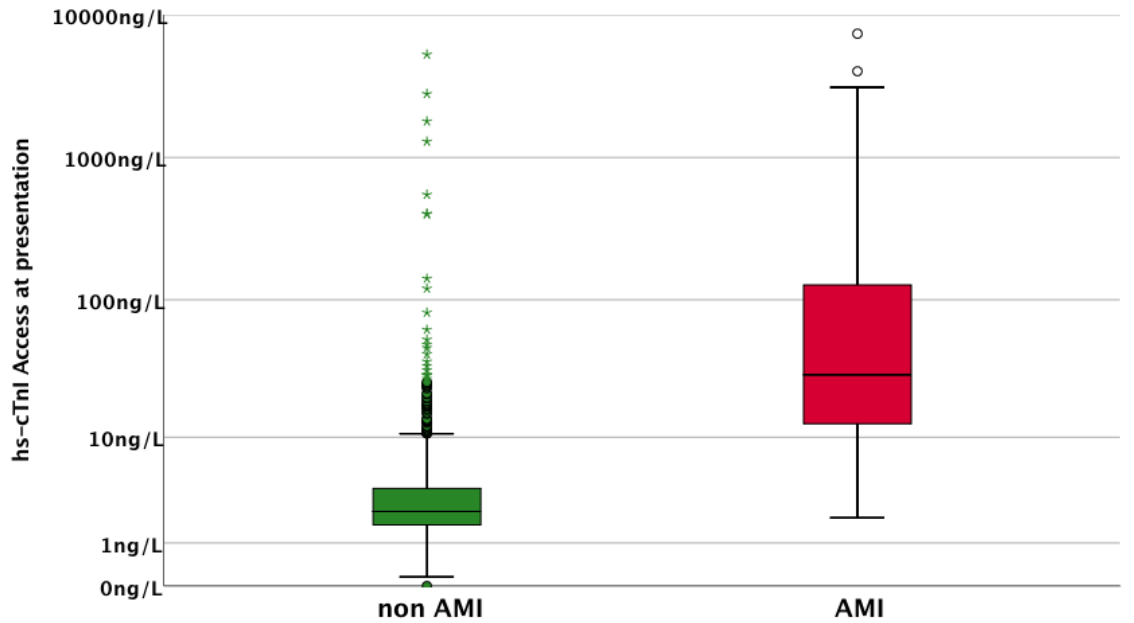
Supplemental Figure 2B **Patient flow of enrolled patients in the validation cohort**

Hs-cTnI denotes high-sensitivity cardiac troponin I; hs-cTnT denotes high-sensitivity cardiac troponin T; STEMI denotes ST-elevation myocardial infarction.



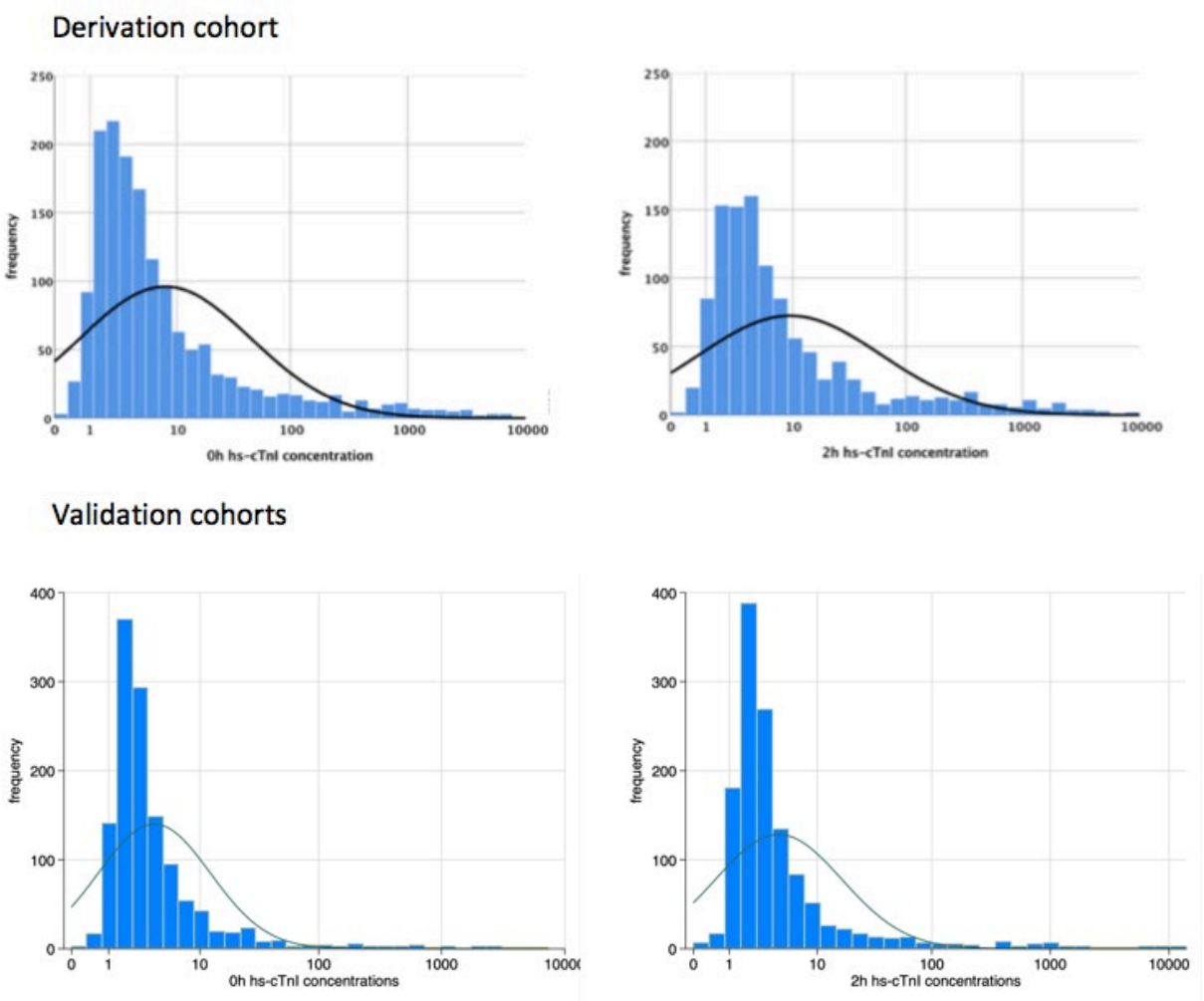
Supplemental Figure 3A **Boxplots showing Concentrations of hs-cTnI-Access at Presentation according to the final diagnosis the derivation cohort**

Boxes represent medians and interquartile ranges (IQRs), while whiskers display the smallest and the largest non-outliers. Rings display outliers further than 1.5 IQRs and stars display outliers further than 3 IQRs from the respective end of the box. AMI denotes acute myocardial infarction; hs-cTnI denotes high-sensitivity cardiac troponin I.



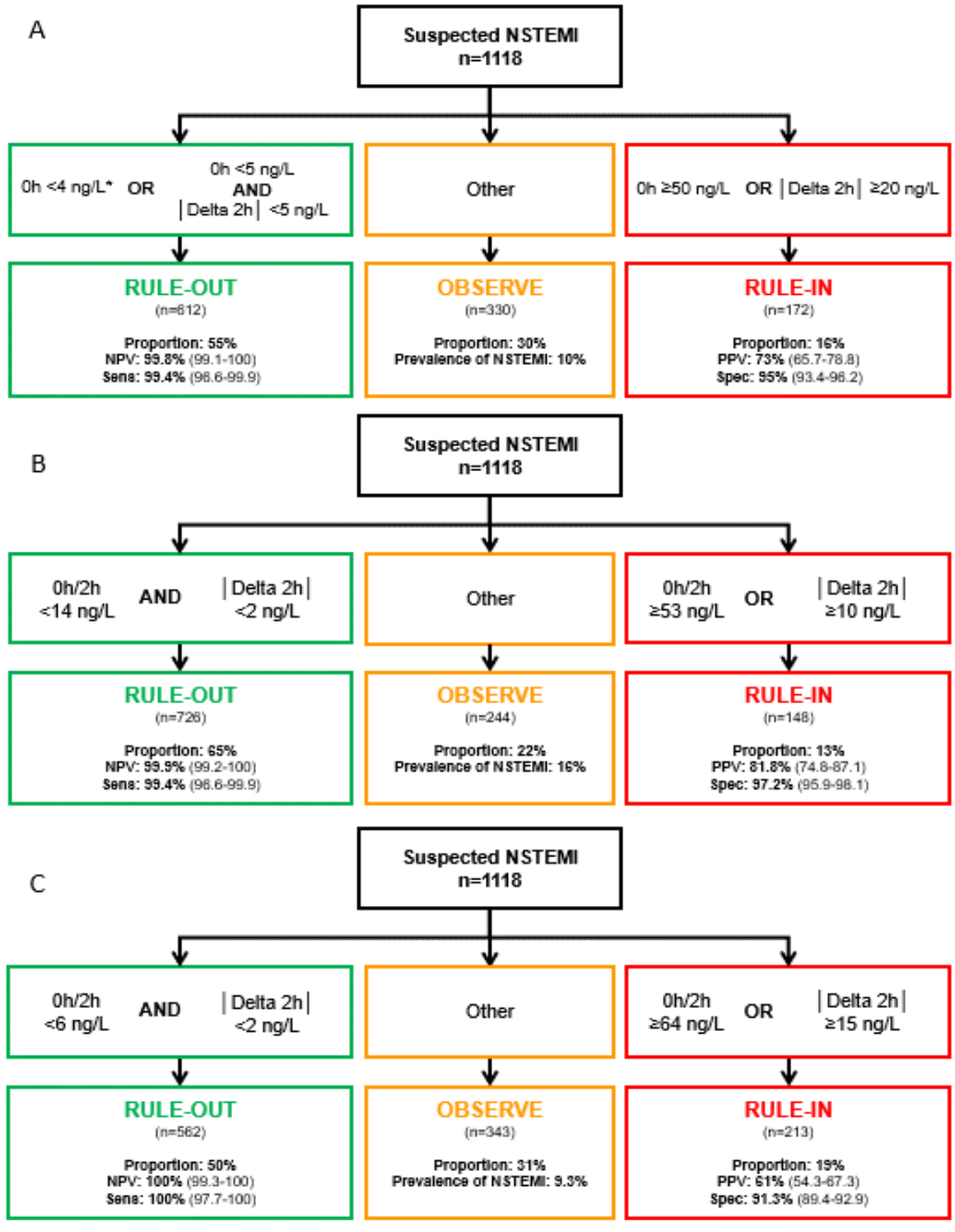
Supplemental Figure 3B **Boxplots showing Concentrations of hs-cTnI-Access at Presentation according to the final diagnosis the validation cohort**

Boxes represent medians and interquartile ranges (IQRs), while whiskers display the smallest and the largest non-outliers. Rings display outliers further than 1.5 IQRs and stars display outliers further than 3 IQRs from the respective end of the box. AMI denotes acute myocardial infarction; hs-cTnI denotes high-sensitivity cardiac troponin I



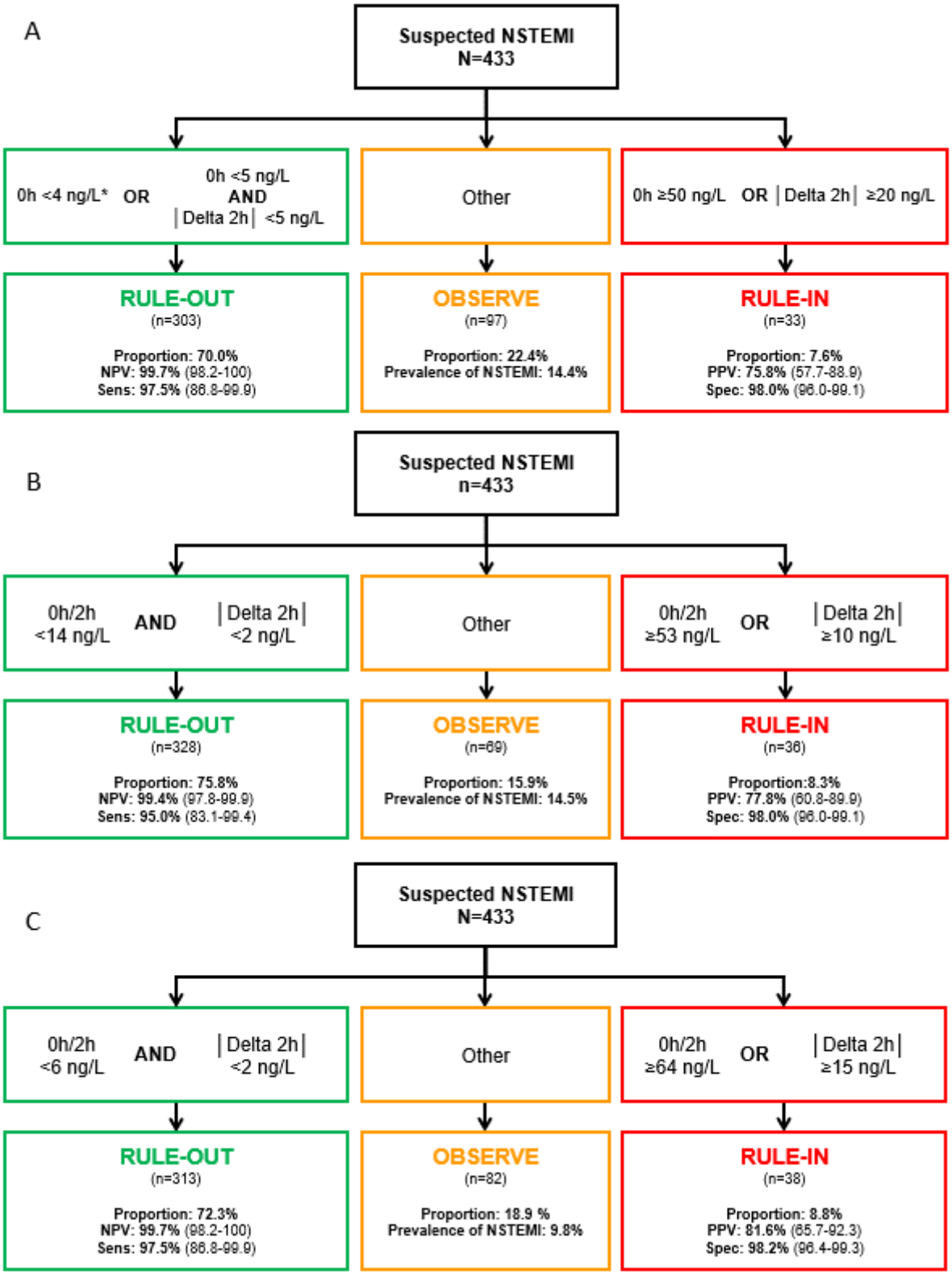
Supplemental Figure 4 **Histograms**

Histograms highlighting the distribution of hs-cTnI concentrations at presentation and after 2h in the derivation and the validations cohorts.


A
Suspected NSTEMI
n=1118
0h <4 ng/L* OR
0h <5 ng/L
AND
|Delta 2h| <5 ng/L
Other
0h ≥50 ng/L OR |Delta 2h| ≥20 ng/L
RULE-OUT
(n=612)
Proportion: 55%
NPV: 99.8% (99.1-100)
Sens: 99.4% (96.6-99.9)
OBSERVE
(n=330)
Proportion: 30%
Prevalence of NSTEMI: 10%
RULE-IN
(n=172)
Proportion: 16%
PPV: 73% (65.7-78.8)
Spec: 95% (93.4-98.2)
B
Suspected NSTEMI
n=1118
0h/2h
<14 ng/L
AND
|Delta 2h|
<2 ng/L
Other
0h/2h
≥53 ng/L
OR
|Delta 2h|
≥10 ng/L
RULE-OUT
(n=726)
Proportion: 65%
NPV: 99.9% (99.2-100)
Sens: 99.4% (96.6-99.9)
OBSERVE
(n=244)
Proportion: 22%
Prevalence of NSTEMI: 16%
RULE-IN
(n=148)
Proportion: 13%
PPV: 81.8% (74.8-87.1)
Spec: 97.2% (95.9-98.1)
C
Suspected NSTEMI
n=1118
0h/2h
<6 ng/L
AND
|Delta 2h|
<2 ng/L
Other
0h/2h
≥64 ng/L
OR
|Delta 2h|
≥15 ng/L
RULE-OUT
(n=562)
Proportion: 50%
NPV: 100% (99.3-100)
Sens: 100% (97.7-100)
OBSERVE
(n=343)
Proportion: 31%
Prevalence of NSTEMI: 9.3%
RULE-IN
(n=213)
Proportion: 19%
PPV: 61% (54.3-67.3)
Spec: 91.3% (89.4-92.9)

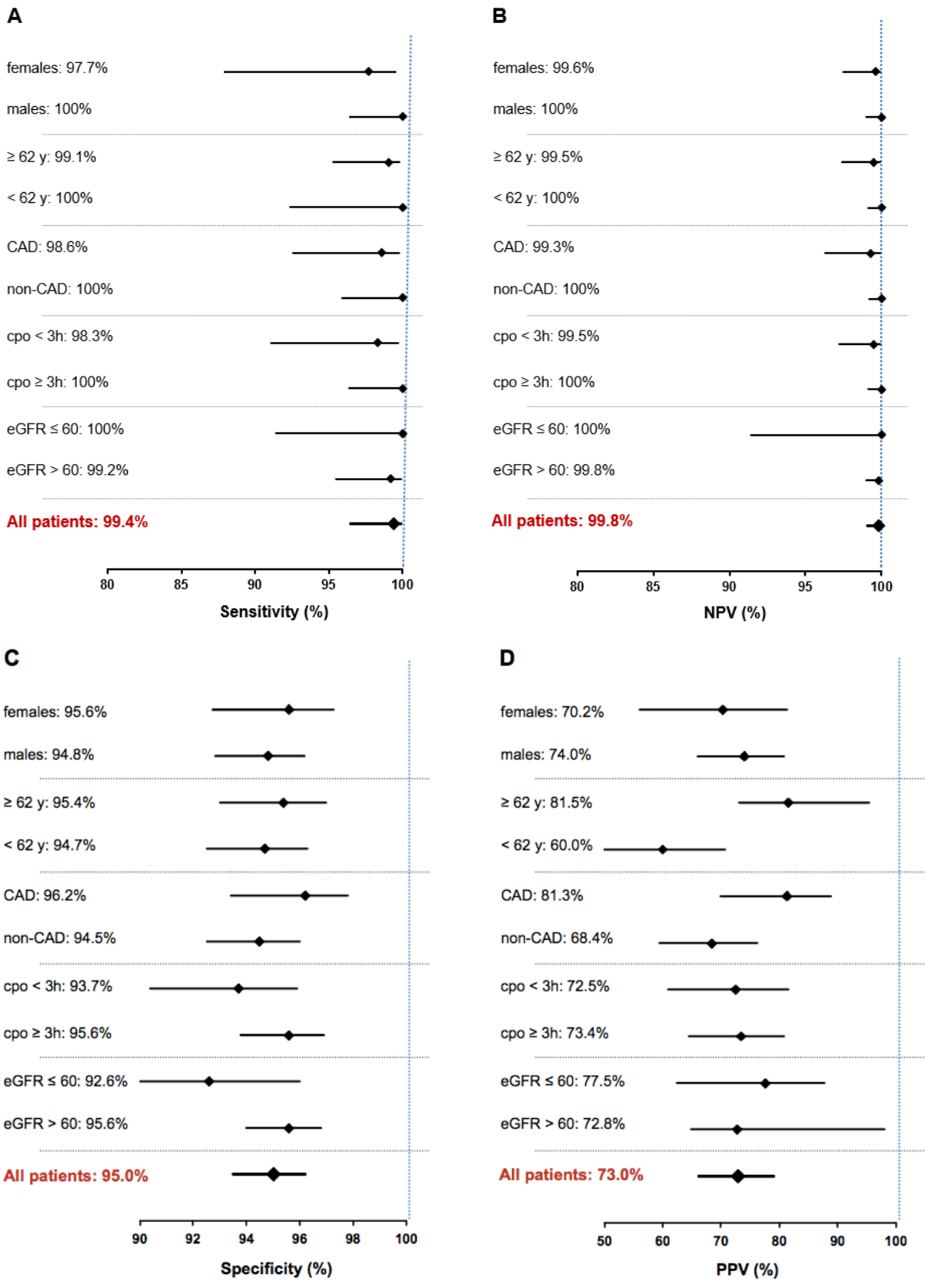
Supplemental Figure 5A **Direct Comparison of the hs-cTnI-Access 0/2h-algorithm with the hs-cTnT-Elecsys and hs-cTnI-Architect 0/2h-algorithms in the derivation cohort**

Direct comparison of the diagnostic performance of (A) the hs-cTnI-Access 0/2h-algorithm with (B) the hs-cTnT-Elecsys 0/2h-algorithm and (C) the hs-cTnI-Architect 0/2h-algorithm in the derivation cohort. NSTEMI denotes non-ST-elevation myocardial infarction; 0h/2h denotes based on zero-hour or two-hour blood sample obtained at presentation to the ED and after two-hours; Delta 2h│ denotes absolute (unsigned) change of high-sensitivity cardiac troponin I within two hours; NPV denotes negative predictive value; Sens. denotes sensitivity; PPV denotes positive predictive value; Spec. denotes specificity; * denotes chest pain onset <2 hours


A
Suspected NSTEMI
N=433
0h <4 ng/L* OR 0h <5 ng/L AND |Delta 2h| <5 ng/L
Other
0h ≥50 ng/L OR |Delta 2h| ≥20 ng/L
RULE-OUT
(n=303)
Proportion: 70.0%
NPV: 99.7% (98.2-100)
Sens: 97.5% (86.8-99.9)
OBSERVE
(n=97)
Proportion: 22.4%
Prevalence of NSTEMI: 14.4%
RULE-IN
(n=33)
Proportion: 7.6%
PPV: 75.8% (57.7-88.9)
Spec: 98.0% (96.0-99.1)
B
Suspected NSTEMI
n=433
0h/2h <14 ng/L AND |Delta 2h| <2 ng/L
Other
0h/2h ≥53 ng/L OR |Delta 2h| ≥10 ng/L
RULE-OUT
(n=328)
Proportion: 75.8%
NPV: 99.4% (97.8-99.9)
Sens: 95.0% (83.1-99.4)
OBSERVE
(n=69)
Proportion: 15.9%
Prevalence of NSTEMI: 14.5%
RULE-IN
(n=36)
Proportion:8.3%
PPV: 77.8% (60.8-89.9)
Spec: 98.0% (96.0-99.1)
C
Suspected NSTEMI
N=433
0h/2h <6 ng/L AND |Delta 2h| <2 ng/L
Other
0h/2h ≥64 ng/L OR |Delta 2h| ≥15 ng/L
RULE-OUT
(n=313)
Proportion: 72.3%
NPV: 99.7% (98.2-100)
Sens: 97.5% (86.8-99.9)
OBSERVE
(n=82)
Proportion: 18.9 %
Prevalence of NSTEMI: 9.8%
RULE-IN
(n=38)
Proportion: 8.8%
PPV: 81.6% (65.7-92.3)
Spec: 98.2% (96.4-99.3)

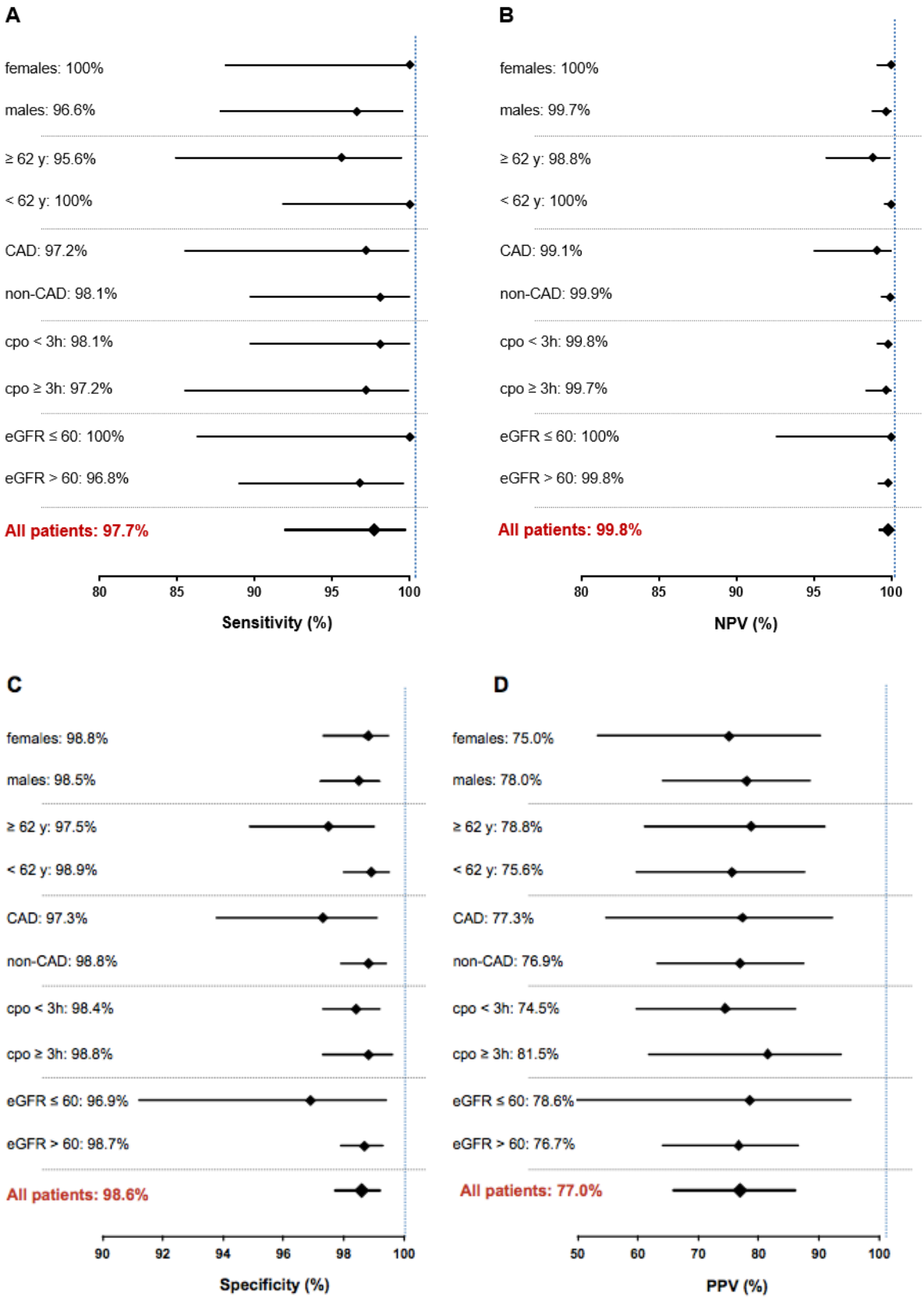
Supplemental Figure 5B **Direct Comparison of the hs-cTnI-Access 0/2h-algorithm with the hs-cTnT-Elecsys and hs-cTnI-Architect 0/2h-algorithms in the validation cohort**

Direct comparison of the diagnostic performance of (A) the hs-cTnI-Access 0/2h-algorithm with (B) the hs-cTnT-Elecsys 0/2h-algorithm and (C) the hs-cTnI-Architect 0/2h-algorithm in the derivation cohort. NSTEMI denotes non-ST-elevation myocardial infarction; 0h/2h denotes based on zero-hour or two-hour blood sample obtained at presentation to the ED and after two-hours; Delta 2h$\left|\right.$ denotes absolute (unsigned) change of high-sensitivity cardiac troponin I within two hours; NPV denotes negative predictive value; Sens. denotes sensitivity; PPV denotes positive predictive value; Spec. denotes specificity; * denotes chest pain onset <2 hours


A
females: 97.7%
males: 100%
≥ 62 y: 99.1%
< 62 y: 100%
CAD: 98.6%
non-CAD: 100%
cpo < 3h: 98.3%
cpo ≥ 3h: 100%
eGFR ≤ 60: 100%
eGFR > 60: 99.2%
All patients: 99.4%
80 85 90 95 100
Sensitivity (%)
B
females: 99.6%
males: 100%
≥ 62 y: 99.5%
< 62 y: 100%
CAD: 99.3%
non-CAD: 100%
cpo < 3h: 99.5%
cpo ≥ 3h: 100%
eGFR ≤ 60: 100%
eGFR > 60: 99.8%
All patients: 99.8%
80 85 90 95 100
NPV (%)
C
females: 95.6%
males: 94.8%
≥ 62 y: 95.4%
< 62 y: 94.7%
CAD: 96.2%
non-CAD: 94.5%
cpo < 3h: 93.7%
cpo ≥ 3h: 95.6%
eGFR ≤ 60: 92.6%
eGFR > 60: 95.6%
All patients: 95.0%
90 92 94 96 98 100
Specificity (%)
D
females: 70.2%
males: 74.0%
≥ 62 y: 81.5%
< 62 y: 60.0%
CAD: 81.3%
non-CAD: 68.4%
cpo < 3h: 72.5%
cpo ≥ 3h: 73.4%
eGFR ≤ 60: 77.5%
eGFR > 60: 72.8%
All patients: 73.0%
50 60 70 80 90 100
PPV (%)

Supplemental Figure 6A **Forest plots for algorithm performance in predefined subgroup analyses in the derivation cohort.**

Forest plots indicating sensitivity (A), negative predictive value (NPV, B), specificity (C) and positive predictive value (PPV, D) for predefined subgroup analyses. CAD indicates coronary artery disease; cpo, chest pain onset; and eGFR, estimated glomerular filtration rate.


A
females: 100%
males: 96.6%
≥ 62 y: 95.6%
< 62 y: 100%
CAD: 97.2%
non-CAD: 98.1%
cpo < 3h: 98.1%
cpo ≥ 3h: 97.2%
eGFR ≤ 60: 100%
eGFR > 60: 96.8%
All patients: 97.7%
80 85 90 95 100
Sensitivity (%)
B
females: 100%
males: 99.7%
≥ 62 y: 98.8%
< 62 y: 100%
CAD: 99.1%
non-CAD: 99.9%
cpo < 3h: 99.8%
cpo ≥ 3h: 99.7%
eGFR ≤ 60: 100%
eGFR > 60: 99.8%
All patients: 99.8%
80 85 90 95 100
NPV (%)
C
females: 98.8%
males: 98.5%
≥ 62 y: 97.5%
< 62 y: 98.9%
CAD: 97.3%
non-CAD: 98.8%
cpo < 3h: 98.4%
cpo ≥ 3h: 98.8%
eGFR ≤ 60: 96.9%
eGFR > 60: 98.7%
All patients: 98.6%
90 92 94 96 98 100
Specificity (%)
D
females: 75.0%
males: 78.0%
≥ 62 y: 78.8%
< 62 y: 75.6%
CAD: 77.3%
non-CAD: 76.9%
cpo < 3h: 74.5%
cpo ≥ 3h: 81.5%
eGFR ≤ 60: 78.6%
eGFR > 60: 76.7%
All patients: 77.0%
50 60 70 80 90 100
PPV (%)

Supplemental Figure 6B **Forest plots for algorithm performance in predefined subgroup analyses in the validation cohort.**

Forest plots indicating sensitivity (A), negative predictive value (NPV, B), specificity (C) and positive predictive value (PPV, D) for predefined subgroup analyses. CAD indicates coronary artery disease; cpo, chest pain onset; and eGFR, estimated glomerular filtration rate.