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ORIGINAL CONTRIBUTION

Serial Changes in Highly Sensitive Troponin I Assay and Early Diagnosis of Myocardial Infarction

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Objective

- Diagnostic performance of a highly sensitive troponin I (hsTnI) assay compared with a contemporary troponin I (cTnI) assay
- Serial changes within 3 hours after admission in the diagnosis of acute myocardial infarction (AMI)

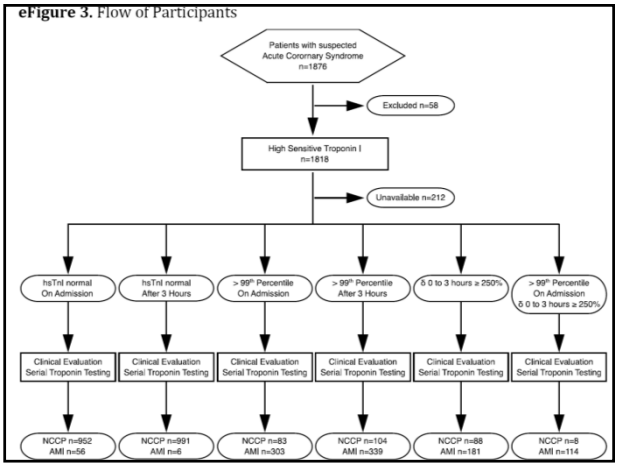
Design, Setting, and Patients

- A total of 1818 patients with suspected acute coronary syndrome
- Chest pain units of the University Heart Center Hamburg, the University Medical Center Mainz, and the Federal Armed Forces Hospital Koblenz, all in Germany
- From January 2007 and December 2008
- Between 18 and 85 years old
- All patients enrolled were Caucasian

Exclusion criteria

- Major surgery or trauma within the previous four weeks
- Pregnancy
- Obvious intravenous drug abuse
- Anemia with Hb level <10 g/dl

eFigure 3. Flow of Participants



Design, Setting, and Patients

- Twelve biomarkers including hsTnI (level of detection, 3.4 pg/mL) and cTnI (level of detection, 10 pg/mL) were measured on admission and after 3 and 6 hours
- Blood was drawn for routine blood work and sample storage on admission and after three and six hours.
- A 12-lead electrocardiogram was obtained on the same time points above
- Conventional troponin assays used for the adjudication of the final diagnosis:
  - cardiac troponin T in Mainz and Hamburg
  - cardiac troponin I in Koblenz

Table 2. Baseline Laboratory Parameters of 1818 Consecutive Patients Presenting With Chest Pain

	No.	Median (IQR)			
		Noncoronary Chest Pain (n = 1165)	Unstable Angina Pectoris (n = 240)	Acute MI (n = 413)	All (N = 1818)
cTnI, pg/mL	1786	5.0 (5.0-5.0)	5.0 (5.0-9.2)	281.0 (59.0-1918.0)	5.0 (5.0-27.0)
hsTnI, pg/mL	1606	4.8 (1.7-9.0)	9.0 (4.5-26.0)	271.5 (60.1-1864.5)	7.4 (3.5-37.8)
Creatine kinase, U/L	1721	74 (51-114)	74 (53-108)	121 (79-224)	82 (56-131)
Creatine kinase MB, ng/mL	1709	1.0 (0.6-1.5)	1.1 (0.7-1.7)	3.3 (1.5-10.5)	1.2 (0.7-2.0)
Myoglobin, µg/L	1705	46.9 (32.4-69.6)	52.4 (35.2-75.7)	130.2 (69.6-283.3)	55.0 (35.5-92.1)
C-reactive protein, mg/L	1778	2.3 (1.1-5.4)	2.3 (1.3-4.5)	3.4 (1.7-8.8)	2.5 (1.3-5.8)
Creatinine, mg/dL	1809	0.94 (0.82-1.08)	0.93 (0.82-1.06)	0.99 (0.88-1.16)	0.95 (0.83-1.09)
eGFR, mL/min/1.73 m^2, mean (SD)	1809	80.1 (21.0)	79.8 (21.1)	75.5 (22.3)	79.0 (21.4)
sVEGFR-1/sFLT-1, pg/mL	1778	302.40 (228.5-7851.6)	294.3 (227.5-8286.6)	5710.7 (301.5-10 649.5)	362.4 (237.0-9055.2)
GDF15, pg/mL	1703	692.2 (495.8-1068.6)	803.7 (606.6-1182.1)	967.1 (662.3-1340.5)	772.9 (534.8-1164.2)
PlGF, pg/mL	1786	16.6 (13.5-20.2)	17.7 (14.6-21.5)	18.1 (14.99-23.0)	17.2 (13.9-20.9)
H-FABP, ng/mL	1696	2.1 (1.5-3.0)	2.2 (1.7-3.1)	8.3 (4.1-21.0)	2.4 (1.6-4.3)
Myeloperoxidase, pmol/L	1782	561.7 (386.5-1231.7)	564.4 (373.4-1114.5)	1070.7 (498.7-1521.3)	645.5 (400.4-1279.8)
GPBB, ng/mL	1679	4.7 (3.7-6.2)	4.9 (3.8-6.5)	5.7 (4.2-8.5)	4.8 (3.8-6.8)
Copeptin, pmol/L	1382	5.4 (2.9-11.9)	5.1 (3.0-11.9)	18.5 (7.0-50.1)	6.7 (3.3-16.5)

Abbreviations: cTnI, contemporary sensitive troponin I; eGFR, estimated glomerular filtration rate; GDF15, growth differentiation factor 15; GPBB, glycogen phosphorylase BB; H-FABP, heart-type fatty acid binding protein; hsTnI, highly sensitive troponin I; IQR, interquartile range; MI, myocardial infarction; PlGF, placental growth factor; sVEGFR-1/sFLT-1, soluble vascular endothelial growth factor receptor 1.

Design, Setting, and Patients

- All patients were followed up for 30 days after initial hospitalization
- Outcomes included death, MI.
- Final diagnosis was based on all available clinical, laboratory, and imaging findings and was adjudicated by **2 independent cardiologists**
- All patients in whom ACS was excluded were categorized as having **noncoronary chest pain**

Troponin assays

- The diagnostic threshold for MI according to the World Health Organization definition is given as 300 pg/mL by the manufacturer
- cTnI
  - the Architect STAT troponin I assay ,Abbott Diagnostics
  - the level of detection is 10 pg/mL
  - range, 0-50000 pg/mL
  - the 99th percentile and the concentration with coefficient of variation of 10% is 32 pg/mL
- hsTnI
  - the Architect STAT High Sensitive Troponin, Abbott Diagnostics
  - the level of detection is 3.4 pg/mL
  - range, 0-50000 pg/mL
  - the 99th percentile is 30 pg/mL
  - the concentration with coefficient of variation of 10% is 5.2 pg/mL

Results

Patient Characteristics

Table 1. Baseline Demographic and Electrocardiographic Characteristics of 1818 Consecutive Patients Presenting With Chest Pain

	No.	No. (%)			
		Noncoronary Chest Pain (n = 1165)	Unstable Angina Pectoris (n = 240)	Acute MI (n = 413)	All (N = 1818)
Age, mean (SD), y	1818	59.7 (14.3)	65.2 (10.5)	64.0 (11.8)	61.4 (13.5)
Male sex	1818	729 (62.6)	165 (68.8)	314 (76.0)	1208 (66.4)
Risk factors					
Body mass index, mean (SD)[a]	1694	27.7 (4.9)	27.9 (4.4)	27.9 (4.6)	27.8 (4.8)
Hypertension	1818	822 (70.6)	204 (85.0)	313 (75.8)	1339 (73.7)
Diabetes mellitus	1746	140 (12.5)	53 (23.0)	80 (20.0)	273 (15.6)
Smoking status					
Current	1802	254 (21.9)	40 (17.1)	143 (35.1)	437 (24.3)
Former	1774	326 (28.5)	76 (33.2)	124 (31.0)	526 (29.7)
Never	1771	564 (49.3)	111 (48.9)	133 (33.2)	808 (45.6)
Hyperlipidemia	1818	824 (70.7)	193 (80.4)	311 (75.3)	1328 (73.0)
Lipids, mean (SD), mg/dL					
Total cholesterol	1605	197.7 (49.0)	196.7 (47.5)	205.0 (50.1)	199.2 (49.1)
HDL cholesterol	1601	51.8 (15.9)	49.3 (14.0)	47.6 (13.8)	50.5 (15.3)
LDL cholesterol	1600	117.2 (40.8)	116.9 (41.9)	129.6 (43.8)	119.9 (41.9)
Parental CAD	1750	379 (33.4)	71 (32.3)	118 (29.9)	568 (32.5)
Known CAD	1771	361 (31.8)	137 (58.5)	136 (33.7)	634 (35.8)

Table 1. Baseline Demographic and Electrocardiographic Characteristics of 1818 Consecutive Patients Presenting With Chest Pain

	No.	No. (%)			
		Noncoronary Chest Pain (n = 1165)	Unstable Angina Pectoris (n = 240)	Acute MI (n = 413)	All (N = 1818)
Electrocardiographic results on admission	1789				
ST-segment elevation		27 (2.3)	6 (2.5)	56 (14.1)	89 (5.0)
ST-segment depression		69 (6.0)	27 (11.3)	109 (27.5)	205 (11.5)
T-wave inversion		295 (25.6)	77 (32.2)	174 (43.8)	546 (30.5)
Left or right bundle-branch block		149 (12.9)	35 (14.6)	61 (15.4)	245 (13.7)
Time between chest pain onset and admission, median (IQR), h	1818	4.2 (2.0-11.7)	4.6 (2.1-15.0)	4.3 (1.9-15.4)	4.3 (2.0-13.0)
<3		446 (38.28)	84 (35.00)	166 (40.19)	696 (38.28)
<6		693 (59.48)	139 (57.92)	237 (57.38)	1069 (58.80)
<12		877 (75.28)	171 (71.25)	289 (69.98)	1337 (73.54)
≥12		288 (24.72)	69 (28.75)	124 (30.02)	481 (26.46)

Abbreviations: CAD, coronary artery disease; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction.
SI conversion factors: To convert cholesterol to mmol/L, multiply values by 0.0258.
[a]Body mass index is calculated as weight in kilograms divided by height in meters squared.

The time between chest pain onset and hospital admission was similar in all diagnosis groups.

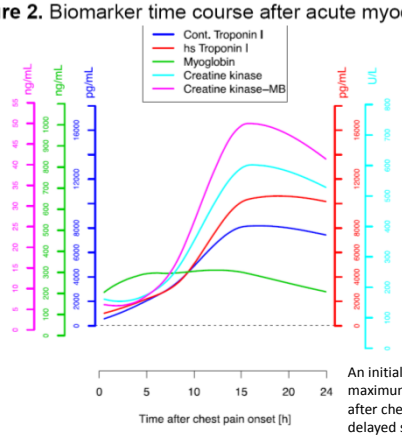
eTable 1. Characteristics of the reference cohorts used for determination of the biomarkers diagnostic cut-off values

Supplementary Table 1	Reference Cohort 1 n=5,000	Reference Cohort 2 n=520
Age [years]	55.5 ± 10.9	51.9 ± 12.1
Gender [% males]	2540 (50.8)	261 (50.2)
Body-mass-index [kg/m²]	27.2 ± 4.8	26.4 ± 4.82
Diabetes mellitus [%]	374 (7.5)	19 (3.7)
Hypertension [%]	2564 (51.3)	249 (48.7)
Dyslipidemia [%]	1462 (29.3)	109 (21.0)
Smoking Status, current [%]	959 (19.2)	100 (19.5)
Family history of AMI [%]	886 (17.7)	135 (26.4)
Prevalent CAD [%]	226 (4.6)	27 (5.3)
Atrial Fibrillation [%]	136 (2.7)	13 (2.6)

eTable 5. 30-day outcome according to diagnosis and high sensitive troponin I level on admission

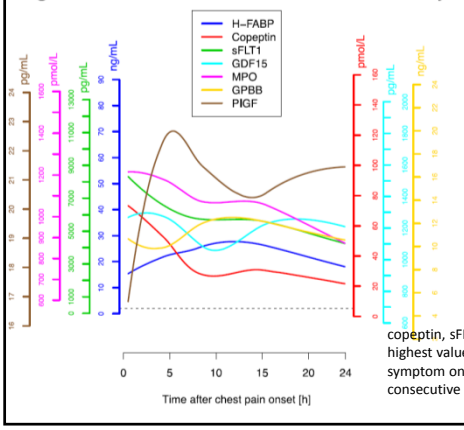
Suppl. Table 5	30-day follow-up		
	Myocardial Infarction n=10	Death n=20	Myocardial Infarction and/or Death n=26
According to gold standard diagnosis			
Non-coronary chest pain	3 (0.2%)	4 (0.2%)	5 (0.3%)
Unstable angina pectoris	1 (0.1%)	0 (0%)	1 (0.1%)
Acute Myocardial Infarction	6 (0.3%)	16 (0.9%)	20 (1.1%)
According to high sensitive troponin I on admission			
hsTnI > LoD	10 (0.6%)	16 (1.0%)	22 (1.4%)
hsTnI > 99th percentile	8 (0.5%)	14 (0.9%)	18 (1.1%)

eFigure 2. Biomarker time course after acute myocardial infarction



An initial rise reaching maximum values 10 to 20 hours after chest pain onset and a delayed subsequent decrease

eFigure 2. Biomarker time course after acute myocardial infarction

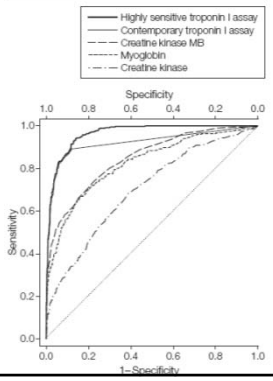


copeptin, sFLT-1 and MPO had highest values directly after symptom onset with a rapid consecutive decline.

Results

Diagnostic Accuracy of Troponin and Other Biomarkers

Figure 1. Receiver Operating Characteristic Curves for Identification of Acute MI by Troponin Assays and Necrosis Markers in the Overall Cohort



eFigure 4. Receiver Operating Characteristic Curves for Identification of Acute MI in the Overall Cohort and Area Under the Receiver Operating Characteristic (AUROC) Curve on Admission According to Chest Pain Onset Time

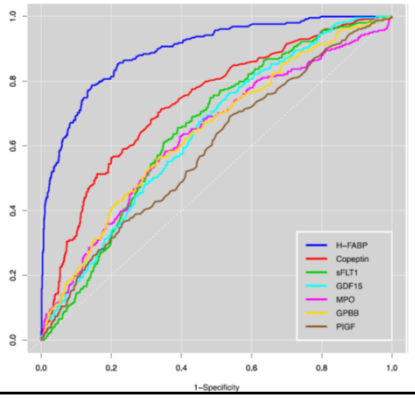
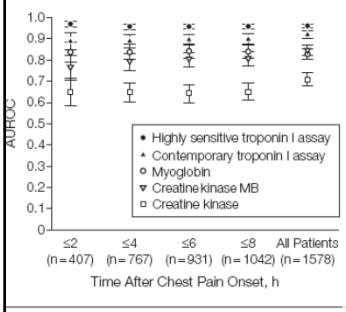


Figure 2. Area Under the Receiver Operating Characteristic (AUROC) Curve on Admission According to Chest Pain Onset Time for Both Troponin I Assays and Necrosis Markers



Error bars indicate 95% CIs

The difference in the diagnostic performance between hsTnI and cTnI was apparent in the first hours after chest pain onset.

Table 3. Diagnostic Performance of Individual Biomarkers and in Combination With hsTnI Assay for Identification of Acute Myocardial Infarction[a]

	AUROC (95% CI)			Relative IDI Addition to Model With hsTnI, % (95% CI)	
	Individual Biomarker	Combined With hsTnI	*P* Value		*P* Value
cTnI					
On admission	0.92 (0.90 to 0.94)				
Change at 3 h[b]	0.89 (0.88 to 0.91)	0.98 (0.98 to 0.99)	<.001	33.4 (24.4 to 44.5)	<.001
hsTnI					
On admission	0.96 (0.95 to 0.97)				
Change at 3 h	0.66 (0.62 to 0.70)	0.99 (0.98 to 0.99)	<.001	31.3 (20.8 to 41.2)	<.001
Creatine kinase	0.71 (0.68 to 0.74)	0.96 (0.95 to 0.97)	.90	0.1 (–0.1 to 1.0)	.07
Creatine kinase MB	0.85 (0.82 to 0.87)	0.96 (0.95 to 0.97)	.90	0.4 (0.0 to 1.5)	.04
Myoglobin	0.83 (0.80 to 0.85)	0.96 (0.95 to 0.97)	.82	2.4 (0.9 to 5.1)	.002
sVEGFR-1/sFLT-1	0.65 (0.62 to 0.68)	0.97 (0.96 to 0.97)	.03	4.0 (2.0 to 7.0)	<.001
GDF15	0.64 (0.61 to 0.68)	0.96 (0.95 to 0.97)	.12	0.2 (–0.2 to 1.3)	.03
PlGF	0.59 (0.56 to 0.63)	0.96 (0.95 to 0.97)	.11	0.1 (0.0 to 1.1)	.39
H-FABP	0.89 (0.87 to 0.91)	0.97 (0.96 to 0.98)	.02	7.4 (4.2 to 13.2)	<.001
Myeloperoxidase	0.63 (0.60 to 0.66)	0.96 (0.95 to 0.97)	.39	1.5 (0.2 to 3.4)	.004
GPBB	0.63 (0.59 to 0.66)	0.96 (0.95 to 0.97)	.99	0.5 (0.0 to 1.6)	.10
Copeptin	0.74 (0.70 to 0.77)	0.97 (0.96 to 0.98)	.01	5.6 (2.5 to 10.6)	<.001

Suppl. Table 3B

	Females n=610			Males n=1208		
	AUC (CI) Individual Marker	AUC (CI) Combination with hs Troponin I	p_{AUC}-Value Combination vs. hs Troponin I	AUC (CI) Individual Marker	AUC (CI) Combination with hs Troponin I	p_{AUC}-Value Combination vs. hs Troponin I
cont. Troponin I	0.97 (0.95,0.98)	-	-	0.96 (0.95,0.97)	-	-
hs Troponin I						
On admission	0.97 (0.95,0.98)	-	-	0.96 (0.95,0.97)	-	-
Δ change 0 to 3 h	0.59 (0.50,0.68)	0.99 (0.98,0.99)	0.001	0.69 (0.64,0.74)	0.98 (0.98,0.99)	< 0.001
Creatine kinase	0.73 (0.67,0.79)	0.97 (0.96,0.98)	0.75	0.68 (0.64,0.72)	0.96 (0.95,0.97)	0.72
Creatine kinase-MB	0.87 (0.82,0.92)	0.97 (0.95,0.98)	0.47	0.83 (0.80,0.86)	0.96 (0.95,0.97)	0.86
Myoglobin	0.85 (0.80,0.89)	0.97 (0.95,0.98)	0.77	0.81 (0.78,0.84)	0.96 (0.95,0.97)	0.69
sFLT1	0.61 (0.55,0.67)	0.97 (0.96,0.99)	0.17	0.66 (0.63,0.70)	0.96 (0.95,0.97)	0.08
GDF15	0.66 (0.60,0.73)	0.97 (0.95,0.98)	0.50	0.64 (0.60,0.68)	0.96 (0.95,0.97)	0.11
PlGF	0.63 (0.57,0.69)	0.97 (0.95,0.98)	0.51	0.57 (0.53,0.61)	0.96 (0.95,0.97)	0.22
H-FABP	0.90 (0.86,0.93)	0.97 (0.96,0.99)	0.06	0.89 (0.87,0.92)	0.97 (0.95,0.98)	0.08
MPO	0.61 (0.54,0.67)	0.97 (0.95,0.98)	0.41	0.64 (0.60,0.68)	0.96 (0.95,0.97)	0.55
GPBB	0.60 (0.54,0.67)	0.97 (0.95,0.98)	0.43	0.63 (0.59,0.66)	0.96 (0.95,0.97)	0.57
Copeptin	0.73 (0.67,0.80)	0.98 (0.97,0.99)	0.07	0.72 (0.69,0.76)	0.96 (0.95,0.97)	0.13

Suppl. Table 3C

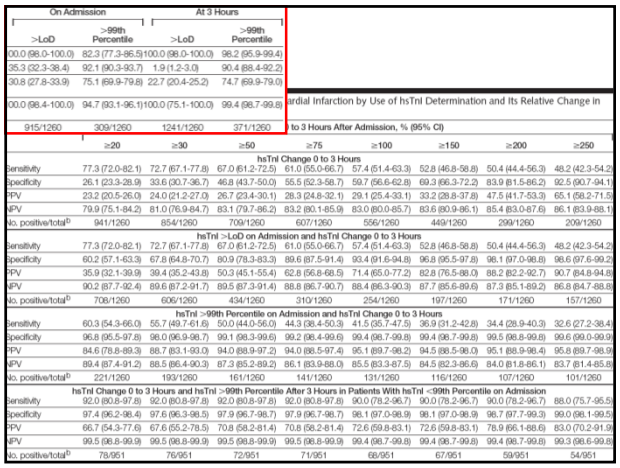
	Patients > 70 years n=524			Patients ≤ 70 years n=1294		
	AUC (CI) Individual Marker	AUC (CI) Combination with hs Troponin I	p_{AUC}-Value Combination vs. hs Troponin I	AUC (CI) Individual Marker	AUC (CI) Combination with hs Troponin I	p_{AUC}-Value Combination vs. hs Troponin I
cont. Troponin I	0.96 (0.94,0.97)	-	-	0.97 (0.96,0.98)	-	-
hs Troponin I						
On admission	0.96 (0.94,0.97)	-	-	0.97 (0.96,0.98)	-	-
Δ change 0 to 3 h	0.69 (0.62,0.76)	0.99 (0.98,1.00)	< 0.001	0.66 (0.61,0.71)	0.98 (0.97,0.99)	< 0.001
Creatine kinase	0.79 (0.75,0.84)	0.96 (0.94,0.98)	0.53	0.68 (0.64,0.72)	0.97 (0.96,0.98)	0.55
Creatine kinase-MB	0.86 (0.82,0.90)	0.96 (0.94,0.98)	0.62	0.84 (0.81,0.87)	0.97 (0.96,0.98)	0.72
Myoglobin	0.86 (0.81,0.90)	0.96 (0.93,0.98)	0.95	0.82 (0.79,0.85)	0.97 (0.96,0.98)	0.74
sFLT1	0.59 (0.53,0.64)	0.96 (0.94,0.98)	0.27	0.67 (0.63,0.70)	0.97 (0.96,0.98)	0.11
GDF15	0.63 (0.57,0.68)	0.96 (0.94,0.97)	0.60	0.65 (0.61,0.68)	0.97 (0.96,0.98)	0.98
PlGF	0.57 (0.51,0.63)	0.96 (0.94,0.97)	0.86	0.59 (0.55,0.63)	0.97 (0.96,0.98)	0.72
H-FABP	0.89 (0.85,0.92)	0.97 (0.95,0.98)	0.01	0.90 (0.87,0.92)	0.97 (0.96,0.98)	0.13
MPO	0.57 (0.51,0.63)	0.96 (0.94,0.98)	0.41	0.65 (0.61,0.69)	0.97 (0.95,0.98)	0.85
GPBB	0.63 (0.57,0.69)	0.96 (0.94,0.98)	0.40	0.62 (0.58,0.66)	0.96 (0.95,0.97)	0.69
Copeptin	0.67 (0.61,0.74)	0.95 (0.93,0.97)	0.09	0.75 (0.71,0.79)	0.97 (0.96,0.98)	0.05

Results

Different Relative Changes in Troponin Concentration in Diagnosis of MI

Table 4. Diagnostic Performance for Identification of Acute Myocardial Infarction by Use of Serial cTnI and hsTnI Determination

	cTnI, % (95% CI)			
	On Admission		At 3 Hours	
	>LoD	>99th Percentile	>LoD	>99th Percentile
Sensitivity	87.4 (83.3-90.8)	79.4 (74.6-83.7)	98.8 (96.9-99.7)	98.2 (96.0-99.3)[1]
Specificity	88.6 (86.6-90.4)	94.5 (93.0-95.7)	78.9 (76.4-81.3)	89.8 (87.8-91.5)
Positive predictive value	69.3 (64.6-73.8)	80.9 (76.2-85.1)	58.0 (53.8-62.2)	73.9 (69.5-78.0)
Negative predictive value	96.0 (94.6-97.1)	94.0 (92.4-95.3)	99.5 (98.8-99.9)	99.4 (98.7-99.8)[1]
No. positive/total[a]	411/1430	320/1430	555/1430	433/1430
	hsTnI, % (95% CI)			
	On Admission		At 3 Hours	
	>LoD	>99th Percentile	>LoD	>99th Percentile
	100.0 (98.0-100.0)	82.3 (77.3-86.5)	100.0 (98.0-100.0)	98.2 (95.9-99.4)
	35.3 (32.3-38.4)	92.1 (90.3-93.7)	1.9 (1.2-3.0)	90.4 (88.4-92.2)
	30.8 (27.8-33.9)	75.1 (69.9-79.8)	22.7 (20.4-25.2)	74.7 (69.9-79.0)
	100.0 (98.4-100.0)	94.7 (93.1-96.1)	100.0 (75.1-100.0)	99.4 (98.7-99.8)[1]
	915/1260	309/1260	1241/1260	371/1260



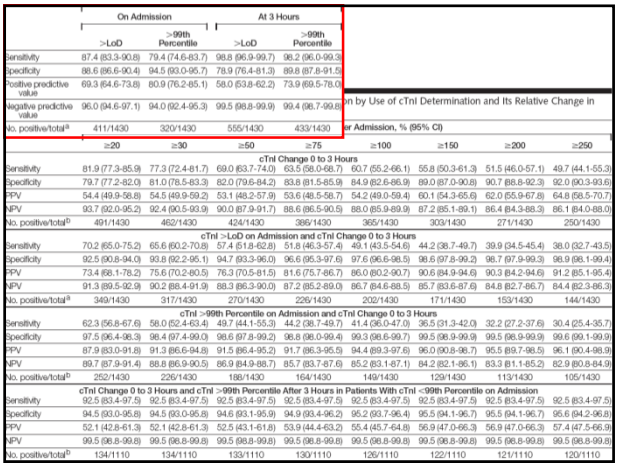
On Admission / At 3 Hours

>LoD	>99th Percentile	>LoD	>99th Percentile
100.0 (98.0-100.0)	82.3 (77.3-86.5)	100.0 (98.0-100.0)	98.2 (95.9-99.4)
35.3 (32.3-38.4)	92.1 (90.3-93.7)	1.9 (1.2-3.0)	90.4 (88.4-92.2)
30.8 (27.8-33.9)	75.1 (69.9-79.8)	22.7 (20.4-25.2)	74.7 (69.9-79.0)
100.0 (98.4-100.0)	94.7 (93.1-96.1)	100.0 (75.1-100.0)	99.4 (98.7-99.8)
915/1260	309/1260	1241/1260	371/1260

ardial Infarction by Use of hsTnI Determination and Its Relative Change in

to 3 Hours After Admission, % (95% CI)

	≥20	≥30	≥50	≥75	≥100	≥150	≥200	≥250
hsTnI Change 0 to 3 Hours								
Sensitivity	77.3 (72.0-82.1)	72.7 (67.1-77.8)	67.0 (61.2-72.5)	61.0 (55.0-66.7)	57.4 (51.4-63.3)	52.8 (46.8-58.8)	50.4 (44.4-56.3)	48.2 (42.3-54.2)
Specificity	26.1 (23.3-28.9)	33.6 (30.7-36.7)	46.8 (43.7-50.0)	55.5 (52.3-58.7)	59.7 (56.6-62.8)	69.3 (66.3-72.2)	83.9 (81.5-86.2)	92.5 (90.7-94.1)
PPV	23.2 (20.5-26.0)	24.0 (21.2-27.0)	26.7 (23.4-30.1)	28.3 (24.8-32.1)	29.1 (25.4-33.1)	33.2 (28.8-37.8)	47.5 (41.7-53.3)	65.1 (58.2-71.5)
NPV	79.9 (75.1-84.2)	81.0 (76.9-84.7)	83.1 (79.7-86.2)	83.2 (80.1-85.9)	83.0 (80.0-85.7)	83.6 (80.9-86.1)	85.4 (83.0-87.6)	86.1 (83.9-88.1)
No. positive/total[b]	941/1260	854/1260	709/1260	607/1260	556/1260	449/1260	299/1260	209/1260
hsTnI >LoD on Admission and hsTnI Change 0 to 3 Hours								
Sensitivity	77.3 (72.0-82.1)	72.7 (67.1-77.8)	67.0 (61.2-72.5)	61.0 (55.0-66.7)	57.4 (51.4-63.3)	52.8 (46.8-58.8)	50.4 (44.4-56.3)	48.2 (42.3-54.2)
Specificity	60.2 (57.1-63.3)	67.8 (64.8-70.7)	80.9 (78.3-83.3)	89.6 (87.5-91.4)	93.4 (91.6-94.8)	96.8 (95.5-97.8)	98.1 (97.0-98.8)	98.6 (97.6-99.2)
PPV	35.9 (32.1-39.9)	39.4 (35.2-43.8)	50.3 (45.1-55.4)	62.8 (56.8-68.5)	71.4 (65.0-77.2)	82.8 (76.5-88.0)	88.2 (82.2-92.7)	90.7 (84.8-94.8)
NPV	90.2 (87.7-92.4)	89.6 (87.2-91.7)	89.5 (87.3-91.4)	88.8 (86.7-90.7)	88.4 (86.3-90.3)	87.7 (85.6-89.6)	87.3 (85.1-89.2)	86.8 (84.7-88.8)
No. positive/total[b]	708/1260	606/1260	434/1260	310/1260	254/1260	197/1260	171/1260	157/1260
hsTnI >99th Percentile on Admission and hsTnI Change 0 to 3 Hours								
Sensitivity	60.3 (54.3-66.0)	55.7 (49.7-61.6)	50.0 (44.0-56.0)	44.3 (38.4-50.3)	41.5 (35.7-47.5)	36.9 (31.2-42.8)	34.4 (28.9-40.3)	32.6 (27.2-38.4)
Specificity	96.8 (95.5-97.8)	98.0 (96.9-98.7)	99.1 (98.3-99.6)	99.2 (98.4-99.6)	99.4 (98.7-99.8)	99.4 (98.7-99.8)	99.5 (98.8-99.8)	99.6 (99.0-99.9)
PPV	84.6 (78.8-89.3)	88.7 (83.1-93.0)	94.0 (88.9-97.2)	94.0 (88.5-97.4)	95.1 (89.7-98.2)	94.5 (88.5-98.0)	95.1 (88.9-98.4)	95.8 (89.7-98.9)
NPV	89.4 (87.4-91.2)	88.5 (86.4-90.3)	87.3 (85.2-89.2)	86.1 (83.9-88.0)	85.5 (83.3-87.5)	84.5 (82.3-86.6)	84.0 (81.8-86.1)	83.7 (81.4-85.8)
No. positive/total[b]	221/1260	193/1260	161/1260	141/1260	131/1260	116/1260	107/1260	101/1260
hsTnI Change 0 to 3 Hours and hsTnI >99th Percentile After 3 Hours in Patients With hsTnI <99th Percentile on Admission								
Sensitivity	92.0 (80.8-97.8)	92.0 (80.8-97.8)	92.0 (80.8-97.8)	92.0 (80.8-97.8)	90.0 (78.2-96.7)	90.0 (78.2-96.7)	90.0 (78.2-96.7)	88.0 (75.7-95.5)
Specificity	97.4 (96.2-98.4)	97.6 (96.3-98.5)	97.9 (96.7-98.7)	97.9 (96.7-98.7)	98.1 (97.0-98.9)	98.1 (97.0-98.9)	98.7 (97.7-99.3)	99.0 (98.1-99.5)
PPV	66.7 (54.3-77.6)	67.6 (55.2-78.5)	70.8 (58.2-81.4)	70.8 (58.2-81.4)	72.6 (59.8-83.1)	72.6 (59.8-83.1)	78.9 (66.1-88.6)	83.0 (70.2-91.9)
NPV	99.5 (98.8-99.9)	99.5 (98.8-99.9)	99.5 (98.8-99.9)	99.5 (98.8-99.9)	99.4 (98.7-99.8)	99.4 (98.7-99.8)	99.4 (98.7-99.8)	99.3 (98.6-99.8)
No. positive/total[b]	78/951	76/951	72/951	71/951	68/951	67/951	59/951	54/951



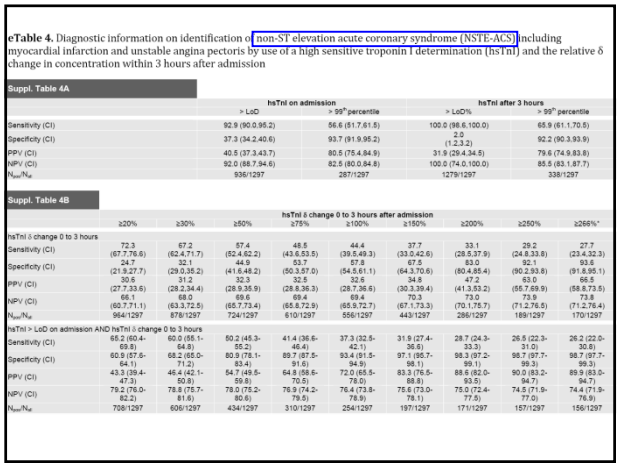
On Admission / At 3 Hours

	>LoD	>99th Percentile	>LoD	>99th Percentile
Sensitivity	87.4 (83.3-90.8)	79.4 (74.6-83.7)	98.8 (96.9-99.7)	98.2 (96.0-99.3)
Specificity	88.6 (86.6-90.4)	94.5 (93.0-95.7)	78.9 (76.4-81.3)	89.8 (87.8-91.5)
Positive predictive value	69.3 (64.6-73.8)	80.9 (76.2-85.1)	58.0 (53.8-62.2)	73.9 (69.5-78.0)
Negative predictive value	96.0 (94.6-97.1)	94.0 (92.4-95.3)	99.5 (98.8-99.9)	99.4 (98.7-99.8)
No. positive/total[a]	411/1430	320/1430	555/1430	433/1430

by Use of cTnI Determination and Its Relative Change in

er Admission, % (95% CI)

	≥20	≥30	≥50	≥75	≥100	≥150	≥200	≥250
cTnI Change 0 to 3 Hours								
Sensitivity	81.9 (77.3-85.9)	77.3 (72.4-81.7)	69.0 (63.7-74.0)	63.5 (58.0-68.7)	60.7 (55.2-66.1)	55.8 (50.3-61.3)	51.5 (46.0-57.1)	49.7 (44.1-55.3)
Specificity	79.7 (77.2-82.0)	81.0 (78.5-83.3)	82.0 (79.6-84.2)	83.8 (81.5-85.9)	84.9 (82.6-86.9)	89.0 (87.0-90.8)	90.7 (88.8-92.3)	92.0 (90.3-93.6)
PPV	54.4 (49.9-58.8)	54.5 (49.9-59.2)	53.1 (48.2-57.9)	53.6 (48.5-58.7)	54.2 (49.0-59.4)	60.1 (54.3-65.6)	62.0 (55.9-67.8)	64.8 (58.5-70.7)
NPV	93.7 (92.0-95.2)	92.4 (90.5-93.9)	90.0 (87.9-91.7)	88.6 (86.5-90.5)	88.0 (85.9-89.9)	87.2 (85.1-89.1)	86.4 (84.3-88.3)	86.1 (84.0-88.0)
No. positive/total[b]	491/1430	462/1430	424/1430	386/1430	365/1430	303/1430	271/1430	250/1430
cTnI >LoD on Admission and cTnI Change 0 to 3 Hours								
Sensitivity	70.2 (65.0-75.2)	65.6 (60.2-70.8)	57.4 (51.8-62.8)	51.8 (46.3-57.4)	49.1 (43.5-54.6)	44.2 (38.7-49.7)	39.9 (34.5-45.4)	38.0 (32.7-43.5)
Specificity	92.5 (90.8-94.0)	93.8 (92.2-95.1)	94.7 (93.3-96.0)	96.6 (95.3-97.6)	97.6 (96.6-98.5)	98.6 (97.8-99.2)	98.7 (97.9-99.3)	98.9 (98.1-99.4)
PPV	73.4 (68.1-78.2)	75.6 (70.2-80.5)	76.3 (70.5-81.5)	81.6 (75.7-86.7)	86.0 (80.2-90.7)	90.6 (84.9-94.6)	90.3 (84.2-94.6)	91.2 (85.1-95.4)
NPV	91.3 (89.5-92.9)	90.2 (88.4-91.9)	88.3 (86.3-90.0)	87.2 (85.2-89.0)	86.7 (84.6-88.5)	85.7 (83.6-87.6)	84.8 (82.7-86.7)	84.4 (82.3-86.3)
No. positive/total[a]	349/1430	317/1430	270/1430	229/1430	202/1430	171/1430	153/1430	144/1430
cTnI >99th Percentile on Admission and cTnI Change 0 to 3 Hours								
Sensitivity	62.3 (56.8-67.6)	58.0 (52.4-63.4)	49.7 (44.1-55.3)	44.2 (38.7-49.7)	41.4 (36.0-47.0)	36.5 (31.3-42.0)	32.2 (27.2-37.6)	30.4 (25.4-35.7)
Specificity	97.5 (96.4-98.3)	98.4 (97.4-99.0)	98.6 (97.8-99.2)	98.8 (98.0-99.4)	99.3 (98.6-99.7)	99.5 (98.9-99.9)	99.5 (98.9-99.9)	99.6 (99.1-99.9)
PPV	87.9 (83.0-91.8)	91.3 (86.6-94.8)	91.5 (86.4-95.2)	91.7 (86.3-95.5)	94.4 (89.3-97.6)	96.0 (90.8-98.7)	95.5 (89.7-98.5)	96.1 (90.4-98.9)
NPV	89.7 (87.9-91.4)	88.8 (86.9-90.5)	86.9 (84.9-88.7)	85.7 (83.7-87.6)	85.2 (83.1-87.1)	84.2 (82.1-86.1)	83.3 (81.1-85.2)	82.9 (80.8-84.9)
No. positive/total[b]	252/1430	226/1430	188/1430	164/1430	149/1430	129/1430	113/1430	105/1430
cTnI Change 0 to 3 Hours and cTnI >99th Percentile After 3 Hours in Patients With cTnI <99th Percentile on Admission								
Sensitivity	92.5 (83.4-97.5)	92.5 (83.4-97.5)	92.5 (83.4-97.5)	92.5 (83.4-97.5)	92.5 (83.4-97.5)	92.5 (83.4-97.5)	92.5 (83.4-97.5)	92.5 (83.4-97.5)
Specificity	94.5 (93.0-95.8)	94.5 (93.0-95.8)	94.6 (93.1-95.9)	94.9 (93.4-96.2)	95.2 (93.7-96.4)	95.5 (94.1-96.7)	95.5 (94.1-96.7)	95.6 (94.2-96.8)
PPV	52.1 (42.8-61.3)	52.1 (42.8-61.3)	52.5 (43.1-61.8)	53.9 (44.4-63.2)	55.4 (45.7-64.8)	56.9 (47.0-66.3)	56.9 (47.0-66.3)	57.4 (47.5-66.9)
NPV	99.5 (98.8-99.8)	99.5 (98.8-99.8)	99.5 (98.8-99.8)	99.5 (98.8-99.8)	99.5 (98.8-99.8)	99.5 (98.8-99.8)	99.5 (98.8-99.8)	99.5 (98.8-99.8)
No. positive/total[b]	134/1110	134/1110	133/1110	130/1110	126/1110	122/1110	121/1110	120/1110



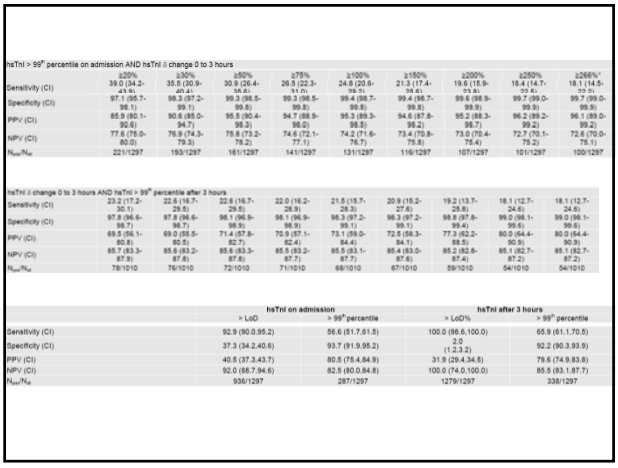
eTable 4. Diagnostic information on identification of non-ST elevation acute coronary syndrome (NSTE-ACS) including myocardial infarction and unstable angina pectoris by use of a high sensitive troponin I determination (hsTnI) and the relative δ change in concentration within 3 hours after admission

Suppl. Table 4A

	hsTnI on admission		hsTnI after 3 hours	
	> LoD	> 99th percentile	> LoD%	> 99th percentile
Sensitivity (CI)	92.9 (90.0-95.2)	56.6 (51.7-61.5)	100.0 (98.6-100.0)	65.9 (61.1-70.5)
Specificity (CI)	37.3 (34.2-40.6)	93.7 (91.9-95.2)	2.0 (1.2-3.2)	92.2 (90.3-93.9)
PPV (CI)	40.5 (37.3-43.7)	80.5 (75.4-84.9)	31.9 (29.4-34.5)	79.6 (74.9-83.8)
NPV (CI)	92.0 (88.7-94.6)	82.5 (80.0-84.8)	100.0 (74.0-100.0)	85.5 (83.1-87.7)
N_{test}/N_{all}	936/1297	287/1297	1279/1297	338/1297

Suppl. Table 4B

	hsTnI δ change 0 to 3 hours after admission								
	≥20%	≥30%	≥50%	≥75%	≥100%	≥150%	≥200%	≥250%	≥266%*
hsTnI δ change 0 to 3 hours									
Sensitivity (CI)	72.3 (67.7-76.6)	67.2 (62.4-71.7)	57.4 (52.4-62.2)	48.5 (43.6-53.5)	44.4 (39.5-49.3)	37.7 (33.0-42.6)	33.1 (28.5-37.9)	29.2 (24.8-33.8)	27.7 (23.4-32.3)
Specificity (CI)	24.7 (21.9-27.7)	32.1 (29.0-35.2)	44.9 (41.6-48.2)	53.7 (50.3-57.0)	57.8 (54.5-61.1)	67.5 (64.3-70.6)	83.0 (80.4-85.4)	92.1 (90.2-93.8)	93.6 (91.8-95.1)
PPV (CI)	30.6 (27.7-33.6)	31.2 (28.2-34.4)	32.3 (28.9-35.9)	32.5 (28.8-36.3)	32.6 (28.7-36.6)	34.8 (30.3-39.4)	47.2 (41.3-53.2)	63.0 (55.7-69.9)	66.5 (58.8-73.5)
NPV (CI)	66.1 (60.7-71.1)	68.0 (63.3-72.5)	69.6 (65.7-73.4)	69.4 (65.8-72.9)	69.4 (65.9-72.7)	70.3 (67.1-73.3)	73.0 (70.1-75.7)	73.9 (71.2-76.5)	73.8 (71.2-76.4)
N_{test}/N_{all}	964/1297	878/1297	724/1297	610/1297	556/1297	443/1297	286/1297	189/1297	170/1297
hsTnI > LoD on admission AND hsTnI δ change 0 to 3 hours									
Sensitivity (CI)	65.2 (60.4-69.8)	60.0 (55.1-64.8)	50.2 (45.3-55.2)	41.4 (36.6-46.4)	37.3 (32.5-42.1)	31.9 (27.4-36.6)	28.7 (24.3-33.3)	26.5 (22.3-31.0)	26.2 (22.0-30.8)
Specificity (CI)	60.9 (57.8-64.1)	68.2 (65.0-71.2)	80.9 (78.1-83.4)	89.7 (87.5-91.6)	93.4 (91.5-94.9)	97.1 (95.7-98.1)	98.3 (97.2-99.1)	98.7 (97.7-99.3)	98.7 (97.7-99.3)
PPV (CI)	43.3 (39.4-47.3)	46.4 (42.1-50.8)	54.7 (49.5-59.8)	64.8 (58.6-70.5)	72.0 (65.5-78.0)	83.3 (76.5-88.8)	88.6 (82.0-93.5)	90.0 (83.2-94.7)	89.9 (83.0-94.7)
NPV (CI)	79.2 (76.0-82.2)	78.8 (75.7-81.6)	78.0 (75.2-80.6)	76.9 (74.2-79.5)	76.4 (73.8-78.9)	75.6 (73.0-78.1)	75.0 (72.4-77.5)	74.5 (71.9-77.0)	74.4 (71.9-76.9)
N_{test}/N_{all}	708/1297	606/1297	434/1297	310/1297	254/1297	197/1297	171/1297	157/1297	156/1297



hsTnI > 99th percentile on admission AND hsTnI δ change 0 to 3 hours

	≥20%	≥30%	≥50%	≥75%	≥100%	≥150%	≥200%	≥250%	≥266%*
Sensitivity (CI)	39.0 (34.2-43.9)	35.5 (30.9-40.4)	30.9 (26.4-35.8)	26.5 (22.3-31.1)	24.8 (20.6-29.5)	21.3 (17.4-25.8)	19.6 (15.9-23.8)	18.4 (14.7-22.5)	18.1 (14.5-22.1)
Specificity (CI)	97.1 (95.7-98.1)	98.3 (97.2-99.1)	99.3 (98.5-99.8)	99.3 (98.5-99.8)	99.4 (98.7-99.8)	99.4 (98.7-99.8)	99.6 (98.9-99.9)	99.7 (99.0-99.9)	99.7 (99.0-99.9)
PPV (CI)	85.9 (80.1-90.6)	90.6 (85.0-94.7)	95.5 (90.4-98.3)	94.7 (88.9-98.0)	95.3 (89.3-98.5)	94.6 (87.8-98.2)	95.2 (88.3-98.7)	96.2 (89.2-99.2)	96.1 (89.0-99.2)
NPV (CI)	77.6 (75.0-80.0)	76.9 (74.3-79.3)	75.8 (73.2-78.2)	74.6 (72.1-77.1)	74.2 (71.6-76.7)	73.4 (70.8-75.8)	73.0 (70.4-75.4)	72.7 (70.1-75.2)	72.6 (70.0-75.1)
N_{test}/N_{all}	221/1297	193/1297	161/1297	141/1297	131/1297	116/1297	107/1297	101/1297	100/1297

hsTnI δ change 0 to 3 hours AND hsTnI > 99th percentile after 3 hours

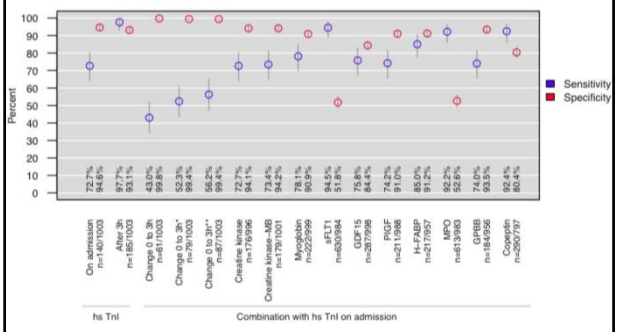
Sensitivity (CI)	23.2 (17.2-30.1)	22.6 (16.7-29.5)	22.6 (16.7-29.5)	22.0 (16.2-28.9)	21.5 (15.7-28.3)	20.9 (15.2-27.6)	19.2 (13.7-25.8)	18.1 (12.7-24.6)	18.1 (12.7-24.6)
Specificity (CI)	97.8 (96.6-98.7)	97.8 (96.6-98.7)	98.1 (96.9-98.9)	98.1 (96.9-98.9)	98.3 (97.2-99.1)	98.3 (97.2-99.1)	98.8 (97.8-99.4)	99.0 (98.1-99.6)	99.0 (98.1-99.6)
PPV (CI)	69.5 (56.1-80.8)	69.0 (55.5-80.5)	71.4 (57.8-82.7)	70.9 (57.1-82.4)	73.1 (59.0-84.4)	72.5 (58.3-84.1)	77.3 (62.2-88.5)	80.0 (64.4-90.9)	80.0 (64.4-90.9)
NPV (CI)	85.7 (83.3-87.9)	85.6 (83.2-87.8)	85.6 (83.3-87.8)	85.5 (83.2-87.7)	85.5 (83.1-87.7)	85.4 (83.0-87.6)	85.2 (82.8-87.4)	85.1 (82.7-87.2)	85.1 (82.7-87.2)
N_{test}/N_{all}	78/1010	76/1010	72/1010	71/1010	68/1010	67/1010	59/1010	54/1010	54/1010

	hsTnI on admission		hsTnI after 3 hours	
	> LoD	> 99th percentile	> LoD%	> 99th percentile
Sensitivity (CI)	92.9 (90.0-95.2)	56.6 (51.7-61.5)	100.0 (98.6-100.0)	65.9 (61.1-70.5)
Specificity (CI)	37.3 (34.2-40.6)	93.7 (91.9-95.2)	2.0 (1.2-3.2)	92.2 (90.3-93.9)
PPV (CI)	40.5 (37.3-43.7)	80.5 (75.4-84.9)	31.9 (29.4-34.5)	79.6 (74.9-83.8)
NPV (CI)	92.0 (88.7-94.6)	82.5 (80.0-84.8)	100.0 (74.0-100.0)	85.5 (83.1-87.7)
N_{test}/N_{all}	936/1297	287/1297	1279/1297	338/1297

Results

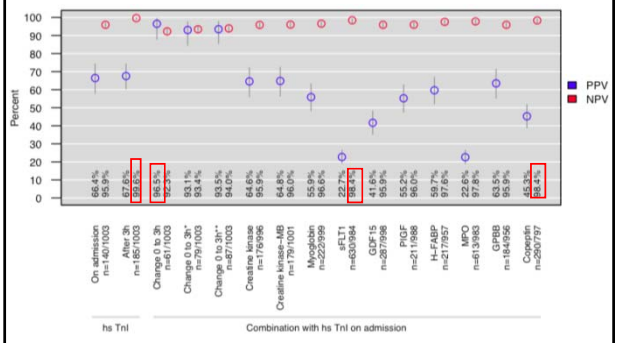
Validation and Clinical Application

eFigure 5. Clinical Application of Troponin, Troponin Change and Combination With an Early Biomarker



δ change cut-off 266%
(*) 82% as the reference change value cut-off
(**) 50% as the reference change value cut-off

eFigure 5. Clinical Application of Troponin, Troponin Change and Combination With an Early Biomarker



δ change cut-off 266%
(*) 82% as the reference change value cut-off
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Comment

Rule-in of MI

- Change in concentration of hsTnI within 3 hours after admission in addition to the 99th percentile diagnostic cutoff provides improved PPV
  - The cTnI assay provided comparable results
- The hsTnI assay provided higher PPV compared with cTnI among the subgroup of patients in this study (n=951) who presented **with initially very low troponin I values**
- Combining a single biomarker with hsTnI on admission **did not** achieve the high PPV

Rule-out of MI

- the 99th percentile cutoff to a second hsTnI or cTNI measurement after 3 hours, which yields an NPV of more than 99%
- If considering the baseline blood draw only, the combination of hsTnI with copeptin or sVEGFR-1/sFLT-1 assessed once on admission provided an NPV of 97% to 98%
- **None** of the individual early biomarkers representing different pathophysiological aspects of an evolving ACS **exceeded the diagnostic performance of hsTnI.**

Stepwise approach

- First, safe rule-out of MI
  - LoD as cutoff for hsTnI on admission
- Second, early and accurate rule-in of MI
  - The 99th percentile as cutoff for hsTnI determined 3 hours after admission

Limitations

- **The final diagnosis** of acute MI was based substantially on **in-house troponin** measurements, a change in troponin levels over time, there is the potential for a type of incorporation bias, which may overestimate the measure of diagnostic accuracy of serial hsTnI levels.
- Second, the number of patients with availability of biomarker values differed, which potentially could affect the results.
- Third, the proportion of patients with MI was rather high compared with that of other studies involving consecutive patients with chest pain, but the number is in line with different European cohorts.
- Still, only white European patients were enrolled might limit the generalizability of the findings to other populations

Conclusions

Conclusions

- Use of hsTnI and cTnI assays in patients with suspected MI provides useful diagnostic information.
- Determinationof hsTnI and cTnI values 3 hours after admission to the emergency department with use of the 99th percentile cutoff provides an NPV > 99%, allowing a safe ruleout of MI
- Application of the relative change in hsTnI or cTnI concentration within 3 hours after admission in combination with the 99th percentile diagnostic cutoff value on admission improves specificity and may facilitate an accurate early rule-in of MI

Thanks for your attetion