
UniversityHospital
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Kardiale Troponine
kritisch betrachtet
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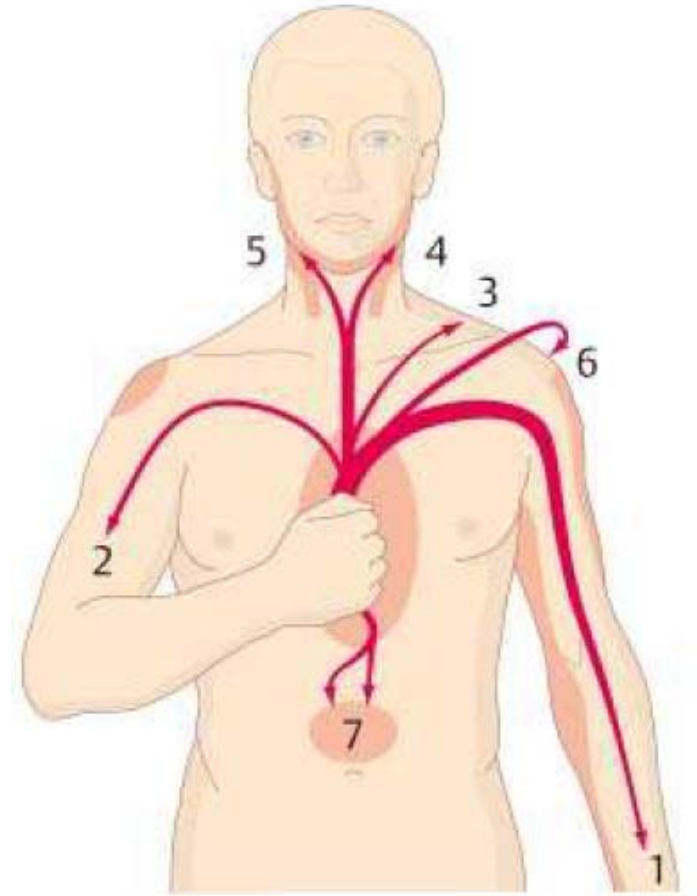
Klinische Zeichen des akuten Herzinfarktes



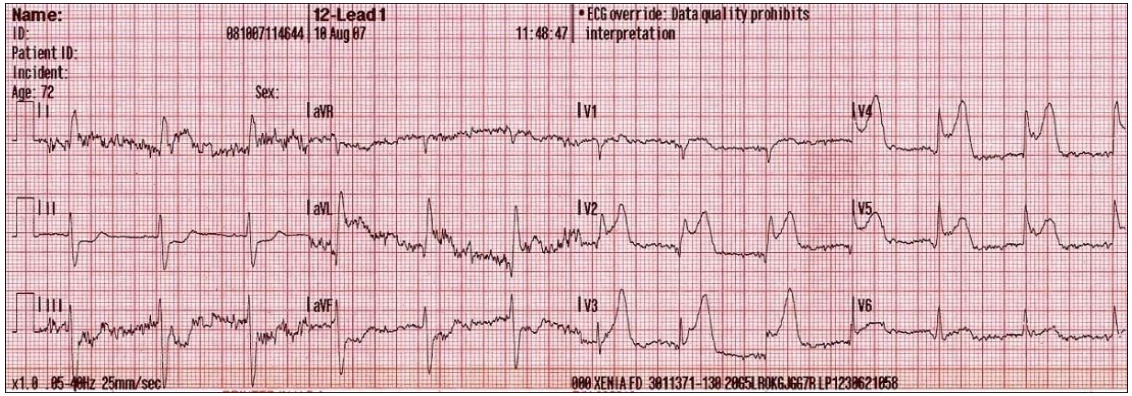
Atypische Symptomatik bei Frauen, älteren Patienten und Diabetikern

Clinical Feature	Likelihood Ratio (95% CI)
Increased likelihood of AMI	
Described as pressure	1.3 (1.2–1.5)
Pain in chest or left arm	2.7*
Chest pain radiation	
To right arm or shoulder	4.7 (1.9–12)
To left arm	2.3 (1.7–3.1)
To both left and right arm	7.1 (3.6–14.2)
To both arms or shoulders	4.1 (2.5–6.5)
Chest pain most important symptom	2.0*
Chest pain associated with exertion	2.4 (1.5–3.8)
Worse than previous angina or similar to prior AMI	1.8 (1.6–2.0)
History of MI	1.5–3.0†
Nausea or vomiting	1.9 (1.7–2.3)
Diaphoresis	2.0 (1.9–2.2)
Third heart sound	3.2 (1.6–6.5)
Hypotension (systolic BP <80 mm Hg)	3.1 (1.8–5.2)
Pulmonary crackles	2.1 (1.4–3.1)
Decreased likelihood of AMI	
Pleuritic chest pain	0.2 (0.1–0.3)
Described as sharp	0.3 (0.2–0.5)
Positional chest pain	0.3 (0.2–0.5)
Reproduced by palpation	0.3 (0.2–0.4)
Inframammary location	0.8 (0.7–0.9)
Not associated with exertion	0.8 (0.6–0.9)

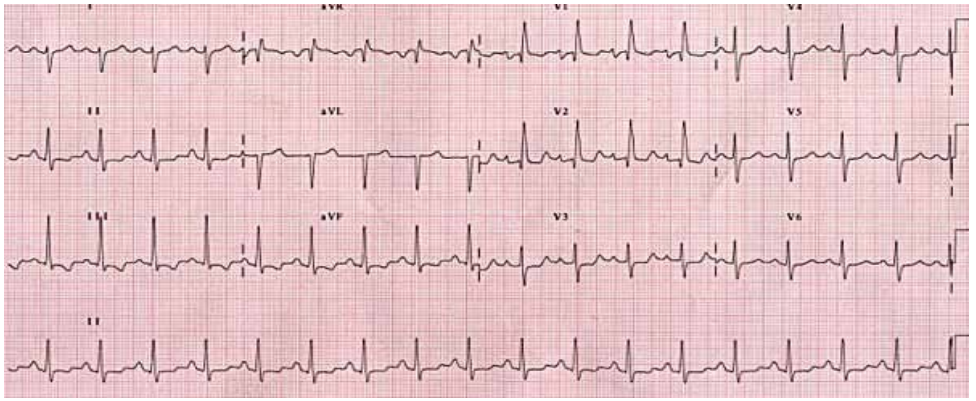
Hollander et al. Circulation 2016; 134:547–564.

Akutes Koronar-Syndrom (ACS)*

ST-Hebungs Myokardinfarkt (STEMI)



Non-ST-Hebungs-ACS



Biomarker der Myokardnekrose

+ → NSTEMI

- → Unstabile Angina Pectoris

*Klassification durch
American College of Cardiologists
& European Society of Cardiology

NSTEMI = non ST-elevation myocardial infarction

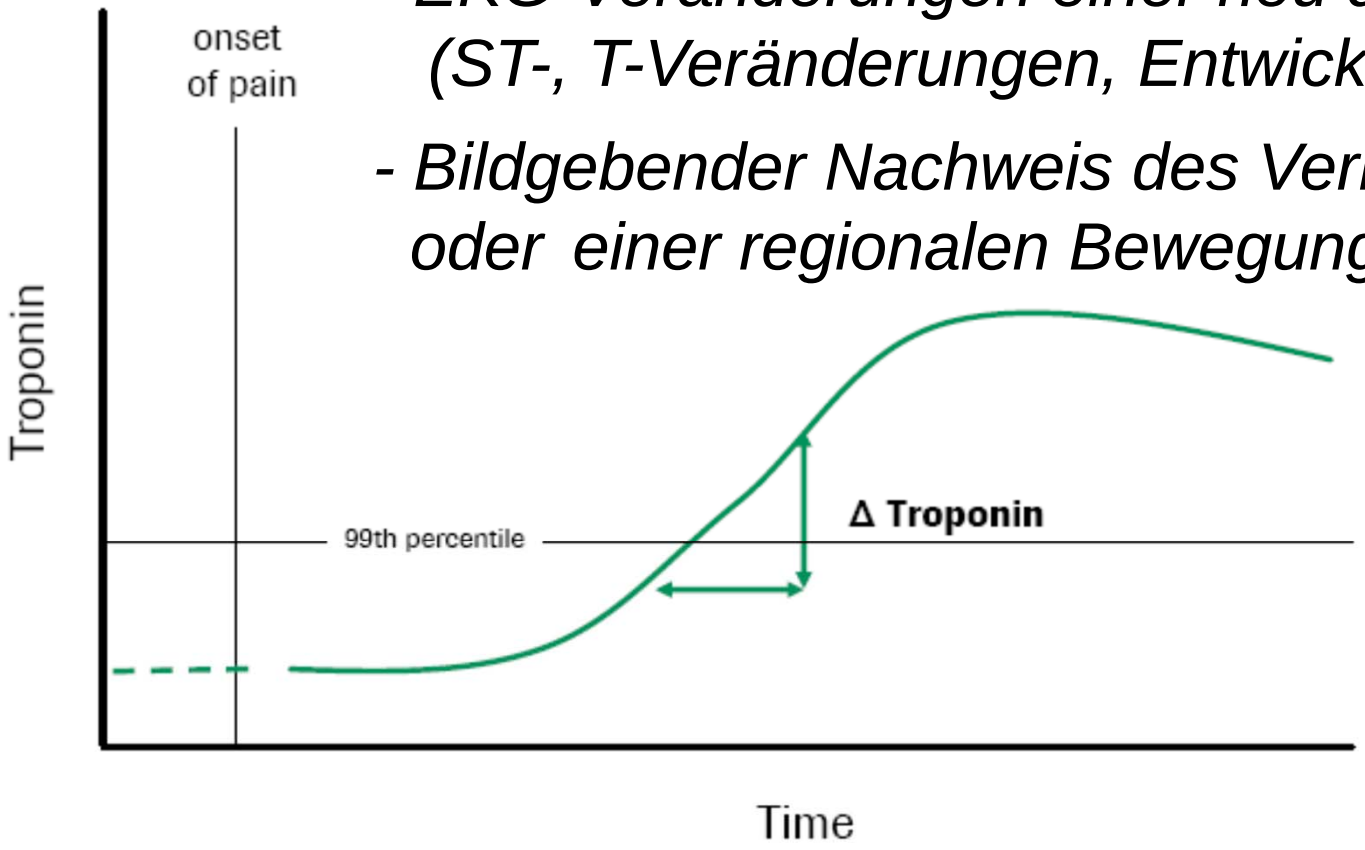
Definition des Akuten Herzinfarktes

(Circulation 2007, 116: 2634-2653 & Eur. Heart J. 2007, 28: 2525-2538)

*Ansteigende oder fallende Troponin-Konzentration im Blut mit mindestens einem Wert > 99. Perzentile**

***und** mindestens einem der nachfolgenden Symptome:*

- *klinische Symptome der kardialen Ischämie*
- *EKG-Veränderungen einer neu aufgetretenen Ischämie (ST-, T-Veränderungen, Entwicklung von Q-Wellen*
- *Bildgebender Nachweis des Verlustes von vitalem Myokard oder einer regionalen Bewegungsstörung der Herzwand*



*Sonderfälle;

Nach PCI (Typ 4a): >3 ULN

Nach Stent (Typ 4b): >3 ULN

Nach ACBP (Typ 5): >5 ULN

Kardiale Troponine – kritische Fragen

- **Sensitiv oder hochsensitiv (AHA/ACC vs ESC)?**
- **cut-off: 99. Perzentile oder limit of detection (LOD)?**
- **Monitoring: 0/1h- oder 0/3h-Algorithmus?**
- **Zentrallabor oder patientennah (POCT)?**

Comparison of the Recent AHA/ACC and ESC Guidelines for the diagnosis of AMI

AHA/ACC 2014 Guidelines	ESC 2015 Guidelines
Diagnosis	
Measure cardiac troponin I or T at presentation and at 3-6 h after symptom onset	Measure cardiac troponin levels by using sensitive or high-sensitivity assays with results within 60 min
Obtain additional troponin levels beyond 6 h in patients with initial normal troponin levels with intermediate- or high-risk features	For rapid rule-out, 2 alternative approaches using the 0 h/1 h or 0 h/3 h algorithms of high-sensitivity troponin assays are recommended
Use of risk scores to assess prognosis in patients with NSTE-ACS	Use established risk scores for prognosis estimation
	In patients with no recurrence of chest pain and normal ECG findings and troponin levels, a noninvasive stress test (preferably with imaging) is recommended to look for ischemia

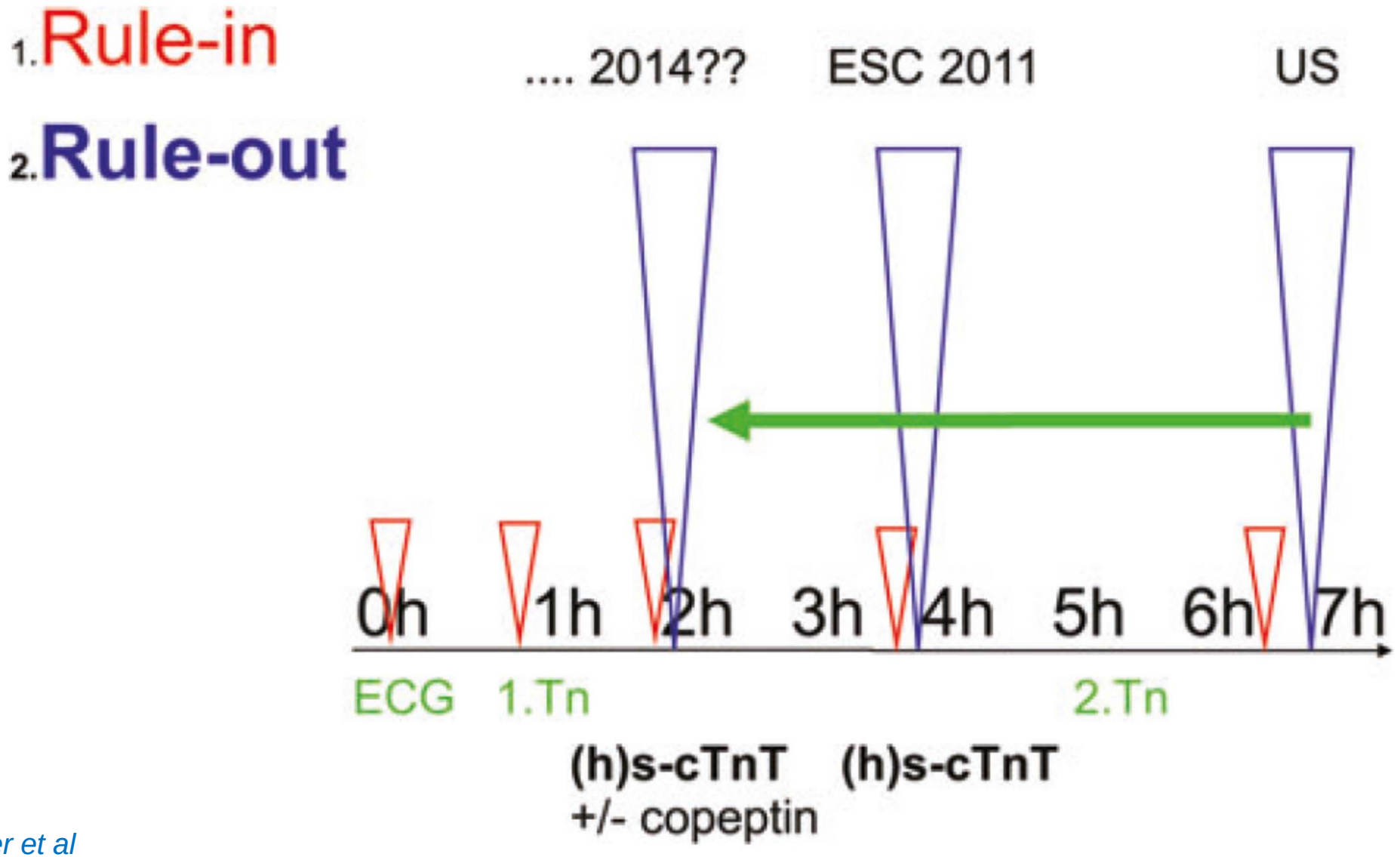
Rodriguez and Mahaffey: Am Coll Cardiol 2016;68:313–21

Kriterien für die analytische Bewertung verschiedener cTroponin-Tests

Acceptance designation	Total imprecision at the 99th percentile, CV%
Guideline acceptable	≤10
Clinically usable	>10 to ≤20
Not acceptable	>20
Assay designation	**Measurable normal values below the 99th percentile, %**
Level 4 (third generation, hs)	≥95
Level 3 (second generation, hs)	75 to <95
Level 2 (first generation, hs)	50 to <75
Level 1 (contemporary)	<50

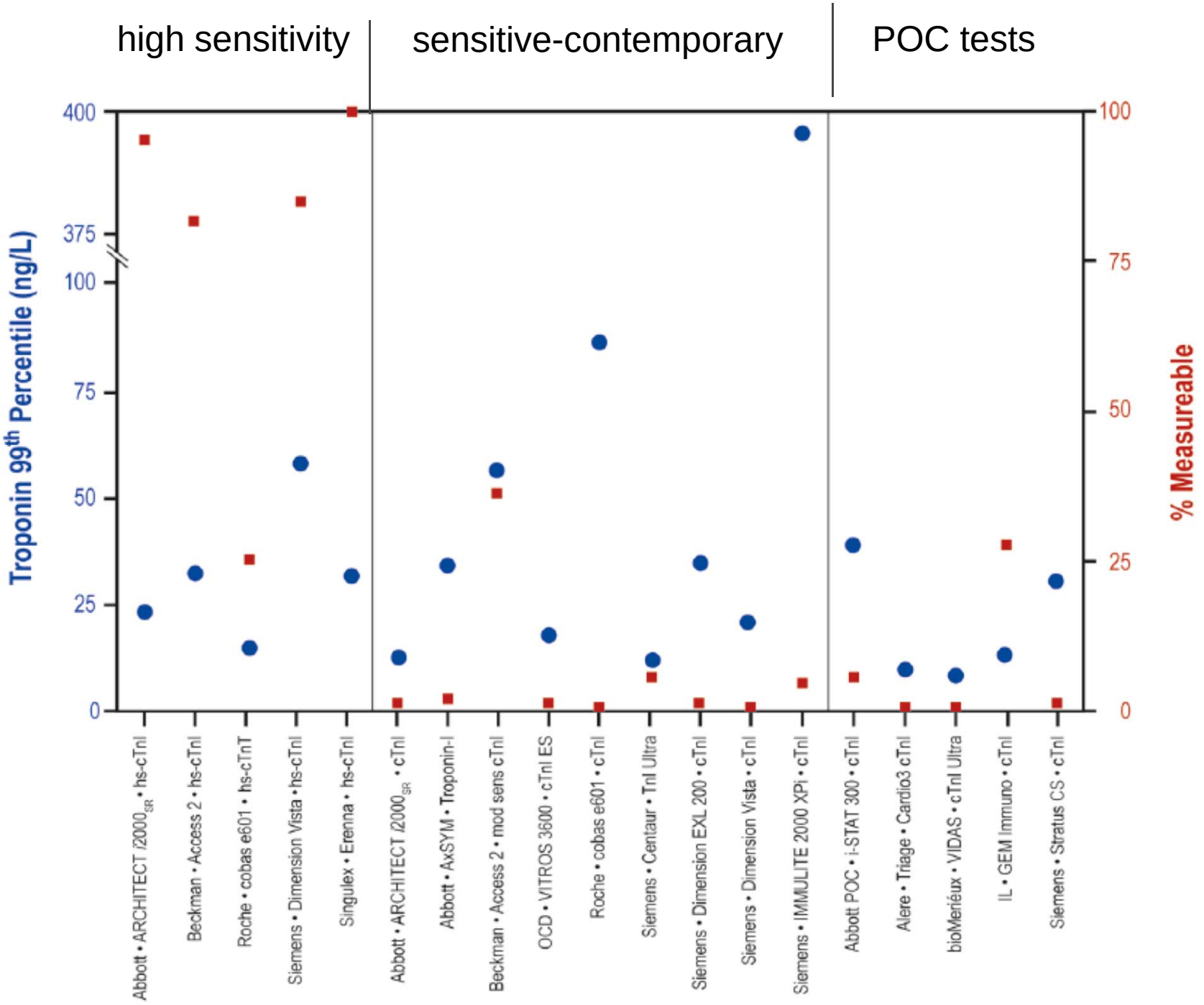
F.S. Apple, Clinical Chemistry 55: 1303–1306 (2009)

Sensitive or high-sensitivity cardiac troponin assays allow more rapid rule-out and more rapid rule-in of AMI

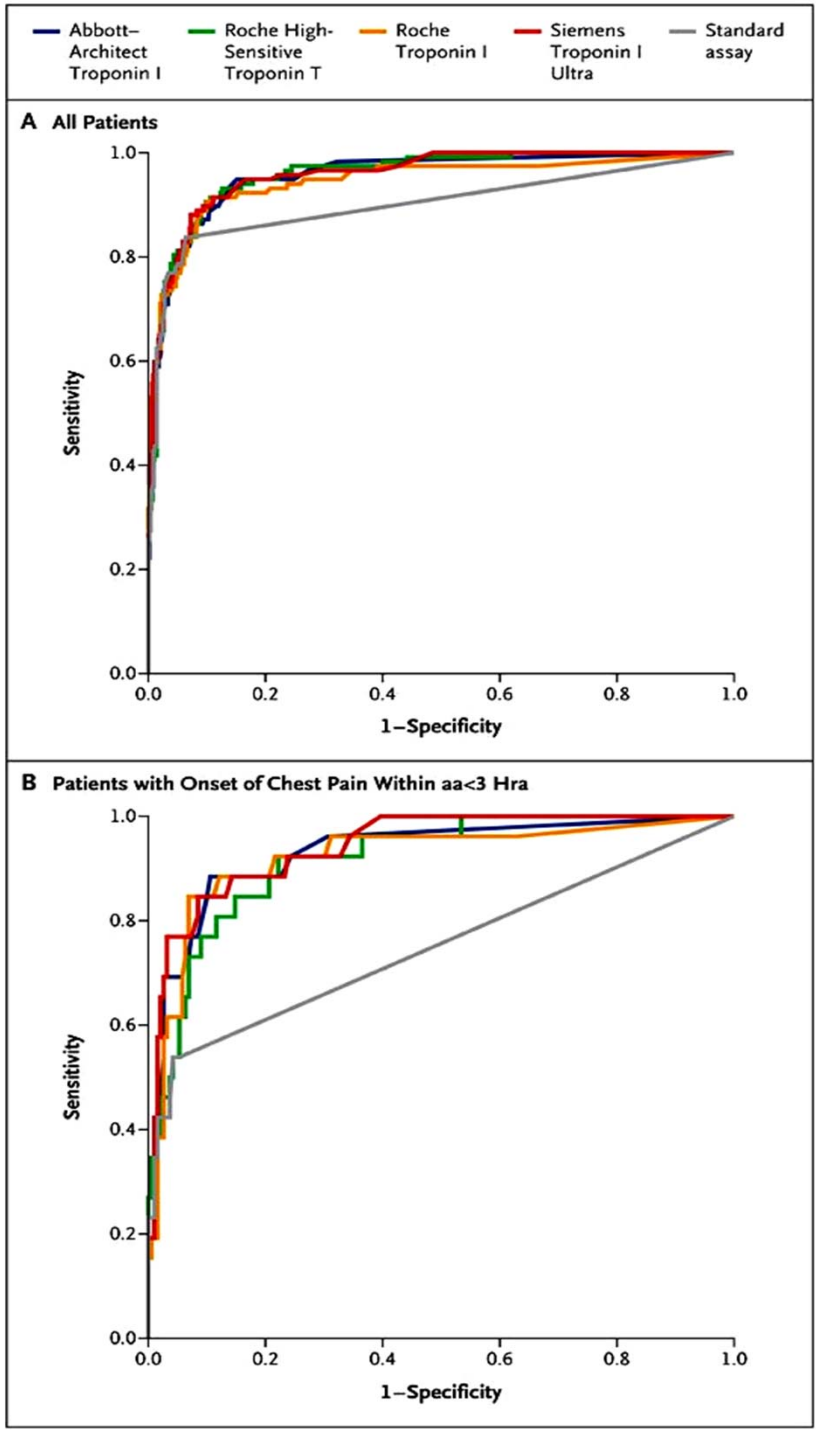


Mueller et al
European Heart Journal (2014) 35, 552–556

99th percentile values and percentage measurable concentrations in a presumably healthy population for 19 cTn assays

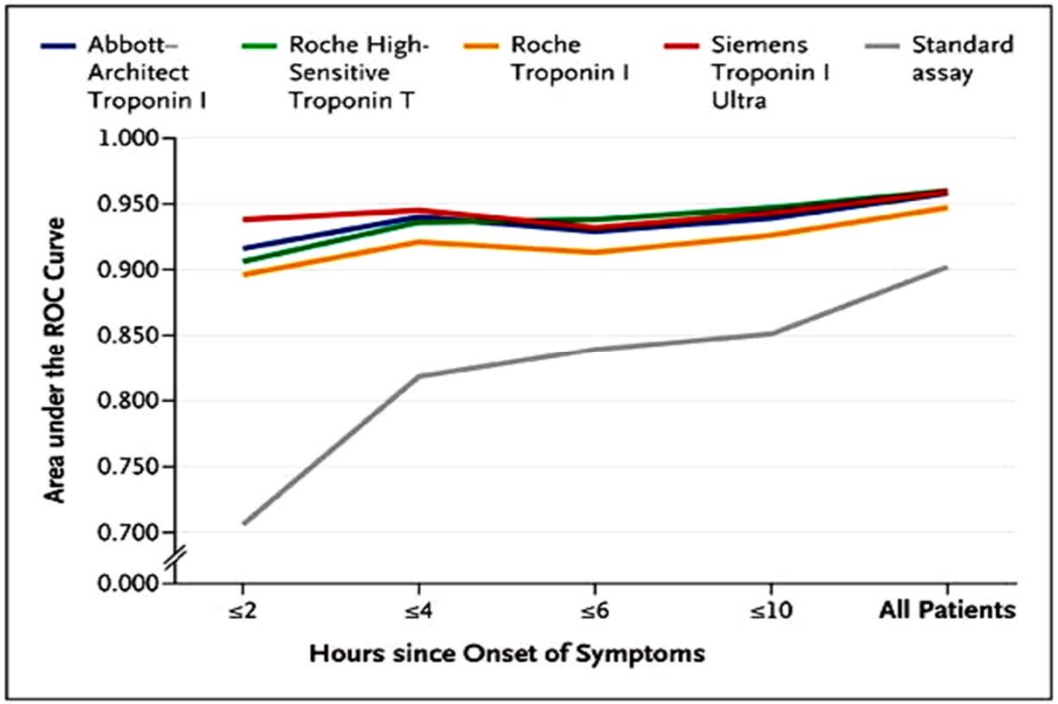


Sandoval et al (2016)
European Heart Journal
Acute Cardiovascular Care, i



Receiver-operating-characteristic Kurven Analysen für konventionelle und sensitive Troponin T Assays (Roche) sowie sensitive Troponin I Assays (Siemens oder Abbott Architect) in Abhängigkeit von der Zeit nach Symptombeginn

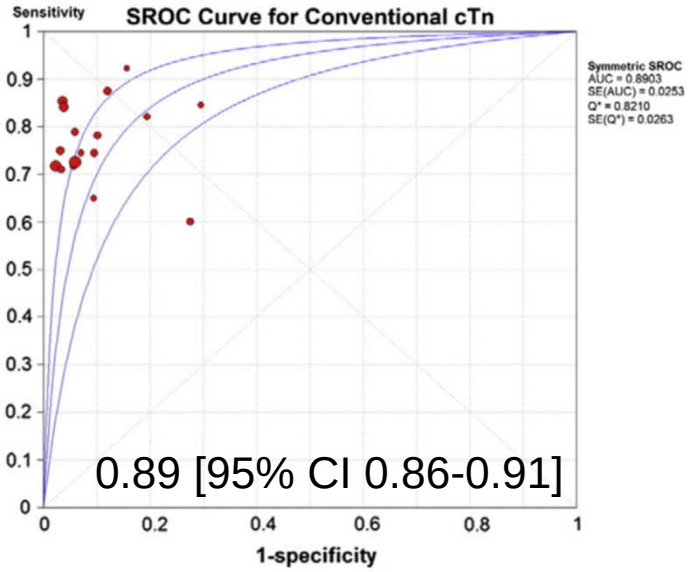
(718 konsekutive Patienten mit Verdacht auf AMI)

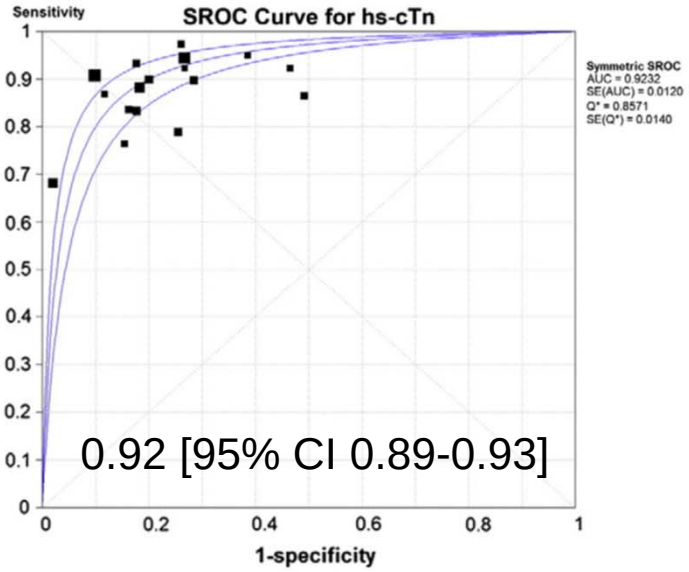


Reichlin et al.; N. Engl. J. Med. 2009; 361: 858-867

Comparison of conventional and high-sensitivity troponin assays in patients with chest pain

A collaborative meta-analysis of 17 studies on 8644 patients





	Baseline cTn	Baseline hs-cTn	Second Serial cTn	Second Serial hs-cTn
Pooled sensitivity	0.749 (0.728-0.769)	0.884 (0.868-0.898)	0.895 (0.867-0.919)	0.928 (0.903-0.948)
Pooled specificity	0.938 (0.932-0.943)	0.816 (0.807-0.826)	0.952 (0.944-0.959)	0.807 (0.794-0.821)
Pooled PPV	0.759 (0.738-0.778)	0.558 (0.539-0.576)	0.758 (0.724-0.790)	0.443 (0.414-0.472)
Pooled NPV	0.935 (0.929-0.940)	0.964 (0.959-0.969)	0.982 (0.977-0.986)	0.985 (0.980-0.990)
Summary positive LR	9.913 (6.648-14.781)	4.393 (3.403-5.673)	13.163 (7.667-22.596)	4.663 (3.576-6.080)
Summary negative LR	0.262 (0.217-0.317)	0.156 (0.116-0.210)	0.137 (0.092-0.204)	0.112 (0.069-0.182)
Summary DOR	41.665 (24.732-70.191)	32.609 (20.477-51.931)	95.503 (45.727-199.46)	49.716 (25.238-97.938)
Area under the SROC curve	0.890 (0.839-0.941)	0.923 (0.899-0.947)	0.951 (0.919-0.983)	0.948 (0.912-0.984)

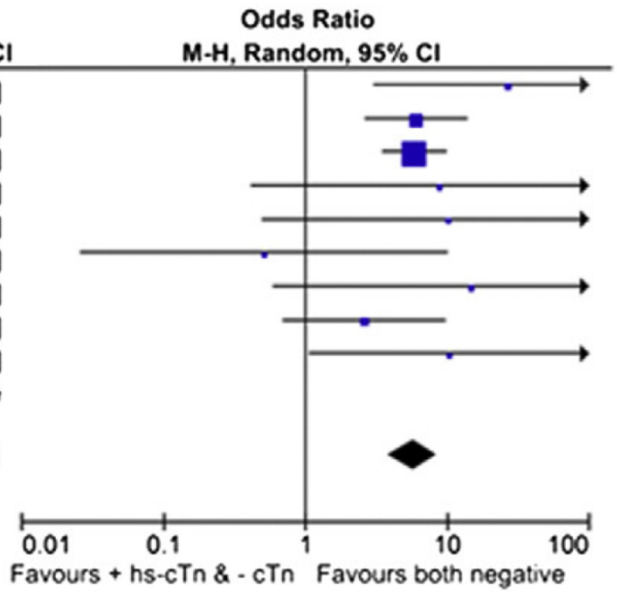
Lipinski et al
Am Heart J 2014;169:6-16.e6

Forest plots comparing death or non-fatal AMI during follow-up between patients with elevation of baseline hs-cTn and negative baseline conventional cTn

death

Study or Subgroup	Pos hs-cTn and Neg cTn Events	Total	Both Negative Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Aldous 2011	5	40	1	189	3.2%	26.86 [3.04, 236.91]
Aldous 2012	13	130	11	608	22.1%	6.03 [2.64, 13.79]
APACE	46	370	23	966	56.7%	5.82 [3.47, 9.75]
Christ 2010	2	39	0	66	1.6%	8.87 [0.41, 189.60]
Collinson 2013	0	10	3	749	1.7%	10.16 [0.49, 209.19]
Eggers 2012	0	55	3	200	1.7%	0.51 [0.03, 9.99]
Freund 2011	1	33	0	160	1.5%	14.82 [0.59, 371.82]
Hammerer-Lercher 2013	3	33	12	324	8.7%	2.60 [0.69, 9.73]
Santalo 2013	3	62	1	205	2.9%	10.37 [1.06, 101.58]
Schreiber 2012	0	83	0	350		Not estimable
Total (95% CI)		**855**		**3817**	**100.0%**	**5.77 [3.91, 8.51]**
Total events	73		54			

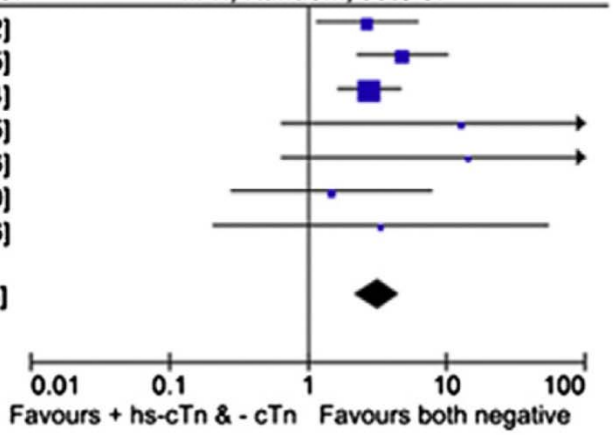
Heterogeneity: Tau² = 0.00; Chi² = 6.68, df = 8 (*P* = .57); I² = 0%
Test for overall effect: Z = 8.84 (*P* < .00001)



Nonfatal AMI

Study or Subgroup	Pos hs-cTn and Neg cTn Events	Total	Both Negative Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Aldous 2011	10	40	21	189	18.5%	2.67 [1.14, 6.22]
Aldous 2012	14	130	15	608	23.3%	4.77 [2.24, 10.15]
APACE	30	370	30	966	48.9%	2.75 [1.63, 4.64]
Christ 2010	3	39	0	66	1.5%	12.75 [0.64, 253.75]
Collinson 2013	0	10	2	749	1.4%	14.24 [0.64, 315.06]
Eggers 2012	2	55	5	200	4.8%	1.47 [0.28, 7.80]
Santalo 2013	1	62	1	205	1.7%	3.34 [0.21, 54.26]
Total (95% CI)		**706**		**2983**	**100.0%**	**3.17 [2.20, 4.56]**
Total events	60		74			

Heterogeneity: Tau² = 0.00; Chi² = 4.12, df = 6 (*P* = .66); I² = 0%
Test for overall effect: Z = 6.21 (*P* < .00001)



Lipinski et al
Am Heart J
2014;169:6-16.e6

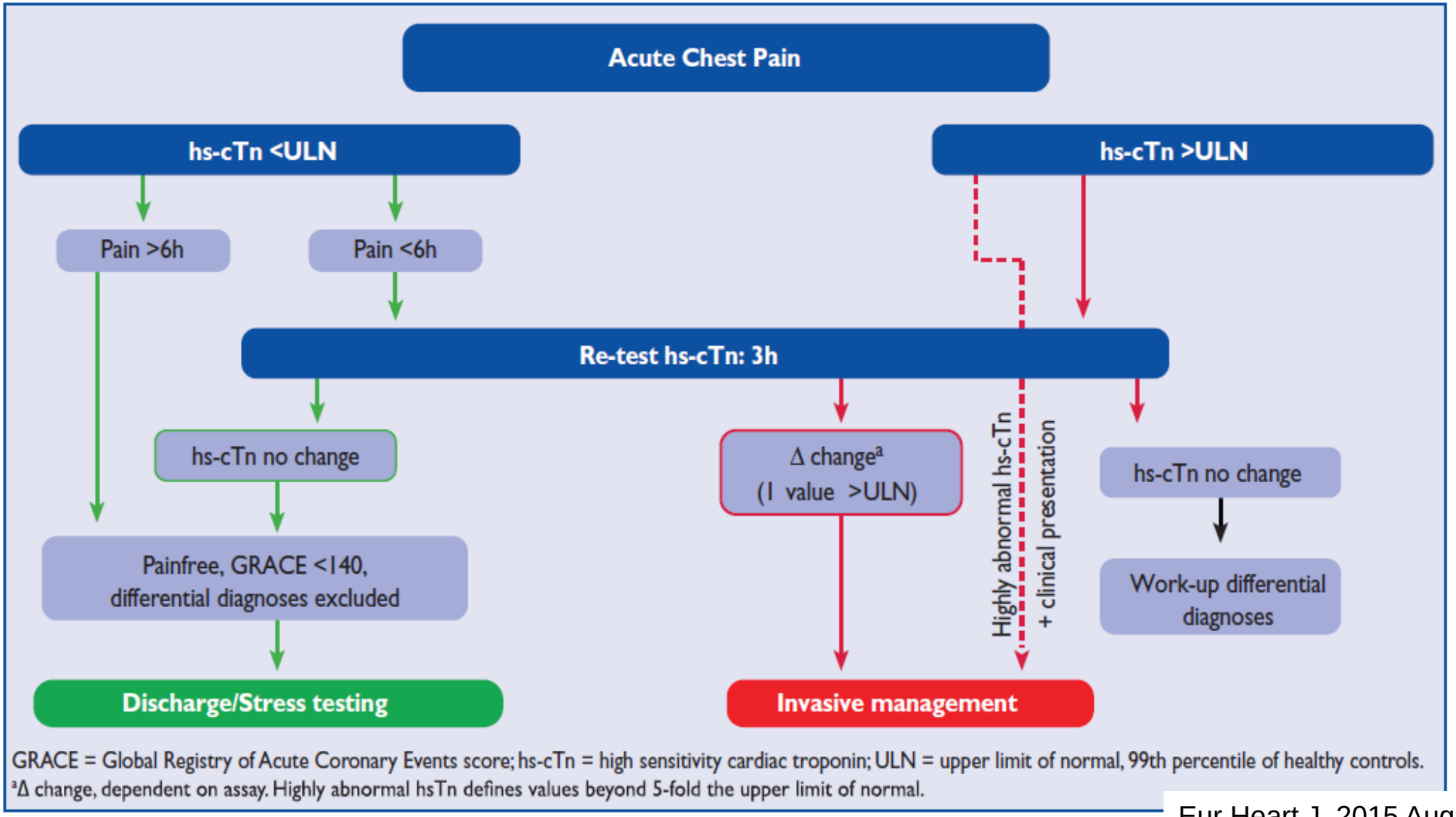
Kardiale Troponine – kritische Fragen:
Sensitiv oder hoch-sensitiv?

- **verbesserter rule-out durch hs-cTn,**
  aber problematisch für rule-in (ungenügende Spezifität / PPV).
- **Verbesserung der Risikovorhersage durch hs-cTn**

Kardiale Troponine – kritische Fragen

-
- **cut-off: 99. Perzentile oder LOD?**

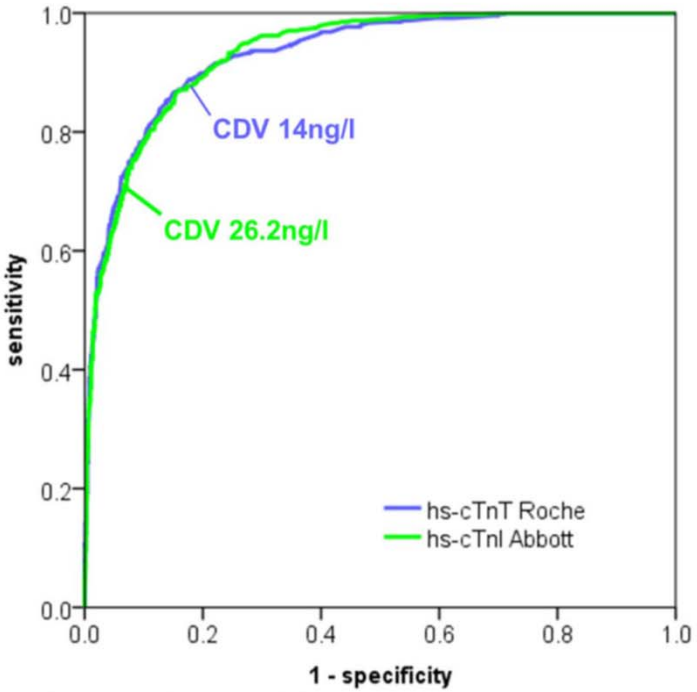
ESC-Guideline zum diagnostischen Vorgehen bei Patienten mit akutem Brustschmerz (0h/3h Rule-Out Algorithmus)



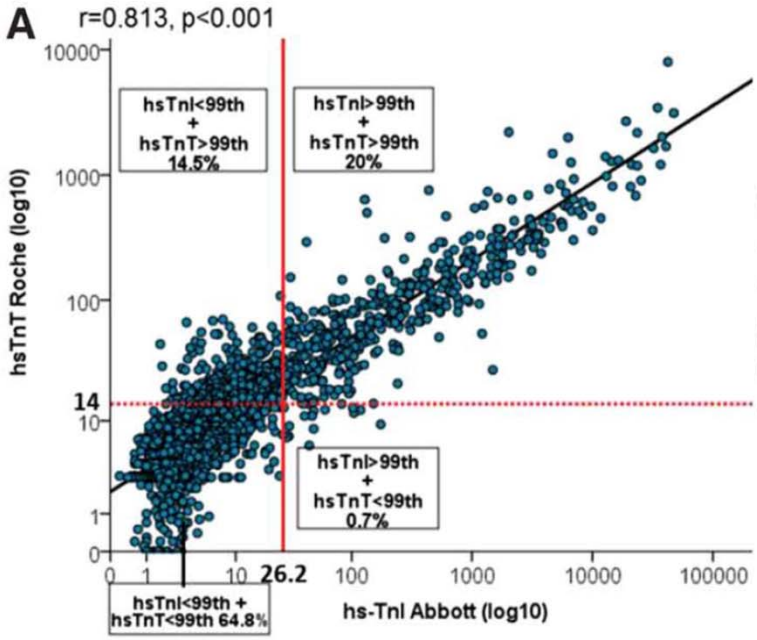
GRACE = Global Registry of Acute Coronary Events score; hs-cTn = high sensitivity cardiac troponin; ULN = upper limit of normal, 99th percentile of healthy controls.
[a]Δ change, dependent on assay. Highly abnormal hsTn defines values beyond 5-fold the upper limit of normal.

Eur Heart J. 2015 Aug 29

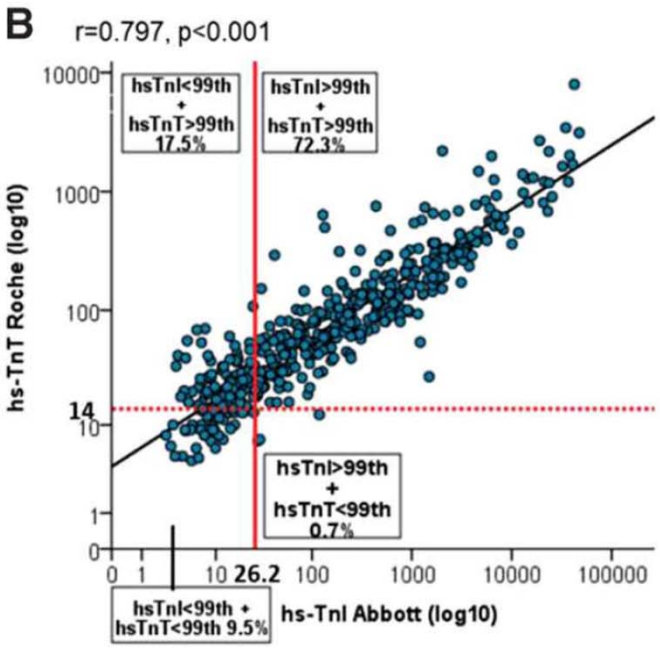
Discordant Diagnosis of Myocardial Infarction by the Currently Recommended 99th Percentile Clinical Decision Values for Cardiac Troponin



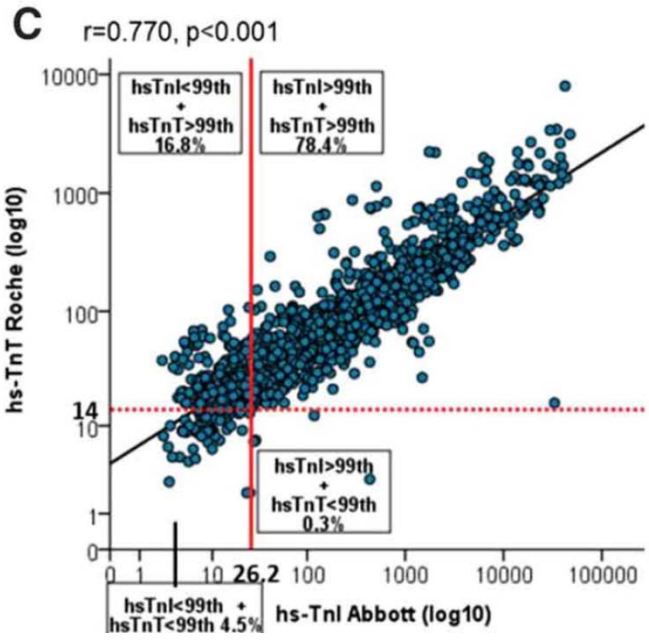
Wildi et al . Circulation. 2015;131:2032-2040.



Total cohort (N = 2300)



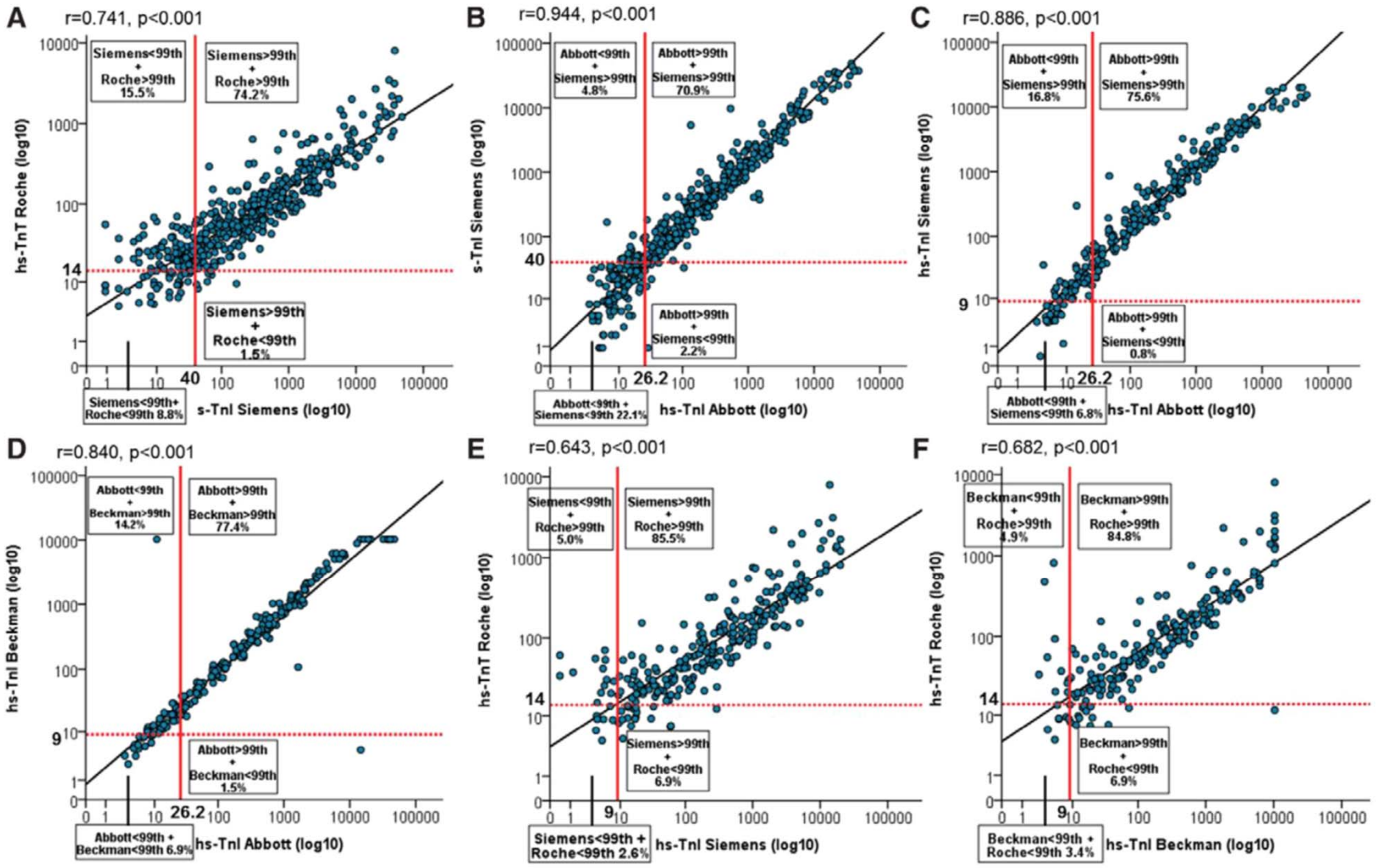
AMI diagnosed with AMI, at first presentation (N = 473)



AMI diagnosed with AMI, at any time (N = 473)

Discordant Diagnosis of Myocardial Infarction by the Currently Recommended 99th Percentile Clinical Decision Values for Cardiac Troponin

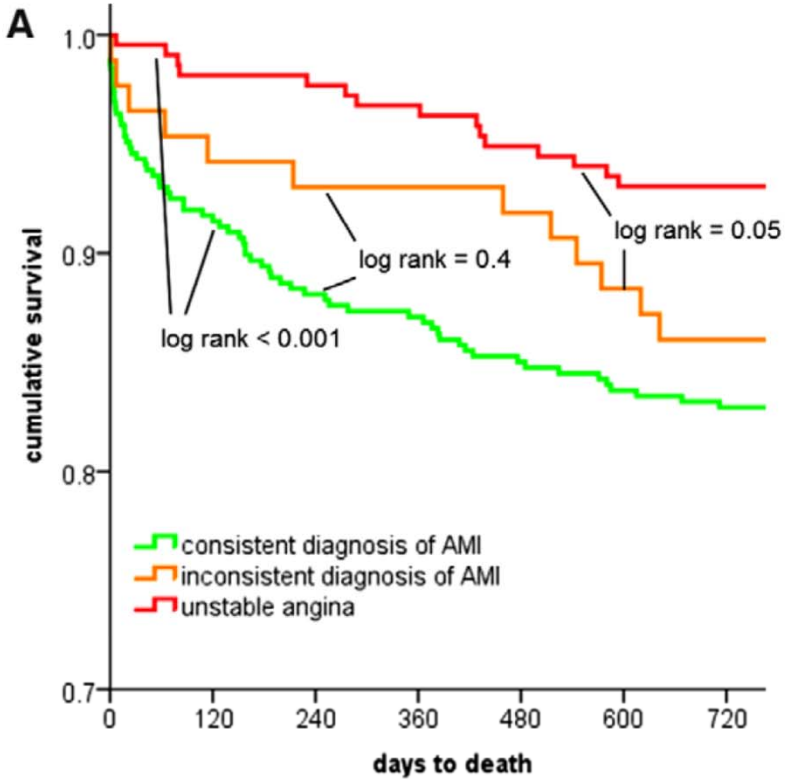
Wildi et al . Circulation. 2015;131:2032-2040.



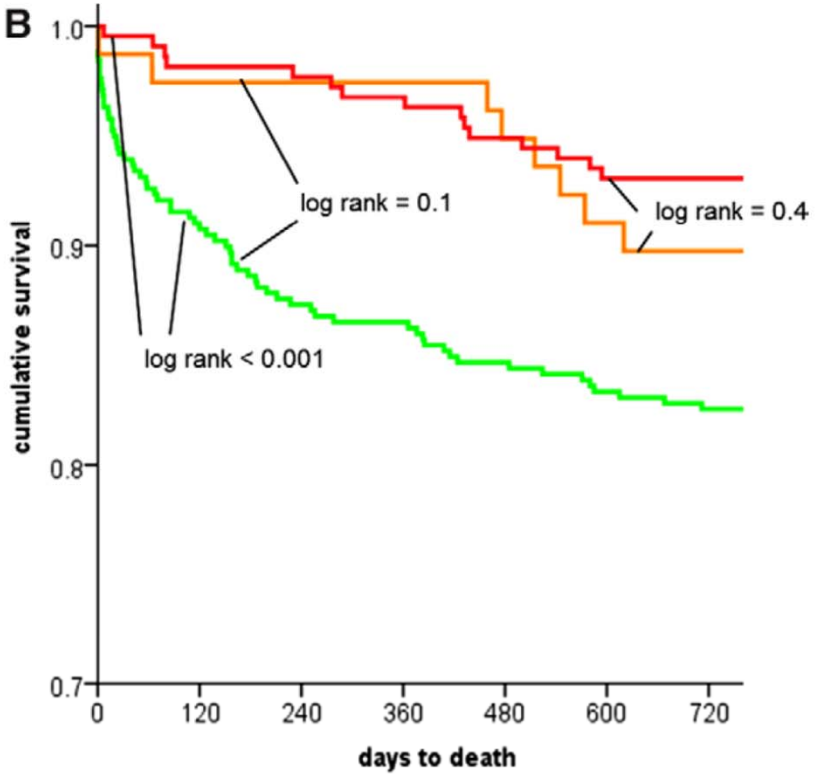
Kaplan–Meier survival curves of ACS patients according to concordant or discordant diagnoses of acute myocardial infarction (AMI) or unstable angina by 99th percentiles of different cardiac troponin assays

Wildi et al . Circulation. 2015; 131:2032-2040.

hs-cTnT (Roche) vs. hs-cTnI (Abbott)



hs-cTnT (Roche) vs. cTnI Ultra (Siemens)



number of patients at risk

unstable angina	216	212	211	209	205	201	201
inconsistent diagnosis of AMI	86	81	80	80	79	76	74
consistent diagnosis of AMI	387	354	341	337	329	324	321

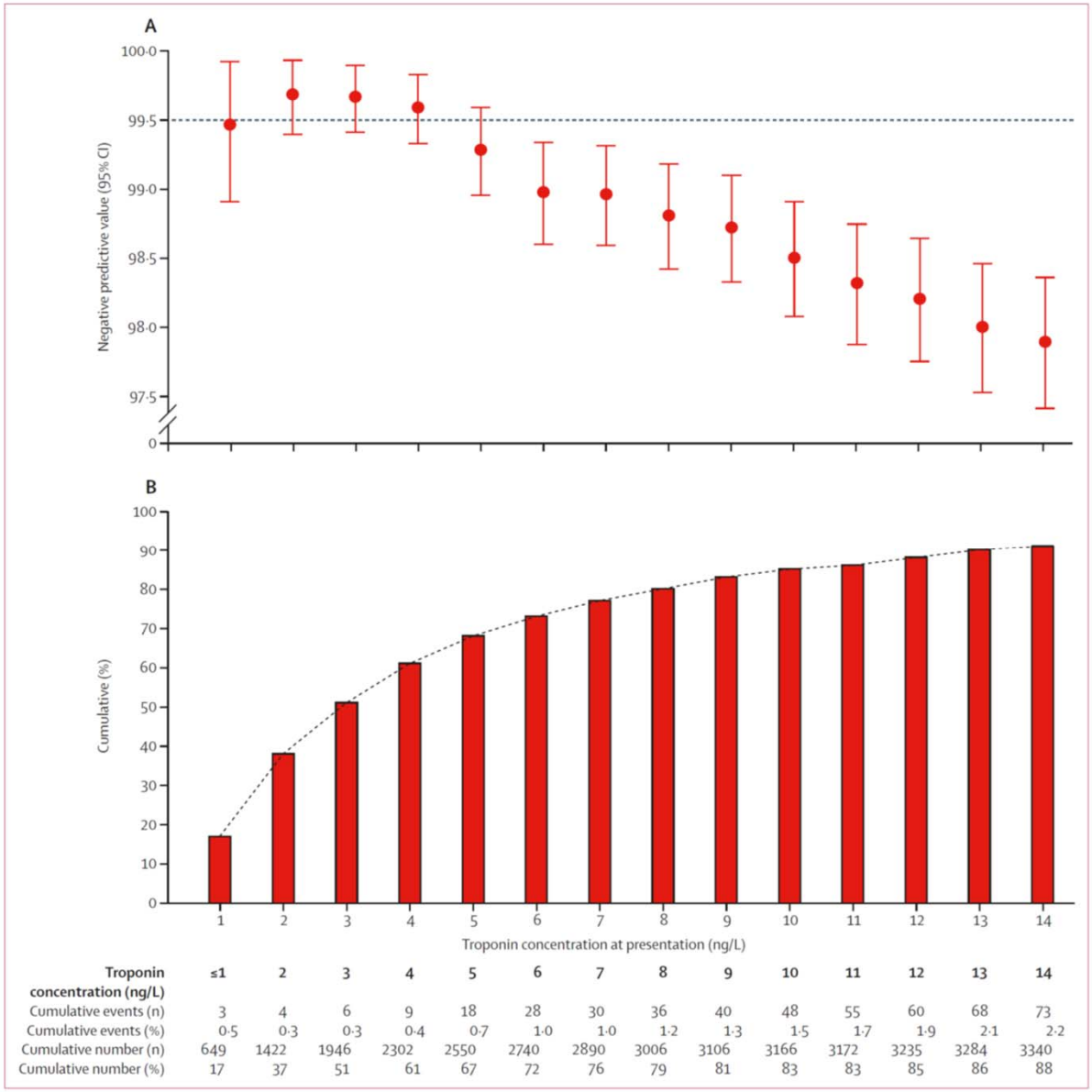
unstable angina	216	212	211	209	205	201	201
inconsistent diagnosis of AMI	78	76	76	76	74	71	70
consistent diagnosis of AMI	378	343	330	327	320	315	312

Biomarker Strategies for Rapid Assessment of Patients With Potential ACS in the ED

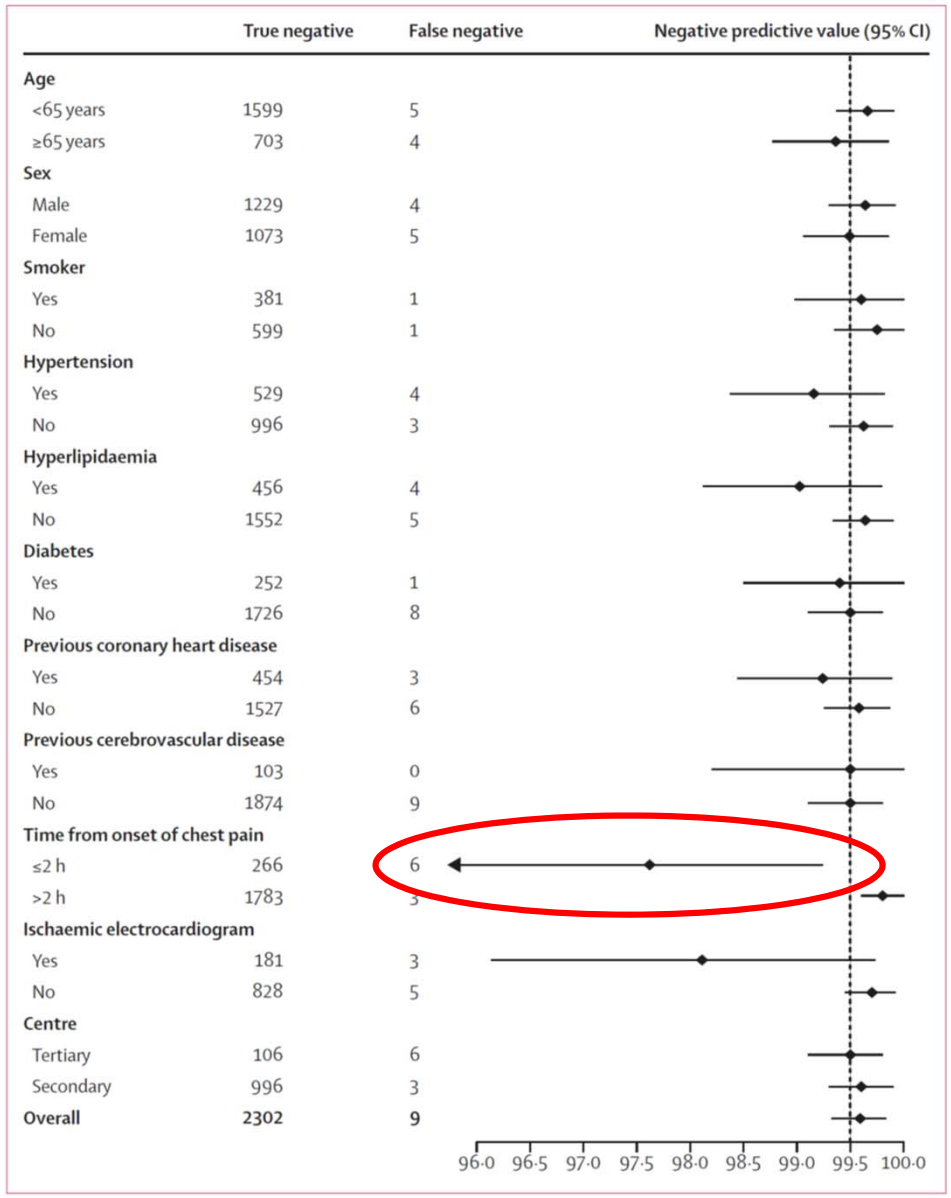
	Very Low cTn	cTn and Copeptin	0- and 1-h Algorithm	0- and 2-h Algorithm	2-h ADP	0- and 3-h ESC
Clinical scoring system	None	None	None	None	TIMI score ≤1 ECG normal at 0 and 2 h	GRACE <140 and pain free
Blood draws, n	1	1	2*	2*	2*	2*
Indication	Rule out	Rule out	Rule out and rule in	Rule out and rule in	Rule out	Rule out and rule in
NPV for AMI, %	98–100	92.4–99 96–99 with hs-cTn	99.1–100	99.5–99.9	99.1–100†	99.6–100
Eligible population size	+(+)	++	+++	+++	++	++(+)
Biomarker rule-out criteria‡						
Using hs-cTnT	hs-cTnT <5 ng/L	hs-cTnT <14 ng/L AND copeptin <10 pmol/L	hs-cTnT<12 ng/L AND 1-h Δ <3	hs-cTnT <14 ng/L at 0 and 2 h AND 2-h Δ <4	hs-cTnT <14 ng/L at 0 and 2 h	hs-cTnT <14 ng/L at 0 and 3 h
Using hs-cTnI	hs-cTnI <2–5 ng/L	hs-cTnI <26 ng/L AND copeptin <10 pmol/L	hs-cTnI <5 ng/L AND 1-h Δ <2	hs-cTnI <6 ng/L at 0 and 2 h AND 2-h Δ <2	hs-cTnI <26 ng/L at 0 and 2 h	hs-cTnI <26 ng/L at 0 and 3h
Biomarker rule-in criteria						
Using hs-cTnT			hs-cTnT ≥52 ng/L OR 1-h Δ ≥5	hs-cTnT ≥53 ng/L OR 2-h Δ ≥10		
Using hs-cTnI			hs-cTnI ≥52 ng/L OR 1-h Δ ≥5	hs-cTnI ≥64 ng/L OR 2-h Δ ≥15		
Feasibility	High	Low; Requires 2 biomarkers requiring different analyzers	High	High	Medium; Requires use of TIMI score	Medium; Requires GRACE score

Hollander et al. Circulation 2016; 134:547–564.

High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome



Troponin concentration (ng/L)	≤1	2	3	4	5	6	7	8	9	10	11	12	13	14
Cumulative events (n)	3	4	6	9	18	28	30	36	40	48	55	60	68	73
Cumulative events (%)	0·5	0·3	0·3	0·4	0·7	1·0	1·0	1·2	1·3	1·5	1·7	1·9	2·1	2·2
Cumulative number (n)	649	1422	1946	2302	2550	2740	2890	3006	3106	3166	3172	3235	3284	3340
Cumulative number (%)	17	37	51	61	67	72	76	79	81	83	83	85	86	88

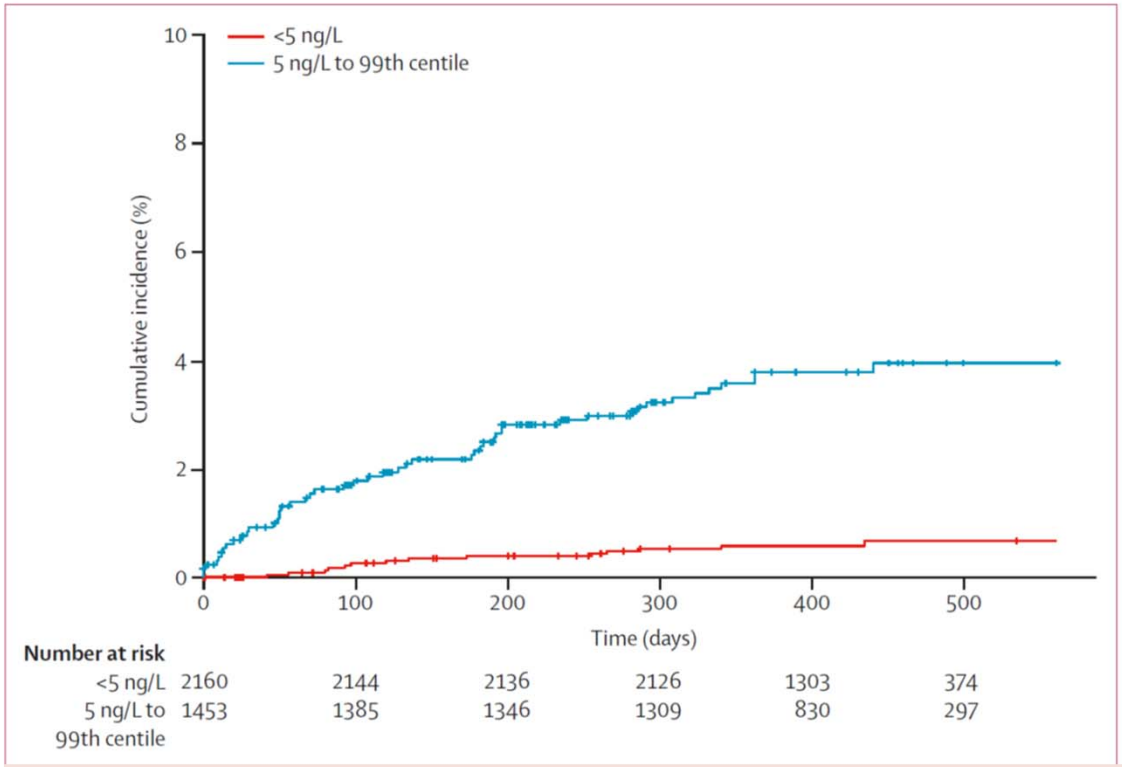


	True negative	False negative
Age		
<65 years	1599	5
≥65 years	703	4
Sex		
Male	1229	4
Female	1073	5
Smoker		
Yes	381	1
No	599	1
Hypertension		
Yes	529	4
No	996	3
Hyperlipidaemia		
Yes	456	4
No	1552	5
Diabetes		
Yes	252	1
No	1726	8
Previous coronary heart disease		
Yes	454	3
No	1527	6
Previous cerebrovascular disease		
Yes	103	0
No	1874	9
Time from onset of chest pain		
≤2 h	266	6
>2 h	1783	3
Ischaemic electrocardiogram		
Yes	181	3
No	828	5
Centre		
Tertiary	106	6
Secondary	996	3
Overall	**2302**	**9**

Shah et al. Lancet 2015; 386: 2481–88.

incidence of myocardial infarction or cardiac death in patients with troponin level below the 99th centile

Goal:
30d incidence of MACE and death < 1%



	<5 ng/L (n=2160)	5 ng/L to 99th centile (n=1453)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Myocardial infarction				
30 days	0 (0·0%)	6 (0·4%)		
1 year	6 (0·3%)	19 (1·3%)	0·21 (0·08–0·51)	0·36 (0·13–0·99)
Cardiac death				
30 days	0 (0·0%)	6 (0·4%)		
1 year	6 (0·3%)	32 (2·2%)	0·14 (0·06–0·31)	0·41 (0·17–0·98)
Myocardial infarction or cardiac death				
30 days	0 (0·0%)	12 (0·8%)		
1 year	12 (0·6%)	48 (3·3%)	0·17 (0·09–0·31)	0·41 (0·21–0·80)

Data are n (%) unless stated otherwise. The hazard ratios are derived from a Cox regression model using all follow-up data. The median follow up was 427 days (IQR 371–489 days).

Shah et al. Lancet 2015; 386: 2481–88.

High-Sensitivity Cardiac Troponin T levels below the Limit of Detection to Exclude Acute Myocardial Infarction: diagnostic performance

Assay and cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
cTnT				
0.01 µg/L[a]	70.9 (59.6–80.6)	92.7 (89.6–95.1)	66.7 (55.5–76.6)	93.9 (91.0–96.1)
hs-cTnT				
14 ng/L[a]	94.9 (87.5–98.6)	72.4 (67.6–76.8)	41.4 (34.2–49.0)	98.6 (96.4–99.6)
5 ng/L[b]	98.7 (93.2–100.0)	24.7 (20.5–29.4)	21.3 (17.2–25.8)	99.0 (94.3–100.0)
3 ng/L[c]	100.0 (95.4–100.0)	6.3 (4.1–9.2)	18.0 (14.5–21.9)	100.0 (85.8–100.0)
14 ng/L and no ECG ischemia[d]	98.7 (93.2–100.0)	61.2 (56.1–66.1)	34.4 (28.2–40.9)	99.6 (97.7–100.0)
<5 ng/L and no ECG ischemia[d]	100.0 (95.4–100.0)	20.8 (16.9–25.2)	20.6 (16.7–25.0)	100.0 (95.5–100.0)
<3 ng/L and no ECG ischemia[d]	100.0 (95.4–100.0)	5.7 (3.6–8.6)	17.9 (14.5–21.8)	100.0 (83.9–100.0)

[a] Cutoff set at the 99th percentile of a reference population.
[b] Cutoff set at the limit of detection of the assay.
[c] Cutoff set at the limit of blank of the assay.
[d] AMI ruled out only if both conditions met.

Body et al. Clinical Chemistry 61:7 983–989 (2015)

High-Sensitivity Cardiac Troponin T Concentrations below the Limit of Detection to Exclude Acute Myocardial Infarction: Prognostic performance (30 days survival)

Assay and cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
cTnT				
0.01 µg/L[a]	62.2 (51.9–71.8)	93.7 (90.7–96.0)	72.6 (61.8–81.8)	90.2 (86.8–93.0)
hs-cTnT				
14 ng/L[a]	89.8 (82.0–95.0)	74.5 (69.7–78.9)	48.6 (41.1–56.2)	96.5 (93.6–98.3)
5 ng/L[b]	99.0 (94.5–100.0)	26.0 (21.6–30.9)	26.4 (22.0–31.3)	99.0 (94.3–100.0)
3 ng/L[c]	100.0 (96.3–100.0)	3.6 (2.3–5.3)	13.3 (10.9–15.9)	100.0 (85.8–100.0)
14 ng/L and no ECG ischemia[d]	94.9 (88.5–98.3)	63.3 (58.1–68.2)	41.0 (34.5–47.7)	97.9 (95.1–99.3)
<5 ng/L and no ECG ischemia[d]	100.0 (96.3–100.0)	21.9 (17.8–26.5)	25.6 (21.3–30.3)	100.0 (95.5–100.0)
<3 ng/L and no ECG ischemia[d]	100.0 (96.3–100.0)	6.0 (3.8–9.0)	22.2 (18.4–26.4)	100.0 (84.6–100.0)

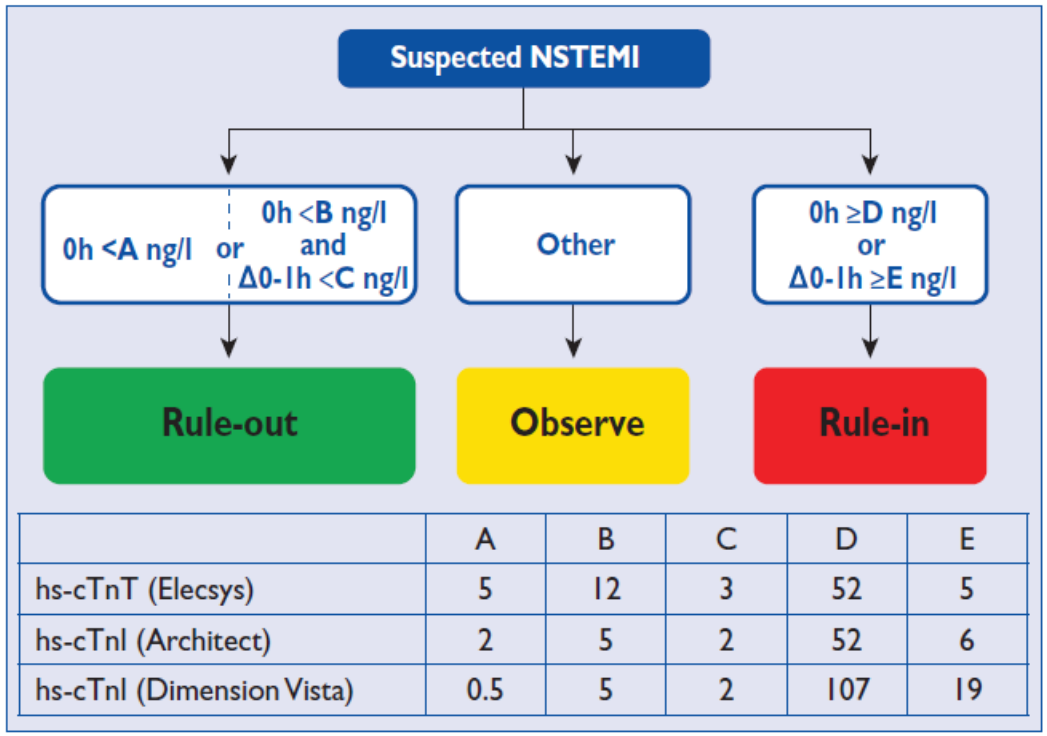
[a] Cutoff set at the 99th percentile of a reference population.
[b] Cutoff set at the limit of detection of the assay.
[c] Cutoff set at the limit of blank of the assay.
[d] AMI ruled out only if both conditions met.

Body et al. Clinical Chemistry 61:7 983–989 (2015)

Kardiale Troponine – kritische Fragen:
cut-off: 99. Perzentile oder LOD?

- **Problem 99. Perzentile: Abhängigkeit von Methoden und Populationen bergen Gefahr diskordanter Diagnosen**
- **LOD: höhere Sensitivität /NPV für rule-out, aber problematisch für rule-in (ungenügende Spezifität / PPV).**
- **LOD: Falsche Sicherheit bei früher Analytik (< 3h nach Beginn der Symptomatik)**

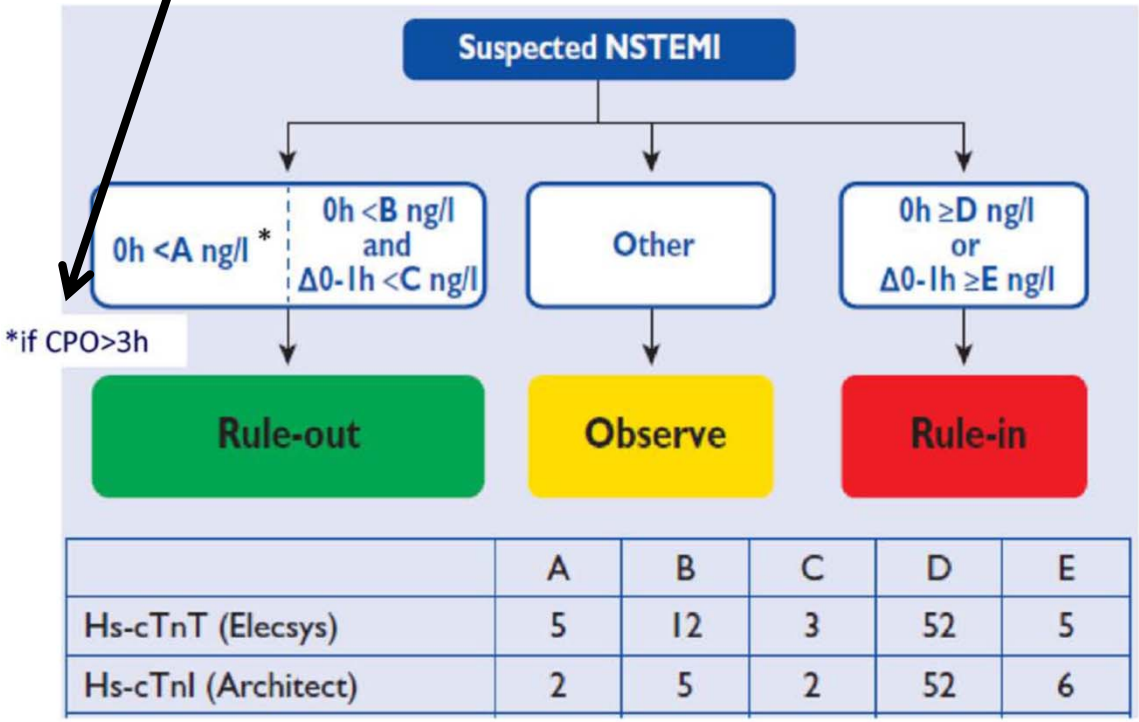
2 Versionen der ESC-Guideline 2015 zum diagnostischen Vorgehen bei Patienten mit Verdacht auf NSTEMI (0h/1h Rule-Out Rule-In Algorithmus)



	A	B	C	D	E
hs-cTnT (Elecsys)	5	12	3	52	5
hs-cTnI (Architect)	2	5	2	52	6
hs-cTnI (Dimension Vista)	0.5	5	2	107	19

Eur Heart J. 2015 Aug 29

CPO = Chest Pain Onset



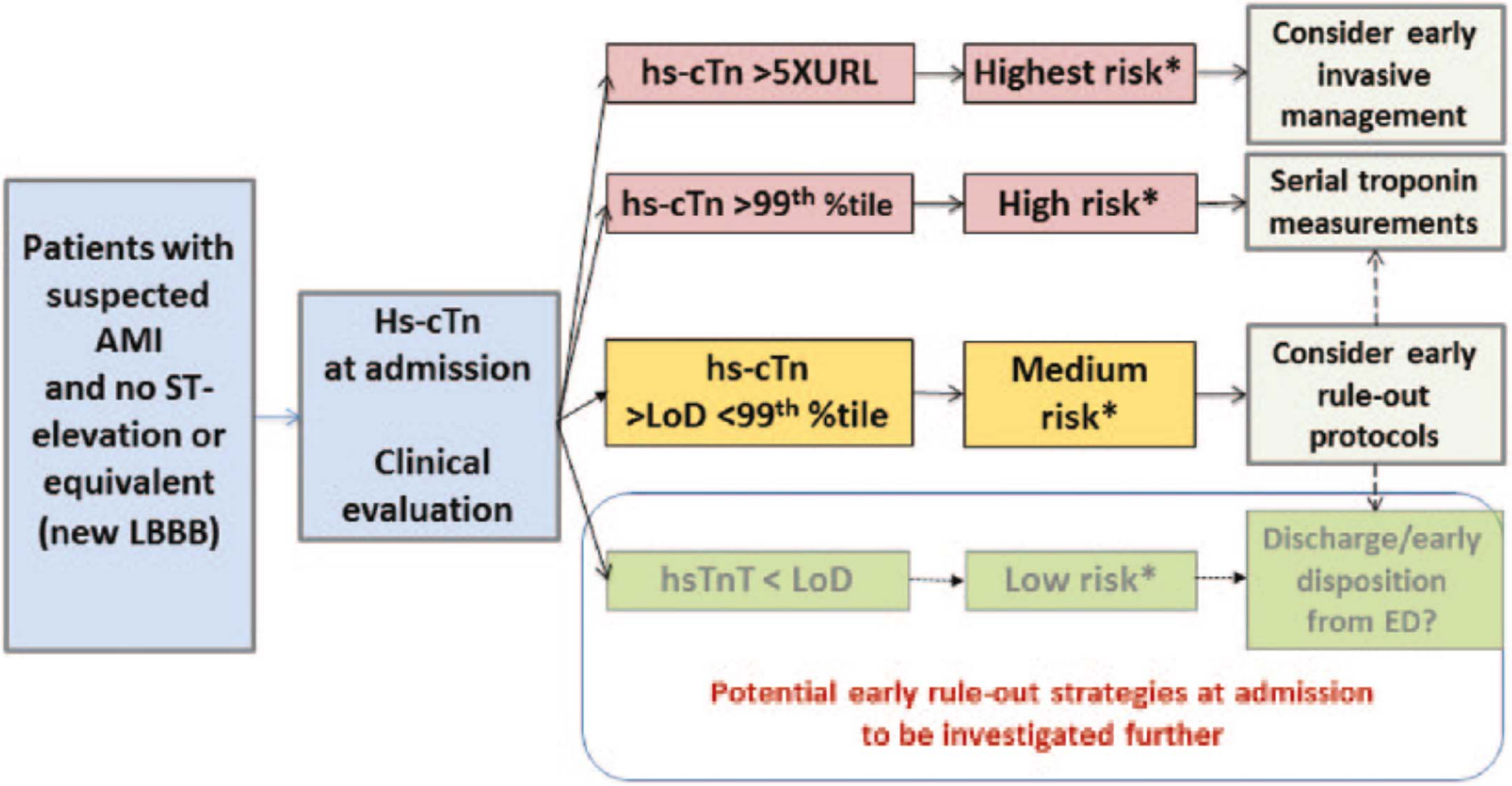
	A	B	C	D	E
Hs-cTnT (Elecsys)	5	12	3	52	5
Hs-cTnI (Architect)	2	5	2	52	6

Hollander et al. Circulation 2016; 134:547–564.

Kardiale Troponine – kritische Fragen

-
-
- **Monitoring: 0/1h oder 0/3h?**

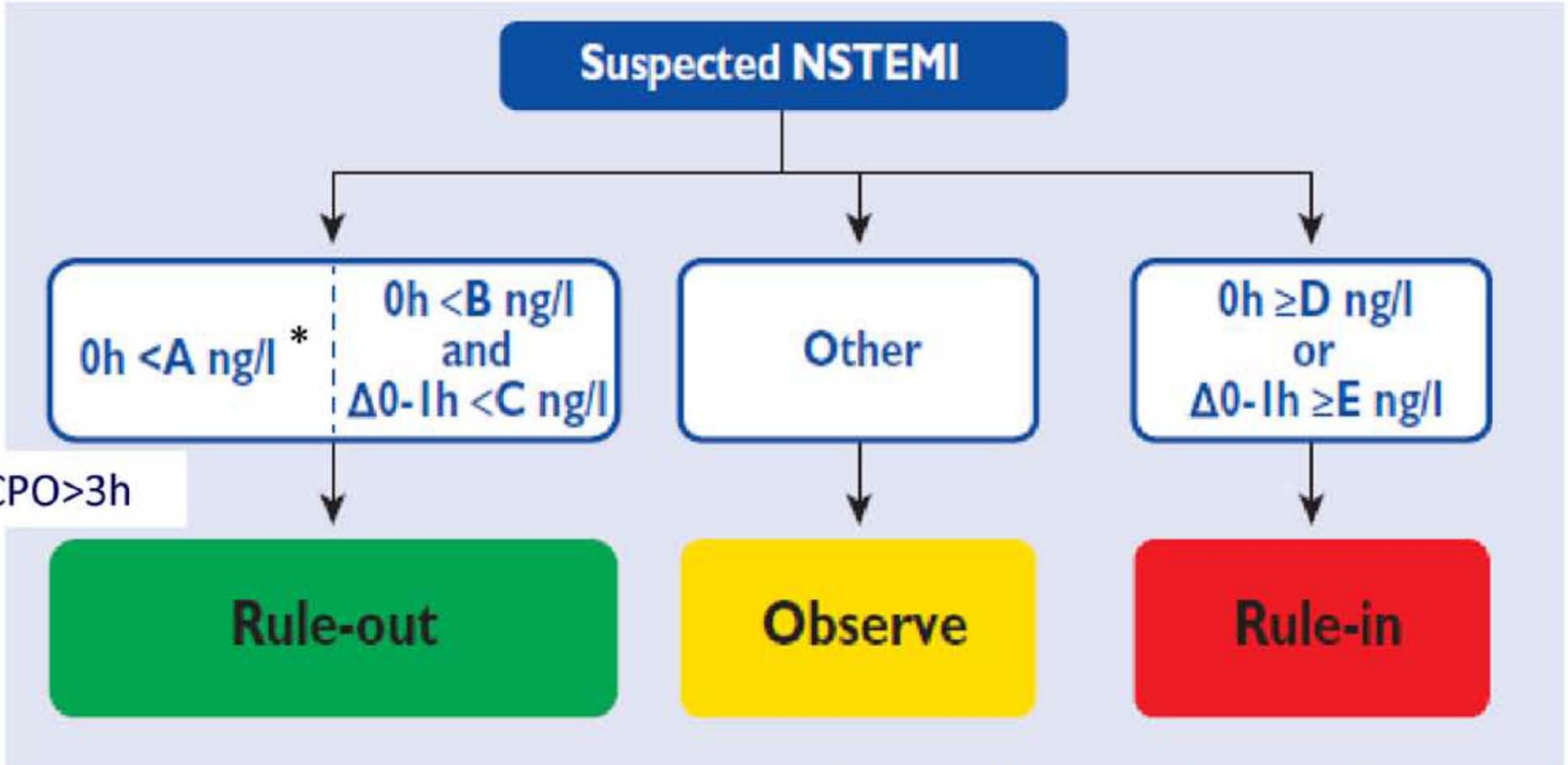
Suggested management flow chart for patients with suspicion of acute myocardial infarction (AMI)



Möckel et al.
European Heart Journal: Acute Cardiovascular Care 2016, in press.

The 0- and 1-hour rule-in and rule-out algorithms using hs-cTn assays in patients presenting with suspected non-ST-elevation myocardial infarction (NSTEMI) to the emergency department

CPO = Chest Pain Onset



	A	B	C	D	E
Hs-cTnT (Elecsys)	5	12	3	52	5
Hs-cTnI (Architect)	2	5	2	52	6

Hollander et al. Circulation 2016; 134:547–564.

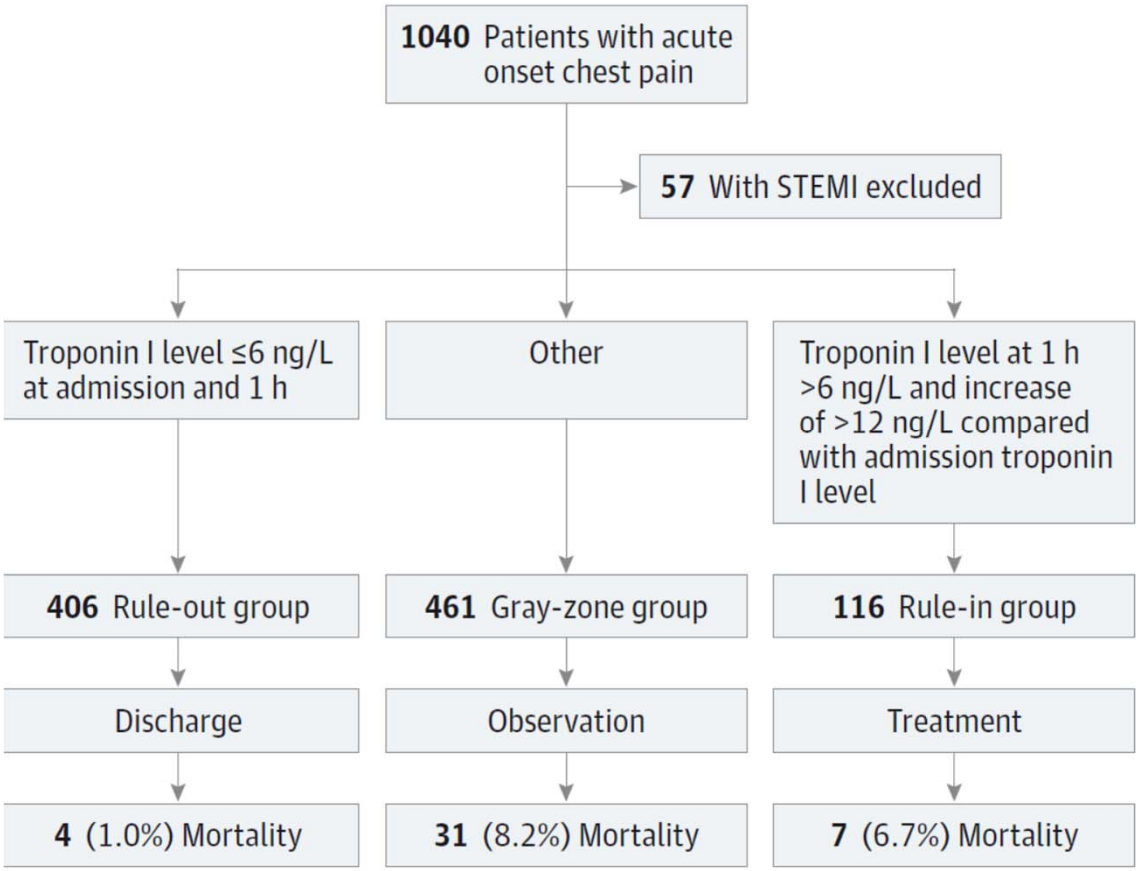
Diagnosis of Myocardial Infarction by hs-Troponin I according to cut-off (LOD vs. 99th percentile) and Algorithm (1h vs 3h)

Rule-out

Troponin I Cutoff Level by Time After Admission	NSTEMI NPV, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)
≤6 ng/L			
Admission only	97.1 (95.2-98.4)	92.2 (87.2-95.7)	61.0 (57.4-64.4)
Admission and 1 h	99.0 (97.5-99.7)[a,b]	97.6 (94.1-99.4)	53.3 (49.7-56.9)
Admission and 3 h	99.5 (98.1-99.9)[c]	98.8 (95.8-99.9)	49.7 (46.1-53.4)
≤27 ng/L (99th Percentile)			
Admission and 1 h	94.8 (93.0-96.3)	77.5 (70.5-83.6)	92.6 (90.5-94.3)
Admission and 3 h	97.0 (95.5-98.1)	87.6 (81.7-92.2)	90.7 (88.4-92.7)

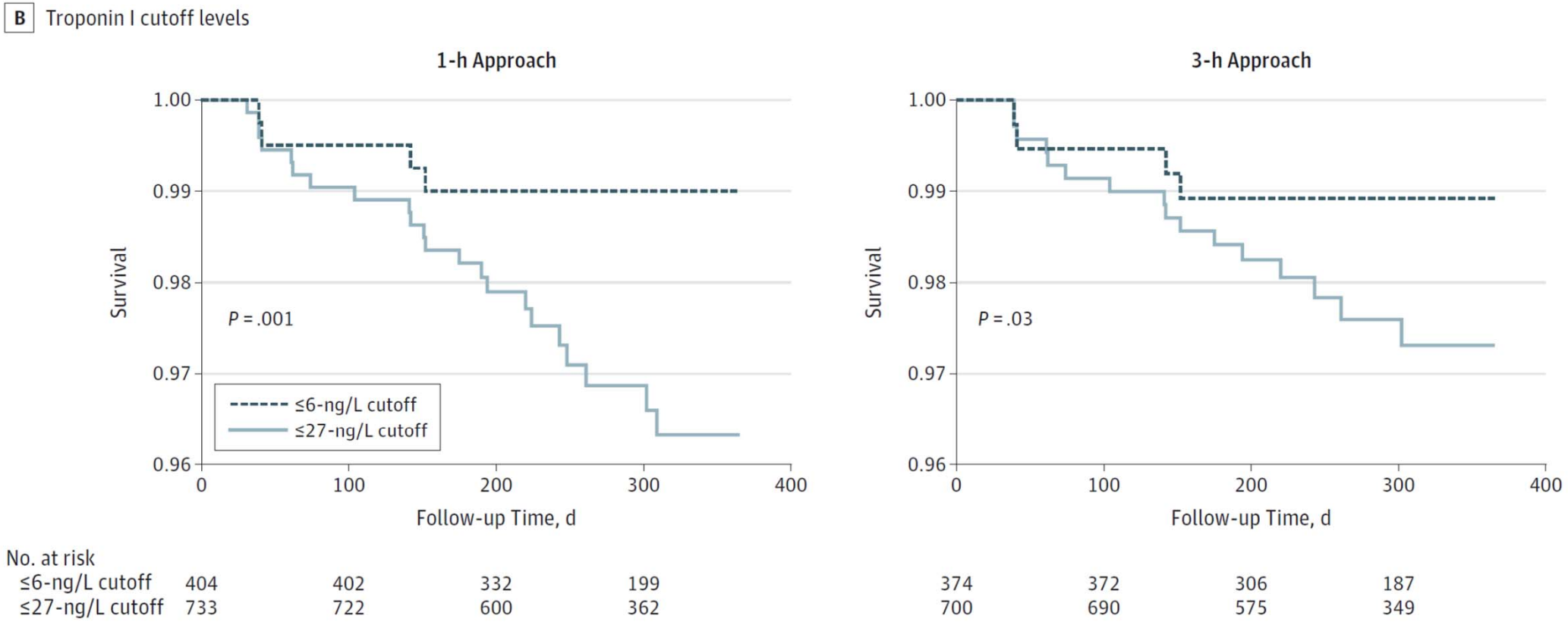
Rule-in

Criteria to Diagnose NSTEMI	NSTEMI (95% CI) PPV, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Troponin I level >6 ng/L at admission	35.2 (30.9-39.7)	92.2 (87.2-95.7)	61.0 (57.4-64.4)
Troponin I level >6 ng/L at 1 h and absolute delta from admission to 1 h ≥12 ng/L	87.1 (79.6-92.6)	59.8 (52.0-67.2)	98.0 (96.7-98.9)
Troponin I level >6 ng/L at 3 h and absolute delta from admission to 3 h ≥12 ng/L	84.6 (78.0-89.9)	77.6 (70.6-83.7)	96.8 (95.3-98.0)



Neumann et al. JAMA Cardiol. 2016;1(4):397-404.

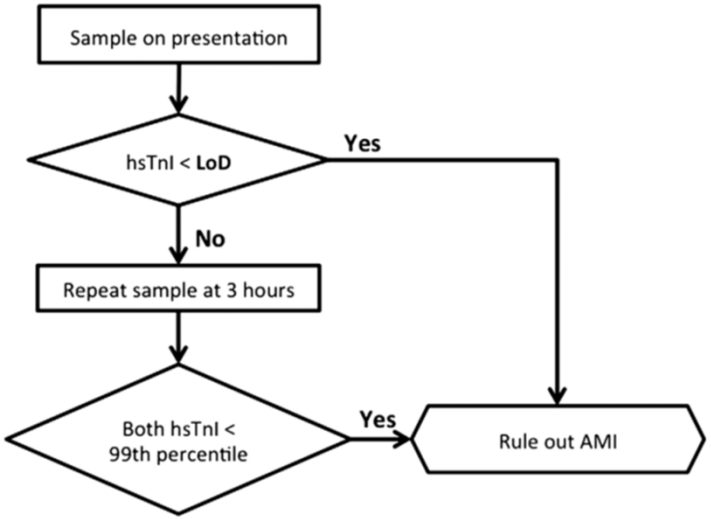
Prognosis of ACS by hs-Troponin I according to cut-off (LOD vs. 99th percentile) and Algorithm (1h vs 3h)



Neumann et al. JAMA Cardiol. 2016;1(4):397-404.

Validation of NICE diagnostic guidance for rule out of myocardial infarction using high-sensitivity troponin tests

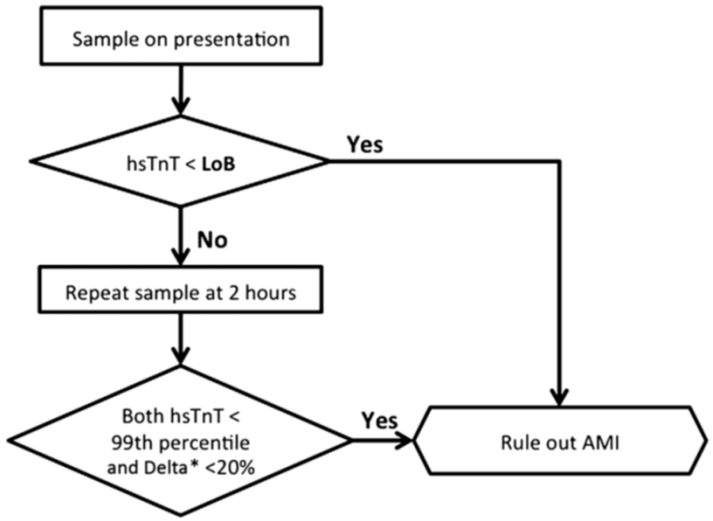
A hsTnI pathway



Hs-cTnI assay

(a)	Combined	
	Ruled out 2506	Ruled in 622
MI at presentation	51 (2.0%)	427 (68.6%)
30-day MACE	267 (10.7%)	457 (73.4%)
NSTEMI	58	427
UAP	209	30

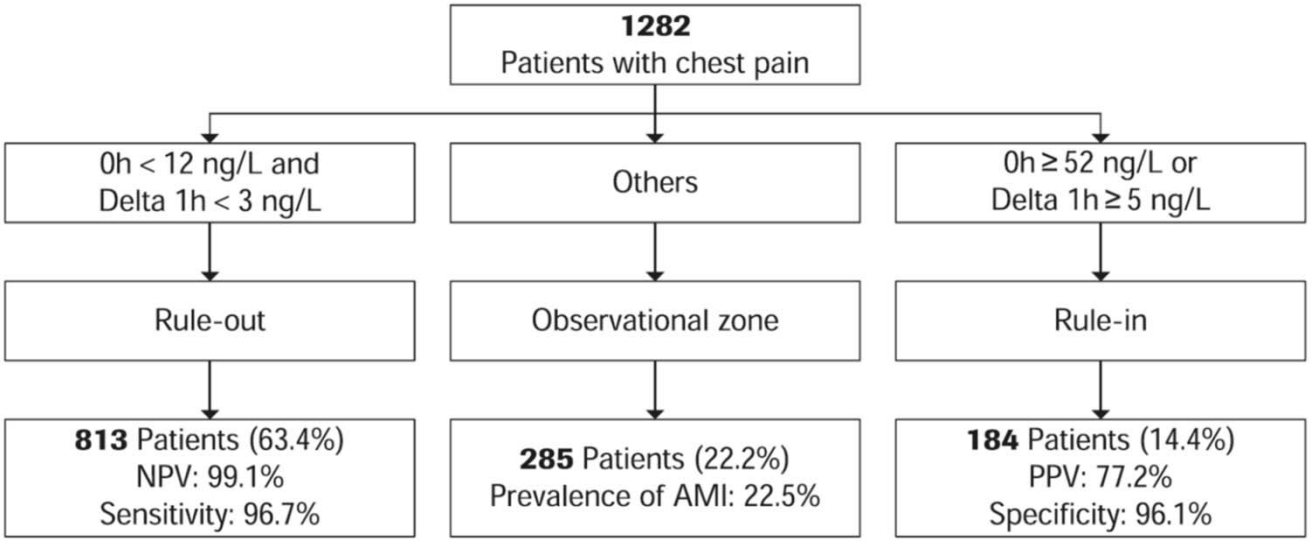
B hsTnT pathway

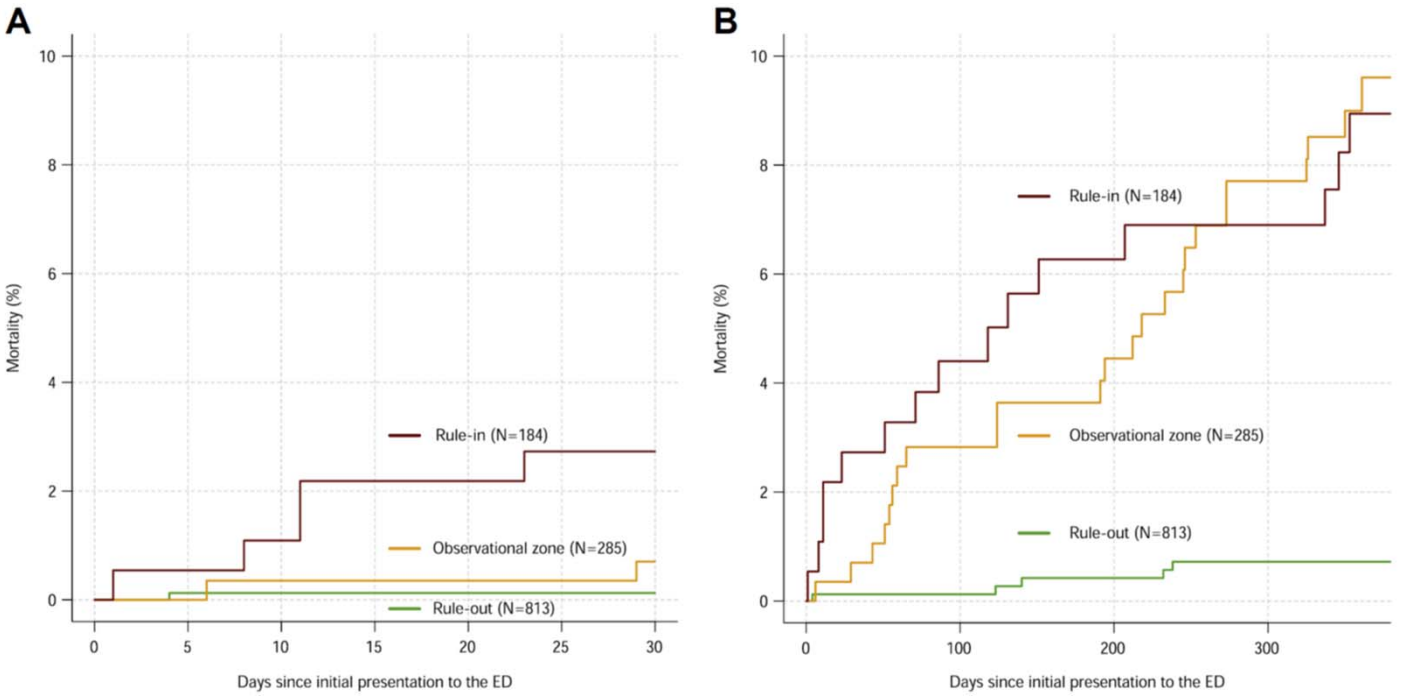


Hs-cTnT assay

(b)	Combined	
	Ruled out 1794	Ruled in 1580
MI at presentation	7 (0.4%)	486 (30.8%)
30-day MACE	153 (8.5%)	621 (39.3%)
NSTEMI	10	492
UAP	143	129

Multicenter Evaluation of a 0-Hour/1-Hour Algorithm in the Diagnosis of Myocardial Infarction With High-Sensitivity Cardiac Troponin T

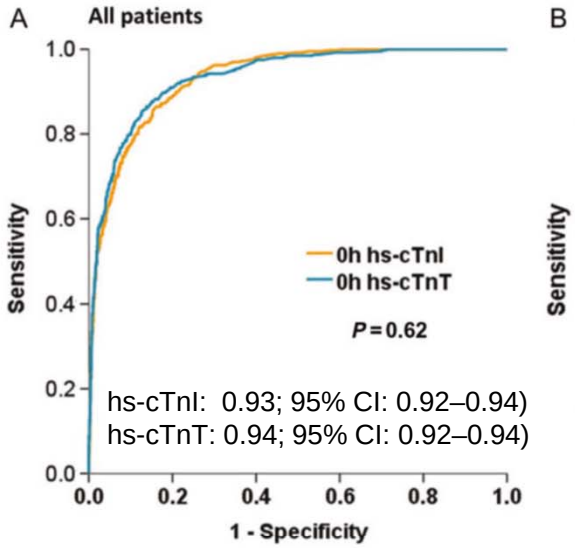


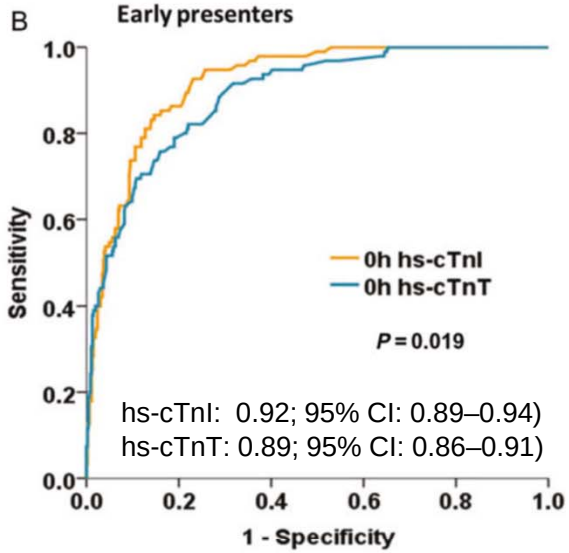


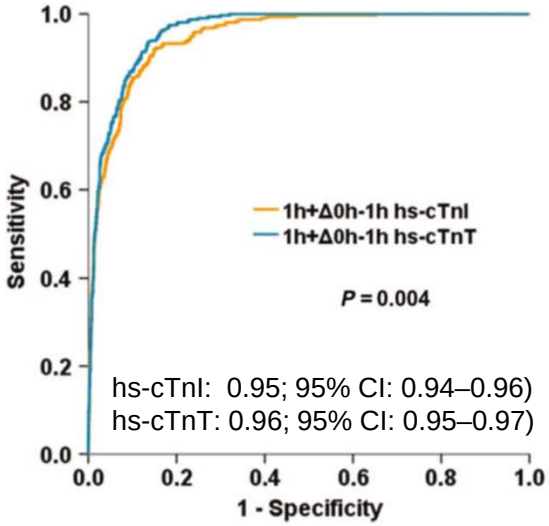
Mueller et al. Ann Emerg Med. 2016;68:76-87

Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction

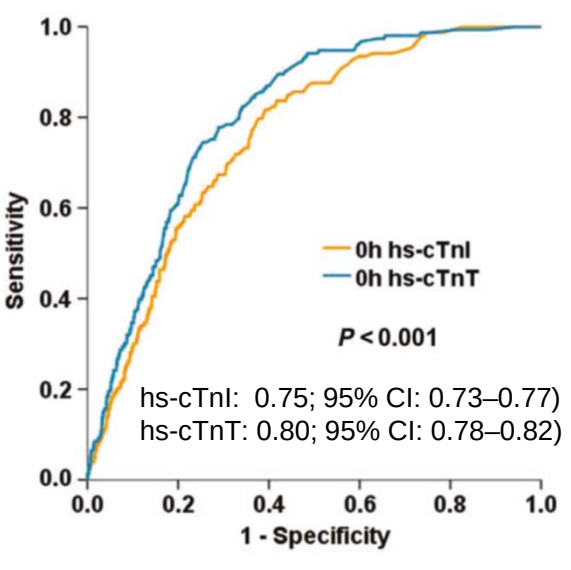
Diagnostic performance: Among 2226 consecutive patients, 18% had an adjudicated final diagnosis of NSTEMI.







Prognostic performance



Gimenez et al, European Heart Journal (2014) 35, 2303–2311

Kardiale Troponine – kritische Fragen:

1h oder 3h Algorithmus?

Cave: bislang nur Beobachtungsstudien, zumeist nur retrospektiv (Biobanken)

Nötig wäre eine randomisierte Studie, Welche die beiden Strategien hinsichtlich outcome vergleicht

	0h/3 h algorithm	0h/1 h algorithm
Negative predictive value for acute MI	98–100%	98–100%
Positive predictive value for acute MI	Unknown, depending on delta change and assay	75–80%
Effectiveness[a]	++	+++
Feasibility	++ requires GRACE score	+++
Challenges	Pain onset cannot be reliably quantified in many patients	Cut-off levels are assay-specific and different from the 99th percentile
Validation in large multicentre studies	+	+++
Additional advantages	Already used clinically	Shorter time to decision

[a]Effectiveness is quantified by the percentage of consecutive chest pain patients clearly classified as rule-out or rule-in of acute MI (i.e., approximately 60% for the 0 h/3 h algorithm and approximately 75% for the 0 h/1 h algorithm).

Eur Heart J. 2015 Aug 29

Kardiale Troponine – kritische Fragen

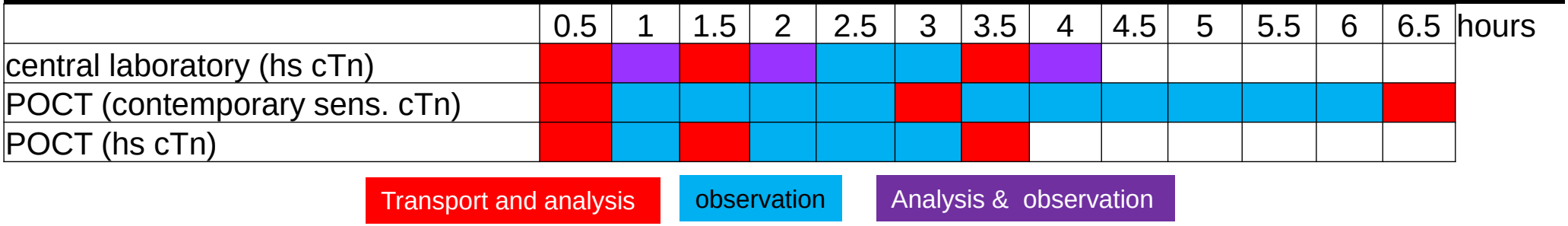
- **Zentrallabor oder POCT?**

Objectives , turn-around-time and clinical implications of point of care testing of cardiac markers

Analytical turn-around-time (minutes)						
	sampling	**transport**	**registration**	**centrifugation**	**analysis**	**Σ minutes**
central laboratory	< 5	10 - 30	< 5	10	10 - 20	**45 to >60**
POCT	< 5		< 5		10 - 20	**<30**

Potential gain of point of care testing of cardiac markers
Decreased turn around time
Decrease the delay of diagnosis (rule-out and rule-in)
Decrease the delay of treatment (rule-in)
Decrease the length of stay in the emergency department (rule-out)
Decrease the length of stay in the chest pain unit (rule-out)

Clinical turn-around-time



Kriterien für die analytische Bewertung verschiedener cTroponin-Tests

Acceptance designation	Total imprecision at the 99th percentile, CV%
Guideline acceptable	≤10
Clinically usable	>10 to ≤20
Not acceptable	>20
Assay designation	**Measurable normal values below the 99th percentile, %**
Level 4 (third generation, hs)	≥95
Level 3 (second generation, hs)	75 to <95
Level 2 (first generation, hs)	50 to <75
Level 1 (contemporary)	<50

F.S. Apple, Clinical Chemistry 55: 1303–1306 (2009)

<u>Standard heutiger cTn Tests im Zentrallabor</u>

(Apple & Collinson, Clin. Chem. 2012):

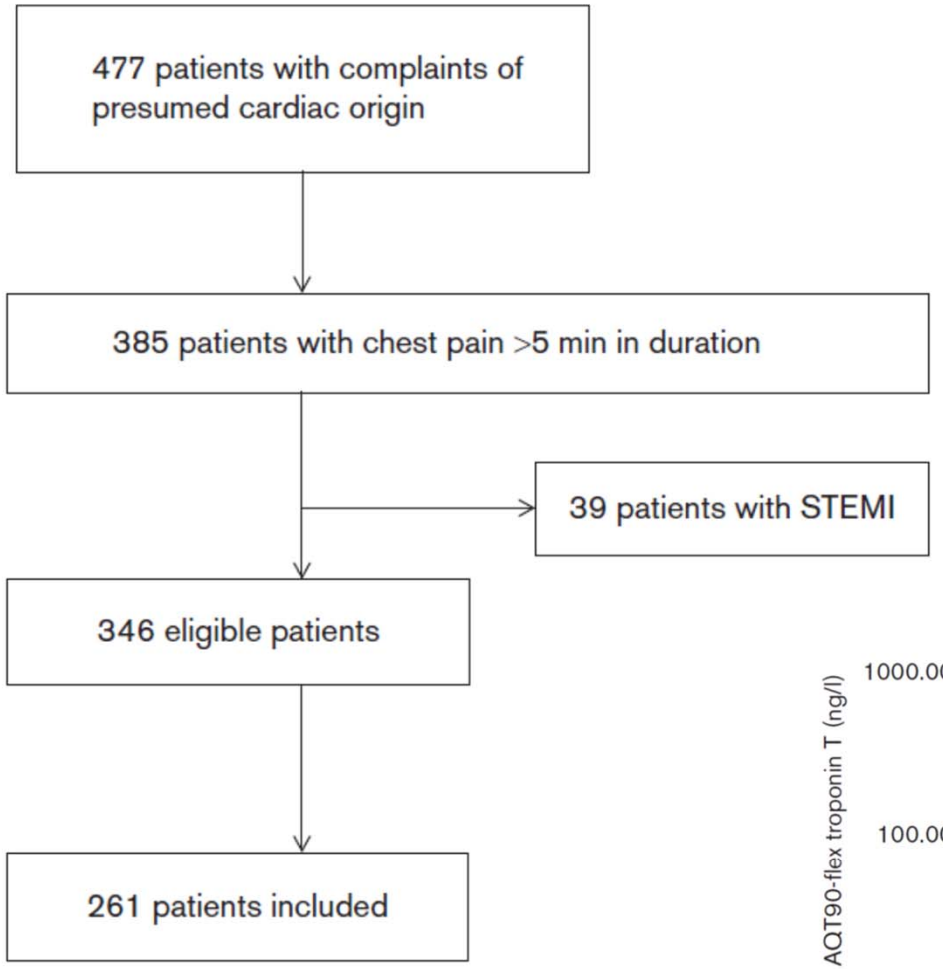
- «guideline-acceptable» oder «clinically usable»
- Level 2 oder level 3

<u>Standard heutiger cTn POCT Tests</u>

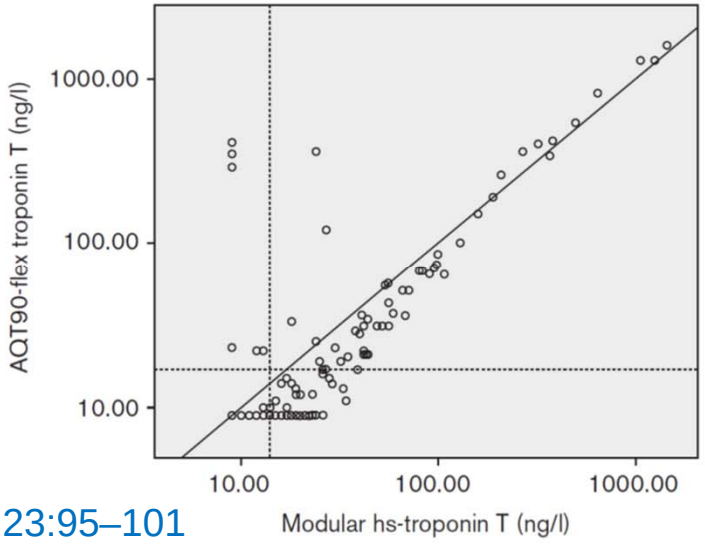
(Amundson & Apple, Clin. Chem. Lab. Med. 2015):

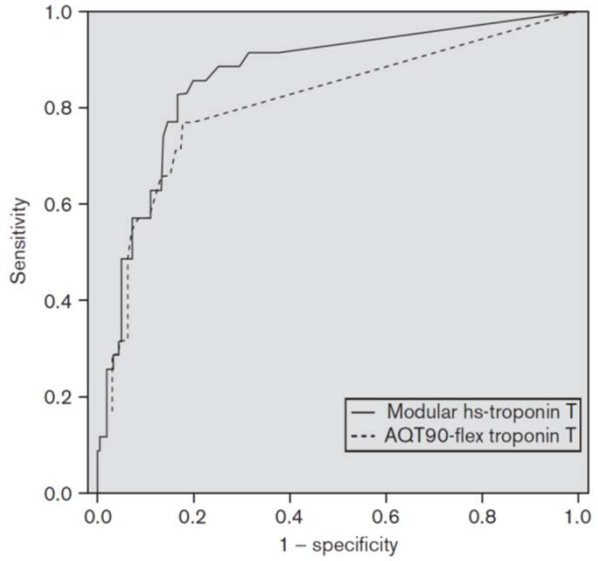
- «not acceptable» (bioMerieux Vidas)
- «clinically usable» (Alere Triage Panel TnI, *laut Herstellerangaben, also nicht in unabhängigen Studien geprüft*)
- wegen fehlender Angaben nicht beurteilbar
  chiniline-i chroma, Dxpress reader, Eurolyser Smart,
  Roche cardiac reader, Roche cobas h232, Samsung LABGEO)

Point-of-care troponin T is inferior to high-sensitivity troponin T for ruling out acute myocardial infarction in the emergency department



	Laboratory-based modular hs-cTnT	Point-of-care AQT90-flex cTnT	*P*
99th percentile (ng/l)	14	17	–
Sensitivity	91 (75–98)%	68 (49–82)%	0.008
Specificity	75 (69–80)%	87 (82–91)%	< 0.001
NPV	98 (95–100)%	95 (91–97)%	–
PPV	35 (26–46)%	43 (30–58)%	–
LR (–)	0.12 (0.04–0.35)	0.37 (0.23–0.60)	–
LR (+)	3.63 (2.83–4.65)	5.37 (3.57–8.07)	–
AUC	0.88 (0.84–0.92)	0.82 (0.77–0.87)	0.05





ter Avest et al,
European Journal of Emergency Medicine 2016, 23:95–101

Comparison of five point-of-care troponin assays for their diagnostic performance

Manufacturer	Siemens	Radiometer		Mitsubishi	Alere
POC System	**Stratus CS 200** 	**AQT90 FLEX** 		**Pathfast** 	**Triage Cardio with Next Generation TnI** 
Troponin	I	T	I	I	I
Measuring range (ng/l)	30-50000	10-25000	10-50000	1-50000	10-10000
99. percentile (ng/l)	70	17	23	20	20
CV (%) at 99. percentile	<10	15	12	5	<17
CV=10% at concentration (ng/l)	60	26	27	3	37
Specimen	Heparin whole blood or plasma	Heparin and EDTA whole blood or plasma	Heparin and EDTA whole blood or plasma	Heparin and EDTA whole blood or plasma	EDTA whole blood or plasma
Sample volume	200 µl plasma or 2-2.5 ml whole blood	2 ml	2 ml	100 µl	250 µl
Classification	guideline acceptable	-	clinically usable	guideline acceptable	clinically usable

Suh, Hof, Keller-Lang, von Eckardstein, Gawinecka, submitted

Imprecision and accuracy of five point-of-care troponin assays

POC System	Control material	Target cTn concentration (ng/L)	Measured mean cTn concentration (ng/L)	Bias (%)	CV%
PATHFAST™	QC level 1	73	81	11	7.7
	QC level 2	1370	1266	-7.6	8.0
Stratus CS 200	QC level 2	942	944	0.2	2.9
	QC level 3	3890	3977	2.2	4.5
AQT90 FLEX cTnI	MC1	36	31	-15	11
	MC2	1120	1127	0.6	3.7
AQT90 FLEX cTnT	TnT1	56	56	0.8	5.1
	TnT2	853	884	3.6	2.8
Triage MeterPro	Triage total level 1	40	54	34	13

Suh, Hof, Keller-Lang, von Eckardstein, Gawinecka, submitted

Kriterien für die analytische Bewertung verschiedener cTroponin-Tests

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Level 4 (third generation, hs)	≥95
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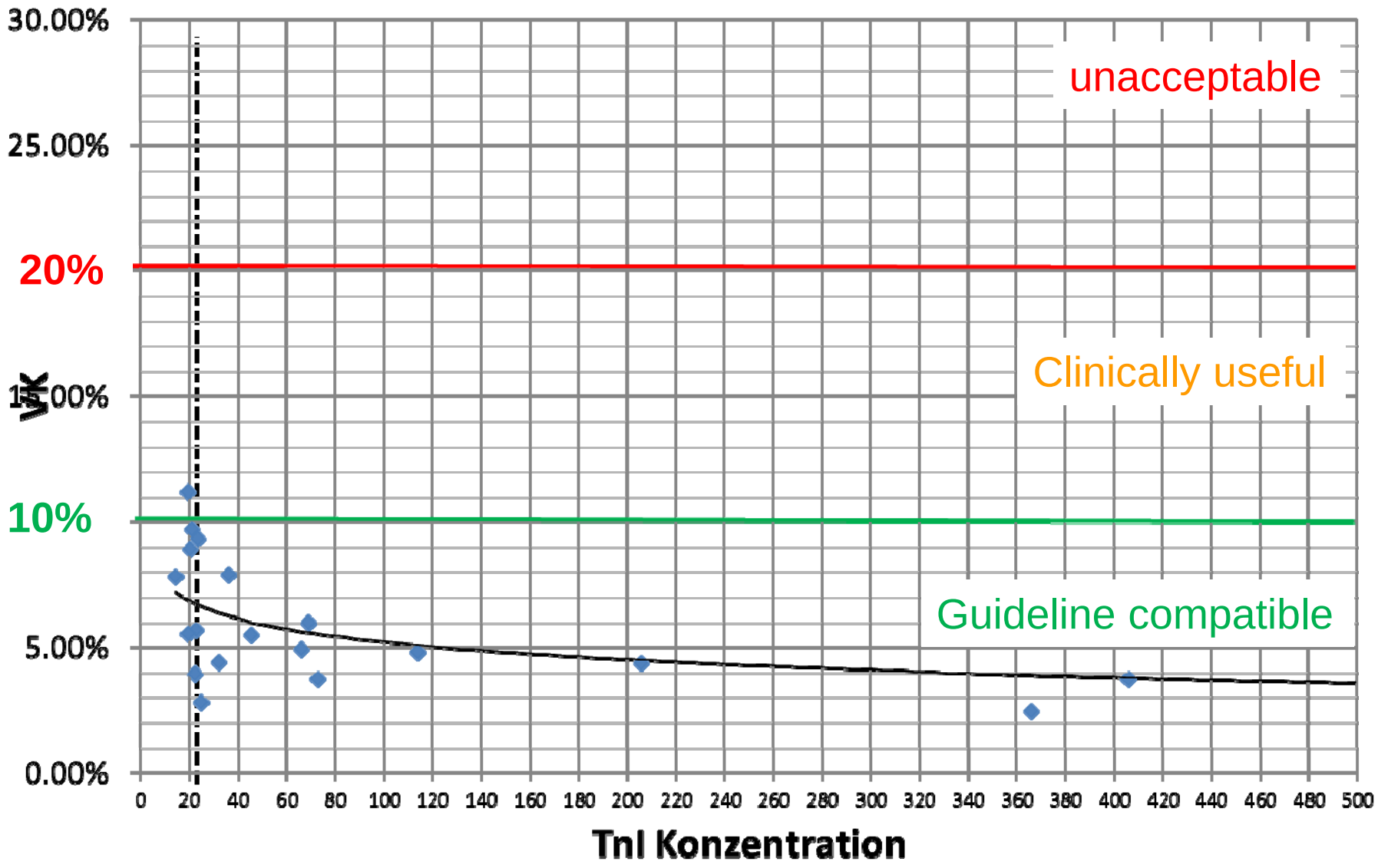
Level 2 (first generation, hs)	50 to <75
Level 1 (contemporary)	<50

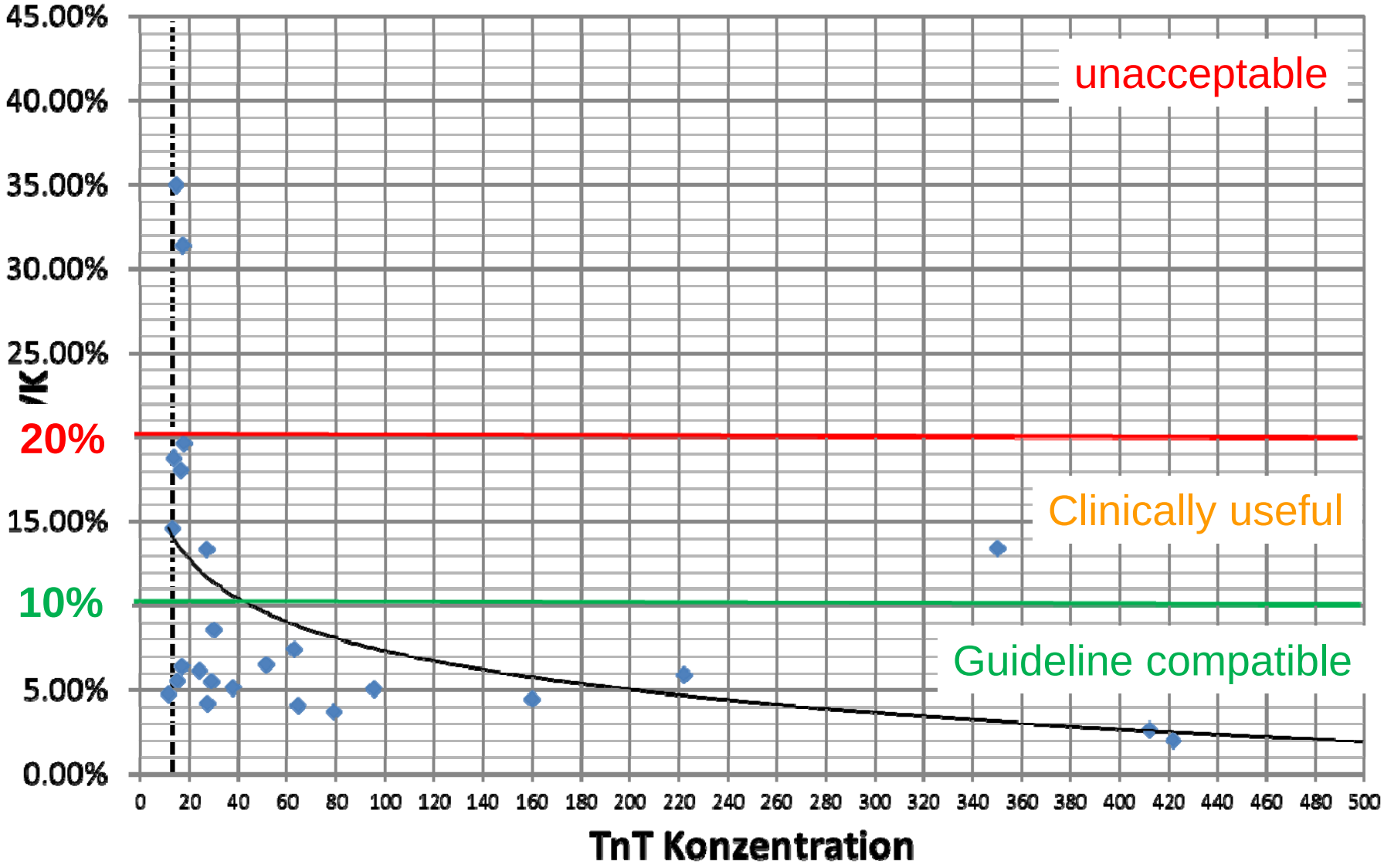
F.S. Apple, Clinical Chemistry 55: 1303–1306 (2009)

Functional Assay Sensitivity of a "guideline conform" POC troponin assay



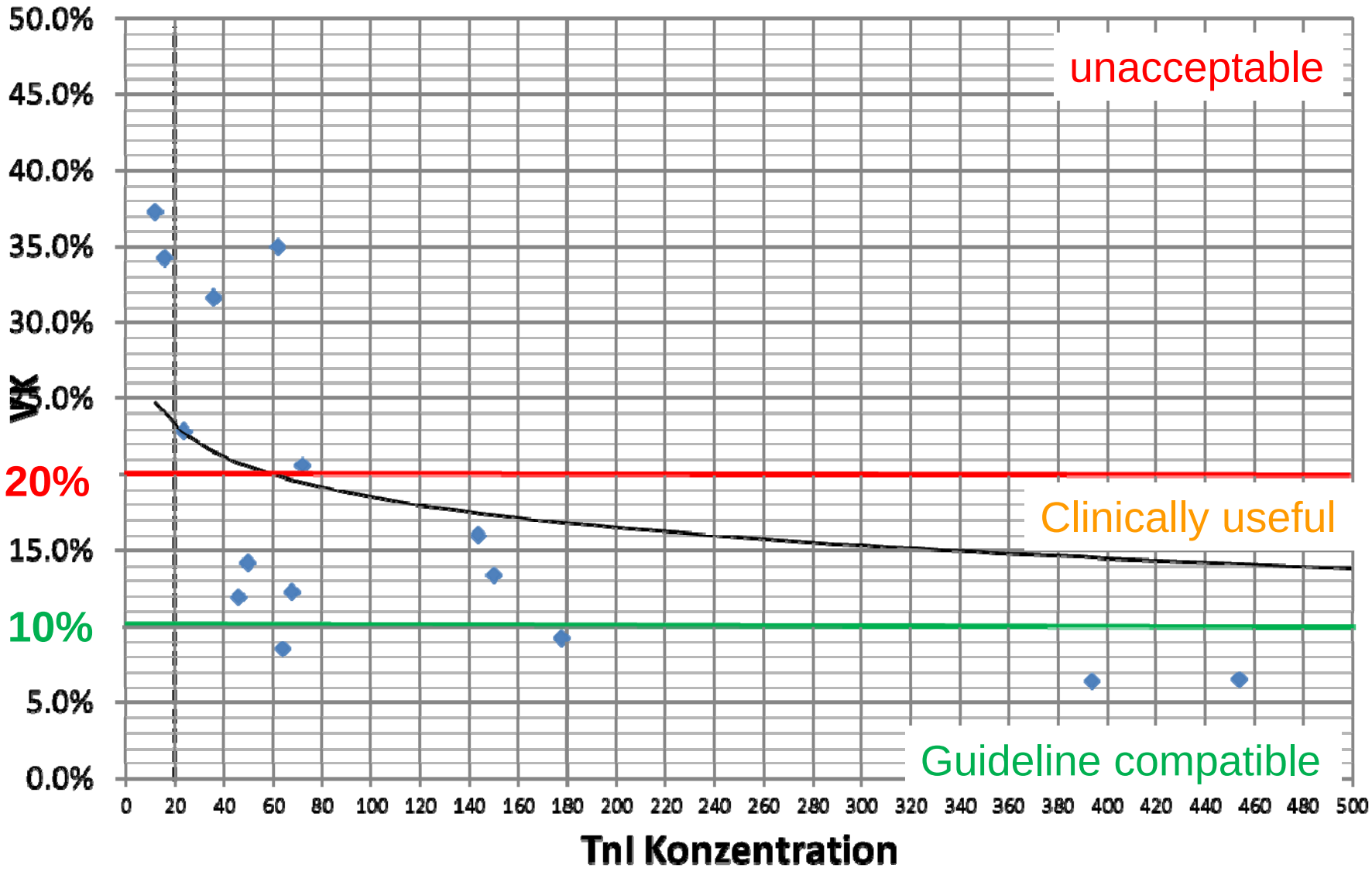
Suh, Hof, Keller-Lang, von Eckardstein, Gawinecka, submitted

Functional Assay Sensitivity of a "clinically useful" POC troponin assay



Suh, Hof, Keller-Lang, von Eckardstein, Gawinecka, submitted

Functional Assay Sensitivity of an unacceptable POC troponin assay



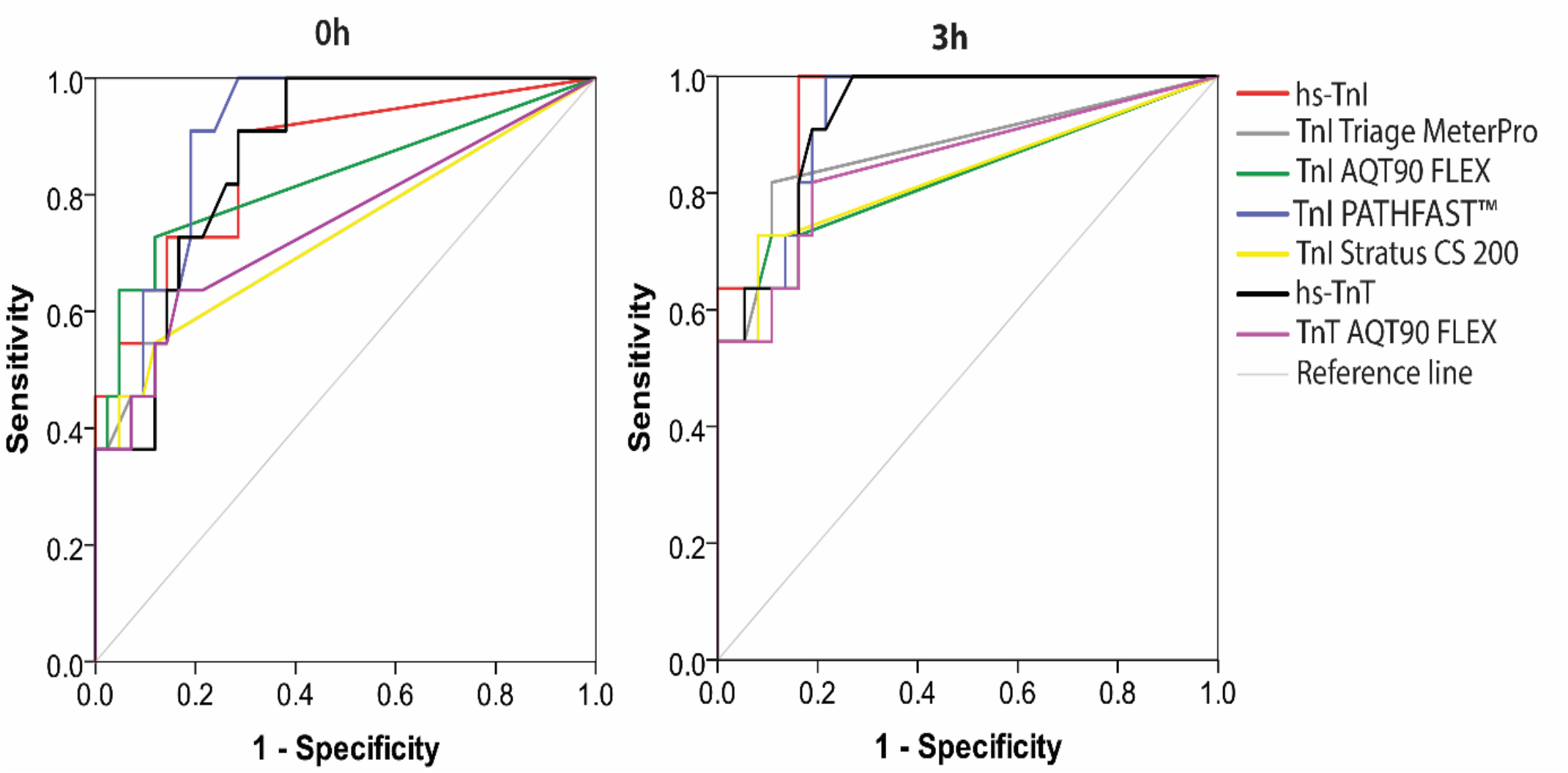
Suh, Hof, Keller-Lang, von Eckardstein, Gawinecka, submitted

Analytical performance of five point-of-care troponin assays according to Apple's scorecard

	PATHFAST™		Stratus CS 200		AQT90 FLEX cTnI		AQT90 FLEX cTnT		Triage MeterPro	
	claimed	measured	claimed	measured	claimed	measured	claimed	measured	claimed	measured
99th percentile (ng/L)*	20	-	70	-	23	-	17		20	-
CV (%) at 99th percentile	5	11.5	<10	9.2	12	7.4	15	16	<17	40
10% Functional assay sensitivity (ng/L)	3	24	60	64	27	16	26	31	37	840
Classification	guideline accep-table	clinically usable	guideline accep-table	guideline accep-table	clinically usable	guideline accep-table	-	clinically usable	clinically usable	Not accep-table

Suh, Hof, Keller-Lang, von Eckardstein, Gawinecka, submitted

Diagnostic performance of cTn assays in the diagnosis of myocardial infarction according to the 0/3h ESC algorithm



Suh, Hof, Keller-Lang, von Eckardstein, Gawinecka, submitted

Diagnostic performance of cTn assays in the diagnosis of myocardial infarction according to the 0/3h ESC algorithm: 0h

Assay	Cut-off (ng/L)	n#	0h				
			AUC (95%CI)	Sensitivity*	Specificity*	NPV§	PPV¥
hs-cTnI	26	13/68	0.86 (0.75-0.96)	62%	88%	92%	50%
Triage MeterPro	20	10/41	0.71 (0.53-0.89)	50%	93%	88%	63%
AQT90 FLEX cTnI	23	13/63	0.84 (0.71-0.96)	46%	94%	89%	60%
PATHFAST™	20	12/63	0.90 (0.82-0.97)	67%	91%	93%	57%
Stratus CS 200	70	13/63	0.76 (0.62-0.90)	39%	92%	88%	50%
hs-cTnT	14	13/68	0.88 (0.80-0.95)	92%	71%	98%	38%
AQT90 FLEX cTnT	17	13/63	0.74 (0.59-0.89)	46%	87%	89%	43%

Suh, Hof, Keller-Lang, von Eckardstein, Gawinecka, submitted

Diagnostic performance of cTn assays in the diagnosis of myocardial infarction according to the 0/3h ESC algorithm: 3hours

Assay	Cut-off (ng/L)	n#	3h				
			AUC (95%CI)	Sensitivity*	Specificity*	NPV§	PPV¥
hs-cTnI	26	13/68	0.96 (0.92-1.00)	77%	87%	95%	53%
Triage MeterPro	20	10/41	0.86 (0.72-1.00)	70%	88%	92%	58%
AQT90 FLEX cTnI	23	13/63	0.86 (0.72-0.99)	69%	92%	94%	64%
PATHFAST™	20	12/63	0.94 (0.89-1.00)	75%	87%	95%	53%
Stratus CS 200	70	13/63	0.86 (0.73-0.99)	77%	92%	95%	67%
hs-cTnT	14	13/68	0.94 (0.88-0.99)	100%	72%	100%	41%
AQT90 FLEX cTnT	17	13/63	0.87 (0.75-0.99)	62%	86%	92%	47%

Suh, Hof, Keller-Lang, von Eckardstein, Gawinecka, submitted

Kardiale Troponine – kritische Fragen:
Zentrallabor oder POCT?

- **funktionelle Assay-Sensitivitätsgrenzen gegenwärtiger cTn POC Tests zumeist unbekannt oder nicht publiziert**
- **zumeist allenfalls *contemporary* sensitiv (also *«clinically useful»* aber nicht *«guideline-konform»*): Mehrzahl der POC Tests für Anwendung der ESC guidelines (0/1h- oder 0/3h-Algorithmen) ungeeignet**
- **gegenwärtige cTn-POC Tests bringen zumeist gegenüber Zentrallabor keinen Zeitgewinn im klinischen Entscheidungs-prozess.**
- **hs-cTn POC Tests erforderlich**