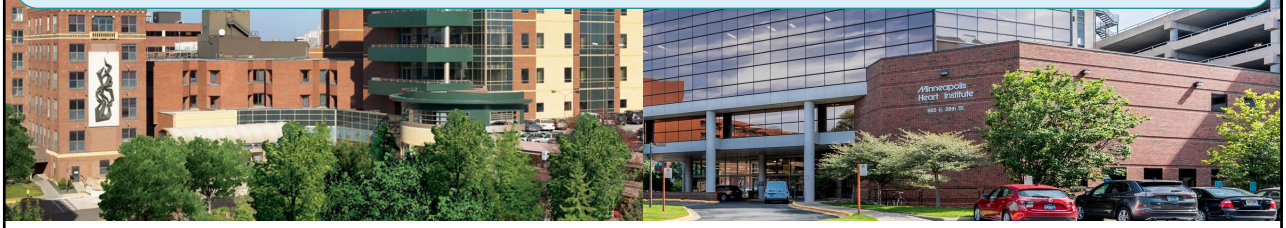
1

MHIF Cardiovascular Grand Rounds – December 5th, 2022.

Implementation of High-Sensitivity Cardiac Troponin T: The Time is Now



Yader Sandoval, MD, FACC, FSCAI
Interventional Section, Minneapolis Heart Institute, Abbott Northwestern Hospital
Center for Coronary Artery Disease, Minneapolis Heart Institute Foundation, Minneapolis, MN.
Adjunct Associate Professor of Medicine, Mayo Clinic College of Medicine and Science

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DISCLOSURES

- Abbott Diagnostics: advisory board
- Roche Diagnostics: advisory board, speaker
- Patent #20210401347 (machine learning models for ECG-based troponin level detection)

1. Hs-cTnT implementation: why and when?

Allina transition to Roche instrumentation → Early 2023

- ❑ Allina's fleet of **chemistry analyzers are at the end of life** with increasing downtimes.
- ❑ New instrumentation will provides improved TATs, reducing critical lab turnaround times
- ❑ New instruments offer largest test menu (190 assays), consolidating platforms and reducing send outs.
- ❑ **Go-live date for Roche implementation** → January 3rd, 2023.

How does this impact cardiology practice?

- ❑ Cardiac troponin testing: transition from conventional Abbott's cTnI to Roche's Gen 5 cTnT (hs-cTnT).
- ❑ Natriuretic peptide testing: transition from Abbott's BNP to Roche's NT-proBNP.

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Allina Health Multidisciplinary High-Sensitivity Cardiac Troponin T Implementation Team

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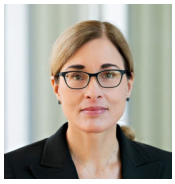
Dr. Anthony
Laboratory Medicine


Dr. O'Laughlin
Emergency Medicine


Dr. Sandoval
Cardiology


Dr. Bradley
Cardiology


Dr. Katz
Laboratory Medicine


Dr. Lefebvre
Internal Medicine


Dr. Drexel
Cardiology


Greg Kerola
CV Project Manager

Weekly 1-hour meetings every Thursday at 7 a.m. since mid-September 2022

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Laboratory Medicine
- Dr. Lauren Anthony
- Dr. Brenda Katz
- Diana K. Weyhrauch
- Dean A. Derhaag
- Lawrence R. Rothstein
- Heather Grussing (Lab Project Manager)

Emergency Medicine
- Dr. Daniel O' Laughlin
- Wendy Baumgardt

Cardiology
- Dr. Yader Sandoval
- Dr. Steven Bradley
- Dr. Todd Drexel
- Dr. Cavalcante

Cardiovascular Emergencies
- Greg Kerola (CV Project Manager)
- Louise V. Anderson
- Will O. Belzer

Internal Medicine
- Dr. Anthony J. Lefebvre
- Dr. Daniel Pollman (IM resident)

Clinical Nursing Specialist
- Roberta Wagner

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2. What is a high-sensitivity cardiac troponin assay?

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CARDIAC TROPONIN ASSAYS

	Contemporary cTn Assay	High Sensitivity cTn Assay
Analytical sensitivity	▪ Measure cTn in **LESS** than 50% of a healthy cohort.	▪ Measure cTn in **≥ 50%** of a healthy men and women.
Imprecision	▪ Acceptable CV≤20% at 99th URL.	▪ **CV<10%** at the 99th URL
"Healthy" reference cohort		
	Reportable measured concentration in <50%.	Reportable measured concentration >50%.

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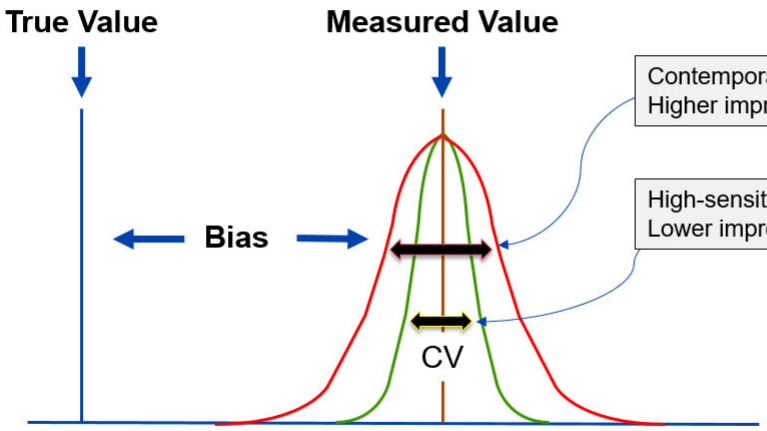
Total Imprecision: Coefficient of Variation (CV)



Adapted from Fierdoz O. Essential laboratory knowledge for the clinician. Continuing Medical Education, [S.l.], v. 30, n. 7, p. 244-248, jun. 2012.

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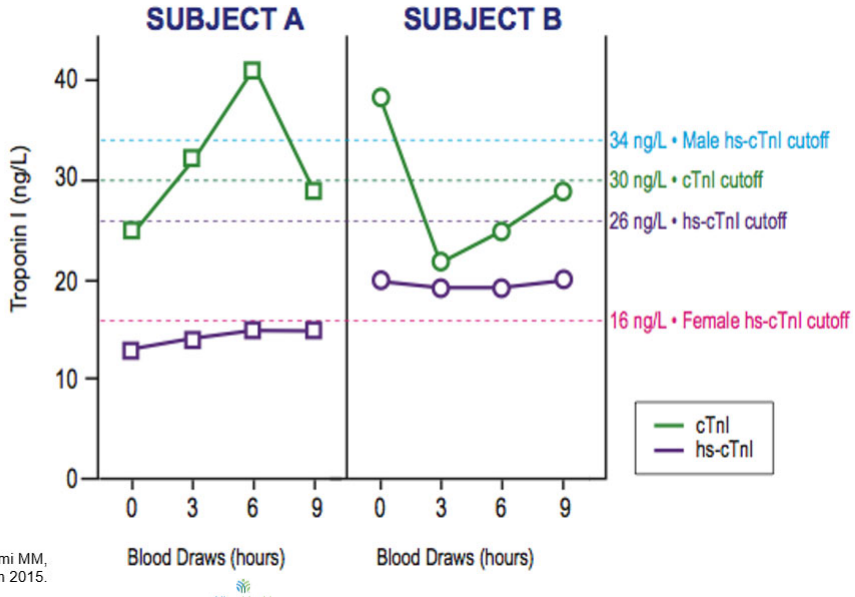
Less "analytical noise"



Sandoval Y, Smith SW, Schulz KM, Murakami MM, Love SA, Nicholson J, Apple FS. Clin Chem 2015.

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Key Message: not all cTn assays are created equal – KNOW YOUR ASSAY

Manufacturer | Assay type | Analytical sensitivity | Imprecision (%CV) | Lowest reportable value (LoQ) | 99th percentile

Hs-assays	LoD, ng/L	20% CV (LoQ), ng/L	99th URL, ng/L	%CV at 99th URL	% >LOD	Epitopes/antibodies	Detection tag
Abbott ARCHITECT hs-cTnI	1.7	2.3	17/35	5.0/4.1	85%	C: 24-40; D: 41-49	Acridinium
Beckman Coulter Access hs-cTnI (Li heparin plasma)	1-2	0.9-2.3	11.6/19.8	4.2/3.6	>50%	C: 41-49; D: 24-40	ALP
Roche TnT Gen 5 STAT	3; 5 for e411	6	14/22	<10	55.1%	C: 125-131; D: 136-147	Ruthenium
Siemens ATELLICA	1.6	2.5	38.6/53.5	<4	75%	C:41-50, 171-190, D:29-34	Luminescence

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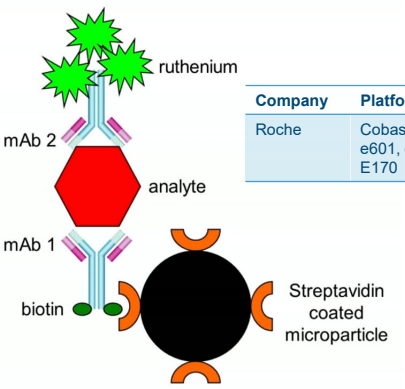
US FDA 510k cleared hs-cTn assays

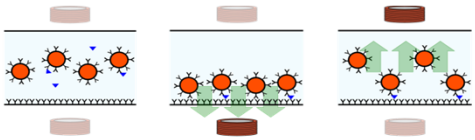
Cardiac Troponin T: 1 manufacturer



Company	Platforms	Assay
Roche	Cobas e601, e602, E170	TnT Gen 5 STAT

C: 87-91
D: 23-29

Cardiac Troponin I: multiple companies



Company / Platform / Assay	Capture (C) & Detection (D) antibodies
Abbott ARCHITECT hs-cTnI	C: 24-40; D: 41-49
Beckman Coulter / Access 2 hs-cTnI (plasma)	NA
Beckman Coulter / Access 2 hs-cTnI (serum)	NA
Beckman Coulter / DxI Access hs-cTnI (plasma)	NA
Beckman Coulter / DxI Access hs-cTnI (serum)	NA
Siemens ATELLICA High Sensivity TnI (TNIH)	C: 41-50, 171-190; D: 29-34
Siemens ADVIA Centaur XP/XPT/CP High Sensitivity TnI (TNIH)	C: 41-50, 171-190; D: 29-34
Siemens Dimension VISTA High Sensitivity TnI (TNIH)	C: 41-50, 171-190; D: 29-34
Siemens Dimension ExL High Sensitivity TnI (TNIH)	C: 41-50, 171-190; D: 29-34

Figure (left) from Jeffrey W. Meesen, PhD – Troponin and ACS, December 15th, 2017; Figure (right) for illustration/educational purposes courtesy of Fred S. Apple, PhD
Information regarding hs-cTn assays per IFCC C-CB website.

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3. Background: why?

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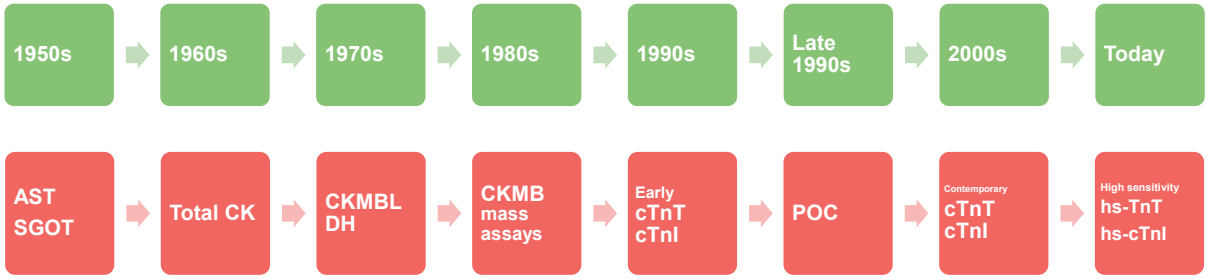
Evolution of Cardiac Biomarkers



* Please note that hs-cTn assays have been used clinically outside the US for more than 10 years.

Lewandroski KB. Clin Lab Med 2014; Ladenson JH. Clin Chem 2012.

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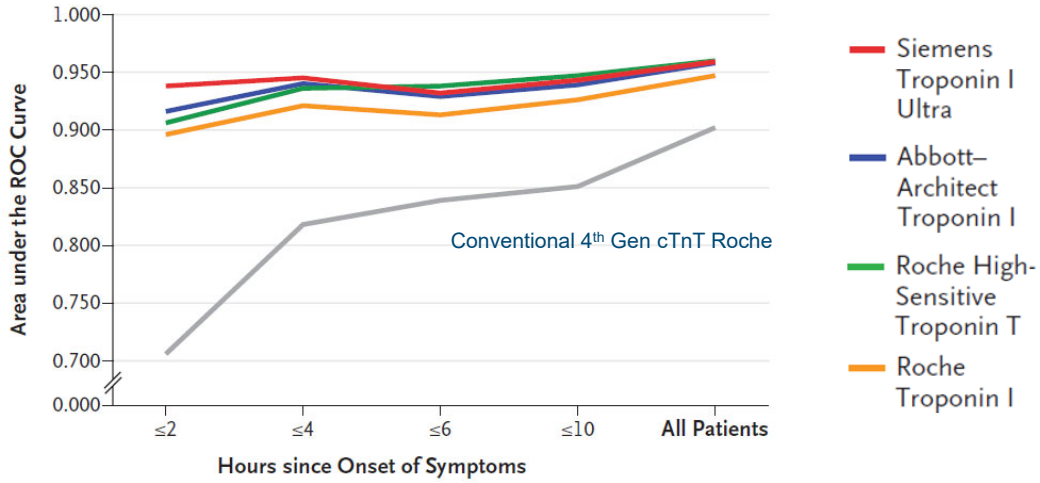
The case to improve the diagnostic performance of cardiac troponin assays



Reichlin T et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009; 361: 858-67.

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Limitations of Contemporary cTn Assays

Delayed increase of circulating levels for 3-4 hours, often requiring sampling for 6-12 hours.

Delays in Excluding Disease

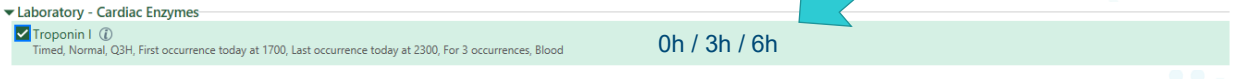
- Delays in **rule-out** interferes with evaluation of alternative diagnoses and contributes to expensive overcrowding in the ED.

Delays in Diagnosing Disease

- Delays in **rule-in** hold back prompt use of evidence-based therapies.

Reichlin et al. Arch Intern Med 2012.

The present ANW ACS admission order set



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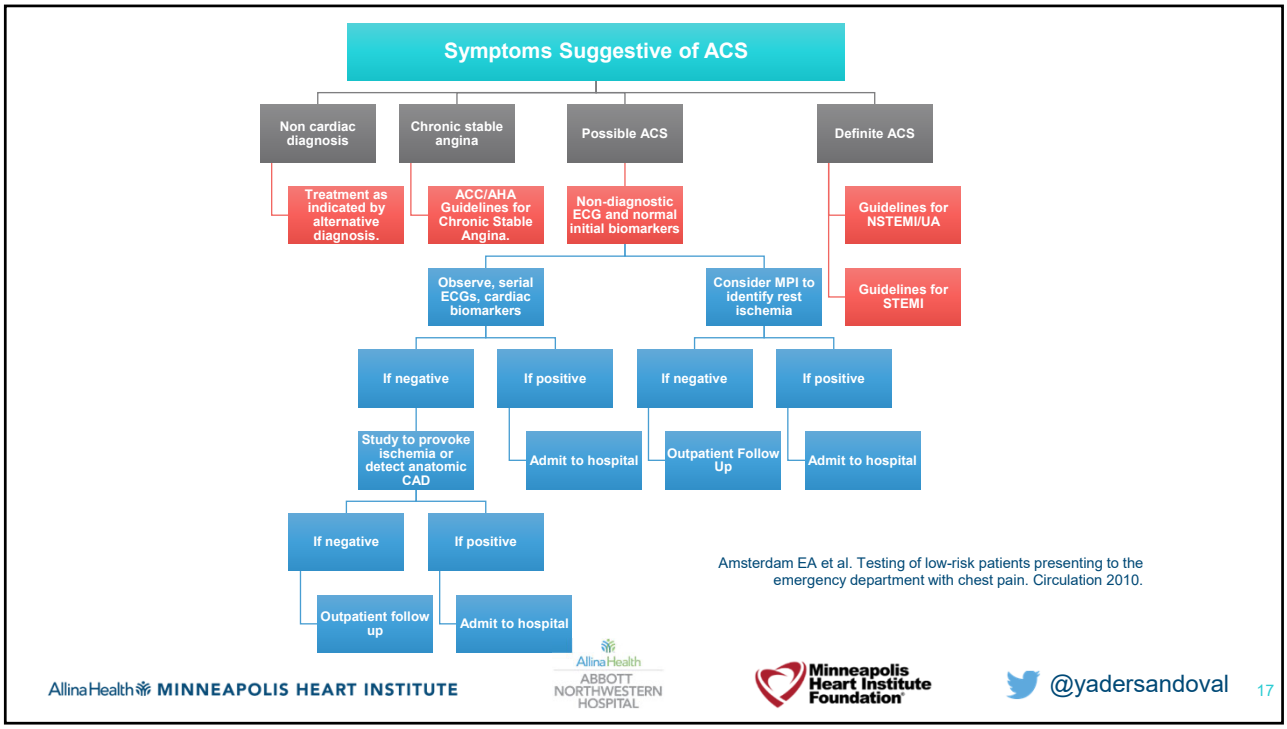
Symptoms Suggestive of ACS
Non cardiac diagnosis
Chronic stable angina
Possible ACS
Definite ACS
Treatment as indicated by alternative diagnosis.
ACC/AHA Guidelines for Chronic Stable Angina.
Non-diagnostic ECG and normal initial biomarkers
Guidelines for NSTEMI/UA
Observe, serial ECGs, cardiac biomarkers
Consider MPI to identify rest ischemia
Guidelines for STEMI
If negative
If positive
If negative
If positive
Study to provoke ischemia or detect anatomic CAD
Admit to hospital
Outpatient Follow Up
Admit to hospital
If negative
If positive
Outpatient follow up
Admit to hospital
Amsterdam EA et al. Testing of low-risk patients presenting to the emergency department with chest pain. Circulation 2010.
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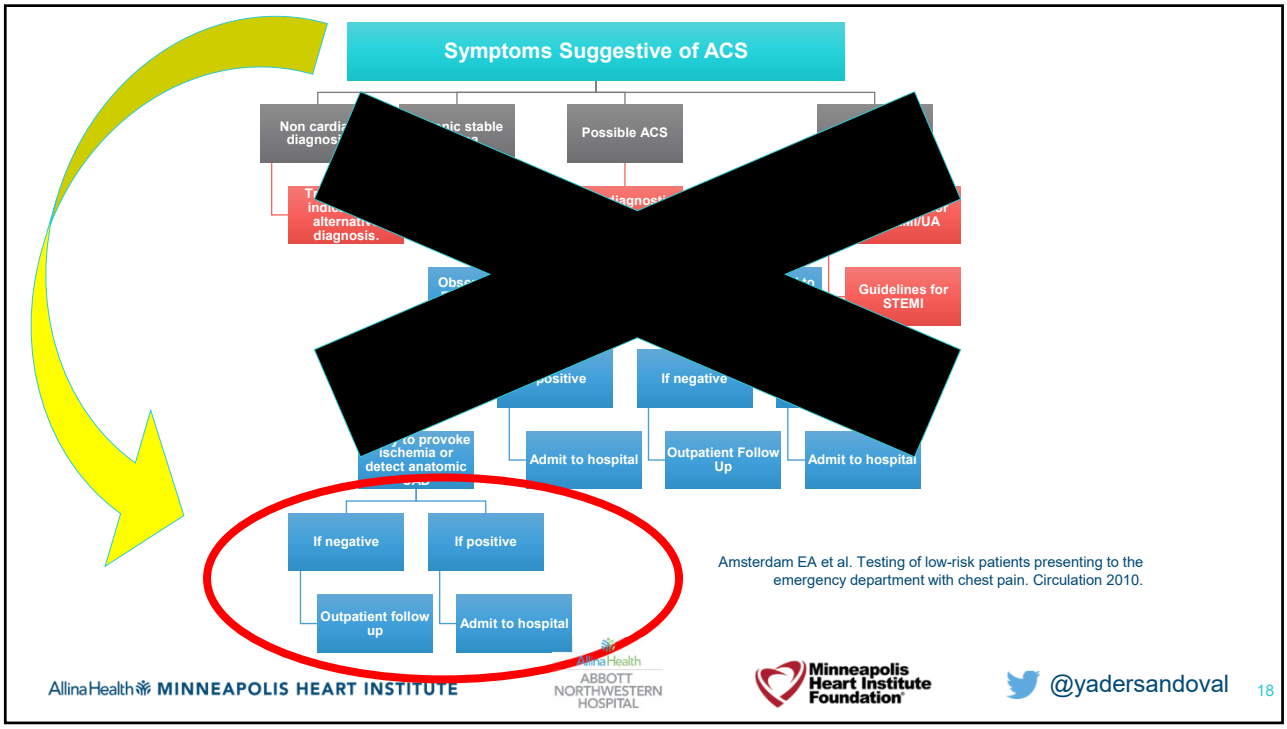
Symptoms Suggestive of ACS
Possible ACS
Guidelines for STEMI
If negative
Admit to hospital
Outpatient Follow Up
If negative
If positive
Outpatient follow up
Admit to hospital
Amsterdam EA et al. Testing of low-risk patients presenting to the emergency department with chest pain. Circulation 2010.
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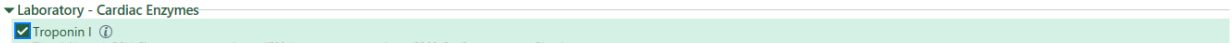
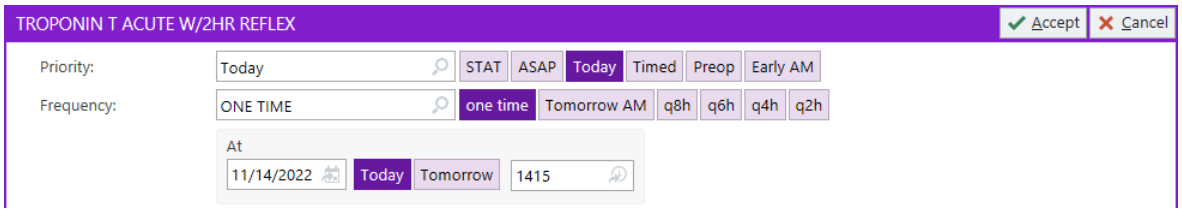
Current approach using conventional cTnI testing:
cTnI q3h (0h/3h/6h) = **~6 hours** (including potential use of POC assays in some EDs)
Lack of standardization and no clear guidance on deltas



Future (early 2023) approach using hs-cTnT testing:
hs-cTnT q2h= 0h +/- 2h (**2h protocol**, 4h sample if needed)
Standardized 0h/2h sampling protocol across the healthcare system with established guideline/algorithm



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4. Evidence: Clinical Trials

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High-sensitivity cardiac troponin risk-stratification RCTs

Extensive data demonstrating that these assays/protocols are excellent in rapidly identifying patients at very-low risk for acute MI and therefore facilitating early rule-out/disposition.

High-STEACS: 7 sites, **31492 patients**

- 0/3h protocol that allows single-sample rule-out if hs-cTnI (Abbott) <5 ng/L (optimized concentration)
- Only 0.3% (56 of 16793) of early rule-out patients had MI or cardiac death at 30-days.

RAPID-TnT: 4 sites, **3378 patients**

- 0/1h protocol that allows single-sample rule out if hs-cTnT (Roche) <5 ng/L
- Among pts. discharged from the ED, 0/1h hs-cTnT had a NPV of 99.6% (99.0-99.9) for 30-day death/MI.

LoDED: 8 sites, **629 patients**

- Single hs-cTn sample <LoD (multiple assays: Roche, Abbott, Beckman)
- No patients with undetectable hs-cTnT had MACE within 30-days.

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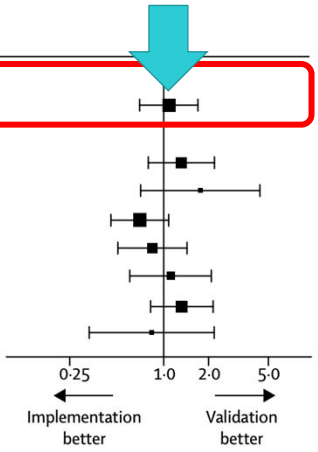
High-STEACS: stepped-wedge, cluster RCT of 48,282 patients across 10 hospitals in Scotland. Does the introduction of a hs-cTnI assay with a sex-specific 99th percentile reduces subsequent MI of CV death in patients with suspected ACS?

	Validation phase		Implementation phase		Odds ratio
	n	%	n	%	95% CI
Primary outcome					
Myocardial infarction or cardiovascular death	105	14·6	131	12·5	1·10 (0·75–1·61)
Secondary outcome					
Myocardial infarction	56	7·8	62	5·9	1·33 (0·81–2·20)
Unplanned revascularisation	18	2·5	25	2·4	1·77 (0·72–4·36)
All-cause death	167	23·2	187	17·8	0·71 (0·46–1·10)
Death from cardiovascular causes	54	7·5	75	7·1	0·86 (0·51–1·45)
Death from cardiac causes	32	4·4	59	5·6	1·13 (0·61–2·09)
Hospital admission with heart failure	91	12·6	113	10·8	1·34 (0·84–2·16)
Ischaemic stroke	24	3·3	17	1·6	0·85 (0·33–2·18)



Use of a high-sensitivity assay was not associated with a lower subsequent incidence of myocardial infarction or cardiovascular death at 1-year.

Shah ASV et al. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. Lancet. 2018 Sep 15;392(10151):919-928.

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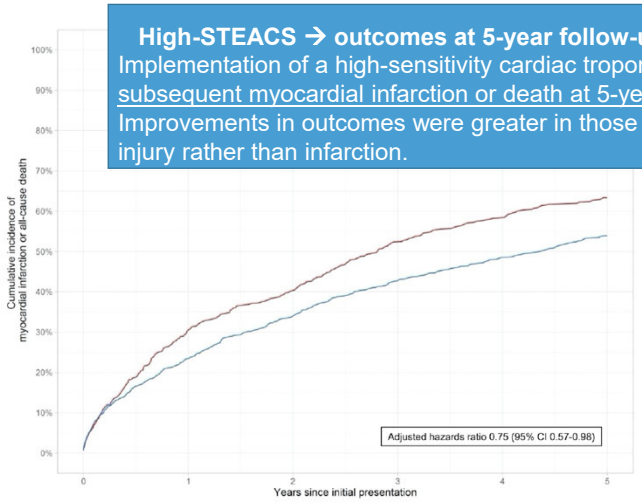
High-STEACS: stepped-wedge, cluster RCT of 48,282 patients across 10 hospitals in Scotland. Does the introduction of a hs-cTnI assay with a sex-specific 99th percentile reduces subsequent MI of CV death in patients with suspected ACS?

High-STEACS → outcomes at 5-year follow-up – data presented at ESC Congress 2022

Implementation of a high-sensitivity cardiac troponin assay was associated with a lower risk of subsequent myocardial infarction or death at 5-years.

Improvements in outcomes were greater in those with a diagnosis of non-ischemic myocardial injury rather than infarction.



5-year outcomes of the High-Sensitive Troponin in the Evaluation of patients with Acute Coronary Syndrome (High-STEACS) trial

Dr Ken Lee
Clinical Lecturer in Cardiology
University of Edinburgh

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5. Guidelines

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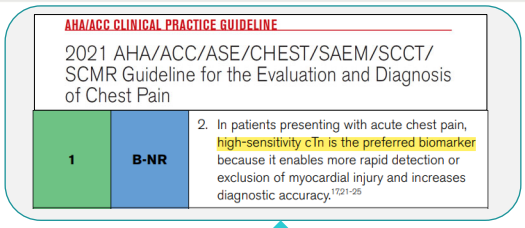
2021 AHA/ACC → High-sensitivity cTn is the preferred biomarker

ESC 2015
0/1h rapid rule-out and rule-in.
Class I, LOE: B

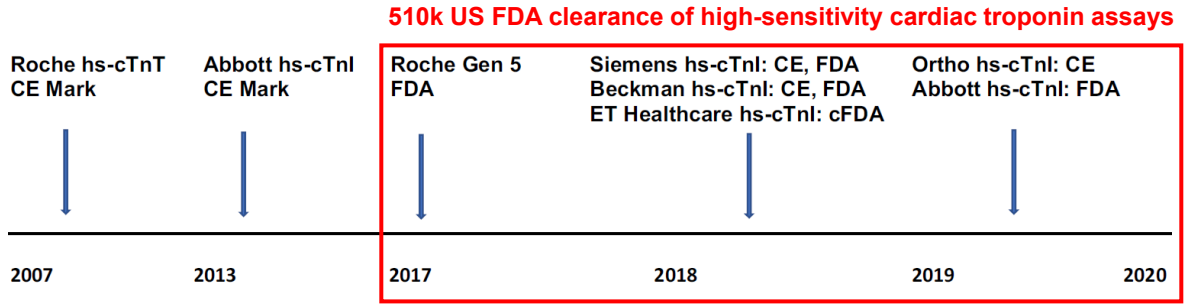


ESC 2011
0/3h rapid-rule out
Class I, LOE: B

ESC 2020
0/1h algorithm - Class I, LOE: B
0/2h algorithm - Class I, LOE: B
0/3h algorithm – Class IIa, LOE: B

6. What is the US experience?

Timeline for regulatory clearance for clinical use of hs-cTn assays



Apple FS et al. Clin Chem 2021; 67: 70-78

Hennepin Healthcare → Abbott hs-cTnI
Ridgeview → Siemens hs-cTnI
UoM and Mayo → Roche hs-cTnT
Allina as of 2023 will transition to Roche's hs-cTnT.

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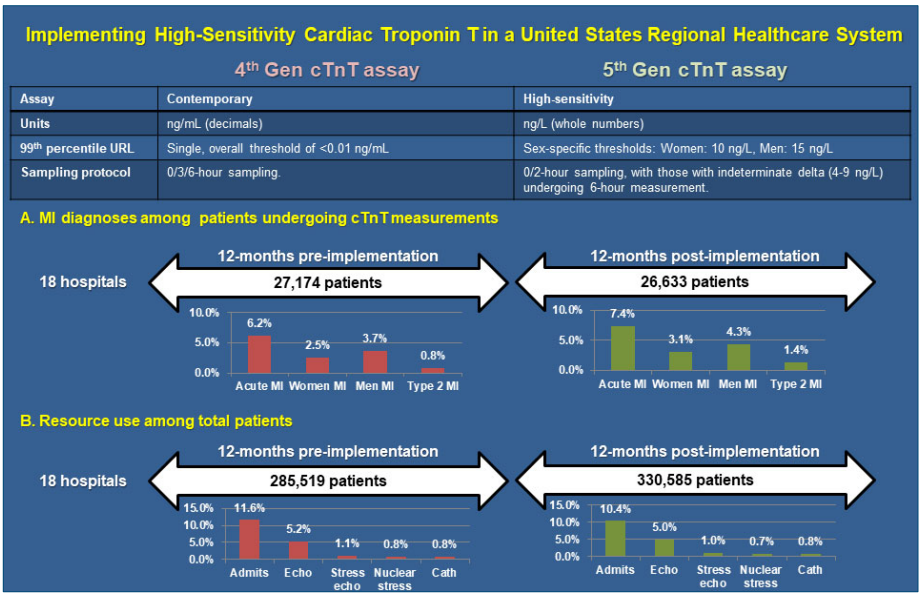
Implementing High-Sensitivity Cardiac Troponin T in a United States Regional Healthcare System

	4th Gen cTnT assay	5th Gen cTnT assay
Assay	Contemporary	High-sensitivity
Units	ng/mL (decimals)	ng/L (whole numbers)
99th percentile URL	Single, overall threshold of <0.01 ng/mL	Sex-specific thresholds: Women: 10 ng/L, Men: 15 ng/L
Sampling protocol	0/3/6-hour sampling.	0/2-hour sampling, with those with indeterminate delta (4-9 ng/L) undergoing 6-hour measurement.



- Small increase in MI diagnoses (ICD-10 codes).
- More type 2 MIs.
- No overall increase in hospital admissions or resource use after hs-cTnT implementation.
- At primary referral hubs, small increase in echocardiography.
- Approximately half of patients had cTn testing in the absence of chest pain

Sandoval et al. Implementing high-sensitivity cardiac troponin T in a US regional healthcare system. Circulation 2020; 141: 1937-1939.

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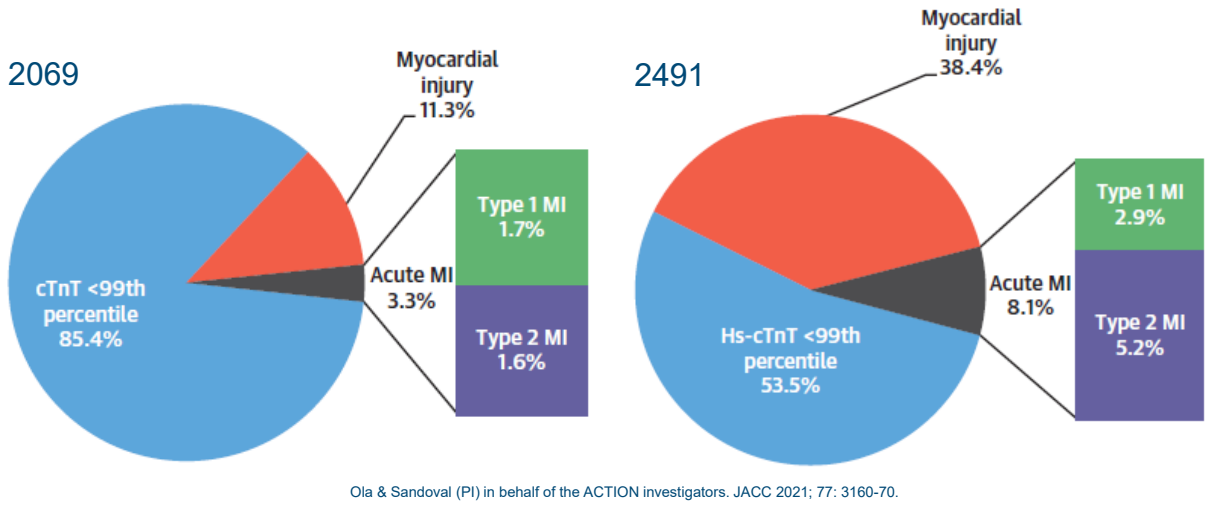
ACTION: Mayo Southwest Wisconsin 5th Gen Troponin T Implementation



Ola & Sandoval (PI) in behalf of the ACTION investigators. JACC 2021; 77: 3160-70.

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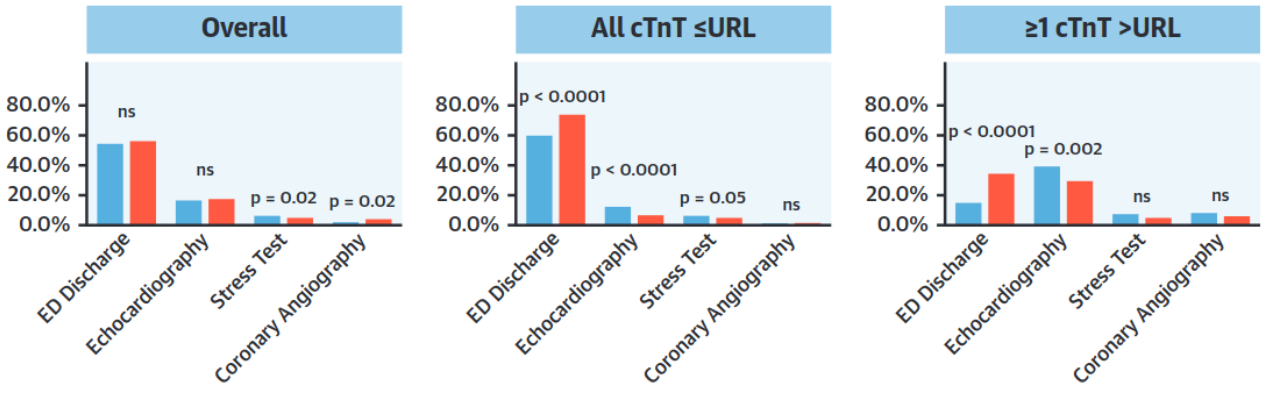
Resource Utilization: Pre vs. Post-implementation



- Except for angiography, overall resource use did not increase.
- Among those without cTnT increases, there were more ED discharges and fewer cardiac stress tests.

Ola & Sandoval (PI) in behalf of the ACTION investigators. JACC 2021; 77: 3160-70.

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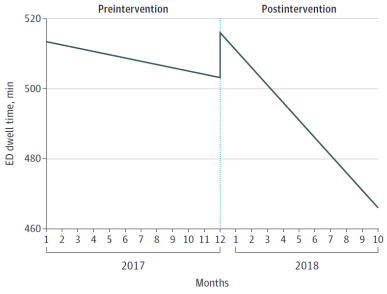
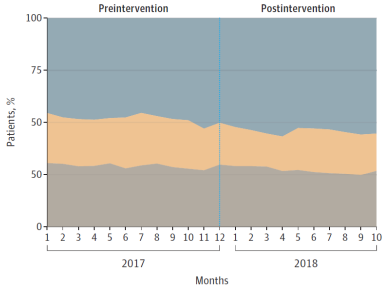
UT Southwestern: 0/1h (+/- 3h) hs-cTnT implementation

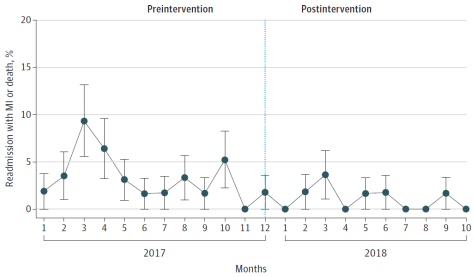
ED dwell time reduced



% patients discharge increased



30d MACE did not differ before/after



Vigen et al. Circulation 2018; 138: 2061-2063 ; Vigen et al. JAMA Netw Open 2020; 3: e203359.

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UC Davis: 0/1h (+/- 3h) hs-cTnT implementation

	Pre-implementation N=1589	Post-implementation N=1616	Adjusted OR
No admission	63%	68%	1.38 (1.18-1.61)
Full admission	28%	24%	0.75 (0.64-0.88)
Cardiology consult or admission	13%	13%	0.91 (0.73-1.12)
NSTEMI	3%	3%	0.95 (0.65-1.40)
UA	2%	2%	0.80 (0.24-2.62)
Cardiac risk stratification	9%	9%	0.95 (0.74-1.22)
Catheterization	10%	10%	1.02 (0.81-1.30

Ford JS et al. Am J Emerg Med 2021; 45: 54-60; Mumma BE et al. Ann Emerg Med 2020; 76: 566-579.

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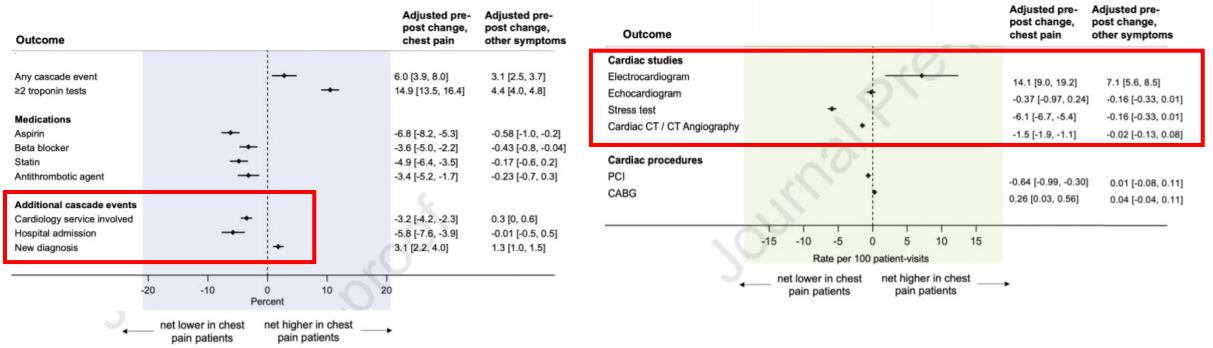
Mass Brigham: 0/1h (+/- 3h) hs-cTnT implementation



Hs-cTnT assay implementation was associated with more net upfront tests yet fewer net stress tests, catheterizations, cardiology evaluations, and hospital admissions in chest pain patients relative to patients with other symptoms.

Baugh et al. Crit Pathw Cardiol 2019; 18: 1-4 ; Ganguli et al. JACC 2021; 77: 3171-9.

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7. Our approach and rationale

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How to use high-sensitivity cardiac troponin T

These guidelines were developed and approved by the multidisciplinary, Allina Health hs-cTnT implementation team. They do not replace clinical judgement.

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Transition from the Abbott cTnI to Roche Gen 5 cTnT (hs-cTnT)

Changes in cardiac troponin results reporting & timing of samples

Decimals, ng/mL Example: 0.032 ng/mL	**Whole rounded numbers, ng/L** Example: 7 ng/L
Overall upper-reference limit cTnI = 0.034 ng/mL	**Sex-specific* 99th percentiles** Males<16 ng/L, Females<11ng/L
Timing of samples 0h / 3h / 6h	**Timing of samples** 0h / 2h protocol, 4h optional

*Sex assigned at birth.

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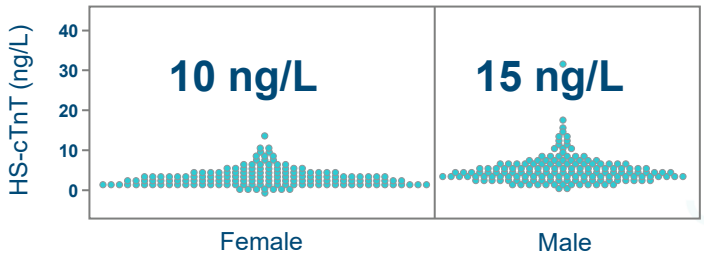
2021 AHA/ACC chest pain guidelines: the 99th percentile URL

COR	LOE	RECOMMENDATIONS
1	C-EO	Clinicians should be familiar with the analytical performance and the 99th percentile upper reference limit that defines myocardial injury for the cTn assay used at their institution.

Sex-specific
99th percentile URLs



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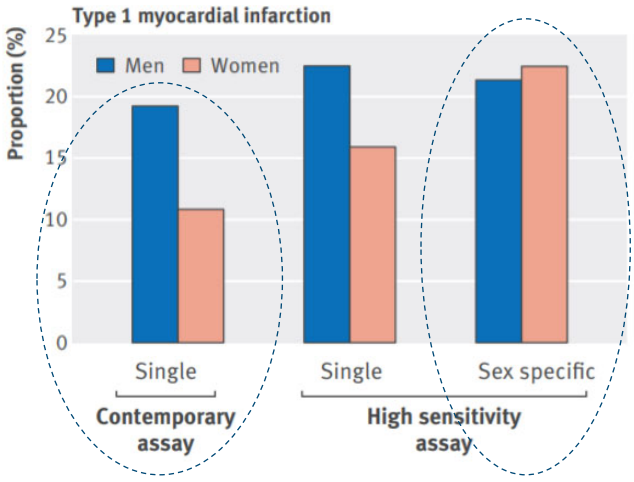
Hs-cTn and the under-diagnosis of MI in women



Shah ASV et al. High-sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. BMJ 2015; 350: g7873.

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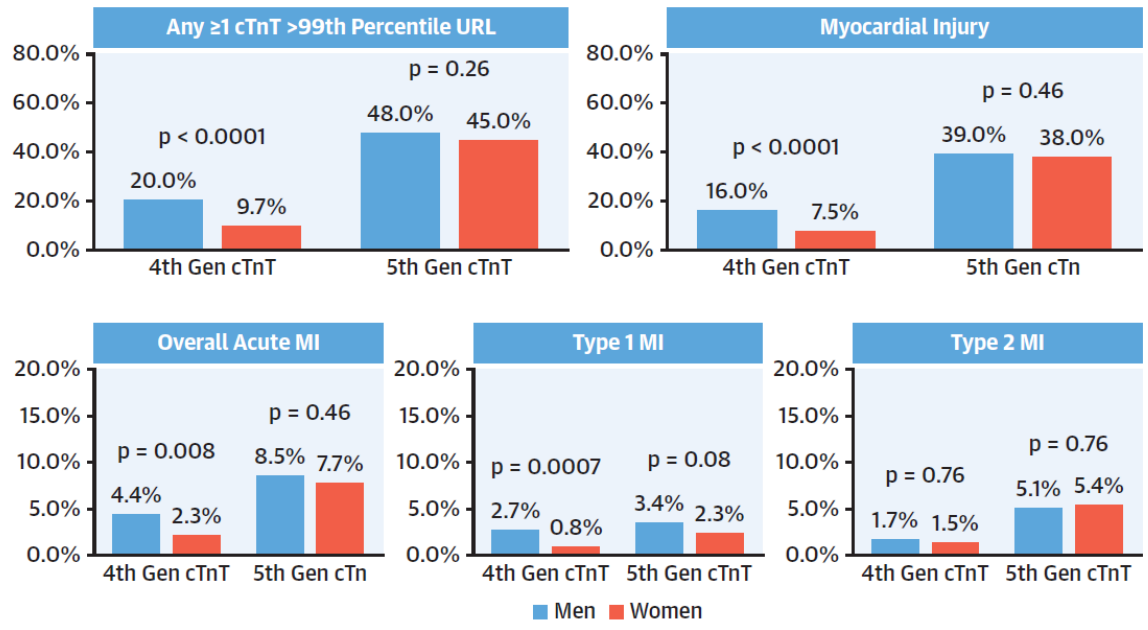

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Ola & Sandoval in behalf of the ACTION investigators. JACC 2021; 77: 3160-70.

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High-sensitivity cardiac troponin T assay results

Test	Result	99th percentile URLs*
Troponin T Gen 5 (hs-cTnT)	<6 ng/L	Male<16 ng/L Female<11 ng/L

*Sex assigned at birth

Lowest reported value by the laboratory
LoQ = limit of quantitation (20% CV)

*Measuring range: 6 to 10000 ng/L
Values below 6 ng/L are reported as <6 ng/L
Values above measuring range are reported as >10000 ng/L

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^Sandoval Y, Jaffe AS. Am J Med 2017; 130: 1358-1365.e1.
*Elecsys Troponin T Gen 5 insert package.

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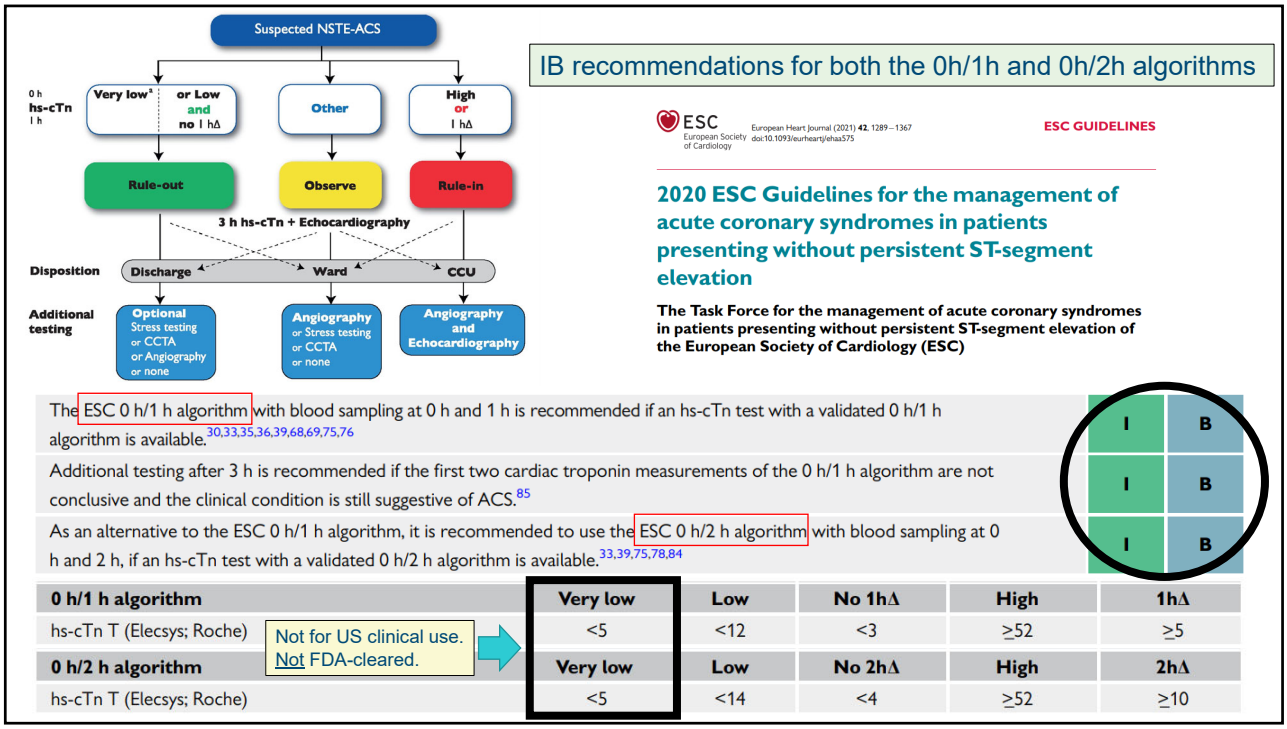
Suspected NSTE-ACS
0 h hs-cTn 1 h
Very low* or Low and no 1 hΔ
Other
High or 1 hΔ
Rule-out
Observe
Rule-in
3 h hs-cTn + Echocardiography
Disposition
Discharge
Ward
CCU
Additional testing
Optional Stress testing or CCTA or Angiography or none
Angiography or Stress testing or CCTA or none
Angiography and Echocardiography
IB recommendations for both the 0h/1h and 0h/2h algorithms
ESC
European Society of Cardiology
European Heart Journal (2021) 42, 1289–1367
doi:10.1093/eurheartj/ehaa575
ESC GUIDELINES
2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation
The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)
The ESC 0 h/1 h algorithm with blood sampling at 0 h and 1 h is recommended if an hs-cTn test with a validated 0 h/1 h algorithm is available.30,33,35,36,39,68,69,75,76
Additional testing after 3 h is recommended if the first two cardiac troponin measurements of the 0 h/1 h algorithm are not conclusive and the clinical condition is still suggestive of ACS.85
As an alternative to the ESC 0 h/1 h algorithm, it is recommended to use the ESC 0 h/2 h algorithm with blood sampling at 0 h and 2 h, if an hs-cTn test with a validated 0 h/2 h algorithm is available.33,39,75,78,84
I B
I B
I B
Not for US clinical use.
Not FDA-cleared.
0 h/1 h algorithm | Very low | Low | No 1hΔ | High | 1hΔ
hs-cTn T (Elecsys; Roche) | <5 | <12 | <3 | ≥52 | ≥5
0 h/2 h algorithm | Very low | Low | No 2hΔ | High | 2hΔ
hs-cTn T (Elecsys; Roche) | <5 | <14 | <4 | ≥52 | ≥10

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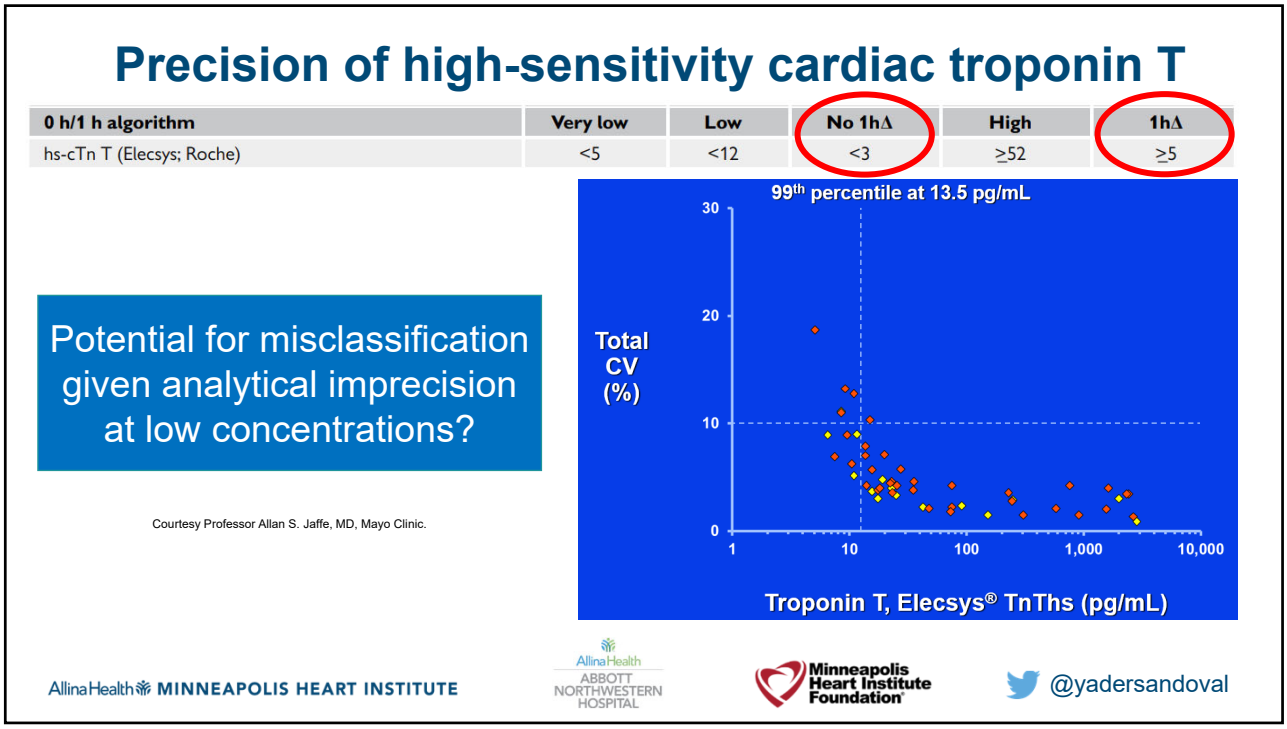
Precision of high-sensitivity cardiac troponin T
0 h/1 h algorithm | Very low | Low | No 1hΔ | High | 1hΔ
hs-cTn T (Elecsys; Roche) | <5 | <12 | <3 | ≥52 | ≥5
Potential for misclassification given analytical imprecision at low concentrations?
Courtesy Professor Allan S. Jaffe, MD, Mayo Clinic.
99th percentile at 13.5 pg/mL
Total CV (%)
30
20
10
0
1
10
100
1,000
10,000
Troponin T, Elecsys® TnThs (pg/mL)
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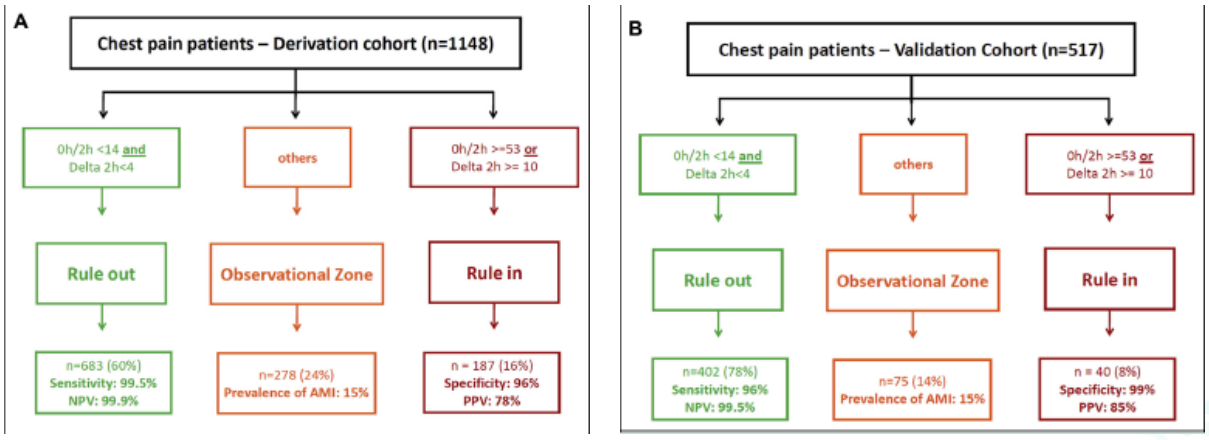
APACE: Derivation and validation of the 0/2h hs-cTnT protocol



Reichlin et al. Am J Med 2015; 128: 369-79.

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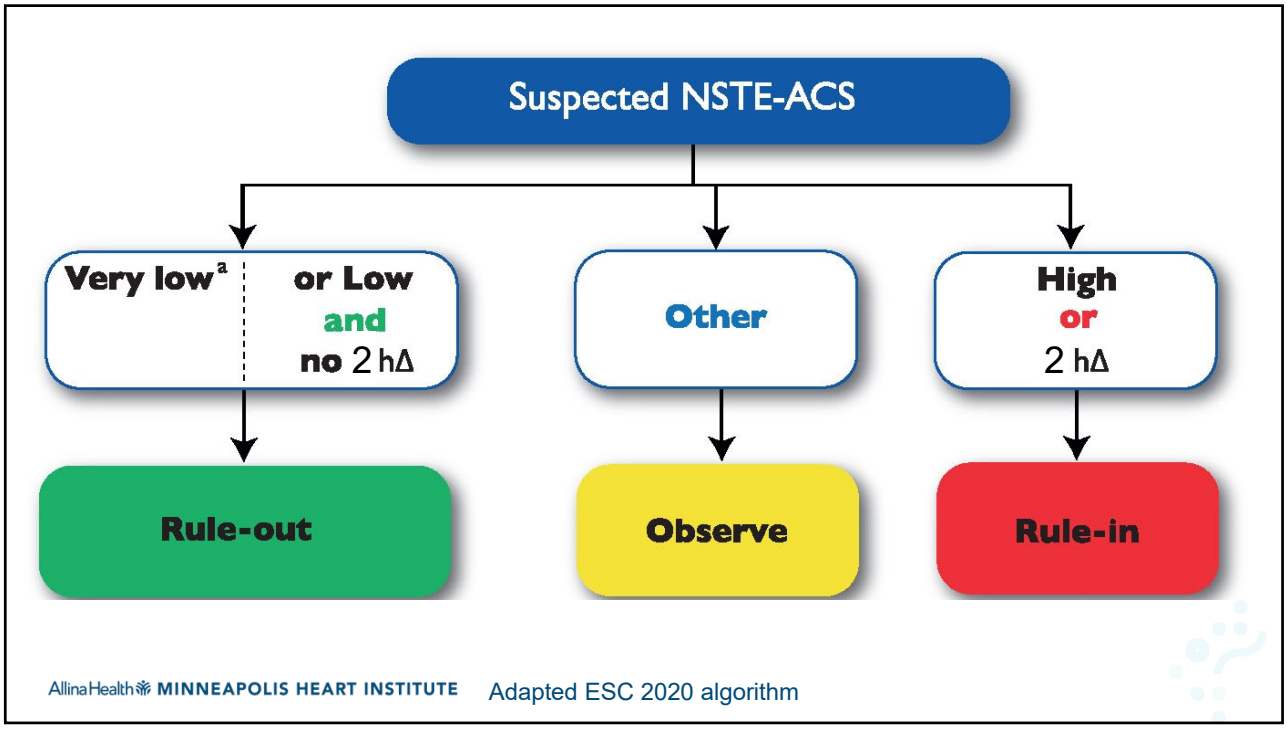

AllinaHealth MINNEAPOLIS HEART INSTITUTE Adapted ESC 2020 algorithm

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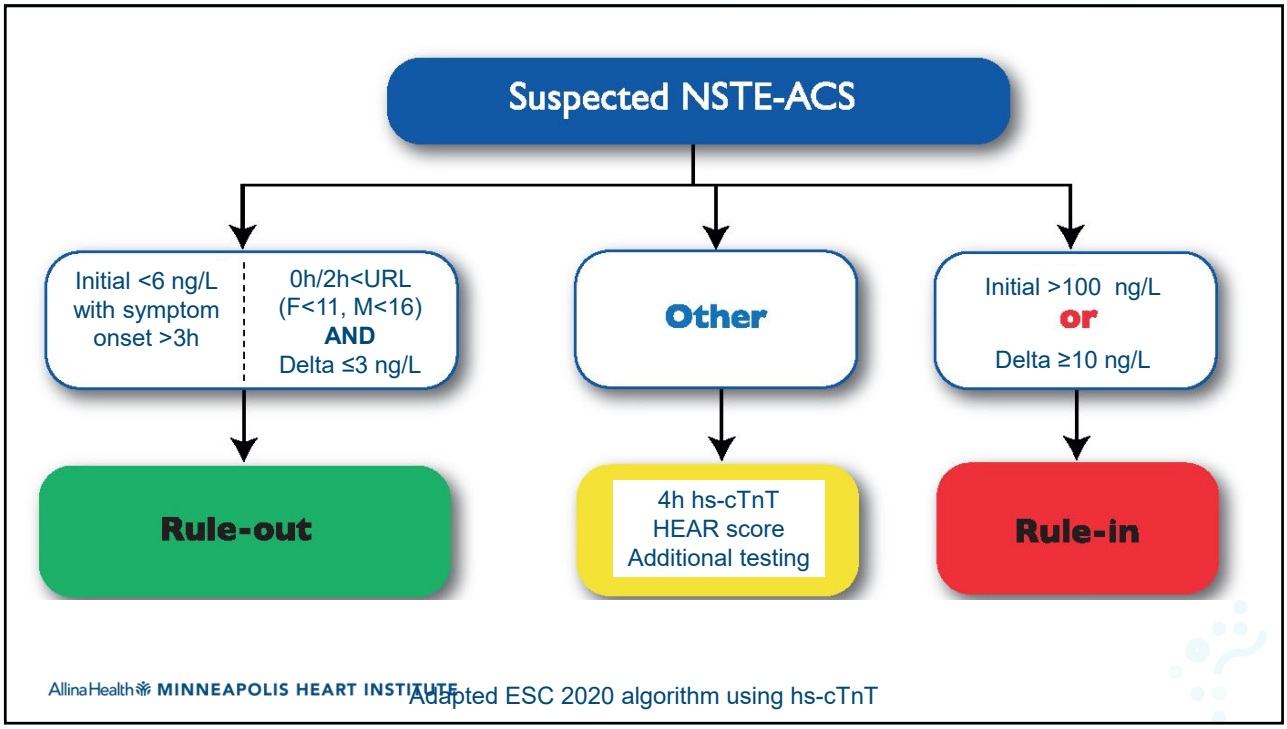
Suspected NSTE-ACS
Initial <6 ng/L with symptom onset >3h
0h/2h<URL (F<11, M<16) AND Delta ≤3 ng/L
Other
Initial >100 ng/L or Delta ≥10 ng/L
Rule-out
4h hs-cTnT HEAR score Additional testing
Rule-in
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Adapted ESC 2020 algorithm using hs-cTnT

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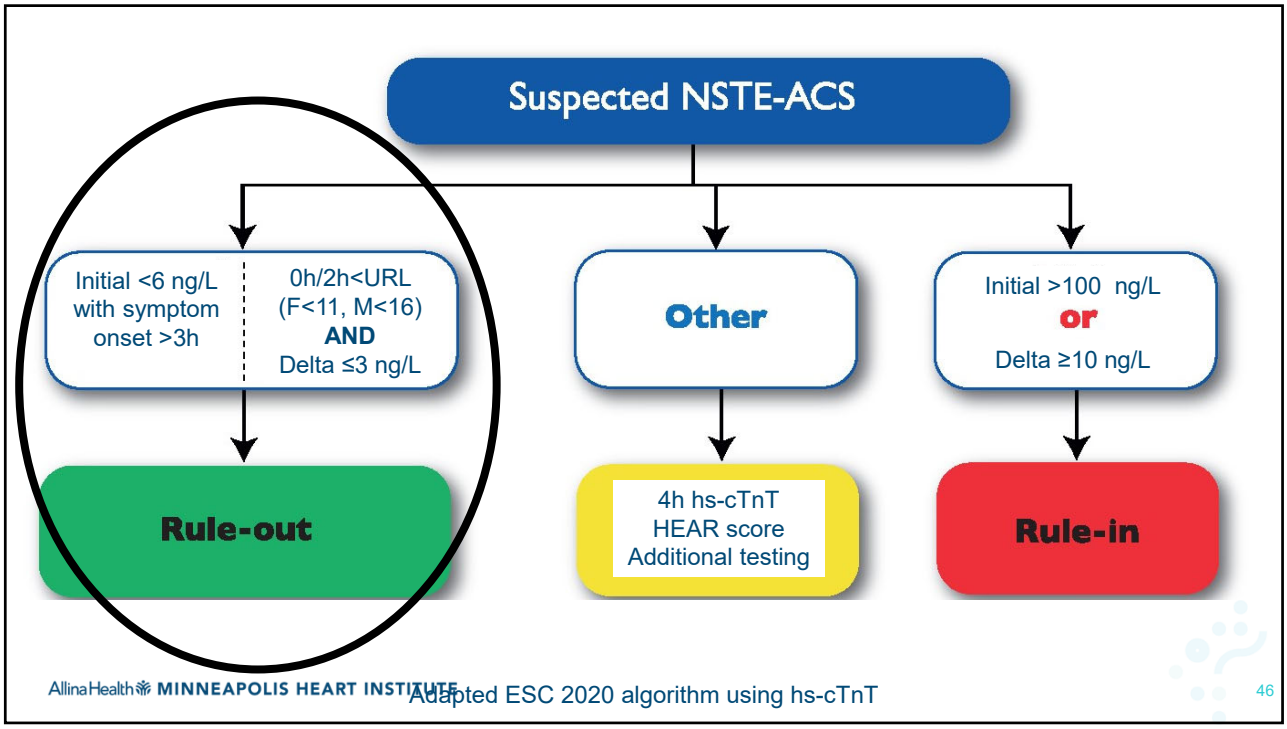
Suspected NSTE-ACS
Initial <6 ng/L with symptom onset >3h
0h/2h<URL (F<11, M<16) AND Delta ≤3 ng/L
Other
Initial >100 ng/L or Delta ≥10 ng/L
Rule-out
4h hs-cTnT HEAR score Additional testing
Rule-in
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Adapted ESC 2020 algorithm using hs-cTnT
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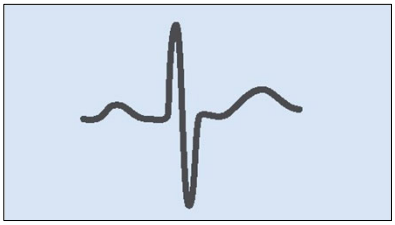
Low-risk: "Ruled-out" for acute MI



Non-ischemic
12-lead electrocardiogram

1. **Single-sample rule-out:**
   a. Initial hs-cTnT<6 ng/L (LoQ)
   b. Symptom onset >3h without recurrence
   c. Non-ischemic ECG.
2. **Serial testing:**
   a. 0h AND 2h hs-cTnT measurements below the sex-specific 99th percentiles (<16 ng/L for men, <11 ng/L for women)
   b. No change/delta: 0h/2h ≤3 ng/L.

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2021 AHA/ACC chest pain guidelines: the single-sample rule-out

COR	LOE	RECOMMENDATIONS
2a	B-NR	For patients with acute chest pain, **a normal ECG**, and symptoms suggestive of ACS that began **at least 3 hours** before ED arrival, **a single hs-cTn concentration that is below the limit of detection on initial measurement (time zero) is reasonable to exclude myocardial injury**.

*Guidelines incorrectly recommend limit of detection, but ACC Chest Pain consensus clarified use of LoQ (not LoD) for single-sample rule-out in US clinical practice.
* There are 3 randomized trials (LoDED, HiSTORIC, and RAPID TnT that incorporate single-sample RO)

2021 AHA/ACC guidelines and 2022 ACC Expert Consensus

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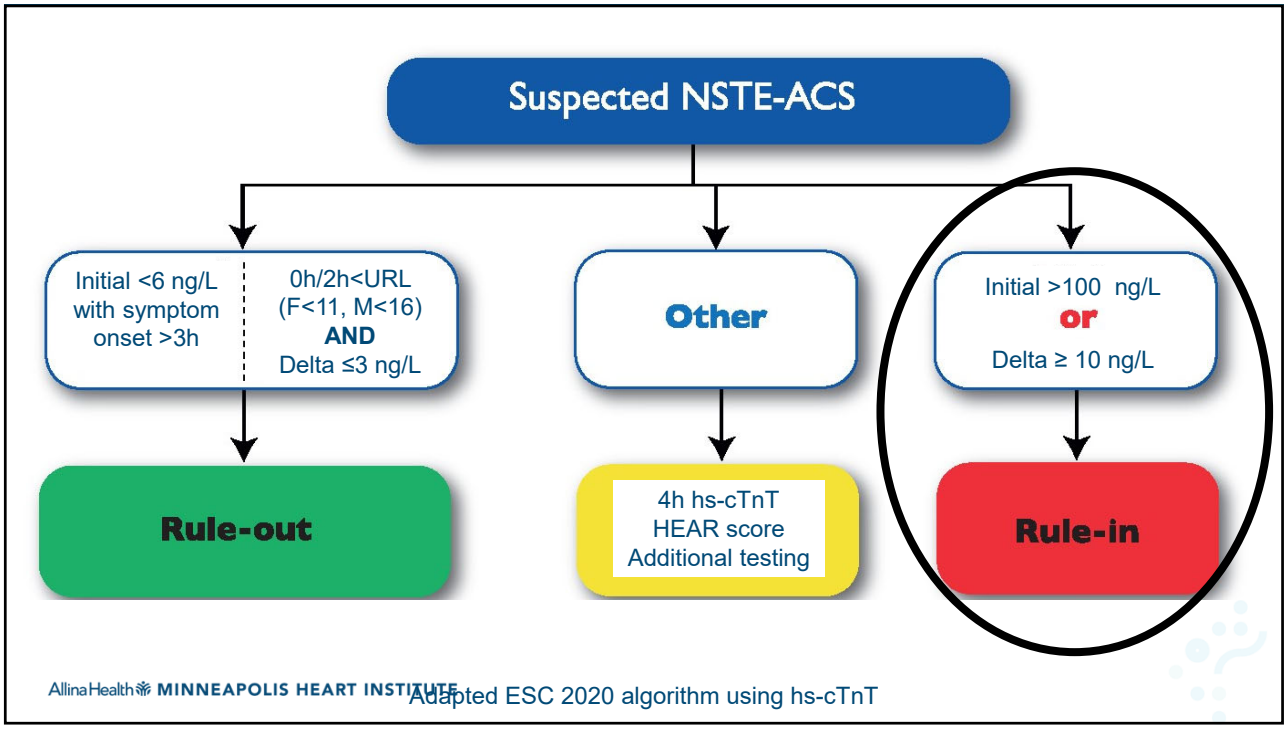

Adapted ESC 2020 algorithm using hs-cTnT

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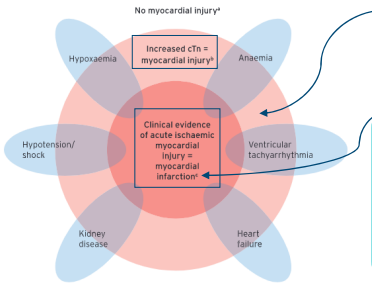
High-risk: does NOT equal to acute MI



- **There are multiple etiologies that can cause hs-cTnT increases above the 99th percentile (i.e. myocardial injury) other than acute myocardial infarction.**
- Clinical context (pre-test probability) and careful clinical evaluation are critical for diagnosis and risk-stratification.

The diagnosis of acute myocardial infarction requires a **rising and/or falling pattern in hs-cTnT concentrations with at least one value above the sex-specific 99th percentile** PLUS *at least one* of the following:

- ❑ Ischemic symptoms
- ❑ New or presumed new significant ST-T wave changes or new LBBB.
- ❑ Development of pathological Q waves.
- ❑ Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- ❑ Identification of intracoronary atherothrombosis or acute angiographic culprit by angiography.

1. **Initial hs-cTnT>100 ng/L without alternative explanation**
   a. In appropriate patients with suspected ACS (I.e.: acute chest pain without alternative explanation for chronic myocardial injury) it correlates with a positive predictive value for acute MI of ~90%.
2. **Serial 0h/2h (or 0h/4h) delta >10 ng/L** identifies higher-risk patients with acute myocardial injury (does not apply in those with initial hs-cTnT >100 ng/L, in which a 20% delta is suggested)

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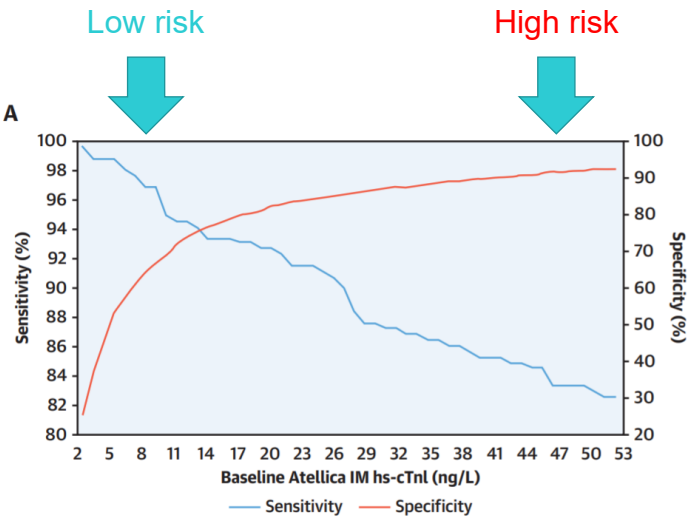

0 h/1 h algorithm	High	1hΔ
hs-cTn T (Elecsys; Roche)	≥52	≥5
hs-cTn I (Architect; Abbott)	≥64	≥6
hs-cTn I (Centaur; Siemens)	≥120	≥12
hs-cTn I (Access; Beckman Coulter)	≥50	≥15
hs-cTn I (Clarity; Singulex)	≥30	≥6
hs-cTn I (Vitros; Clinical Diagnostics)	≥40	≥4
hs-cTn I (Pathfast; LSI Medience)	≥90	≥20
hs-cTn I (TriageTrue; Quidel)	≥60	≥8
0 h/2 h algorithm	**High**	**2hΔ**
hs-cTn T (Elecsys; Roche)	≥52	≥10
hs-cTn I (Architect; Abbott)	≥64	≥15
hs-cTn I (Centaur; Siemens)	≥120	≥20
hs-cTn I (Access; Beckman Coulter)	≥50	≥20
hs-cTn I (Clarity; Singulex)	≥30	TBD
hs-cTn I (Vitros; Clinical Diagnostics)	≥40	TBD
hs-cTn I (Pathfast; LSI Medience)	≥90	TBD
hs-cTn I (TriageTrue; Quidel)	≥60	TBD

Sandoval et al. JACC 2019; 74: 271-282; 2020 ESC NSTEMI guidelines Eur Heart J 2021; 42: 1289-1367.

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Suggested threshold to identify high-risk patients at presentation

Table 2: Diagnostic accuracy of different cut-off points of absolute high-sensitivity cardiac troponin T levels at baseline and changes within the first hour

Cut-off point, ng/L	% (95% CI) Sensitivity	Specificity	Positive predictive value	Negative predictive value
Baseline				
5	99.6 (97.6–100.0)	37.9 (35.0–40.9)	25.4 (22.6–28.4)	99.8 (98.7–100.0)
10	94.4 (90.6–97.0)	70.0 (67.2–72.7)	40.0 (35.9–44.2)	98.3 (97.1–99.1)
14	92.1 (88.4–95.3)	79.4 (76.3–81.3)	48.4 (43.3–53.3)	98.1 (96.5–98.6)
20	80.1 (74.3–85.0)	89.0 (87.0–90.8)	60.7 (54.9–66.2)	95.5 (94.0–96.7)
50	50.2 (43.6–56.8)	97.6 (96.5–98.4)	81.7 (74.3–87.7)	90.2 (88.4–91.9)
100	29.0 (23.2–35.3)	99.3 (98.6–99.7)	89.3 (80.0–95.3)	86.8 (84.8–88.7)

Reichlin et al. CMAJ 2015; 187: E243-E252.

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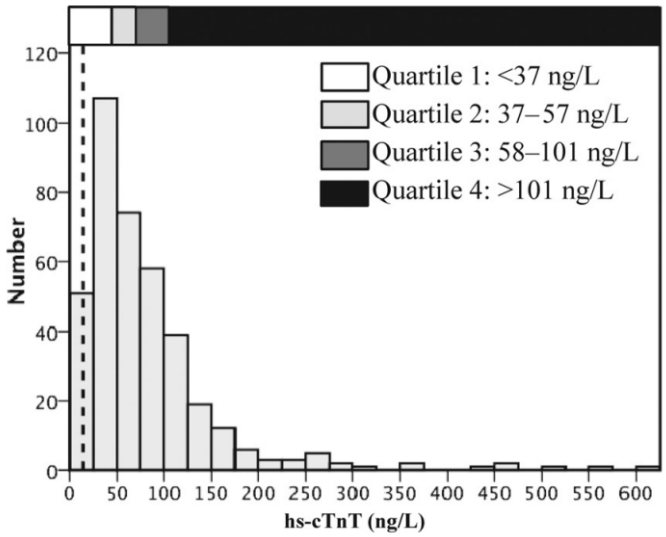
Caveats of high-risk thresholds in unselected populations



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Hassan et al: Clin Chem 60:2, 2014

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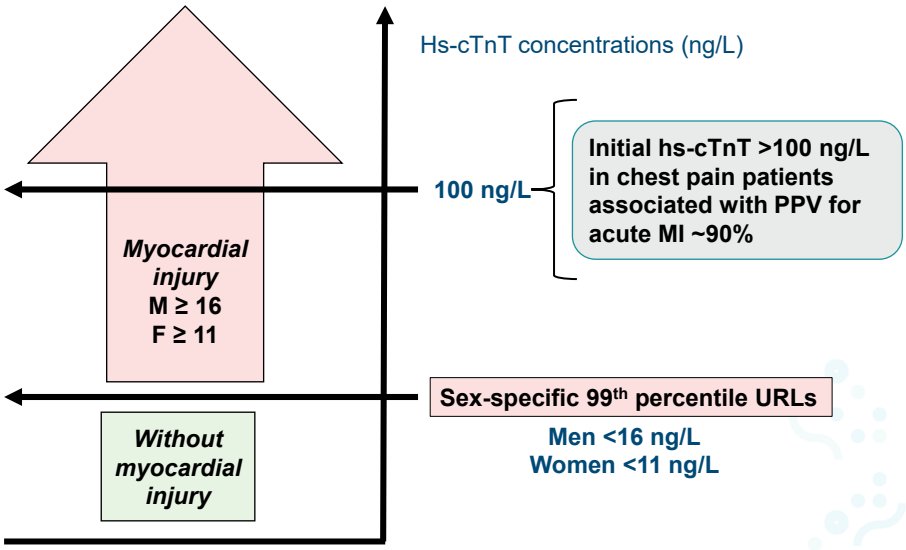
1. Continuous risk marker: the higher the hs-cTn concentration, the higher the risk.
2. Myocardial injury = any hs-cTn > 99th percentile.



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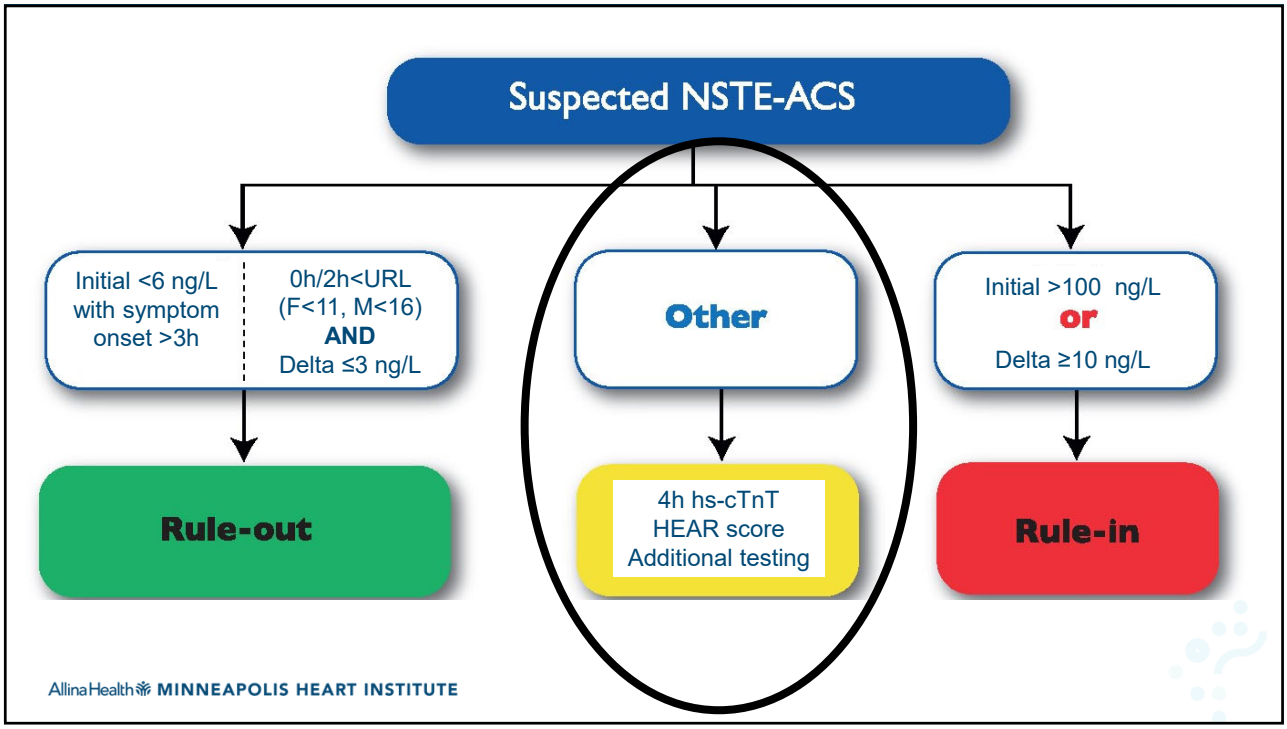

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Intermediate-risk: more evaluation

1. Third hs-cTnT measurement at 4-hours (i.e.: **0h /2h / 4h**).
2. In patients at intermediate-risk, the **HEAR score** can be used to identify patients in whom additional evaluations can be considered.

H	History	
	High suspicion	2
	Moderate suspicion	1
	Low suspicion	0
E	Electrocardiogram	
	ST-segment deviation	2
	Paced, LBBB, RBBB, or LVH	1
	Normal or nonspecific changes	0
A	Age, y	
	>65	2
	45-65	1
	<45	0
R	Cardiac risk factors	
	≥3 or known CAD	2
	1-2	1
	0	0

- HEAR score ≤3 → outpatient follow-up
- HEAR >4 consider additional evaluations such as functional or anatomical non-invasive imaging.

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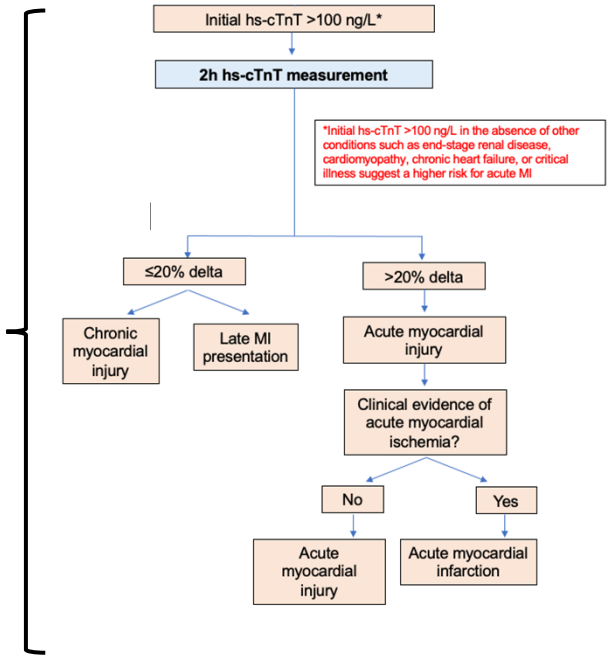
In patients with marked initial increases (>100 ng/L), use % (percent) changes rather than absolute changes (ng/L).

No change ≤20%

Change >20%



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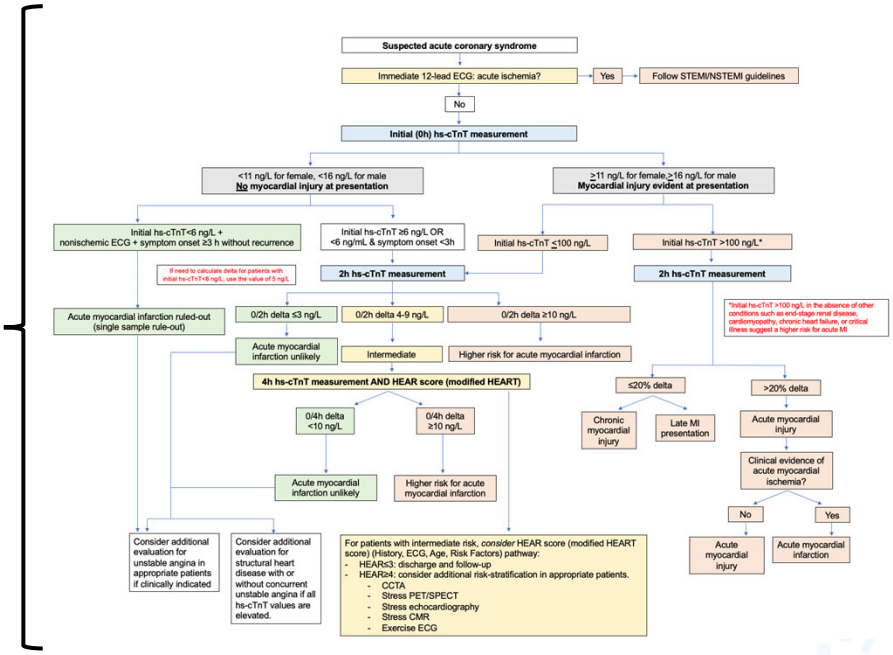
Complete educational algorithm/resource available in the AKN
- **Slide set**
- **Rationale**
- **References**



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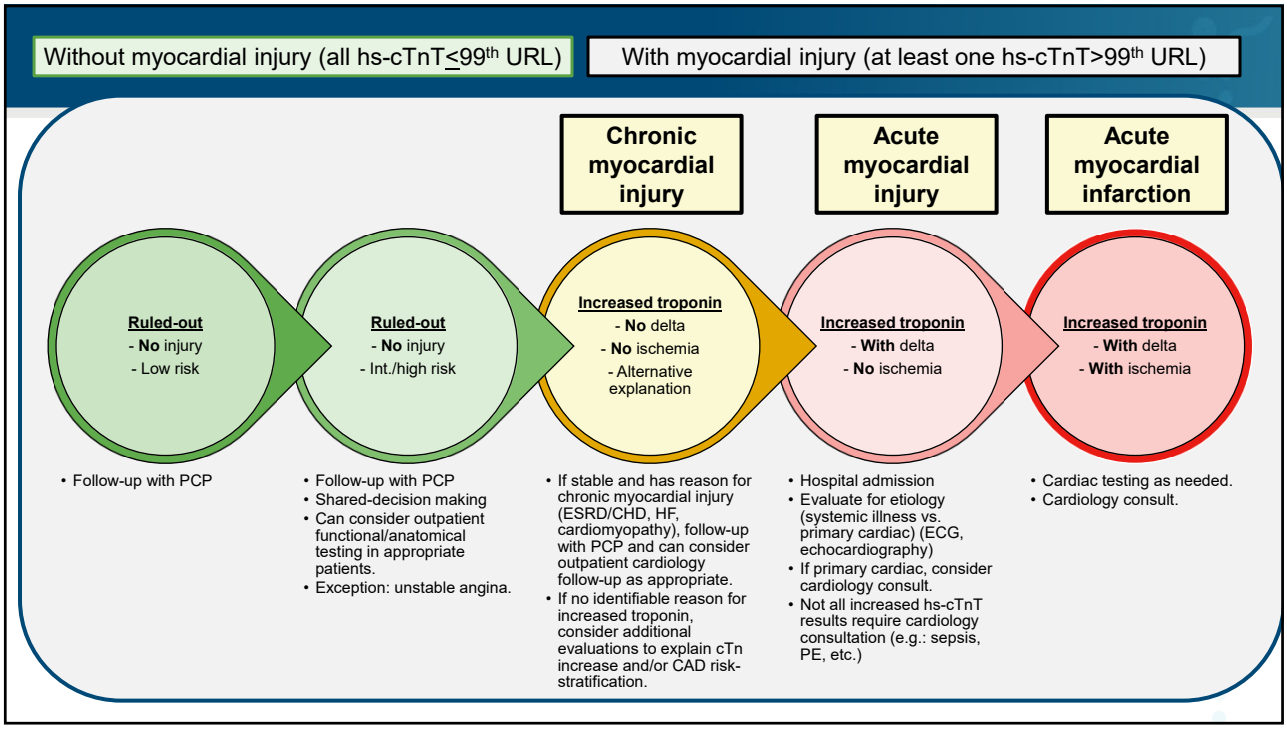

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8. Potential challenges:
Preparation, partnership, and education.

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TROPONIN

YES

High myocardial tissue specificity

NOT

Disease specific

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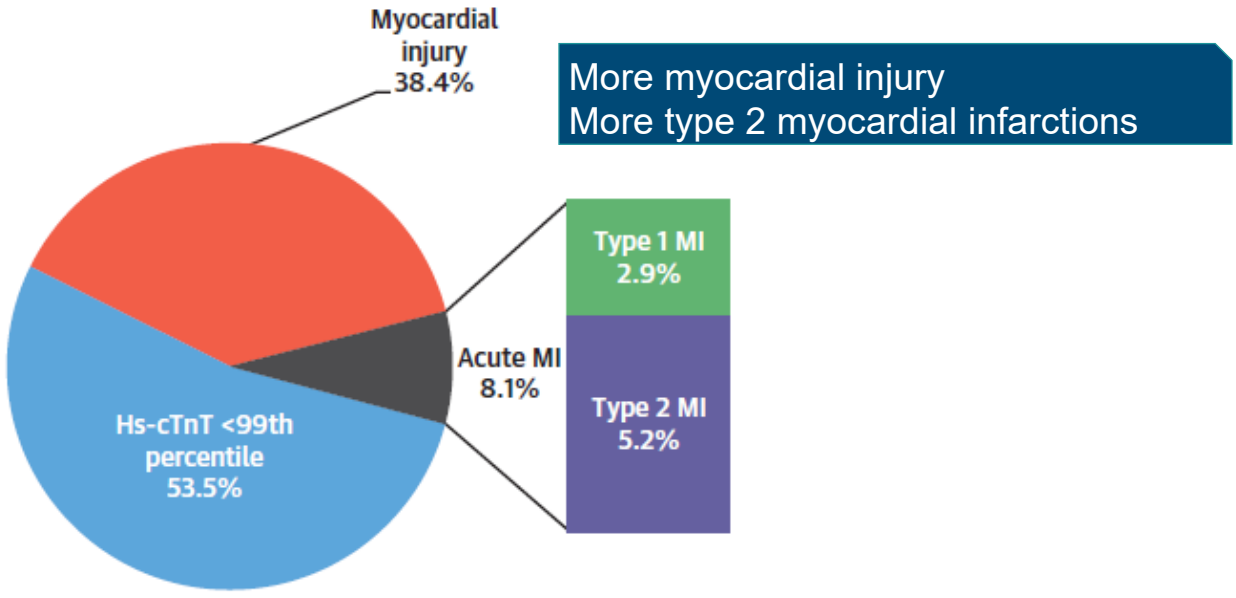

Ola & Sandoval (PI) in behalf of the ACTION investigators. JACC 2021; 77: 3160-70.

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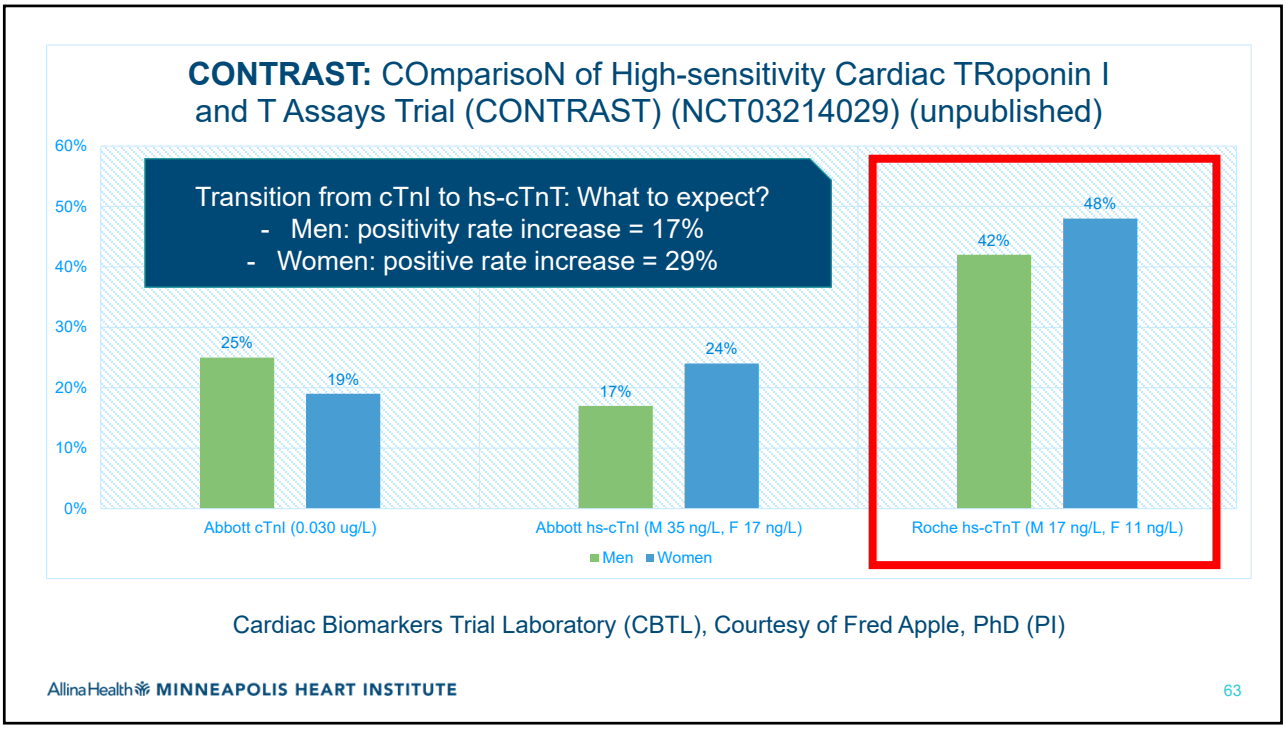
CONTRAST: COmparisoN of High-sensitivity Cardiac TRoponin I and T Assays Trial (CONTRAST) (NCT03214029) (unpublished)
Transition from cTnI to hs-cTnT: What to expect?
- Men: positivity rate increase = 17%
- Women: positive rate increase = 29%
60%
50%
40%
30%
20%
10%
0%
25%
19%
17%
24%
42%
48%
Abbott cTnI (0.030 ug/L)
Abbott hs-cTnI (M 35 ng/L, F 17 ng/L)
Roche hs-cTnT (M 17 ng/L, F 11 ng/L)
Men
Women
Cardiac Biomarkers Trial Laboratory (CBTL), Courtesy of Fred Apple, PhD (PI)
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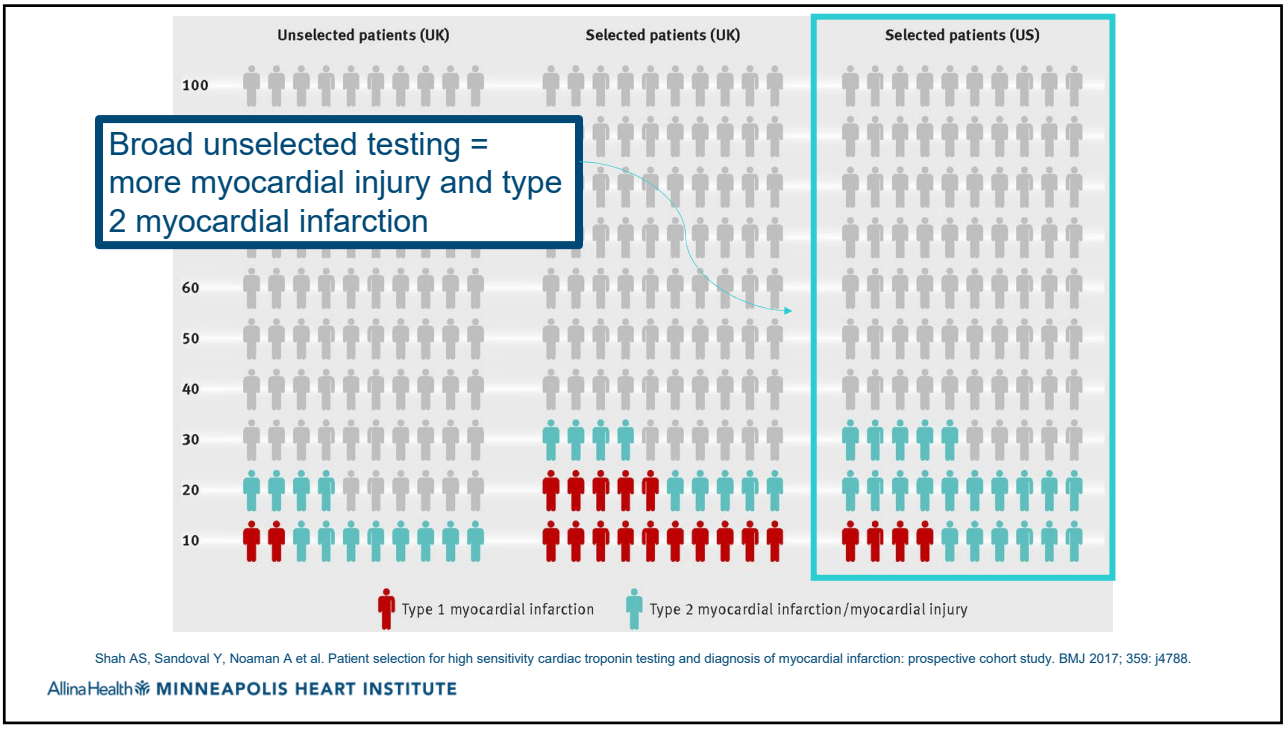
Unselected patients (UK)
Selected patients (UK)
Selected patients (US)
100
60
50
40
30
20
10
Broad unselected testing = more myocardial injury and type 2 myocardial infarction
Type 1 myocardial infarction
Type 2 myocardial infarction/myocardial injury
Shah AS, Sandoval Y, Noaman A et al. Patient selection for high sensitivity cardiac troponin testing and diagnosis of myocardial infarction: prospective cohort study. BMJ 2017; 359: j4788.
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High-STEACS RCT

	All participants (n=48 282)	No myocardial injury		Myocardial injury			
		Validation (n=14 862)	Implementation (n=23 060)	Reclassified by high-sensitivity cardiac troponin I assay		Identified by cardiac troponin I assay	
				Validation (n=720)	Implementation (n=1051)	Validation (n=3396)	Implementation (n=5193)
Primary outcome							
Myocardial infarction* or death from cardiovascular causes	2586 (5%)	367 (2%)	479 (2%)	105 (15%)	131 (12%)	634 (19%)	870 (17%)
Secondary outcomes							
Myocardial infarction*	1046 (2%)	163 (1%)	198 (1%)	56 (8%)	62 (6%)	249 (7%)	318 (6%)
Unp vascularisation†	672 (1%)	80 (1%)	182 (1%)	18 (3%)	25 (2%)	147 (4%)	220 (4%)
All- h	4367 (9%)	824 (6%)	1170 (5%)	167 (23%)	187 (18%)	882 (26%)	1137 (22%)
D cardiovascular causes	1693 (4%)	217 (1%)	299 (1%)	54 (8%)	75 (7%)	432 (13%)	616 (12%)
iac causes	1273 (3%)	143 (1%)	191 (1%)	32 (4%)	59 (6%)	349 (10%)	499 (10%)
Hos ssion for heart failure	1700 (4%)	334 (2%)	337 (1%)	91 (13%)	113 (11%)	371 (11%)	454 (9%)
Ischaem stroke	546 (1%)	171 (1%)	173 (1%)	24 (3%)	17 (2%)	78 (2%)	83 (2%)
Safety endpoints							
Major haemorrhage‡	195 (<1%)	40 (<1%)	55 (<1%)	5 (1%)	11 (1%)	38 (1%)	46 (1%)
Unplanned hospital admission at 30 days§	8489 (18%)	2450 (17%)	2995 (13%)	208 (29%)	245 (23%)	1190 (35%)	1401 (27%)
Non-cardiovascular death	2673 (6%)	607 (4%)	871 (4%)	113 (16%)	111 (11%)	450 (13%)	521 (10%)

Data are number of patients (%). *Subsequent type 1 or type 4b myocardial infarction. †Defined as urgent or emergency percutaneous coronary intervention or coronary artery bypass grafting from discharge to 1 year later. ‡Bleeding Academic Research Consortium type 3 or type 5. §Excludes type 1 or type 4b myocardial infarction.

Shah ASV et al. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. Lancet 2018; 392: 919-928.

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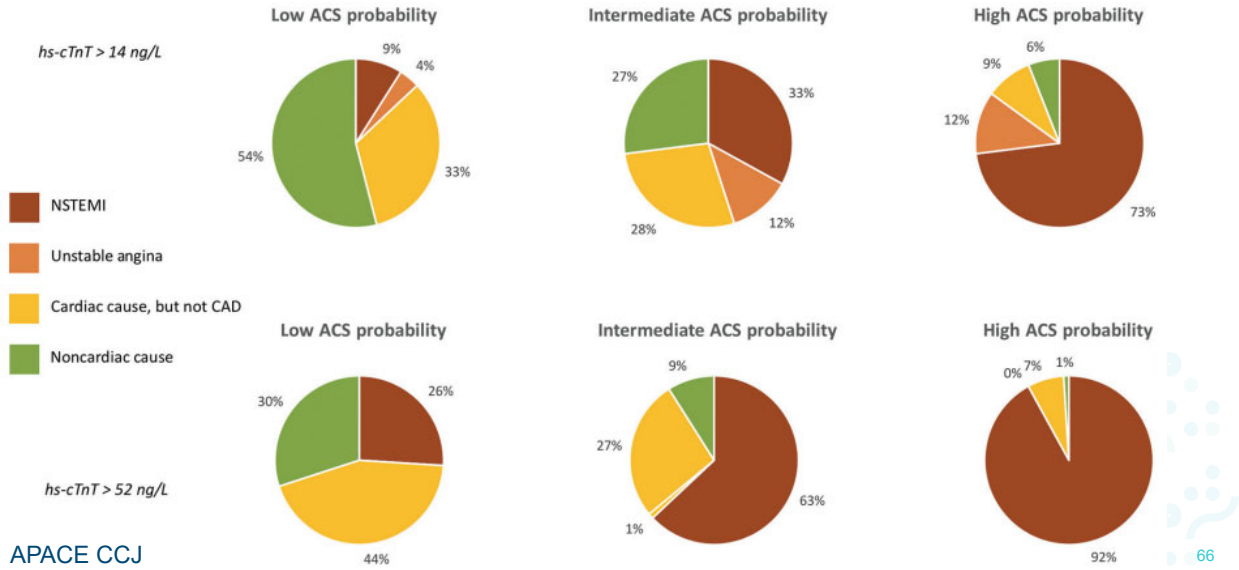
CLINICAL CONTEXT (PRE-TEST PROBABILITY) IS ESSENTIAL



APACE CCJ

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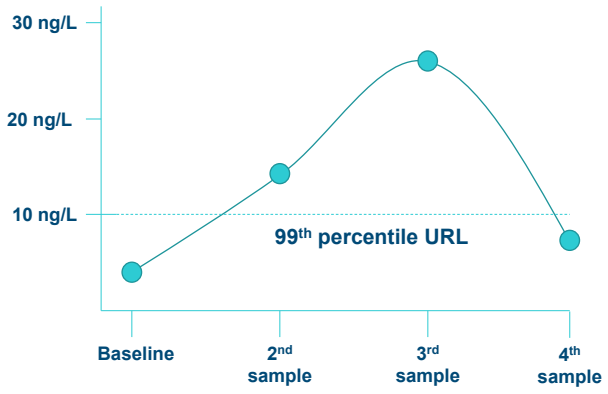
Acute myocardial injury

Significant **rise** and/or **fall** in cTn with ≥1 value >99th percentile URL **without** clear, overt clinical evidence of acute myocardial ischemia.



- **Examples**:
  - Acute heart failure
  - Stress cardiomyopathy
  - Myocarditis
  - Pulmonary embolism
  - Sepsis
  - Critical illness

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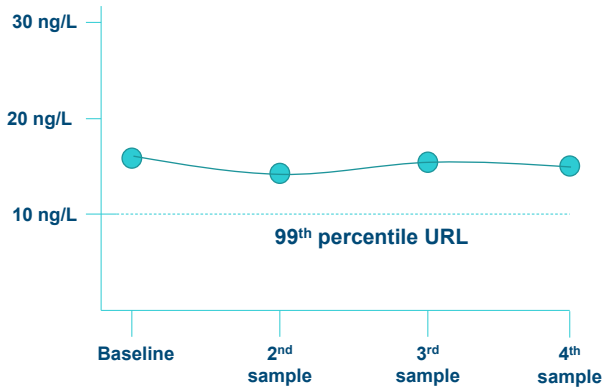
Chronic myocardial injury

Stable, **unchanging** (<20% change) cTn increases >99th percentile without myocardial ischemia.



- **Examples**:
  - Chronic heart failure
  - Cardiomyopathy
  - Chronic kidney disease
  - End-stage renal disease

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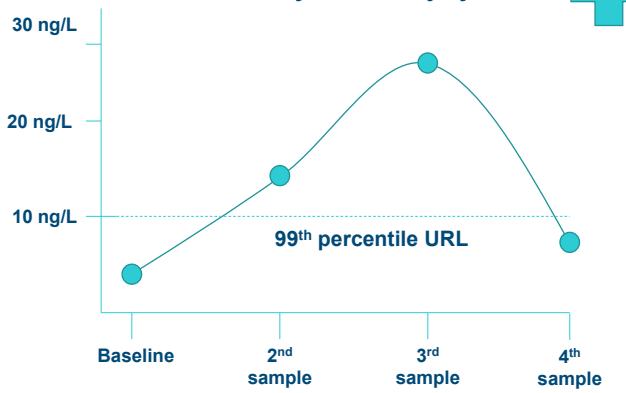
Acute myocardial infarction

Significant **rise** and/or **fall** in cTn with ≥1 value >99th percentile URL with clinical evidence of acute myocardial ischemia.

Acute myocardial injury



Acute myocardial ischemia

- **PLUS** clinical evidence of acute myocardial ischemia as defined by at least 1 of the following:
  - Symptoms.
  - New ischemic ECG changes.
  - Development of pathological Q waves.
  - Imaging
  - Coronary angiography or autopsy

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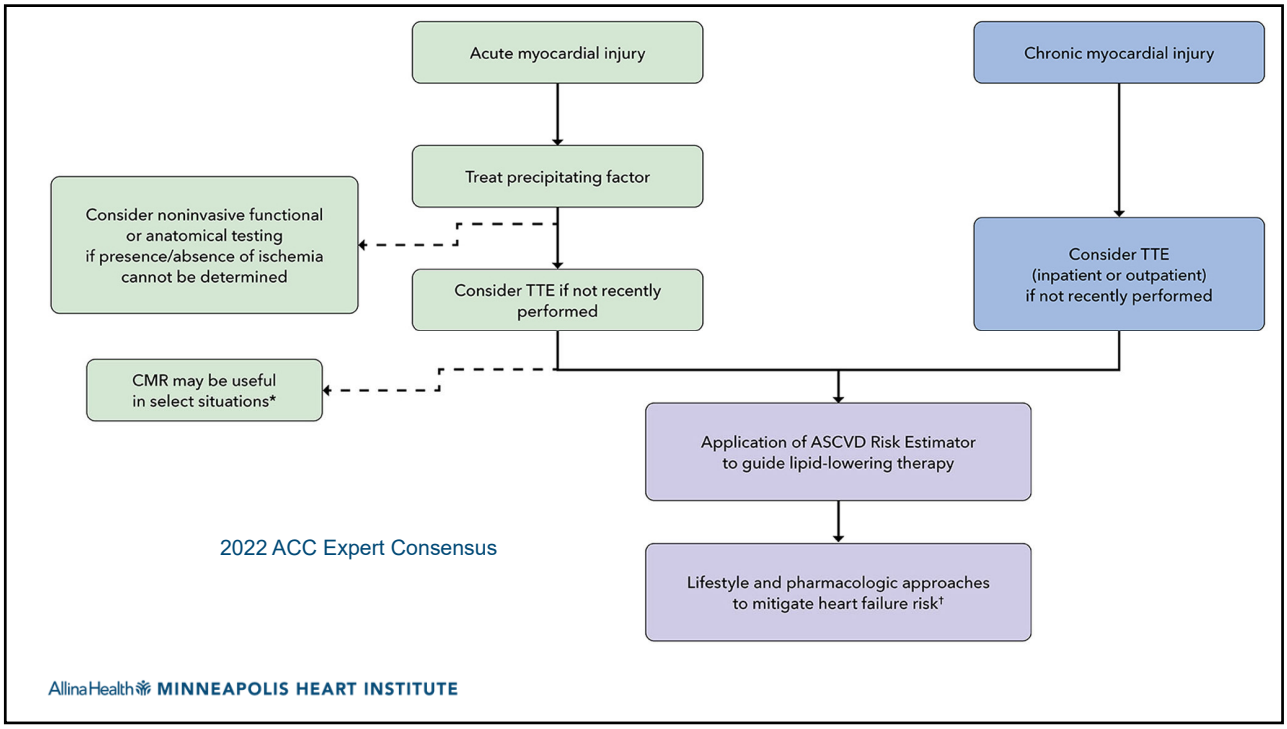

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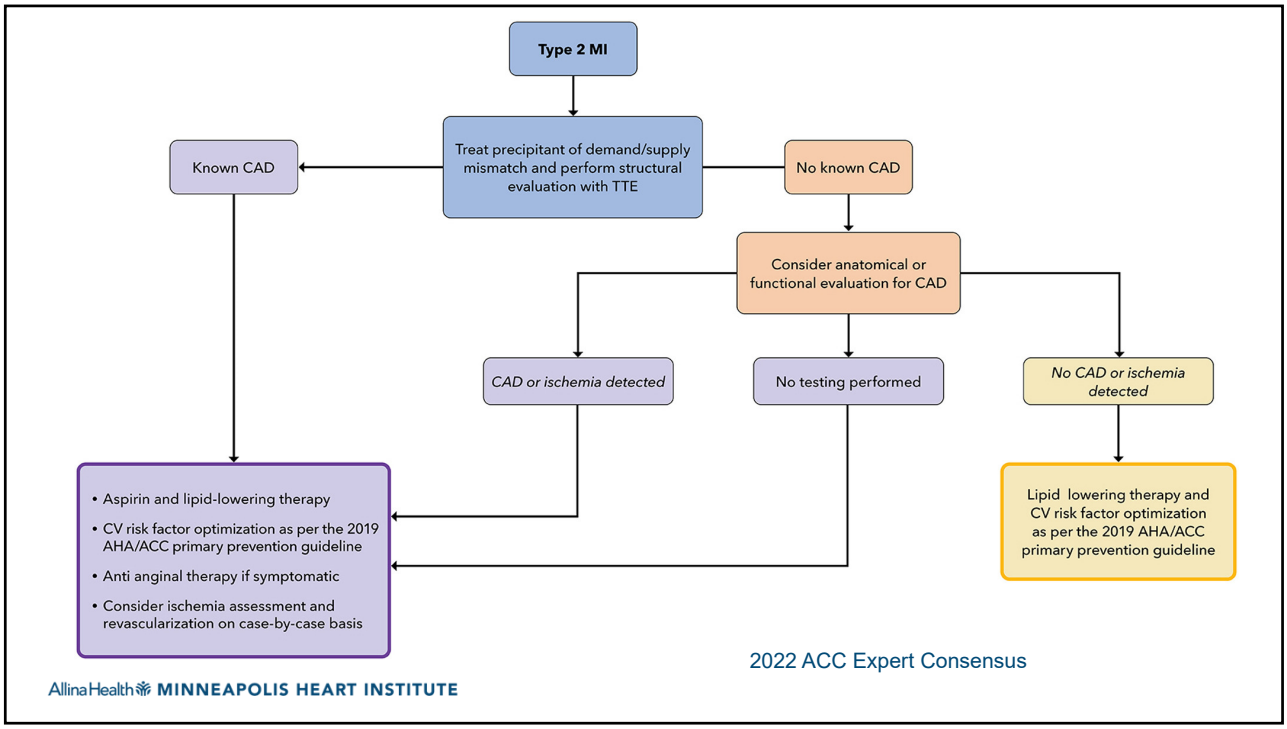

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9. Areas of caution

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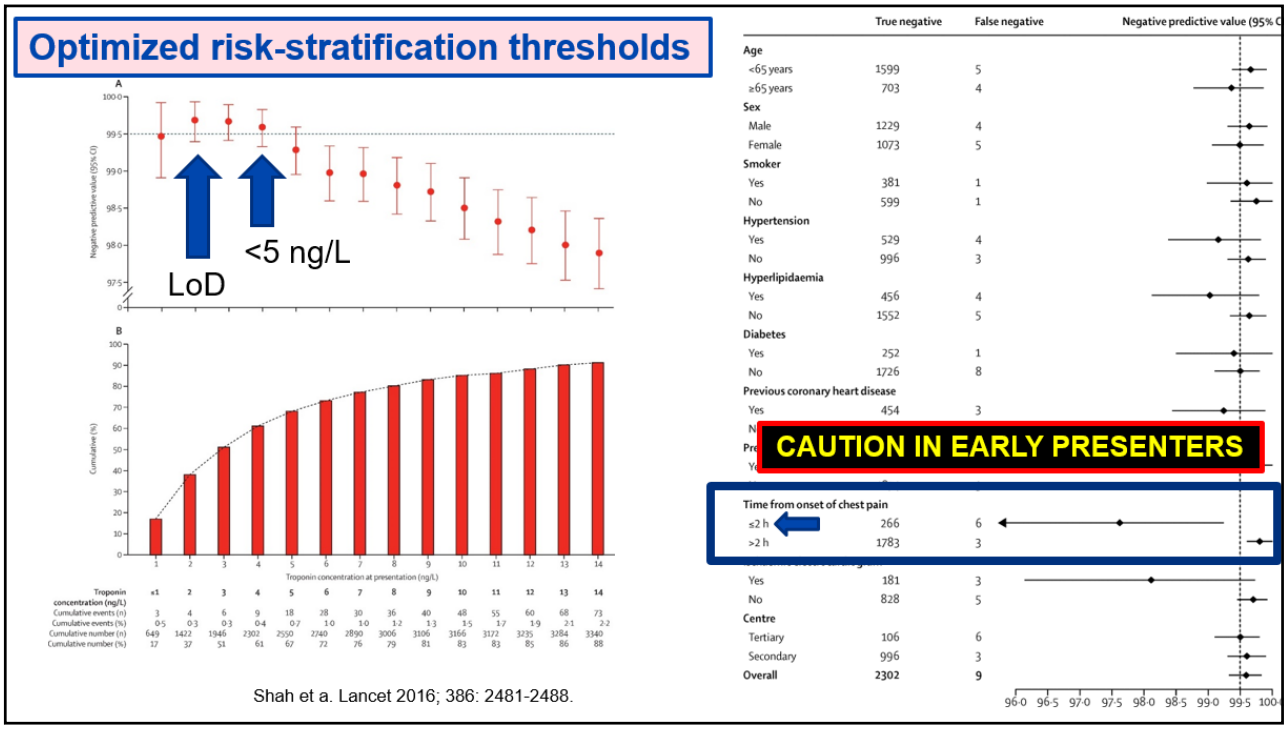
Optimized risk-stratification thresholds
<5 ng/L
LoD
True negative
False negative
Negative predictive value (95% C
Age
<65 years 1599 5
≥65 years 703 4
Sex
Male 1229 4
Female 1073 5
Smoker
Yes 381 1
No 599 1
Hypertension
Yes 529 4
No 996 3
Hyperlipidaemia
Yes 456 4
No 1552 5
Diabetes
Yes 252 1
No 1726 8
Previous coronary heart disease
Yes 454 3
CAUTION IN EARLY PRESENTERS
Time from onset of chest pain
≤2 h 266 6
>2 h 1783 3
Yes 181 3
No 828 5
Centre
Tertiary 106 6
Secondary 996 3
Overall 2302 9
Shah et a. Lancet 2016; 386: 2481-2488.

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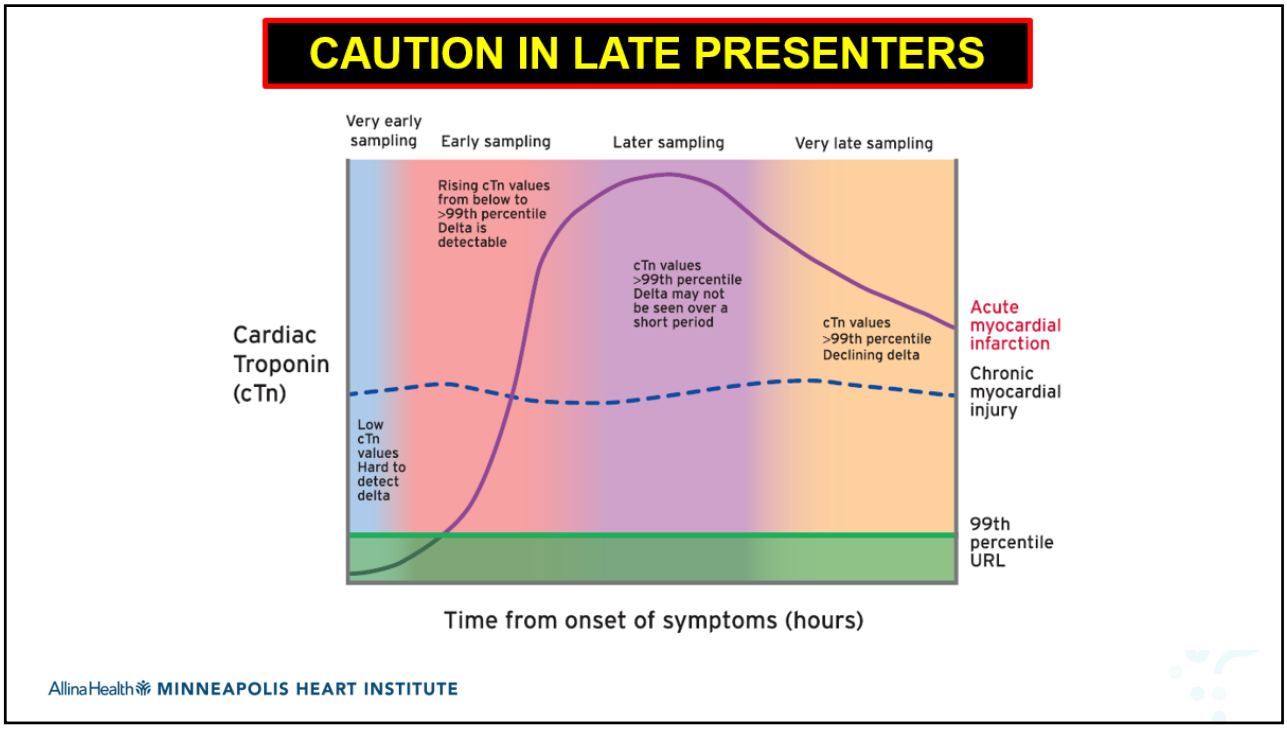
CAUTION IN LATE PRESENTERS
Very early sampling
Early sampling
Later sampling
Very late sampling
Rising cTn values from below to >99th percentile Delta is detectable
cTn values >99th percentile Delta may not be seen over a short period
cTn values >99th percentile Declining delta
Cardiac Troponin (cTn)
Low cTn values Hard to detect delta
Acute myocardial infarction
Chronic myocardial injury
99th percentile URL
Time from onset of symptoms (hours)
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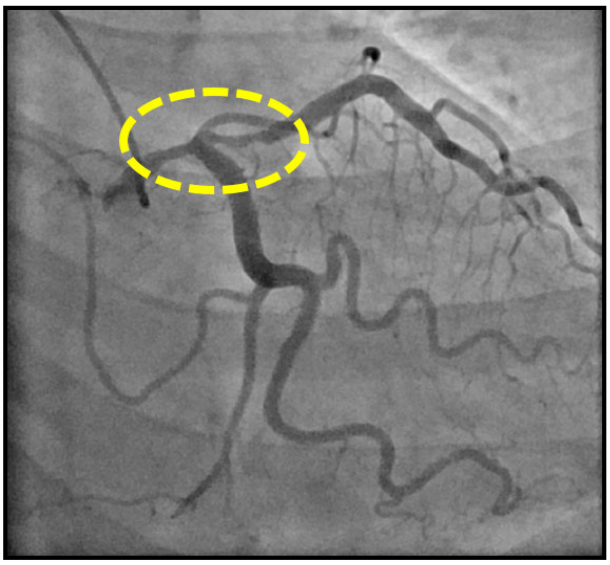
UNSTABLE ANGINA STILL EXISTS



49 year-old F with intermittent chest discomfort for a couple of days.

Baseline hs-cTnT <6 ng/L (LoQ)

2nd hs-cTnT also <6 ng/L

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10. Outpatient applications

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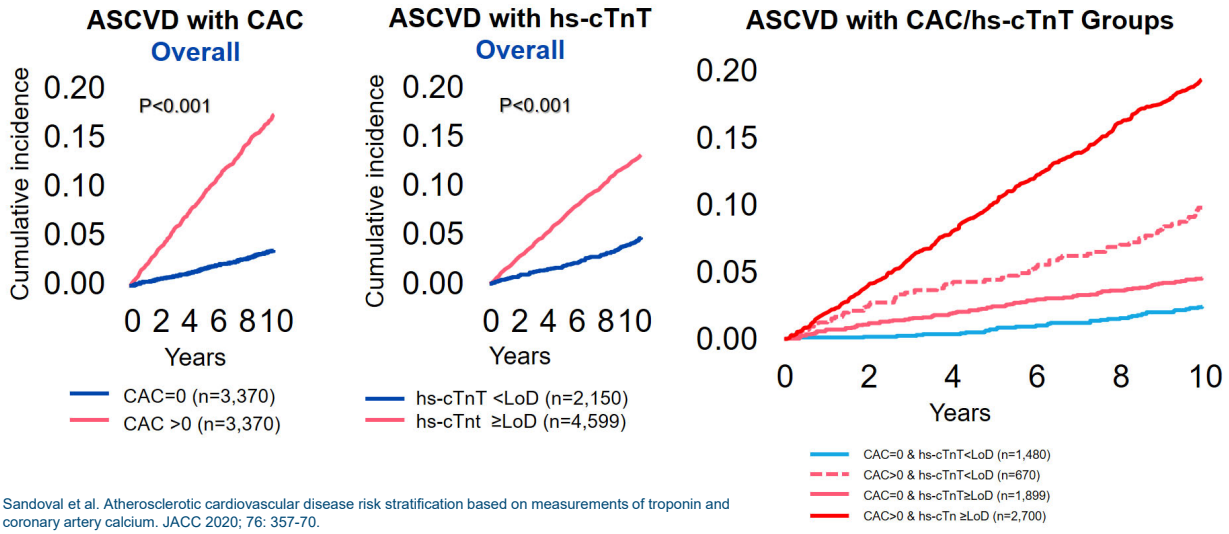
MESA: ASCVD Risk Prediction with CAC and hs-cTnT



Sandoval et al. Atherosclerotic cardiovascular disease risk stratification based on measurements of troponin and coronary artery calcium. JACC 2020; 76: 357-70.

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Circulation

ORIGINAL RESEARCH ARTICLE

Performance of the ABC Scores for Assessing the Risk of Stroke or Systemic Embolism and Bleeding in Patients With Atrial Fibrillation in ENGAGE AF-TIMI 48

Editorial, see p 772

David D. Berg, MD
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BACKGROUND: The ABC (age, biomarker, clinical history)-stroke and ABC-bleeding risk scores incorporate clinical variables and cardiovascular biomarkers to estimate risk of stroke or systemic embolic events and bleeding, respectively, in patients with atrial fibrillation. These scores have been proposed for routine clinical use, but their performance in external cohorts remains uncertain.

METHODS: ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction 48) was a multinational randomized trial of the oral factor Xa inhibitor edoxaban in patients with atrial fibrillation and a $CHADS_2$ score ≥2. We performed a nested prospective biomarker study in 8705 patients, analyzing baseline high-sensitivity troponin T (hsTnT), NT-proBNP (N-terminal 8-type natriuretic peptide), and growth differentiation factor-15 (GDF-15), as well as in serial samples after 12 months. The ABC-stroke (age, prior stroke/transient ischemic attack, hsTnT, NT-proBNP) and ABC-bleeding (age, prior bleeding, hemoglobin, hsTnT, and GDF-15) scores were tested. Hazard ratios were adjusted for estimated glomerular filtration rate and the components of the CHA_2DS_2-VASc and HAS-BLED scores, respectively. Discrimination and reclassification were compared with these established scores.

RESULTS: Median baseline hsTnT, NT-proBNP, and GDF-15 levels were 13.7 ng/L (25th–75th percentiles, 9.6–20.4 ng/L), 811 pg/mL (386–1436 pg/mL), and 1661 pg/mL (1179–2427 pg/mL), respectively. Elevated hsTnT, NT-proBNP, and GDF-15 were independently associated with higher rates of stroke or systemic embolic events, and elevated hsTnT and GDF-15 were independently associated with higher rates of major bleeding (P<0.001 for each). The ABC-stroke and ABC-bleeding scores were well calibrated and yielded higher c indexes than the CHA_2DS_2-VASc score for stroke or systemic embolic events (0.67 [95% CI, 0.65–0.70] versus 0.59 [95% CI, 0.57–0.62]; P<0.001) and HAS-BLED score for major bleeding (0.69 [95% CI, 0.66–0.71] versus 0.62 [95% CI, 0.60–0.64]; P<0.001), respectively. The ABC-stroke and ABC-bleeding scores stratified patients within CHA_2DS_2-VASc and HAS-BLED risk categories (P<0.001 for both). Patients with ABC-bleeding scores predicting a high 1-year risk of bleeding (>2%) derived greater benefit from treatment with edoxaban compared with warfarin.

CONCLUSIONS: The ABC-stroke and ABC-bleeding scores evaluated in this anticoagulated clinical trial cohort were well calibrated and outperformed the CHA_2DS_2-VASc and HAS-BLED scores, respectively. These scores may help identify patients most likely to derive a benefit from treatment with non–vitamin K antagonist oral anticoagulants.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT00781391.

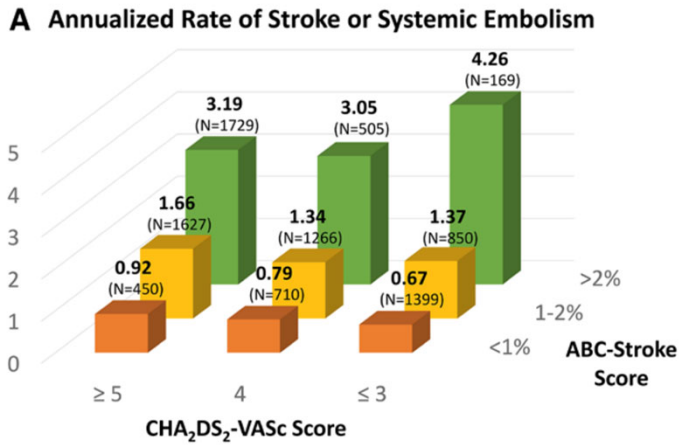
Key Words: atrial fibrillation • biomarkers • hemorrhage • risk assessment • stroke

Sources of Funding, see page 770

https://www.ahajournals.org/journal/circ

Circulation. 2019;139:760–771. DOI: 10.1161/CIRCULATIONAHA.118.038312

ABC-stroke: age, prior stroke/TIA, Hs-cTnT, NT-proBNP



ABC-stroke risk → C statistic of 0.67
CHA_2DS_2-VASc score → C statistic of 0.59

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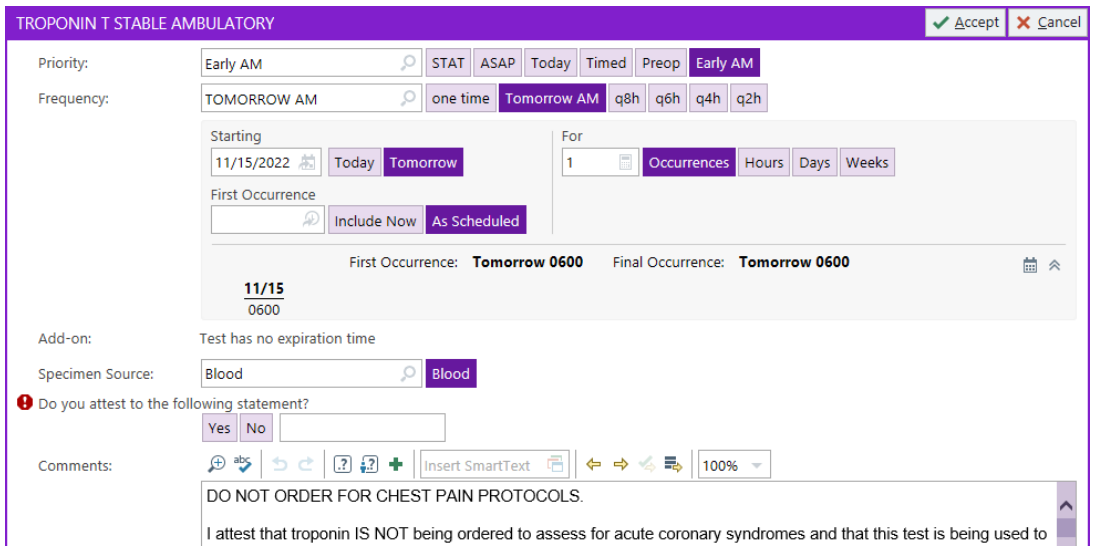

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"When troponin was a lousy assay it was a great test, but now that it's becoming a great assay, it's getting to be a lousy test" – Dr. Robert L. Jesse, MD, PhD; JACC 2010; 55: 2125-8.

PAST – CONTEMPORARY ASSAYS
Binary test: negative vs. positive
Delays in diagnosis due to prolonged sampling
More samples needed
More analytical noise; more false positives.
More uncertainty about 'low-risk' which contributed to additional risk-stratification in ruled-out patients
No randomized trials
Limited MI vs. no MI scope
Overall threshold, MI under-diagnosis in women

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"When troponin was a lousy assay it was a great test, but now that it's becoming a great assay, it's getting to be a lousy test" – Dr. Robert L. Jesse, MD, PhD; JACC 2010; 55: 2125-8.

PAST – CONTEMPORARY ASSAYS	PRESENT – HIGH-SENSITIVITY ASSAYS
Binary test: negative vs. positive	Continuous biomarker: barometer of CV health
Delays in diagnosis due to prolonged sampling	Rapid diagnosis, most within 1-3 hours
More samples needed	Less samples needed
More analytical noise; more false positives.	Less analytical noise; less false positives.
More uncertainty about 'low-risk' which contributed to additional risk-stratification in ruled-out patients	Less uncertainty about 'low-risk' which reduces additional testing in ruled-out patients
No randomized trials	Multiple RCTs
Limited MI vs. no MI scope	Multiple applications, including emerging outpatient CV applications
Overall threshold, MI under-diagnosis in women	Sex-specific thresholds, improved diagnosis in women

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Take-home Points

1. Clinical trials and practice guidelines recommend high-sensitivity cardiac troponin assays as the preferred test to evaluate patients with suspected ACS.
2. Main advantages: rapid triage and disposition in the emergency department.
3. Main challenges: increased "positivity" rate – how to deal with acute/chronic myocardial injury and type 2 myocardial infarction.
4. Key intervention for successful implementation: education, education, education.
5. Clinical context and pre-test probability remain essential.
6. Increasing number of application of hs-cTn testing in the outpatient setting.

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Mark your calendars: MHIF GR on NT-proBNP with Dr. James Januzzi

AllinaHealth | Minneapolis Heart Institute Foundation | CLINICAL EDUCATION

Minneapolis Heart Institute Foundation® Cardiovascular Grand Rounds

Title: NT-proBNP
Speaker: James Januzzi, MD, FACC, FESC
Hutter Family Professor of Medicine, Harvard Medical School
Cardiologist, Massachusetts General Hospital
Trialist, Baim Institute for Clinical Research
Date: February 13, 2023
Time: 7:00 - 8:00 AM
Location: Minneapolis Heart Institute Building, Suite 100, MHIF Learning Center
Webinar - visit www.mplsheart.org/grandrounds for login information

OBJECTIVES

At the completion of this activity, the participants should better be able to:

1. List the differential diagnosis of an elevated NT-proBNP.
2. Discuss optimal diagnostic cut-offs for the biomarker.
3. Recite similarities and differences between BNP and NT-proBNP.

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Contact: yader.sandoval@allina.com

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