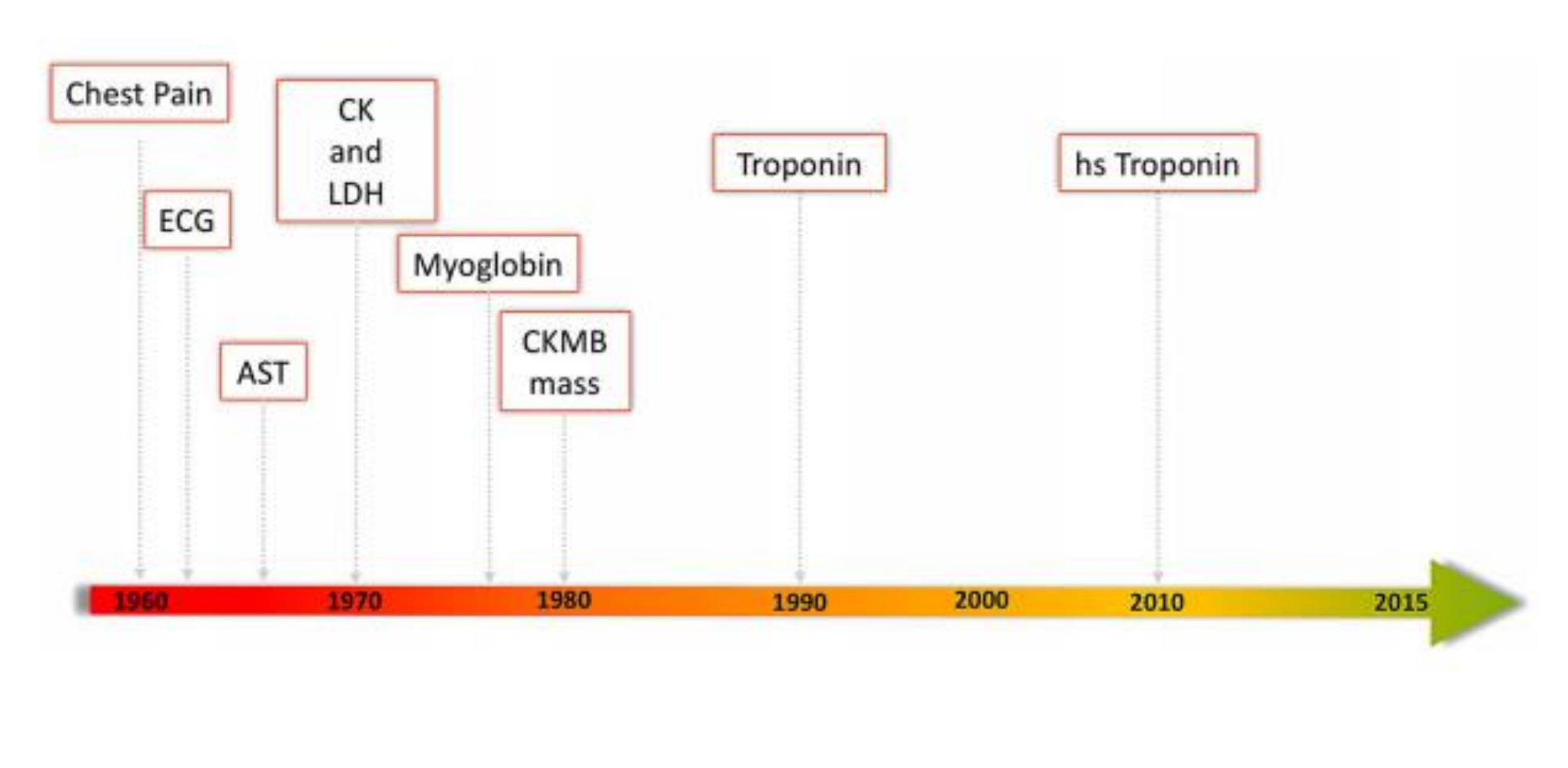
Troponins in Emergency department

Introduction

- The thorough evaluation and accurate diagnosis of the myriad of disorders that cause chest pain is of utmost importance for the emergency department (ED) physician.
- Early detection of cardiac troponins (cTns) specifically can alter patient dispositions from the ED.
- High sensitivity cardiac troponins" (hs-cTn) are promising for potentially detecting previously-missed clinically significant myocardial damage.

Fox WR et al. Clin Exp Emerg Med 2016;3(1):1-8

Timeline of development of cardiac biomarkers



Garg P et al. Intern Emerg Med;2017: 12:147–155

Troponins

- Troponin is a component of the contractile apparatus within skeletal and cardiac myocytes.
- Along with calcium ions, troponin proteins regulate and facilitate the interaction between actin and myosin filaments for muscle contraction.
- Cardiac troponin (cTn) is a complex comprising three subunits:

1. Troponin T attaches the troponin complex to the actin filament
2. Troponin C acts as the calcium binding site
3. Troponin I inhibits interaction with myosin heads in the absence of sufficient calcium ions.

Garg P et al. Intern Emerg Med;2017: 12:147–155

Troponins

- Troponin C is synthesised in skeletal and cardiac muscle.
- Troponin T and I isoforms are highly specific and sensitive to cardiac myocytes and, therefore, are known as cardiac troponins (cTn).
- The detection of cTn-T or cTn-I in the blood stream is a highly specific marker for cardiac damage .
- 92–95% of troponin is attached to the actin thin filaments in the cardiac sarcomere, and the remaining 5–8% is free in the myocyte cytoplasm.
- Free, unbound cTn constitutes the 'early releasable troponin pool' (ERTP) . ERTP is thought to be released immediately following myocyte injury

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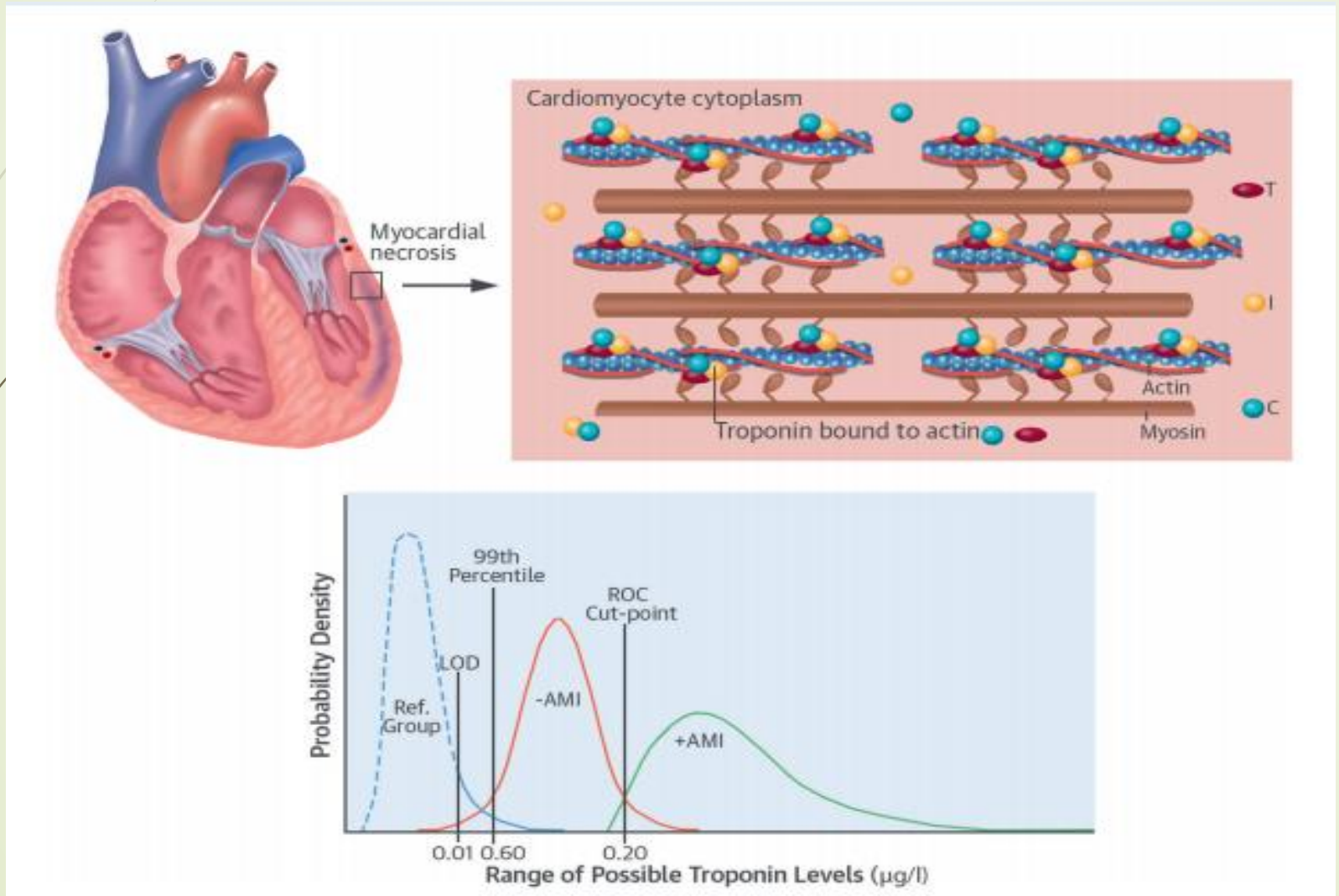
Troponin Isoforms

Table Isoforms of the troponin subunits with their respective genes and expression sites

Troponin I (TnI)		Troponin T (TnT)		Troponin C (TnC)	
Isoform *(Gene)*	**Expression site**	**Isoform *(Gene)***	**Expression site**	**Isoform *(Gene)***	**Expression site**
Fast-skeletal 'fsTnI' *(TNNI2)*	Fast-twitch skeletal muscle	**Fast-skeletal 'fsTnT' *(TNNT3)***	Fast-twitch skeletal muscle	**Fast-skeletal 'fsTnC' *(TNNC2)***	Fast-twitch skeletal muscle
Slow-skeletal 'ssTnI' *(TNNI1)*	Slow-twitch skeletal muscle	**Slow-skeletal 'ssTnT' *(TNNT1)***	Slow-twitch skeletal muscle	**Slow-skeletal 'ssTnC' or 'cTnC' *(TNNC1)***	Slow-twitch skeletal muscle and cardiac muscle
Cardiac 'cTnI' *(TNNI3)*	Cardiac muscle	**Cardiac 'cTnT' *(TNNT2)***	Cardiac muscle		

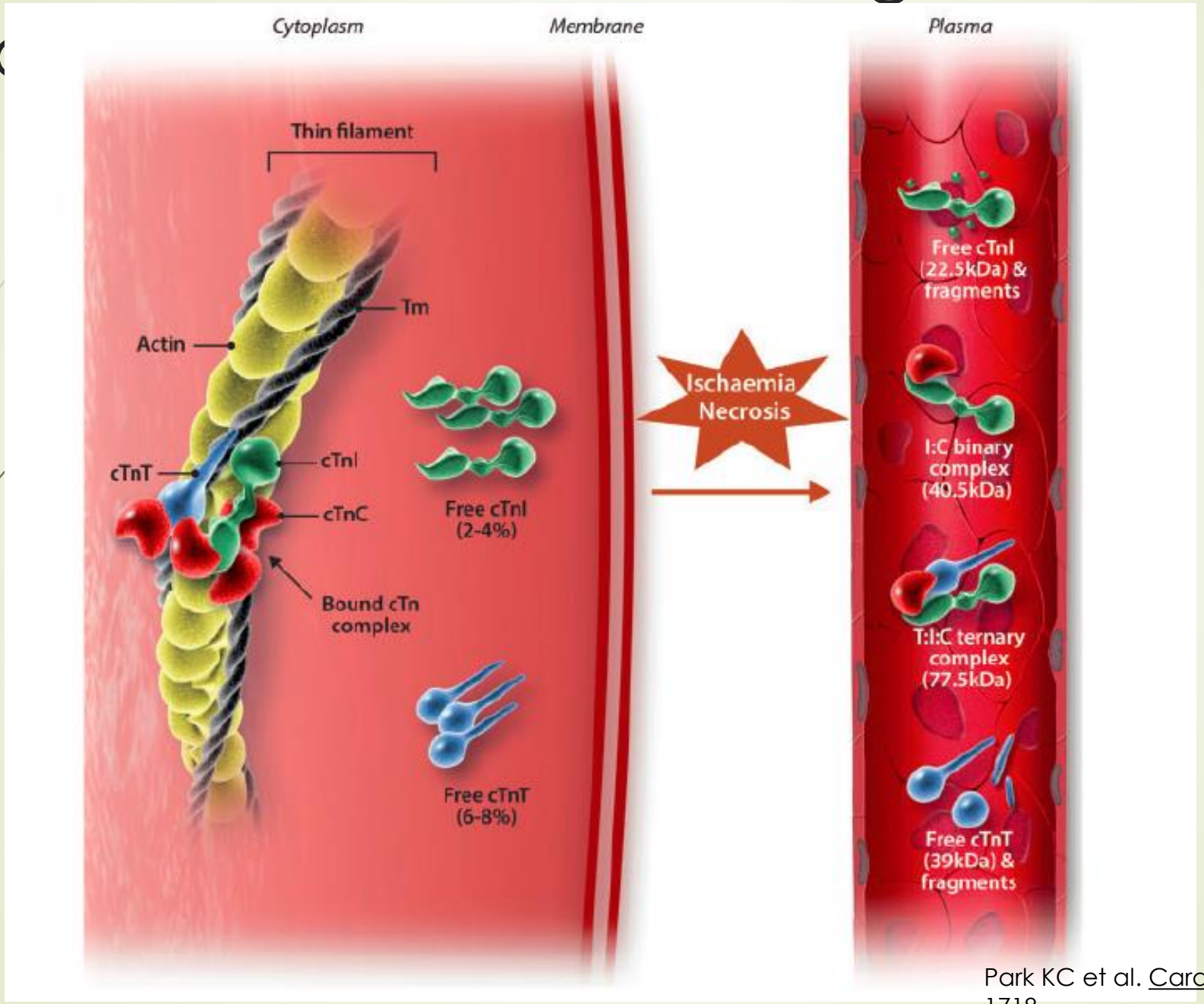
Park KC et al. Cardiovasc Res. 2017 Dec 1;113(14):1708-1718.

Troponins in MI



Brush, Jr., J.E. et al. J Am Coll Cardiol.

Troponin forms released during ischemic necro



Park KC et al. Cardiovasc Res. 2017;113(14):1708-

High-sensitivity cardiac troponin in MI

- High sensitive-cTn assays detect troponin with higher sensitivity and precision at an earlier point of time.[1]

- The negative predictive value of hs-cTn assays is 95% for Acute Myocardial infarction(AMI) exclusion in patients tested on arrival at the Emergency department, repeated at 3 h, rises to nearly 100%.[1]

- Shah et al. demonstrated that using lower cutoffs for hs-cTn I (5 ng/L) identifies low-risk patients for the composite outcome of index myocardial infarction with an NPV of 99.6% (95% CI 99.3–99.8%) .[2]

1. Garg P et al. Intern Emerg Med;2017: 12:147–155.
2. Shah ASV et al. 2015; Lancet 386:2481–2488

High-sensitivity cardiac troponin in MI

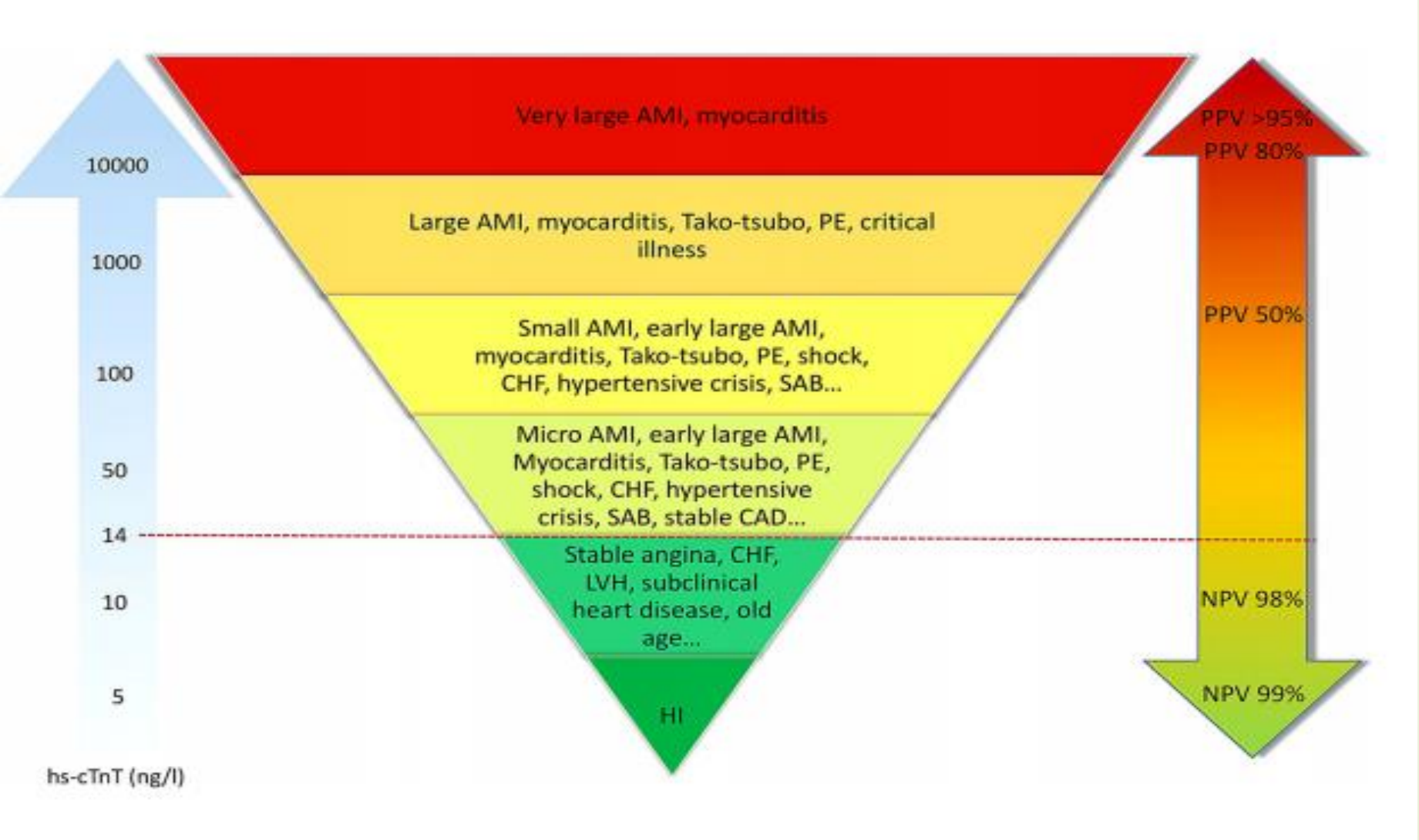
- A systematic review and meta-analysis demonstrated that 'lower cutoffs' (3–5 ng/L versus 14 ng/L) for a single baseline hs-cTn T measurement.

Improve sensitivity for Acute MI markedly, and can be used as a rule-out test in patients presenting more than 3 h after symptom onset

- hs-cTn facilitates earlier exclusion of Acute MI, contributing to reduced length of stay, and earlier treatment resulting in improved outcomes

Garg P et al. Intern Emerg Med;2017: 12:147–155

High-sensitivity cardiac troponin



AMI- acute myocardial infarction

CAD - Coronary artery disease

CHF- Congestive heart failure

HI -healthy individual

LVH - Left ventricular hypertrophy

PE- Pulmonary embolus

SAB -Staphylococcus aureus bacteramia

NPV -Negative predictive value

PPV – Positive predictive value

Garg P et al. Intern Emerg Med;2017: 12:147–155

Mechanisms of elevated cardiac troponins

- Direct cardiac damage :

1. Infiltrative cardiac diseases – Direct myocyte compression and regional loss of myocardium
2. Chemotherapy – Cardiotoxicity

Park KC et al. Cardiovasc Res. 2017 Dec 1;113(14):1708-1718.

Mechanisms of elevated cardiac troponins

- Myocardial strain (excessive wall stress):

1. CHF – Myocardial wall stress
2. Systemic hypertension – Increased LV after load (pressure overload)
3. Aortic stenosis - Increased LV after load (pressure overload)
4. Pulmonary artery hypertension - Increased LV after load (pressure overload)
5. Valvular regurgitation – Increased LV/RV preload (Volume overload)
6. Chronic Kidney Disease and End Stage Renal Disease – Chronic RAAS activation and excessive sympathetic activity(Volume and pressure overload).

Park KC et al. Cardiovasc Res. 2017 Dec

Mechanisms of elevated cardiac troponins

- Myocardial ischemia (reduced myocardial oxygen supply)

1. CHF and adverse cardiac remodeling –a)capillary inadequacy and impaired coronary reserve. b)Sub endocardial ischemia
2. Coronary artery disease – a) endothelial dysfunction and atherosclerosis, b) clinically silent microinfarcts.
3. Systemic hypotension –decreased perfusion pressure
4. Hypovolemia –decreased –decrease filling pressure/output
5. Anemia –reduced myocardial oxygen supply
6. Diabetes mellitus- Macrovascular complications (endothelial dysfunction and coronary artery disease)

Park KC et al. Cardiovasc Res. 2017 Dec 1;113(14):1708-1718.

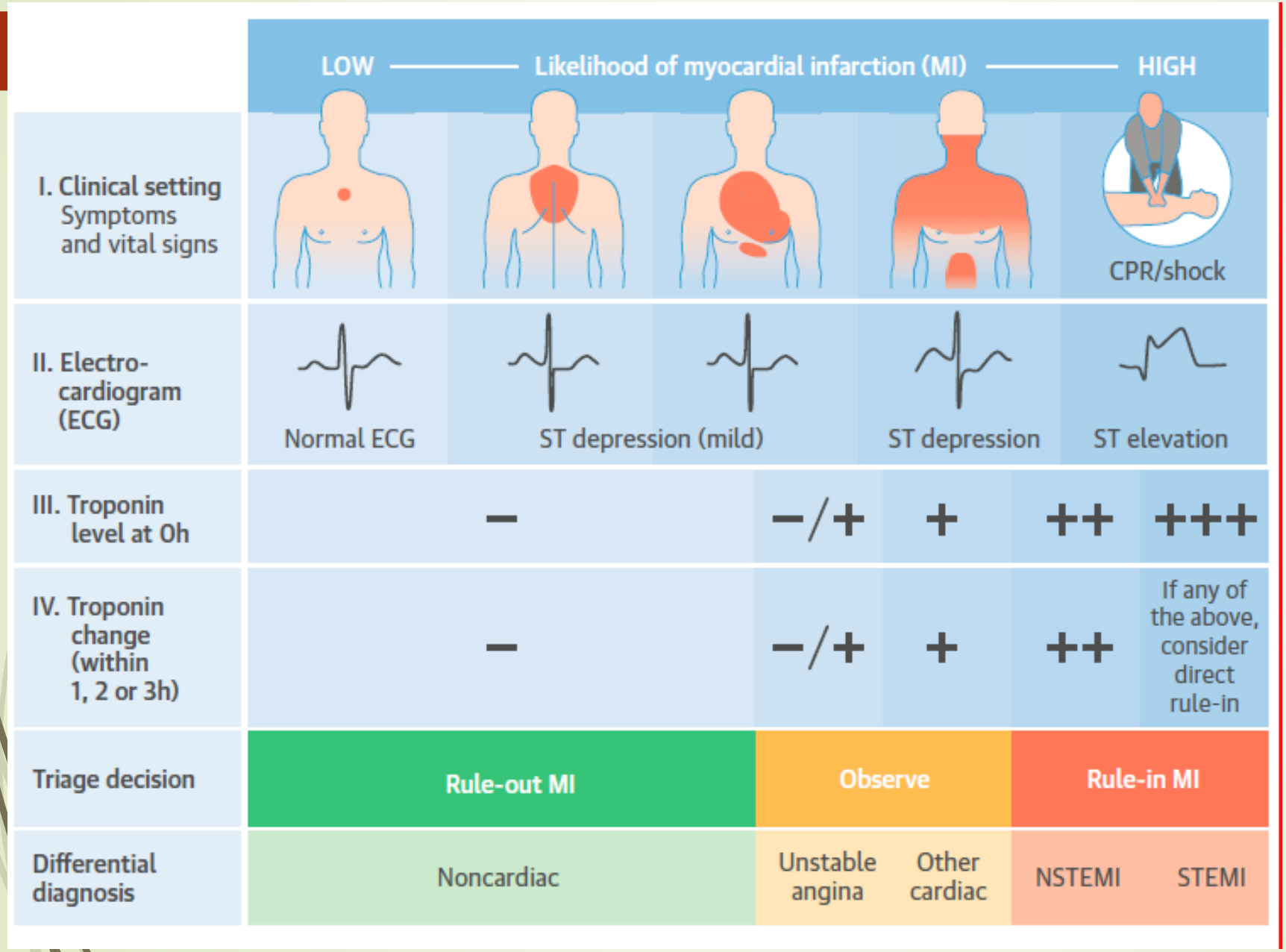
Mechanisms of elevated cardiac troponins

- Demand ischemia (Increased myocardial oxygen demand) –

1. CHF and cardiac remodeling – a) Diastolic stiffening and contractile dysfunction –Collagen deposition and focal fibroses. b) sub endocardial ischemia
2. Atrial fibrillation – Increased myocardial oxygen consumption.
3. Chronic Kidney Disease and End Stage Renal Disease – excessive sympathetic activity and catecholamine release
4. Post stroke - excessive sympathetic activity and catecholamine release

Park KC et al. Cardiovasc Res. 2017 Dec 1;113(14):1708-1718.

Initial assessment in ACS



Twerenbold, R. et al. J Am Coll Cardiol. 2017;70(8):984–1012

Biomarkers for assessment in ACS

TABLE 2 Summary of Biomarker Strategies for Rapid Assessment of Patients With Potential ACS in the ED

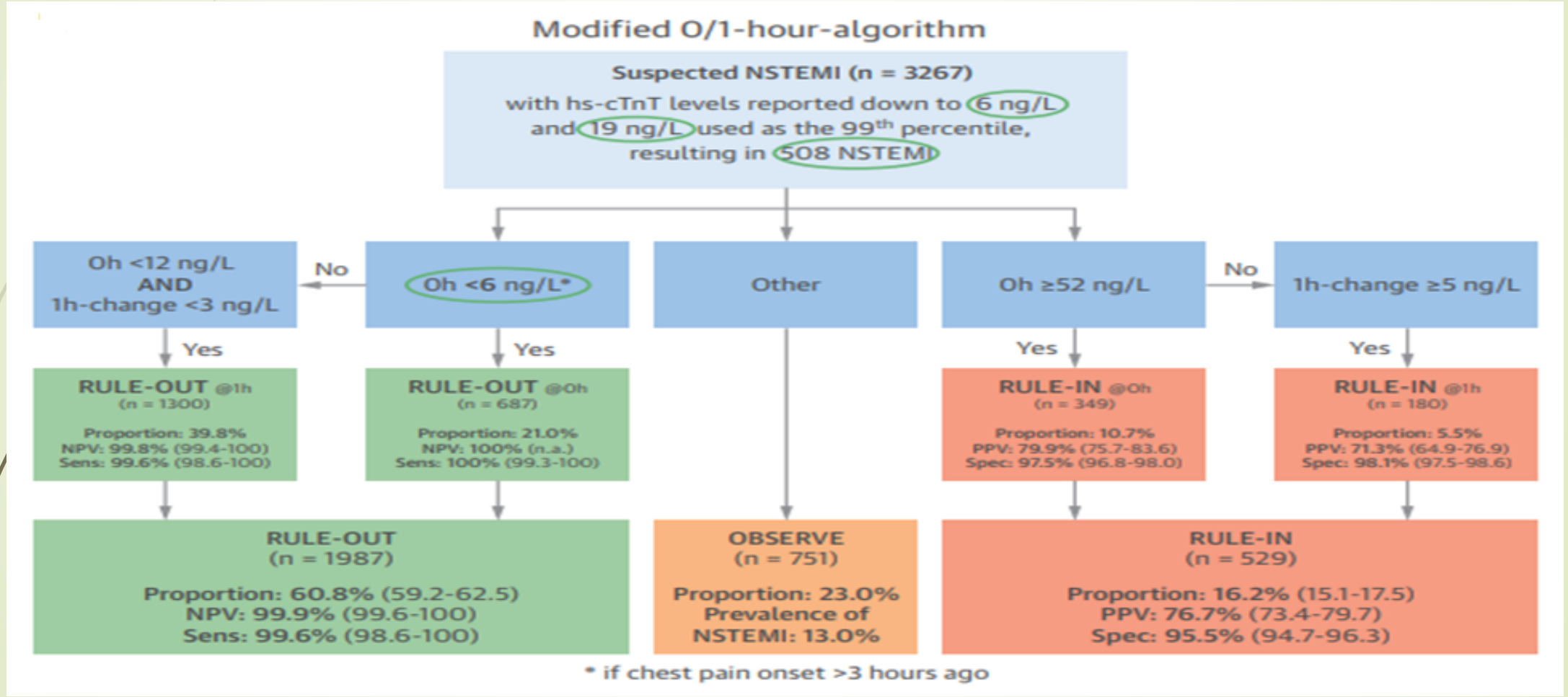
	Very Low cTn	0/1h-ESC Algorithm	Alternative 1h Algorithm	0/2h Algorithm	2h-ADP	0/3h-ESC Algorithm
Clinical scoring system	None	None	None	None	TIMI score ≤1 ECG Normal at 0 h/2 h	GRACE <140 and Pain Free
Number of blood draws	1	1 or 2	2	1 or 2	2	1 or 2
Indication	Rule-out	Rule-out and rule-in	Rule-out and rule-in	Rule-out and rule-in	Rule-out	Rule-out and rule-in
Negative predictive value for MI	98.5%-100%	99.1%-100%	99.2%-99.6%	99.5%-99.9%	99.1%-100%*	99.6%-100%
Eligible population size	+(+)	+++	+++	+++	++	++(+)
Biomarker rule-out criteria†						
High-sensitivity cardiac troponin T (hs-cTnT)	hs-cTnT <5 ng/l	hs-cTnT 0 h <12 ng/l AND 1-h change <3 ng/l	n.a.	hs-cTnT 0 h and 2 h <14 ng/l AND 2-h change <4 ng/l	hs-cTnT 0 h and 2 h <14 ng/l	hs-cTnT 0 h and 3 h <14 ng/l
High-sensitivity cardiac troponin I (hs-cTnI)	hs-cTnI 0 h <2-5 ng/l	hs-cTnI 0 h <5 ng/l AND 1-h change <2 ng/l	hs-cTnI 0 h ≤6 ng/l AND hs-cTnI 1 h ≤6 ng/l	hs-cTnI 0 h and 2 h <6 ng/l AND 2-h change <2 ng/l	hs-cTnI 0 h and 2 h <26 ng/l	hs-cTnI 0 h and 3 h <26 ng/l
Biomarker rule-in criteria†						
Using hs-cTnT	n.a.	hs-cTnT 0 h ≥52 ng/l OR 1-h change ≥5 ng/l	n.a.	hs-cTnT 0h ≥53 ng/l OR 2-h change ≥10 ng/l	n.a.	
Using hs-cTnI	n.a.	hs-cTnI 0 h ≥52 ng/l OR 1-h change ≥6 ng/l	hs-cTnI 1 h >6 ng/l AND 1-h change ≥12 ng/l	hs-cTnI 0 h ≥64 ng/l OR 2-h change ≥15 ng/l	n.a.	
Feasibility	High	High	High	High	Medium; requires use of TIMI score	Medium; requires GRACE score

Eligible population size is quantified by the percentage of consecutive chest pain patients eligible for this early triage strategy. + =20%; ++ =40%; +++ =50% to 75%. *For major adverse cardiac events (death, MI, major arrhythmias). †Characteristics are provided for the hs-cTnT (Elecsys) and hs-cTnI (Architect). Cutoff levels differ for other hs-cTn assays becoming available for clinical use in the future.

ACS = acute coronary syndrome; ADP = accelerated diagnostic pathway; cTn = cardiac troponin; ECG = electrocardiogram; ED = emergency department; ESC = European Society of Cardiology; GRACE = Global Registry of Acute Coronary Events; hs = high-sensitivity; LOD = lower limit of detection; MI = myocardial infarction; RCT = randomized controlled trial; TIMI = Thrombolysis In Myocardial Infarction.

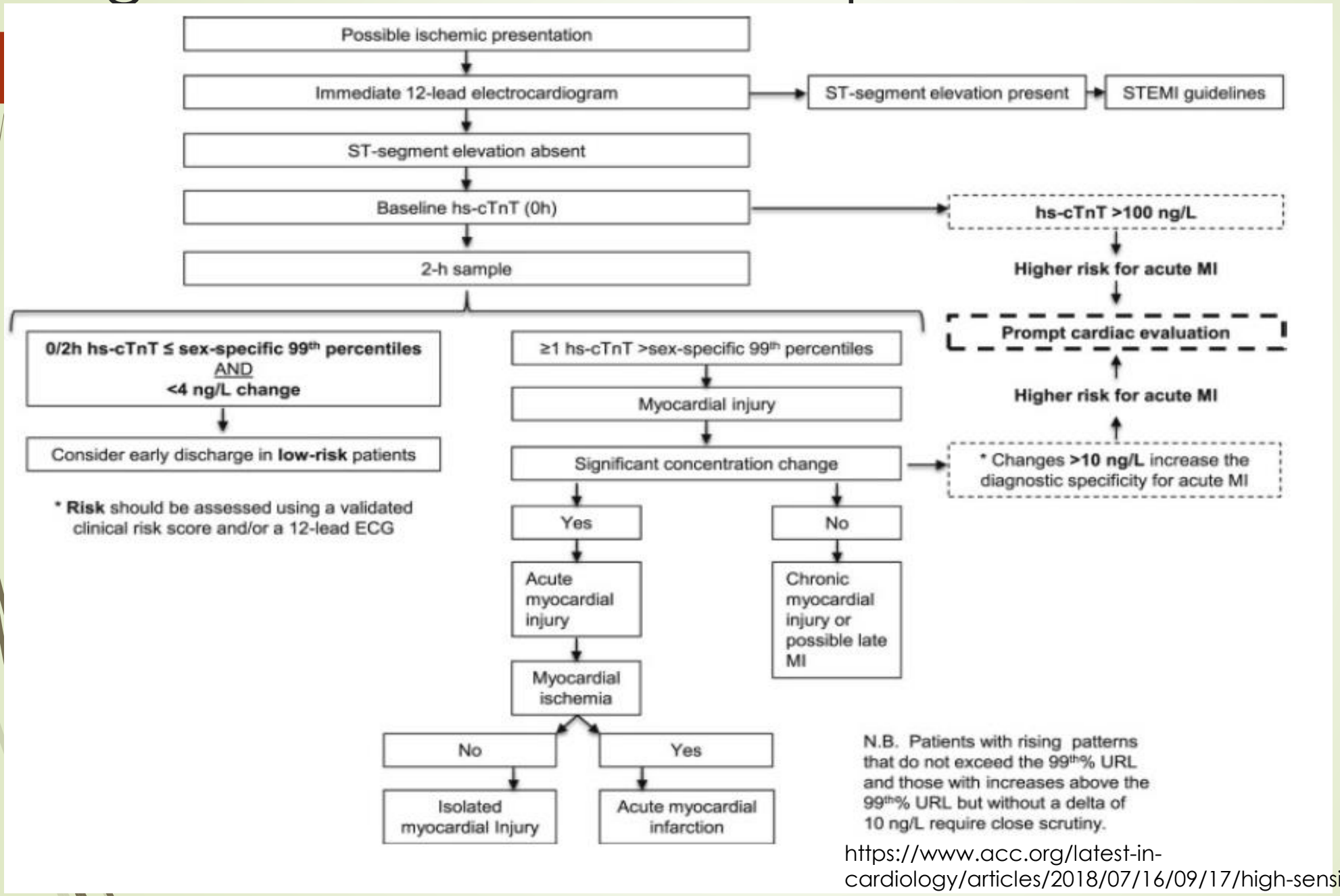
Twerenbold R et al. J Am Coll Cardiol. 2017;70(8):996-1012

ESC algorithm for assessment of troponin levels in MI



Twerenbold R et al. J Am Coll Cardiol. 2017;70(8):996-1012

High sensitive Cardiac troponin in MI



https://www.acc.org/latest-in-cardiology/articles/2018/07/16/09/17/high-sensitivity-cardiac-

Other Cardiac causes of troponin elevation

- **The American Heart Association/ American College of Cardiology** Non - ST elevation myocardial infarction (NSTEMI) – troponin to be tested at the time of arrival ,6 hours after the first to confirm the diagnosis.[1]
- **Congestive heart failure:** In acute exacerbation, an elevated troponin the higher the troponin, the higher the mortality, regardless of whether or not the heart failure is due to ischemia.[2]
- **Aortic dissection:** Vrsalovic et al showed that elevated troponins in a patient presenting with an Acute Aortic dissection are at higher risk for poorer outcomes.[3]

1) Vasile VC et al.2017; Curr Cardiol Rep. 19(10): 1-92.
2) Akwe J et al. J Cardiol Curr Res 2017, 10(3): 1-8.
3) Vrsalovic M et al. Int J Cardiol .2016 ;214: 277-278

Other Cardiac causes of troponin elevation

- **Cardiac ablation**: Reichlin et al demonstrated that Troponin levels rose faster in patients undergoing Ventricular Tachycardia ablation when compared to atrial fibrillation ablation.
- **Cardiac contusion**:

1. Rajan et al found that higher troponin I levels were associated with severe arrhythmias and damage to the myocardium
2. Joseph et al showed that a troponin level of greater than 0.2 was significantly more common in the non-survivor group compared to survival group.
3. Velmahos et al with thoracic trauma noted the negative predictive value of cardiac troponins was 21% and the positive predictive value was 94%

1) Reichlin T et al. J Interv Card Electrophysiol.2016; 47(1): 69-74.
2) Rajan GP et al. J Trauma. 2004; 57(4): 801-808;
3) Joseph B et al. Am J Surg .2016;211(6): 982- 988.
4) Velmahos GC et al. J Trauma. 2003; 54(1): 45-50

Other Cardiac causes of troponin elevation

Cardiac infiltrative diseases:

- Hs-cTnT is reliable parameter for cardiac sarcoidosis .[1]
- It has a sensitivity of 87.5% and specificity of 75.0%, positive predictive value (PPV) of 87.5% and negative predictive value (NPV) of 75.0%. .[1]

Arrhythmias:

- Peak troponin levels indicate the presence of severe coronary artery disease (sCAD) in patients presenting with atrial fibrillation (afib).[1]
- Bakshi et al noted that tachycardia was the cause of elevated troponins in 28% of patients without coronary artery disease.[2]

1)Akwe J et al. J Cardiol Curr Res 2017, 10(3): 1-8.
2) Bakshi TK et al. Intern Med J .2002; 32(11): 520-525.

Other Cardiac causes of troponin elevation

Defibrillator shocks:

- Troponin elevation occurs in the majority of patients after inappropriate ICD discharges (ICD shocks cause myocardial injury).[1]
- Miranda et al revealed that patients with cTnI elevation after multiple ICD shocks had higher risk of death or heart failure hospitalization.[2]

Pericarditis/Myocarditis:

- Patients with ECG abnormalities are more likely to have higher troponin levels.[1]
- Imazio M et al. showed that Troponin elevation and myocardial involvement in pericarditis does not portend a worse prognosis.[3]

1) Akwe J et al. J Cardiol Curr Res 2017, 10(3): 1-8.
2) Miranda CH et al. 2014; Am J Emerg Med. 32(9): 1085-1088.
3) Imazio M et al. 2013; Circulation 128(1): 42-49.

Non cardiac causes for Troponin elevation

Acute pulmonary embolism:

- Elevated troponins are found in 30-50% of the patients diagnosed with pulmonary Embolism.[1]
- Konstantinides et al suggested that up to 70.4% of patients who have a Pulmonary Embolism had elevated cTnI were found to have right ventricular dysfunction (RVD) .[2]
- Kilinc et al suggested that high cTnI was higher in massive Pulmonary Embolism (PE) compared with sub-massive and non-massive PE. .[3]

1) Akwe J et al. J Cardiol Curr Res. 2018; 11(1): 1-8
2) Konstantinides S et al. Circulation. 2002 ; 106(10): 1263-1268.
3) Kilinc G et al. J Thorac Dis. 2012; 4(6): 588-593 .

Non cardiac causes for Troponin elevation

End stage renal disease:

- Serum cardiac troponin T (cTnT) concentrations are frequently increased in chronic dialysis patients.[1]
- Mc Lauren showed the prevalence of ischemic heart disease (IHD) in hemodialysis patients as 10–20 times higher than in the general population.[2]

1) Akwe J et al. J Cardiol Curr Res. 2018; 11(1): 1-8.
2) McLaurin MD et al. Clin Chem.1997; 43(6 Pt 1): 976-982.

Non cardiac causes for Troponin elevation

Sepsis/ Systemic Inflammatory Response Syndrome (SIRS):

- Elevated cardiac troponin I (cTnI) is frequently observed in patients with severe sepsis and septic shock.[1]
- TNFa, IL-1β and IL-6 appear play a pivotal role in the release of cardiac troponin in sepsis.[1]
- Ver Elst et al. demonstrated that cTnI positivity was strongly associated with left ventricle dysfunction (LVD), correlated with the degree of hypotension and APACHE II score .[2]

Burns:

- Mehta et al showed that in Patients with total body surface area of burn >30% had significantly higher cTnI rise compared to those with less burn area.[3]

1) Akwe J et al. J Cardiol Curr Res. 2018; 11(1): 1-8.
2)Ver Elst KM et al. Clin Chem.2000;46(5): 650-657.
3) Mehta NJ et al. Int J Cardiol. 2004; 95(1): 13-17.

Non cardiac causes for Troponin elevation

Rhabdomyolysis:

- Punukollu et al. showed that Patients with the cTnI elevation were associated with increased rates of ICU admission, hypotension, sepsis and length of stay compared to those without troponin elevation.[1]

Drug toxicity:

- Christenson ES et al demonstrated high dose anthracycline had increased in troponin levels in breast cancer patients.[2]
- Cardinale D et al showed that an early rise in troponin during trastuzamab was associated with 17.6 times increased risk of cardiotoxicity.[3]

1) Punukollu G et al. Int J Cardiol .2004; 96(1): 35-40.
2) Christenson ES et al. Clin Biochem. 2015 ; 48(4-5): 223-235.
3) Cardinale D et al. J Clin Oncol. 2010; 28(25): 3910- 3916.

Errors in cardiac troponin testing

Main Sources of Analytical Error in Cardiac Troponin Testing

- Heterophile antibodies
  - Heterophile antibodies cause errors, more often elevations
  - Antibodies targeting assay reagents are rare but have strong effects
- Anti-Tn antibodies
  - Rarely cause false-negative results
  - Rarely impair clearance leading to an artificially elevated result
- Endogenous forms of assay components
  - Can be a result of supplementation (eg, biotin)
  - Signal-generating enzymes (eg, alkaline phosphatase) can affect results when extremely elevated
- Nonreproducible false elevations
  - Some are due to instrument malfunction, without preanalytical factors
- Calibration drift
  - Quality control and/or assurance procedures must be designed to detect shifts near diagnostic thresholds
- Poor standardization and harmonization
  - Considerable inter-assay variability challenges comparing results and thresholds
  - This is a bigger challenge for cardiac troponin I because of the variety of assays and antibodies
- Varying analytic sensitivity

Herman DS et al. Am J Clin Pathol. 2017 ; 148 (4) :281-295

Errors in cardiac troponin testing

Main Sources of Postanalytical Error in Cardiac Troponin Testing

- Myocardial infarction diagnostic threshold
  - Most use the guideline 99th percentile of healthy reference population
  - Variable selection criteria for "healthy reference" population
  - Poor precision in determination of 99th percentile due to sample size
- Detecting change
  - Approximate interpretations delay and likely impair accurate diagnosis
- Reporting units
  - Inconsistent unit use causes confusion and affects assessment of magnitude
- Lower limit of reportable range
  - Use of limit of quantification makes it easier for laboratory to ensure result quality
  - Use of limit of quantification impairs detection of early changes and conservative rule-out strategies

Herman DS et al. Am J Clin Pathol. 2017 ; 148 (4) :281-295

Case scenarios

1) A 51-year-old woman with a history of mild hypertension and mild hyperlipidemia had presented with a 2-h episode of substernal chest discomfort for the first time.

- She was receiving a statin but refused treatment for hypertension.
- She was an avid runner and had never had chest discomfort previously. The discomfort occurred at rest and radiated to her arms and her neck.
- Her electrocardiogram (ECG)3 revealed minor ST segment and T-wave changes in the inferior and lateral leads.
- Her initial cardiac troponin T (cTnT) concentration was 0.04 g/L (99th-percentile upper reference
- limit,0.01g/L) but increased to 0.32g/L and then to 0.76 g/L. An emergent coronary angiogram was interpreted as normal with the exception of slow flow in the circumflex coronary artery.
- An echocardiogram was normal.

Case scenarios

2) A 62-year-old woman was referred for evaluation of atypical chest pain and an equivocal stress test result.

- She had a history of hypertension and smoking for 25 years.
- Her chest discomfort was mild and radiated to the right shoulder. It occurred at rest and during exercise but had not changed in intensity or duration for 2 months.
- Her ECG was normal.
- The cTnT concentration measured with the fourth-generation assay on the day of a computed tomography (CT) angiography evaluation was 0.01g/L (99th-percentile upper reference limit, 0.01 g/L).
- A cTnT concentration measured with a high-sensitivity cTnT (hs-cTnT) assay of the same sample was mildly increased (15 ng/L; 99th-percentile value for women, 10 ng/L).
- CT angiography revealed 3-vessel coronary artery disease with noncalcified (soft) plaque in the middle portion of the left anterior descending coronary artery and several calcified, lesions in other vessels.

Case scenarios

3) A man, 54 years of age, was transferred from a peripheral hospital. He had risk factors of hypertension, type 2 diabetes mellitus.

- He presented with an episode of severe chest pain at rest, in the context of a 2 week history of exertional chest pain. His chest pain was described as dull and heavy, associated with shortness of breath and diaphoresis.
- Electrocardiogram (ECG) demonstrated sinus rhythm with T wave inversion in the anterior leads. His serum troponin I was elevated at 9.92 µg/L (normal < 0.03 µg/L). Coronary angiogram was performed. It demonstrated a severe ulcerated plaque in the proximal left anterior descending (LAD) artery. The left circumflex artery was of moderate calibre with minor disease. The right coronary artery was dominant with a distal 70% stenosis

Case scenarios

4) A woman, 53 years of age, presented to hospital with an episode of severe chest pain associated with shortness of breath. Her cardiac risk factors included hypertension and a family history of premature coronary artery disease.

- Recently she had been experiencing significant stress at work.
- Her ECG demonstrated sinus rhythm with widespread T wave inversion. Her serum troponin I peaked at 1.61 µg/L (normal <0.03 µg/L). Coronary angiogram was performed, which demonstrated smooth coronary arteries without obstructive lesions.
- Left ventriculogram demonstrated apical ballooning, consistent with Takotsubo or stress cardiomyopathy . Transthoracic echocardiogram confirmed mild-to-moderate segmental left ventricular dysfunction consistent with stress cardiomyopathy.

Summary

- Troponins are biomarkers for diagnosis of Acute MI , Pulmonary edema and other conditions.
- Early detection of cardiac troponins (cTns) specifically can alter patient dispositions from the Emergency Department.
- The troponin assay assist in diagnosis and improve risk stratification for people presenting to the emergency setting with symptoms suggestive of an acute coronary syndrome.
- High-sensitivity cardiac troponins (hs-cTn) are promising for detecting previously-missed clinically significant myocardial damage.
- Cardiac troponins T and I have typically been used for the diagnosis and prognosis of acute coronary syndrome (ACS) but are elevated in several other clinical conditions.