Novità in tema di biomarkers di danno miocardico ischemico

F. Veneziani

Biomarcatori

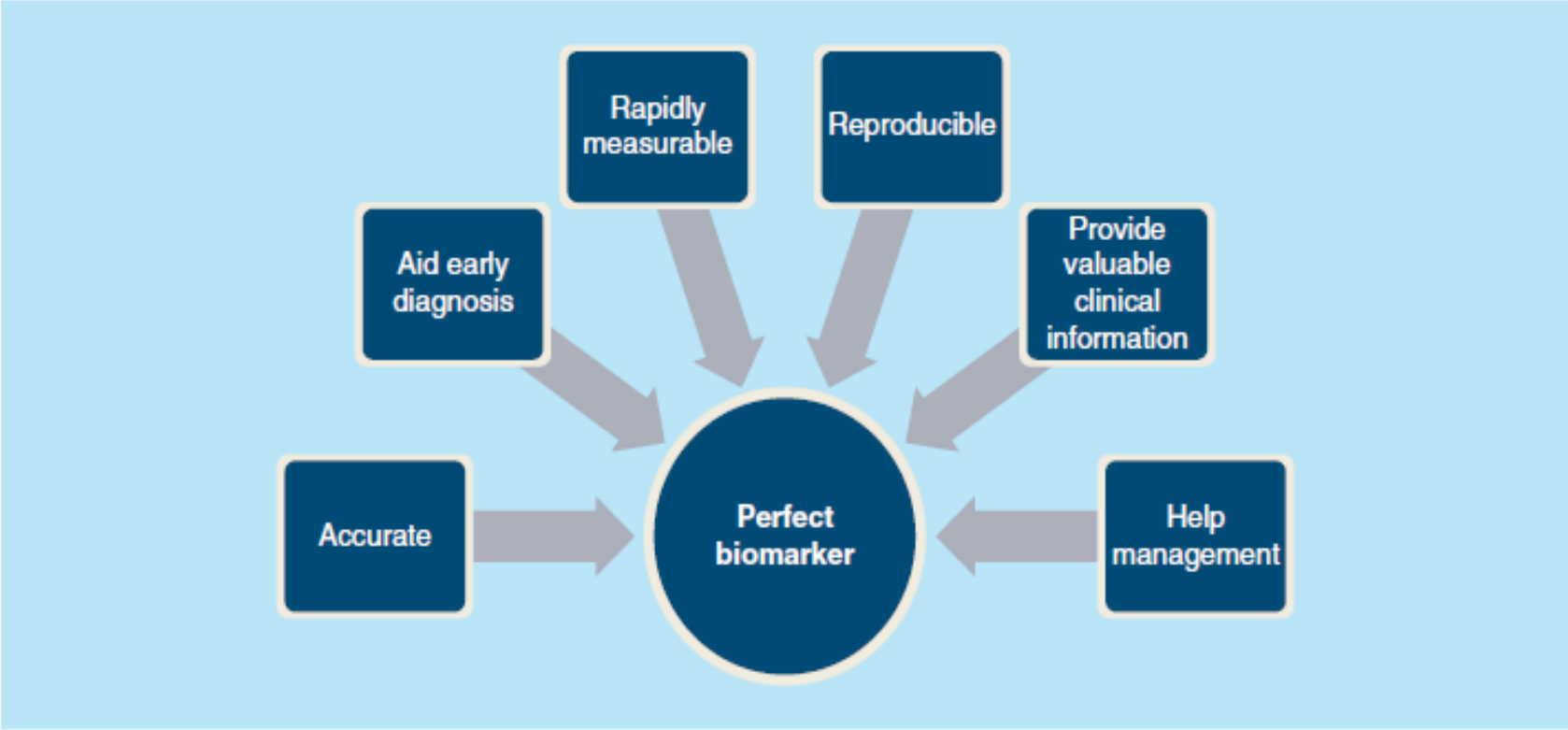


Figure 1. Represents the benchmarks of a perfect biomarker.

Biomarkers in cardiocascular care

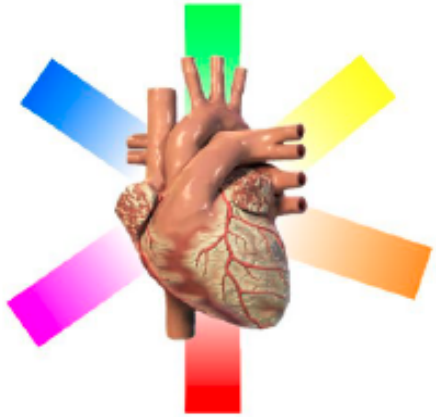
Diagnosis
Prognosis
Monitoring
Personalized Medicine
Companion diagnostics

Myocyte Necrosis

Troponins, FABP, Mgb,
CKMB, GP-BB

Inflammation

hs-CRP, CD40L, ST2,
TNFa, PCT
IL6, PAPP



Metabolic Dysregulation

Metabolites, Cystatin,
Anemia

Genetic Risk

Mutations, SNPs,
Micro-RNA,
DNA-Methylation

Hemodynamic Stress

BNP, NT-proBNP
GDF15, MR-proANP
Copeptin, Troponins

Vascular Damage

CrCl, Cystatin, ET
Microalbuminuria
HbA_{1c}

ESC European Society of Cardiology
European Heart Journal (2018) **00**, 1–33
doi:10.1093/eurheartj/ehy462

EXPERT CONSENSUS DOCUMENT

Fourth universal definition of myocardial infarction (2018)

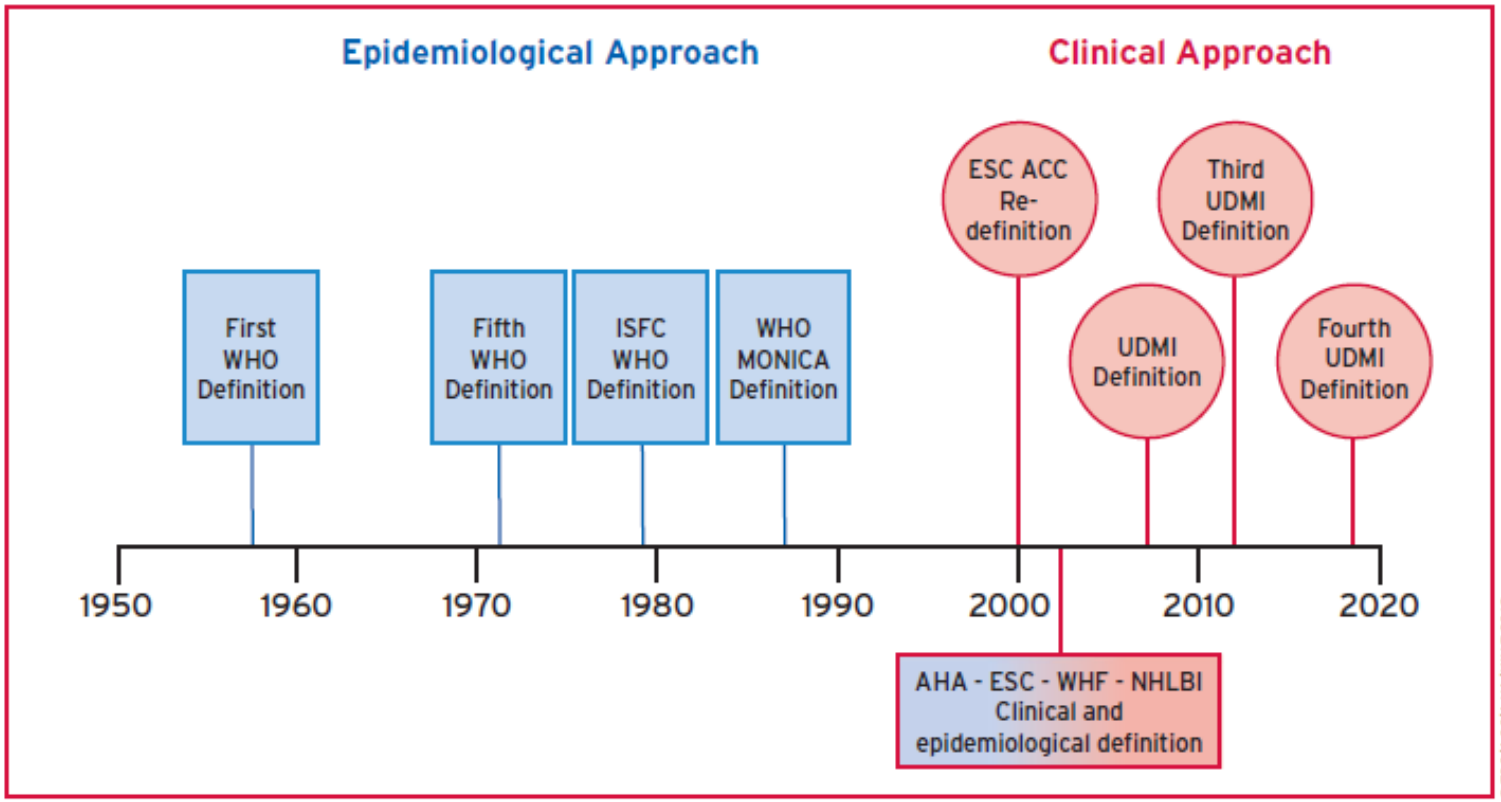
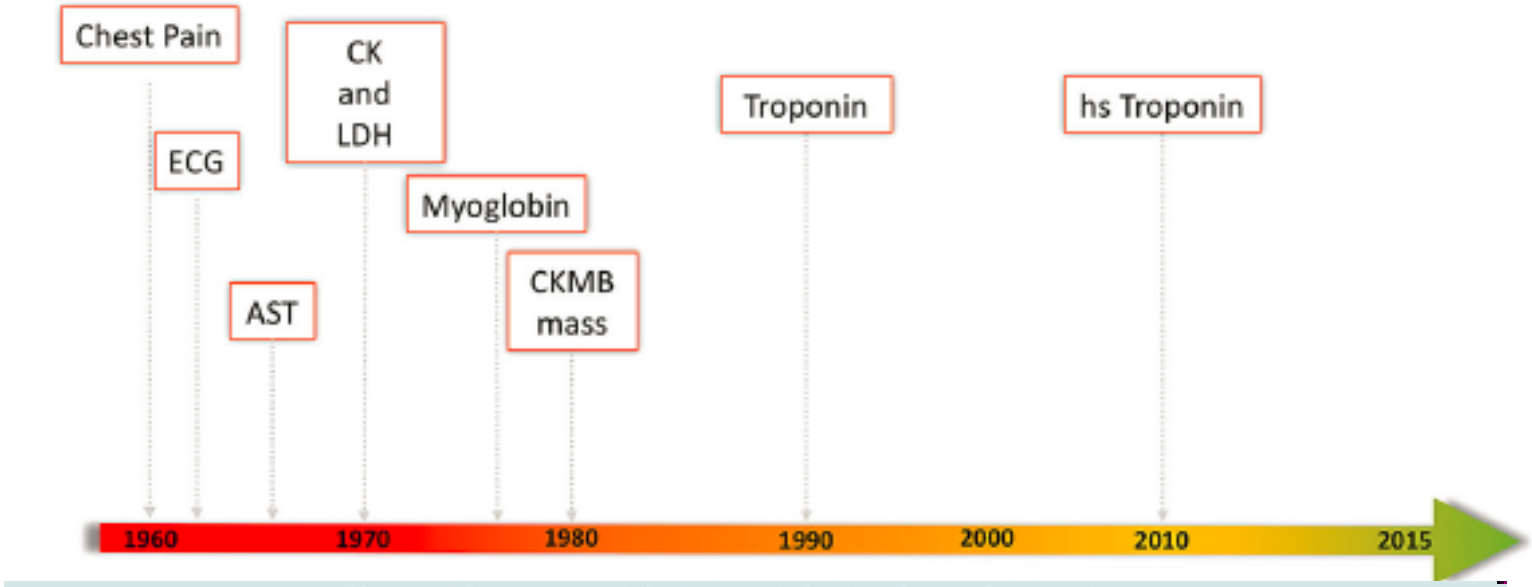
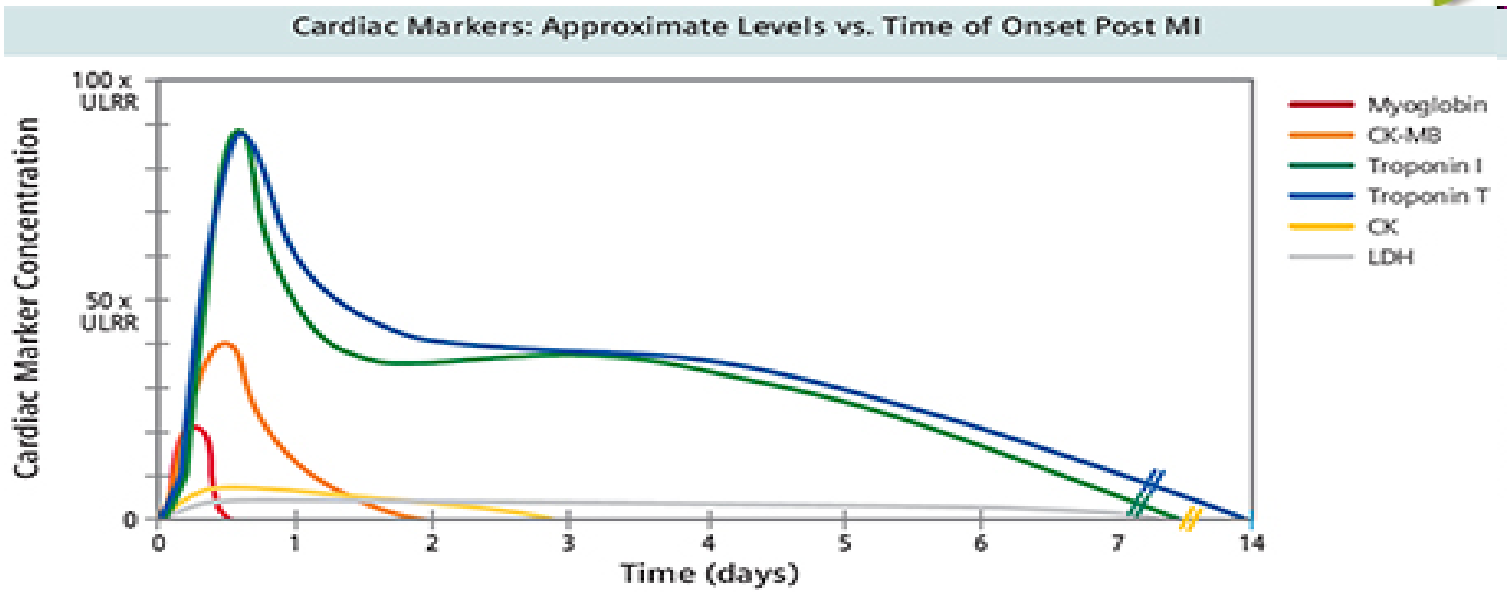


Figure 1 History of documents on the definition of myocardial infarction. ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; ISFC = International Society and Federation of Cardiology; MONICA = MONItoring of trends and determinants in CArdiovascular disease; NHLBI = National Heart, Lung, and Blood Institute; UDMI = Universal Definition of Myocardial Infarction; WHF = World Heart Federation; WHO = World Health Organization.

Timelines of the development of cardiac biomarkers for the diagnosis acute myocardial infarction





DEFINIZIONE E SPECIFICHE DI QUALITA'

- **Si definiscono test di laboratorio ad alta sensibilità (*high sensitivity*) analitica per la misura delle troponine I e T esclusivamente i metodi immunometrici che sono in grado di misurare il 99° percentile della popolazione di riferimento con un errore uguale o inferiore al 10%, come raccomandato da tutte le linee guida nazionali ed internazionali (primo criterio: *conditio sine qua non*).**
- **I metodi ad alta sensibilità sono anche in grado di misurare i livelli circolanti delle troponine, superiori al limite di determinazione del metodo (LOD), in almenno il 50% dei soggetti adulti normali , (secondo criterio di classificazione), sia nei maschi che nelle femmine.**
- **I metodi che misurano il 99° percentile della popolazione di riferimento con un errore inferiore al 20 % (ma maggiore del 10%) si possono ancora utilizzare nella pratica clinica, ma non si devono definire a elevata sensibilità analitica.**
- **I metodi che invece misurano il 99° percentile con un errore maggiore del 20 % non devono più essere utilizzati.**

Box 2
Key definitions relating to analytical performance of cardiac troponin T assays

99th percentile

- Refers to the 99th percentile of cTn concentrations in a sample of apparently healthy individuals
- By convention, this is used to define the upper reference limit of cTn assays

Limit of blank (LoB)

- When analyzing a sample containing no cTn, assays will not always return a result of zero
- The LoB is derived by repeatedly testing a sample that is known to contain no cTn and is equal to the mean plus 1.645 multiplied by the standard deviation of the results obtained

Limit of detection (LoD)

- The lowest concentration of analyte that can be distinguished from the LoB; the LoD will, therefore, be higher than the LoB

Coefficient of variation (CV)

- Measures the precision of an assay and expressed as a percentage
- Equal to the standard deviation divided by the mean of repeated measurements on any given sample

Data from Armbruster D, Pry T. Limit of blank, limit of detection and limit of quantitation. Clin Biochem Rev 2008;29(Supplement 1):S49–52.

Body R et al : Cardiol Clin 2018

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Assay-related issues in the measurement of cardiac troponins☆

Mauro Panteghini *

Department of Clinical Sciences "Luigi Sacco", University of Milan Medical School, Milan, Italy

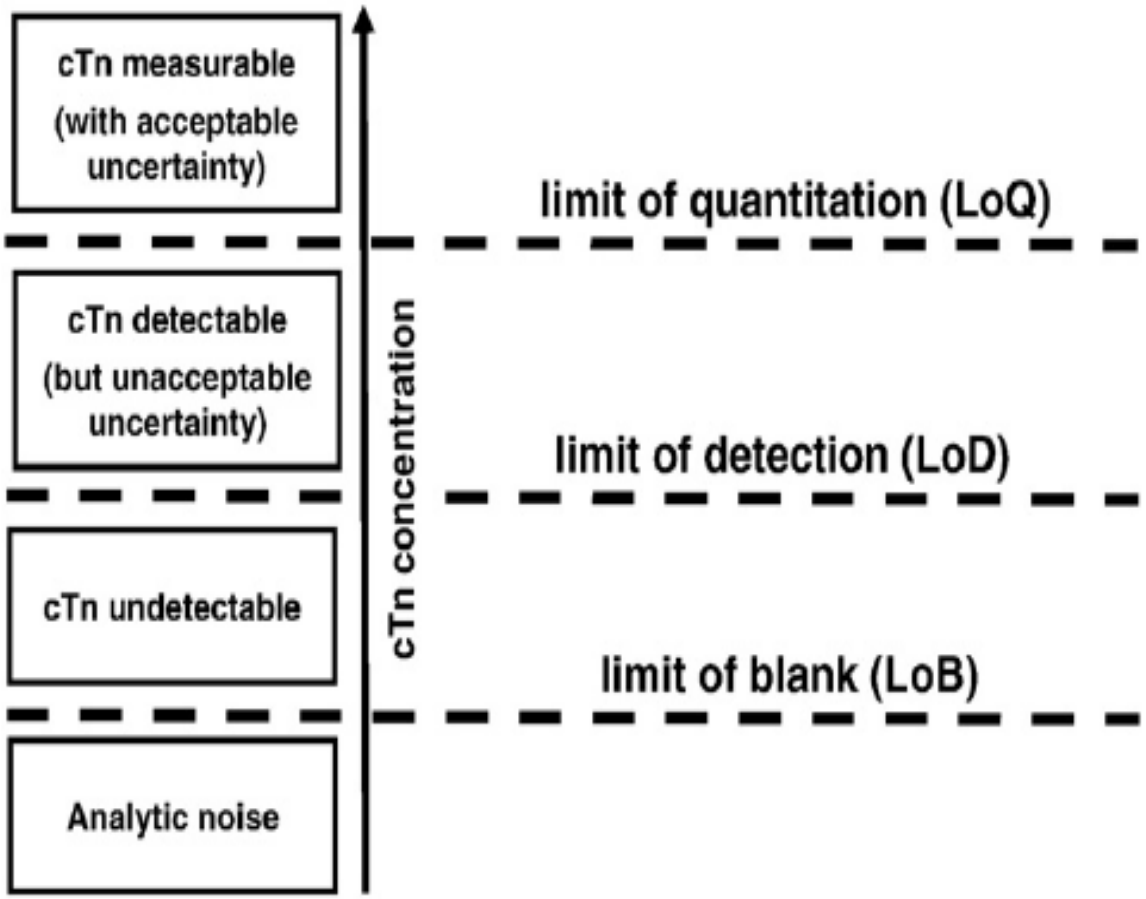


Fig. 2. Limits at low cardiac troponin (cTn) concentrations.

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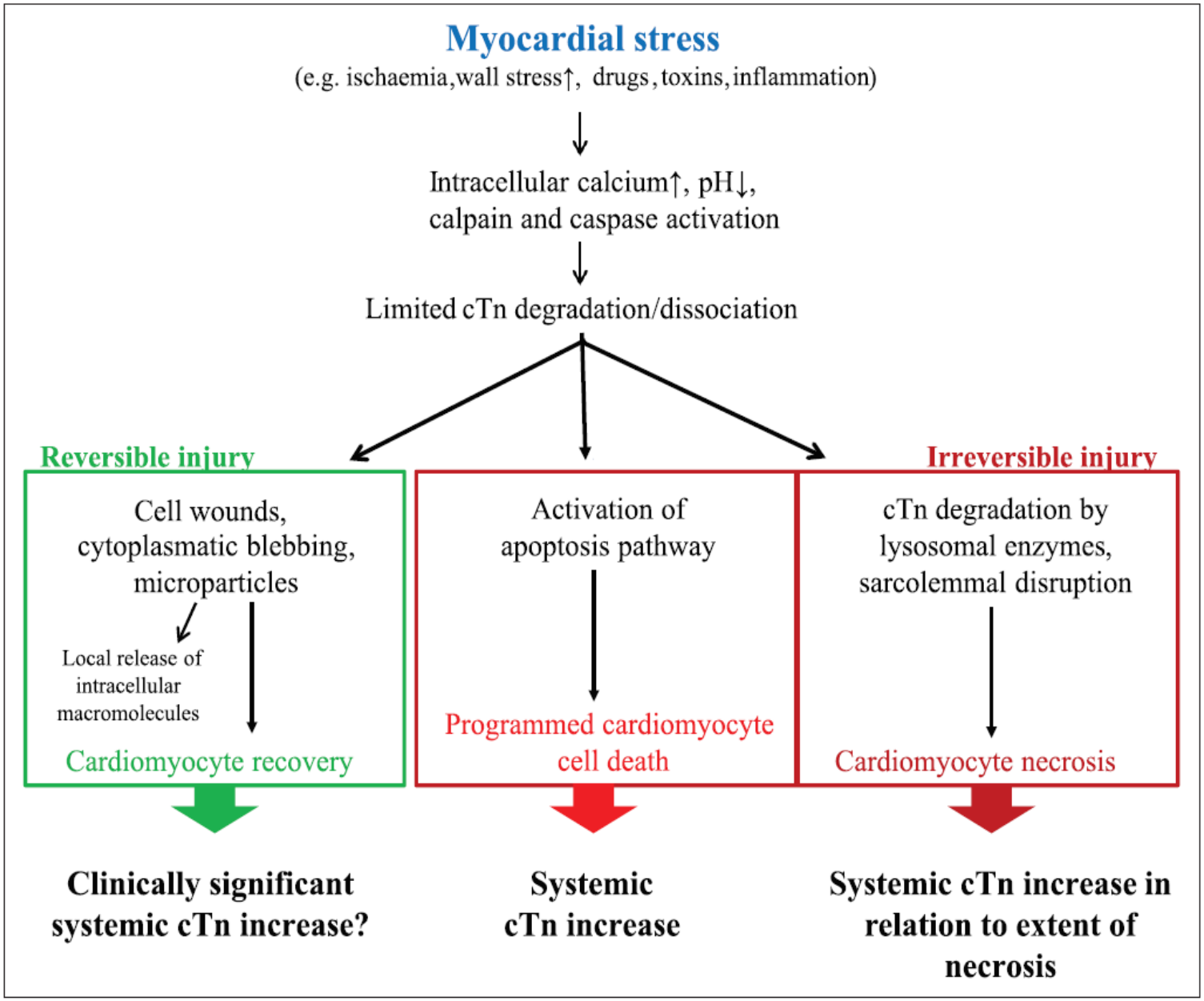
journal homepage: www.elsevier.com/locate/clinbiochem

IFCC educational materials on selected analytical and clinical applications of high sensitivity cardiac troponin assays

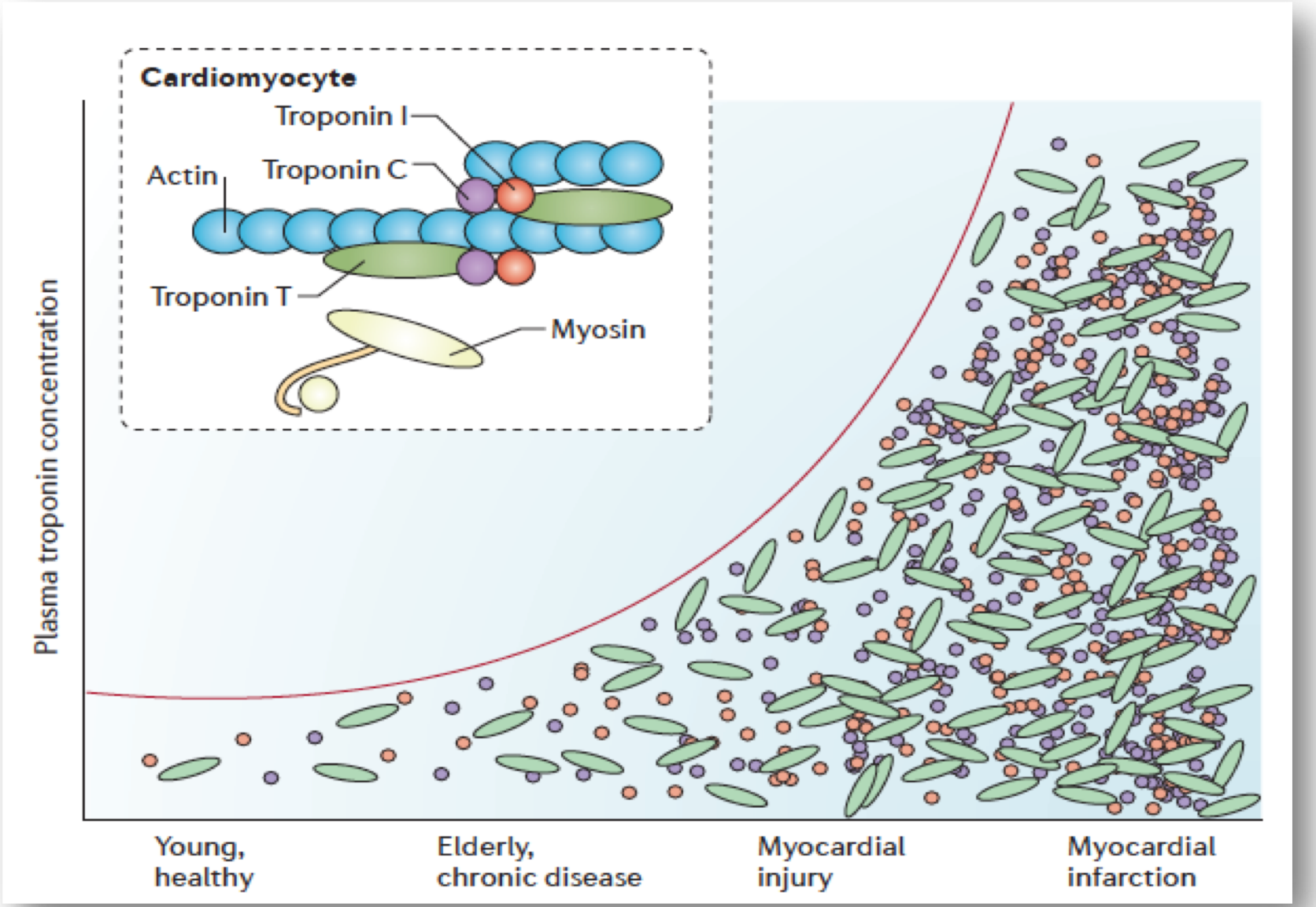
Fred S. Apple [a,*], Allan S. Jaffe [b], Paul Collinson [c,d], Martin Mockel [e], Jordi Ordonez-Llanos [f,1], Bertil Lindahl [g], Judd Hollander [h], Mario Plebani [i], Martin Than [j], M.H.M. Chan [k,1], on behalf of the International Federation of Clinical Chemistry (IFCC) Task Force on Clinical Applications of Cardiac Bio-Markers

Factors that influence an hs-cTn assay's 99th percentile include:

a) age, because cTn values increase with increasing age, especially above 60 y [5];
b) gender, as men have higher values than women [3,4,6];
c) assay method, as the 99th percentile must be determined individually for each assay, as assays are not standardized;
d) specimen type, because the 99th percentile may be different for serum, plasma and/or whole blood.

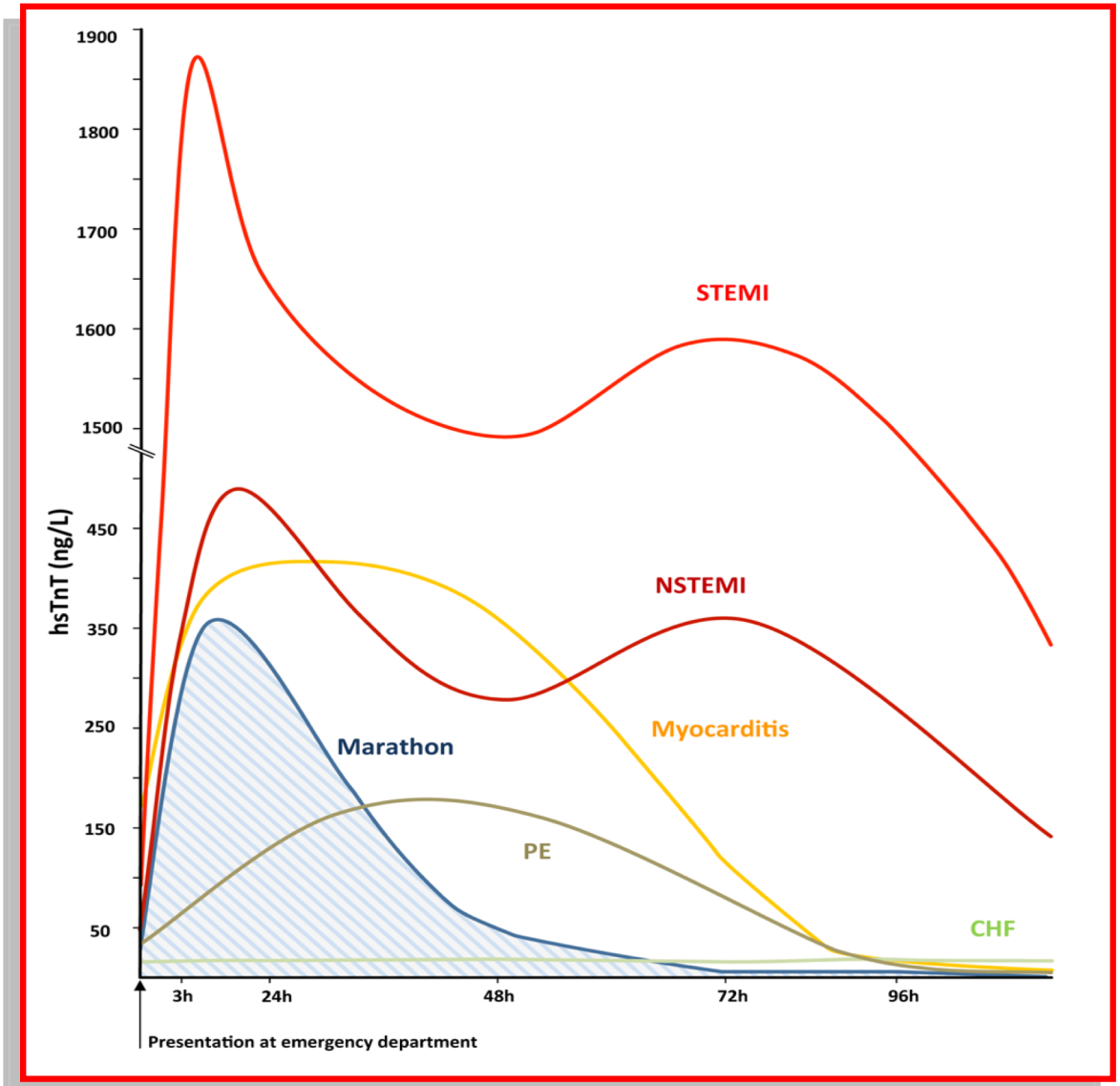

Myocardial stress
(e.g. ischaemia,wall stress↑, drugs,toxins,inflammation)
Intracellular calcium↑, pH↓,
calpain and caspase activation
Limited cTn degradation/dissociation
Reversible injury
Irreversible injury
Cell wounds,
cytoplasmatic blebbing,
microparticles
Local release of
intracellular
macromolecules
Cardiomyocyte recovery
Activation of
apoptosis pathway
Programmed cardiomyocyte
cell death
cTn degradation by
lysosomal enzymes,
sarcolemmal disruption
Cardiomyocyte necrosis
Clinically significant
systemic cTn increase?
Systemic
cTn increase
Systemic cTn increase in
relation to extent of
necrosis

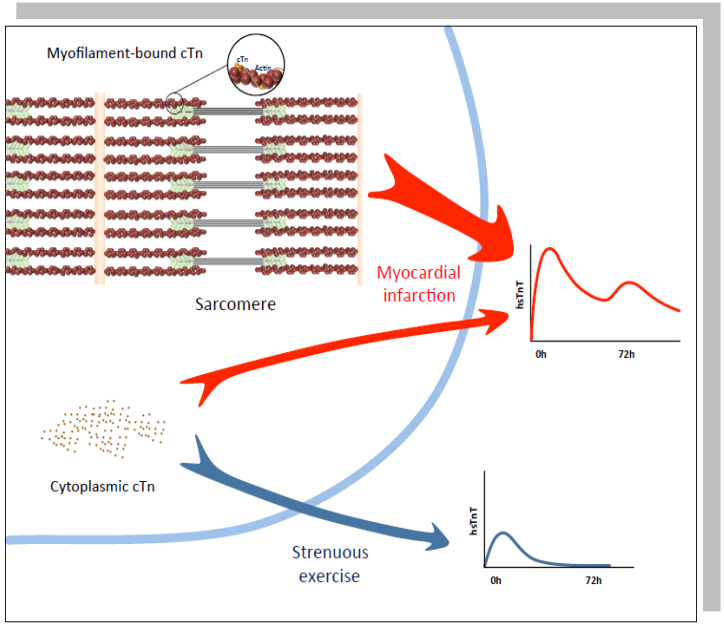
CONTINUUM



Westermann et al 2017

HS troponin after endurance sport





Sedaghat-Hamedani, 2016

ESC European Society of Cardiology

European Heart Journal (2018) **00**, 1–33
doi:10.1093/eurheartj/ehy462

EXPERT CONSENSUS DOCUMENT

Fourth universal definition of myocardial infarction (2018)

1 What is new in the Universal Definition of Myocardial Infarction?

What's new in the universal definition of myocardial infarction?
New concepts
• Differentiation of myocardial infarction from myocardial injury. • Highlighting peri-procedural myocardial injury after cardiac and non-cardiac procedures as discrete from myocardial infarction. • Consideration of electrical remodelling (cardiac memory) in assessing repolarization abnormalities with tachyarrhythmia, pacing, and rate-related conduction disturbances. • Use of cardiovascular magnetic resonance to define aetiology of myocardial injury. • Use of computed tomographic coronary angiography in suspected myocardial infarction.

ESC European Society of Cardiology
European Heart Journal (2018) 00, 1–33
doi:10.1093/eurheartj/ehy462

EXPERT CONSENSUS DOCUMENT

Fourth universal definition of myocardial infarction (2018)

Universal definitions of myocardial injury and myocardial infarction

Criteria for myocardial injury

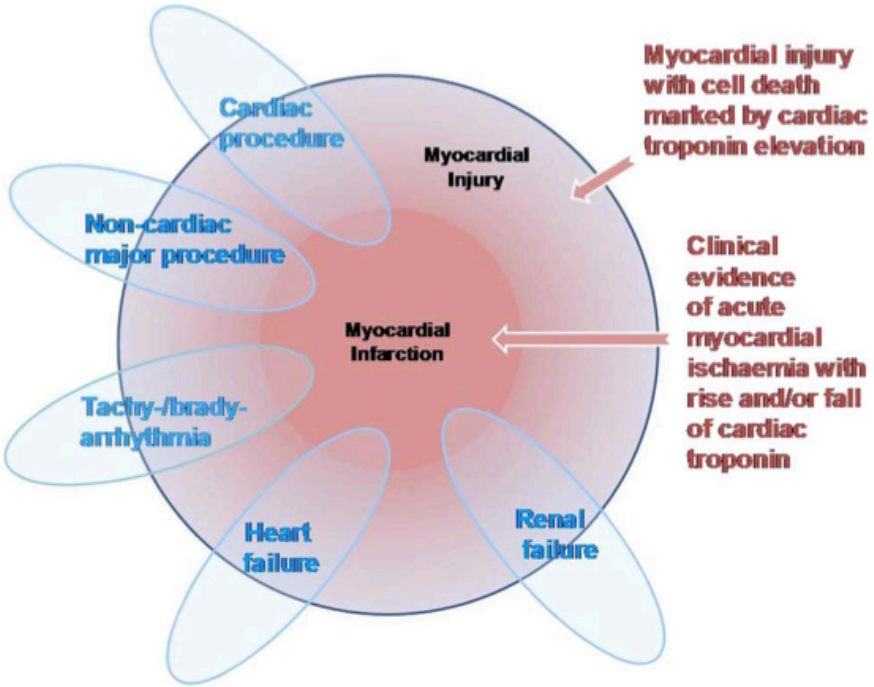
The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.

Criteria for acute myocardial infarction (types 1, 2 and 3 MI)

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:

- Symptoms of myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs).

“Myocardial Injury



Thygesen et al 2012

Marek Kozinski et al 2017

Myocardial injury and myocardial infarction

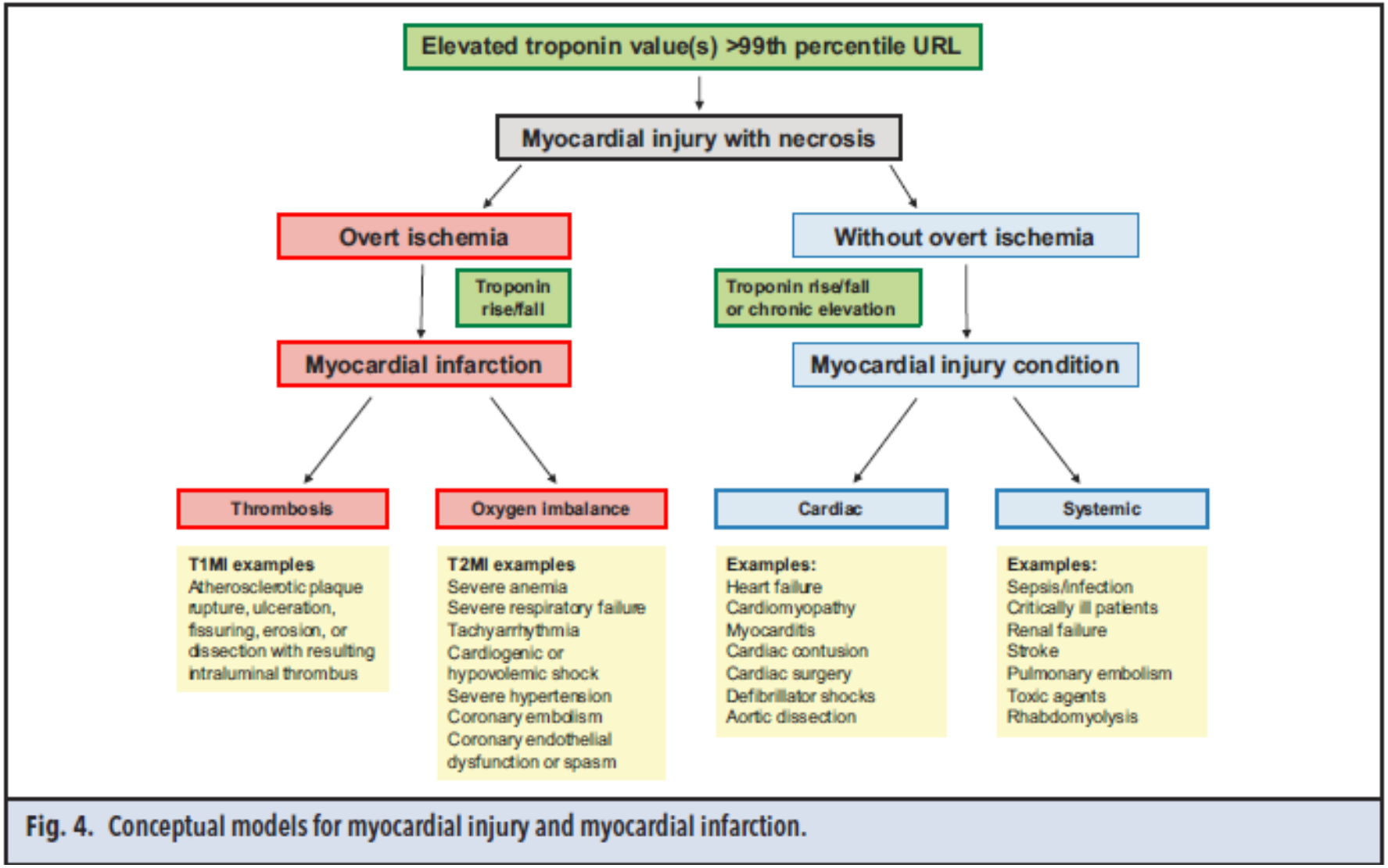
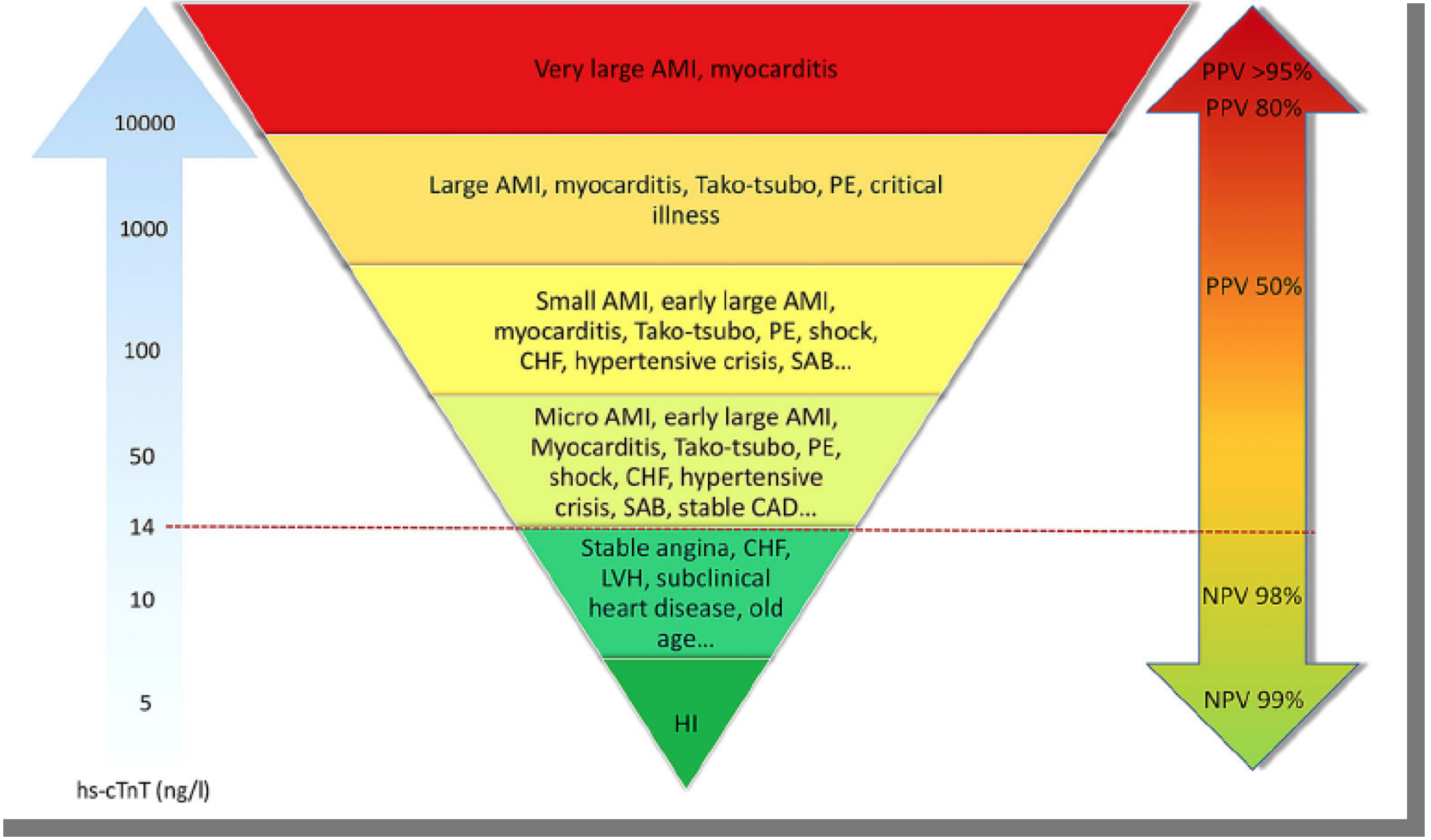


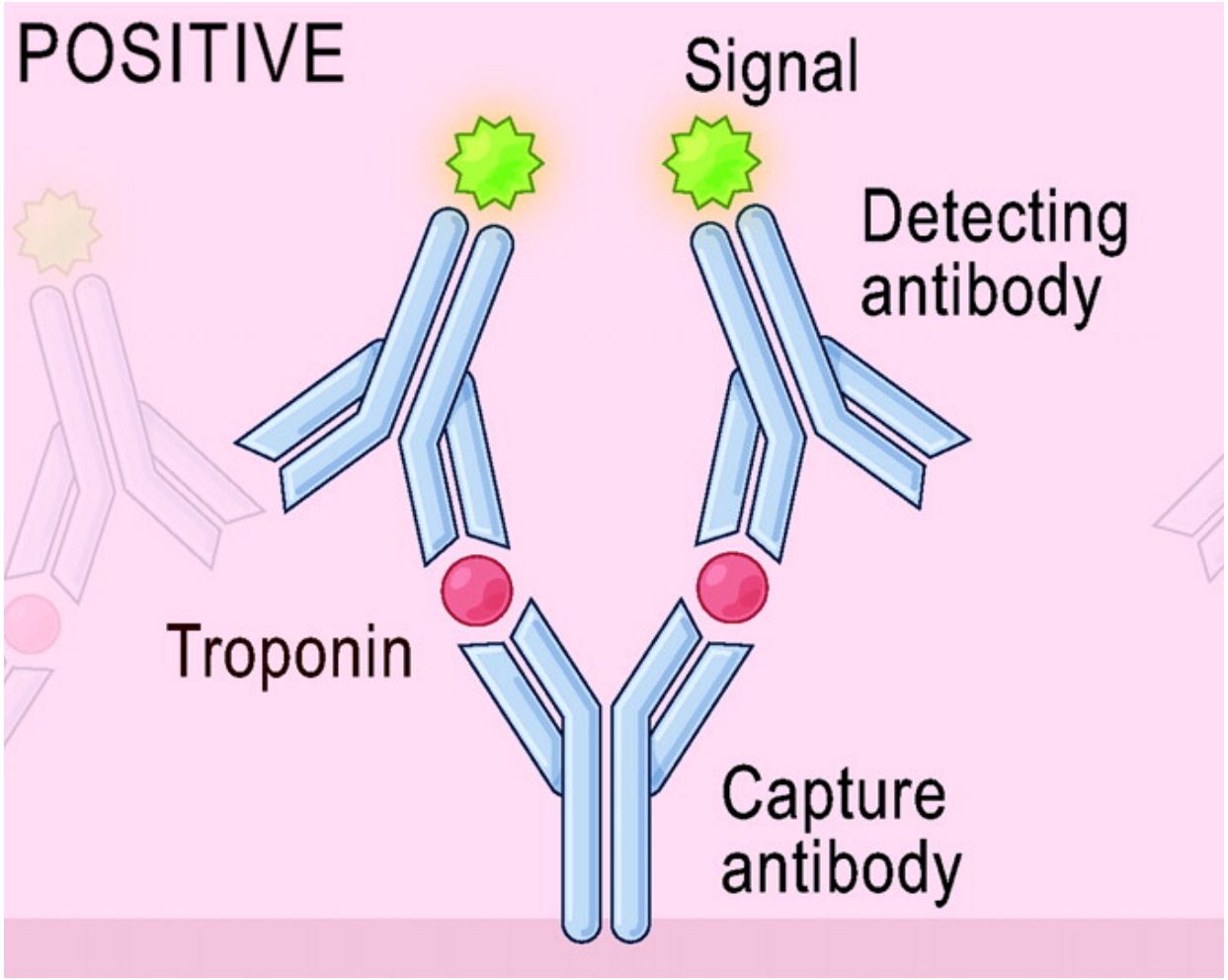
Fig. 4. Conceptual models for myocardial injury and myocardial infarction.

Specificità clinica

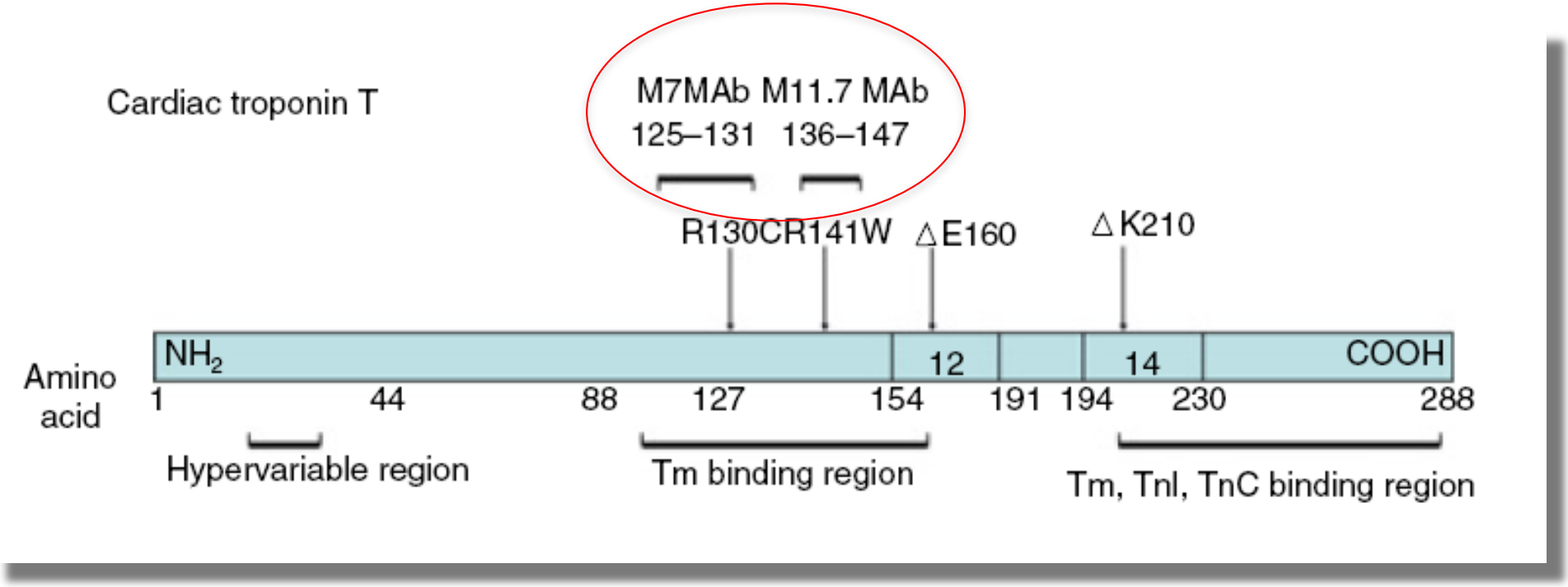


P Garg et al 2017

Specificità analitica

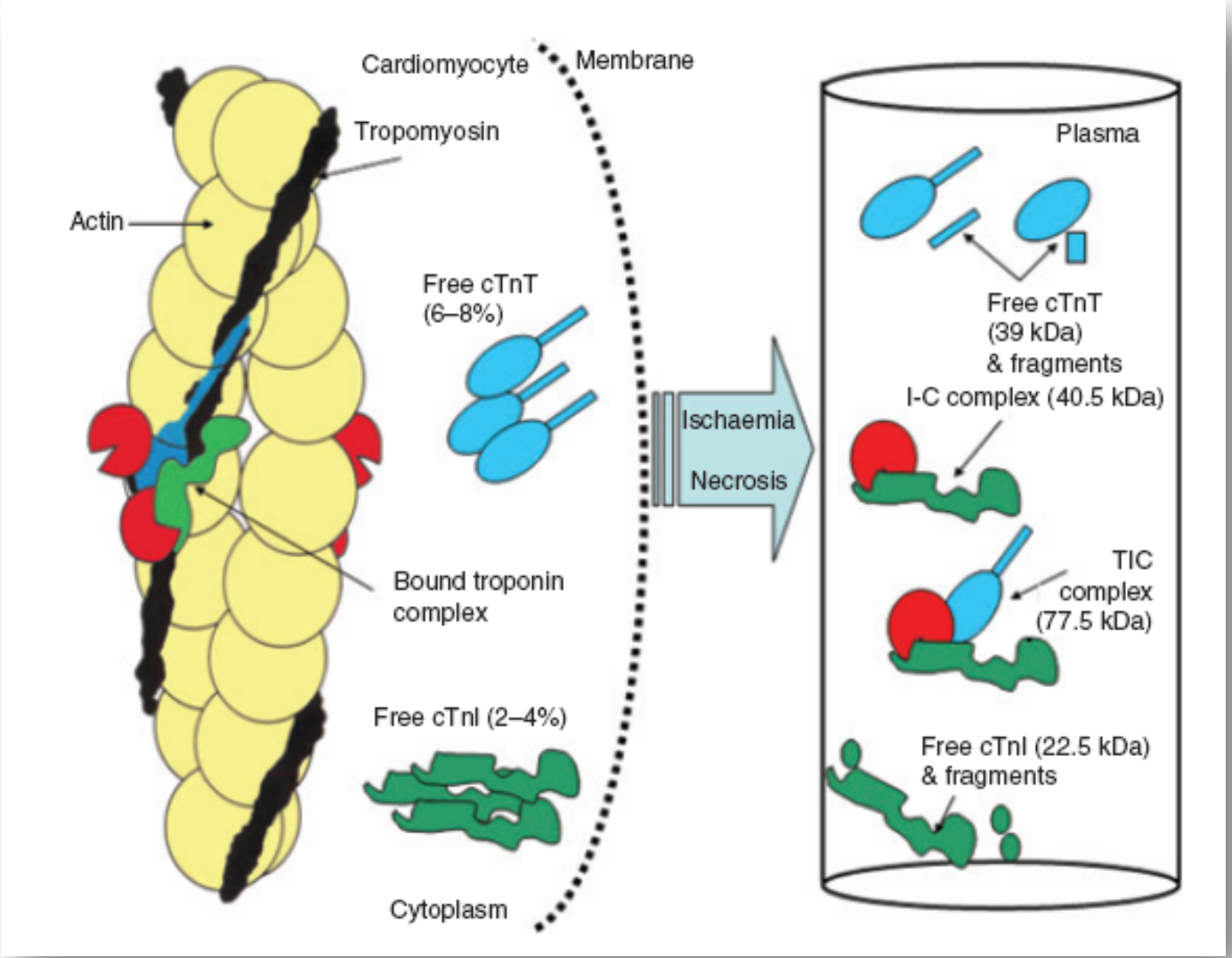


Il metodo per la cTnT



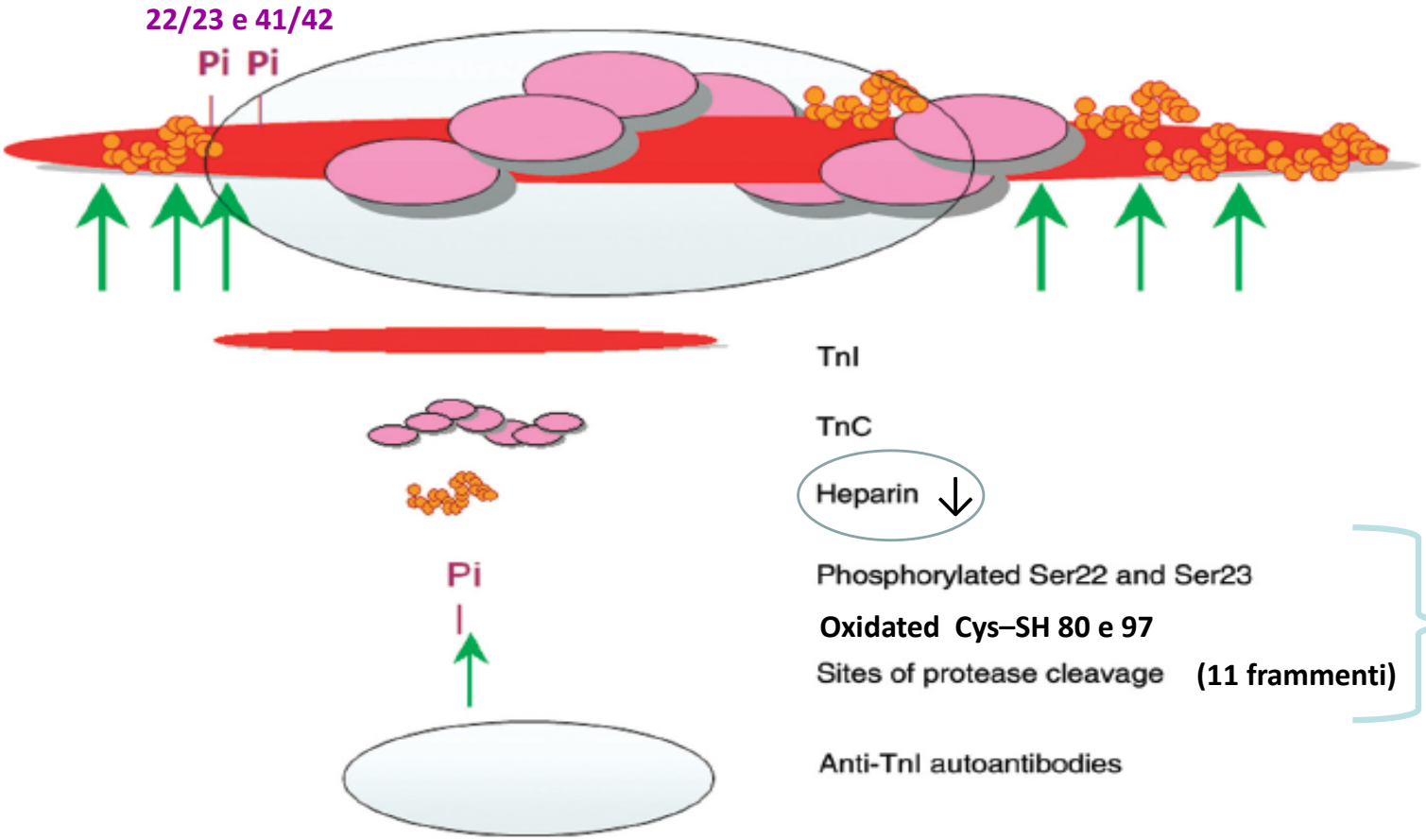
I metodi per cTnI

Specificità analitica cTnI



DC Gaze, PO Collinson 2008

Specificità analitica cTnI



Post-traslazionali

Apple et al 2012

European Heart Journal Advance Access published August 29, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv320

ESC GUIDELINES

2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

Table 3 Clinical implications of high-sensitivity cardiac troponin assays

Compared with standard cardiac troponin assays, high-sensitivity assays:
• Have higher negative predictive value for acute MI.
• Reduce the "troponin-blind" interval leading to earlier detection of acute MI.
• Result in a ~4% absolute and ~20% relative increase in the detection of type 1 MI and a corresponding decrease in the diagnosis of unstable angina.
• Are associated with a 2-fold increase in the detection of type 2 MI.
Levels of high-sensitivity cardiac troponin should be interpreted as quantitative markers of cardiomyocyte damage (i.e. the higher the level, the greater the likelihood of MI):
• Elevations beyond 5-fold the upper reference limit have high (>90%) positive predictive value for acute type 1 MI.
• Elevations up to 3-fold the upper reference limit have only limited (50–60%) positive predictive value for acute MI and may be associated with a broad spectrum of conditions.
• It is common to detect circulating levels of cardiac troponin in healthy individuals.
Rising and/or falling cardiac troponin levels differentiate acute from chronic cardiomyocyte damage (the more pronounced the change, the higher the likelihood of acute MI).

MI = myocardial infarction.

Elevato NPV

Marker quantitativo

Marcatore dinamico

Correlato alla clinica

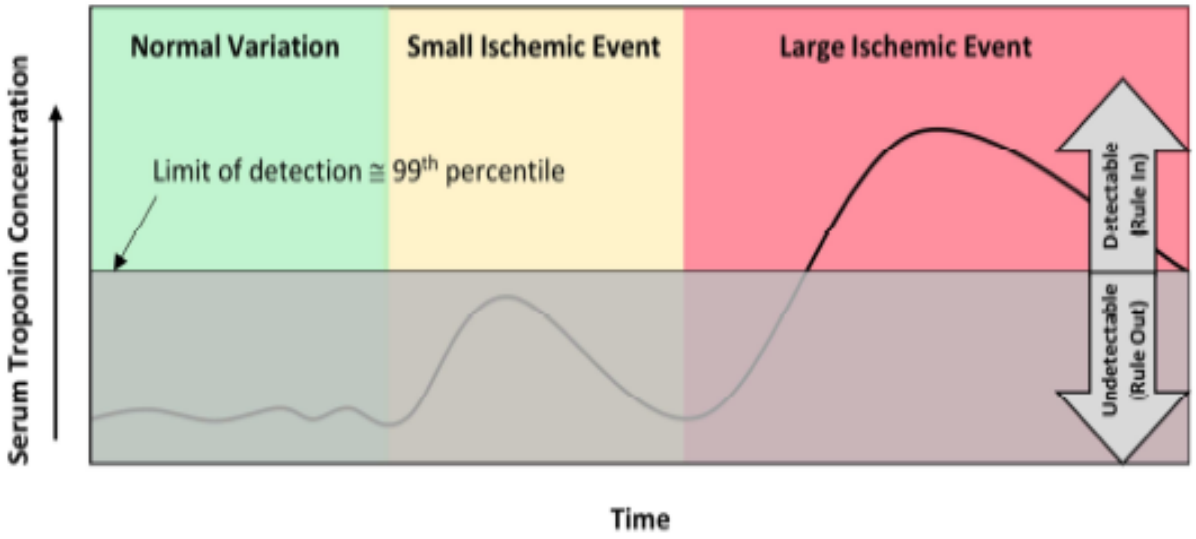


Figure 1a. Conventional troponin assay interpretation.

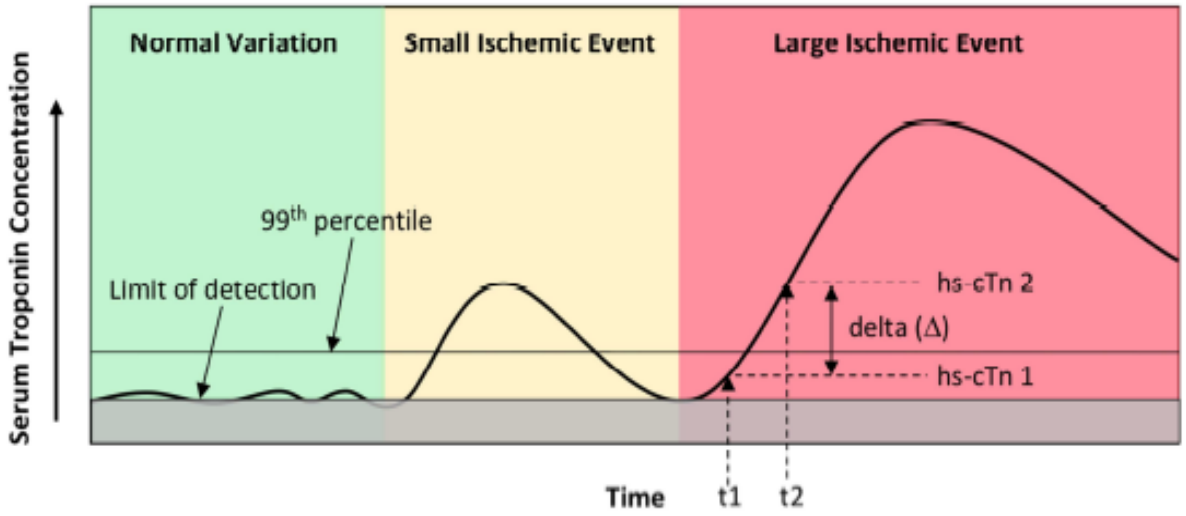


Figure 1b. High-sensitivity troponin assay interpretation.

European Heart Journal Advance Access published August 29, 2015
European Heart Journal
doi:10.1093/eurheartj/ehv320
ESC GUIDELINES

2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

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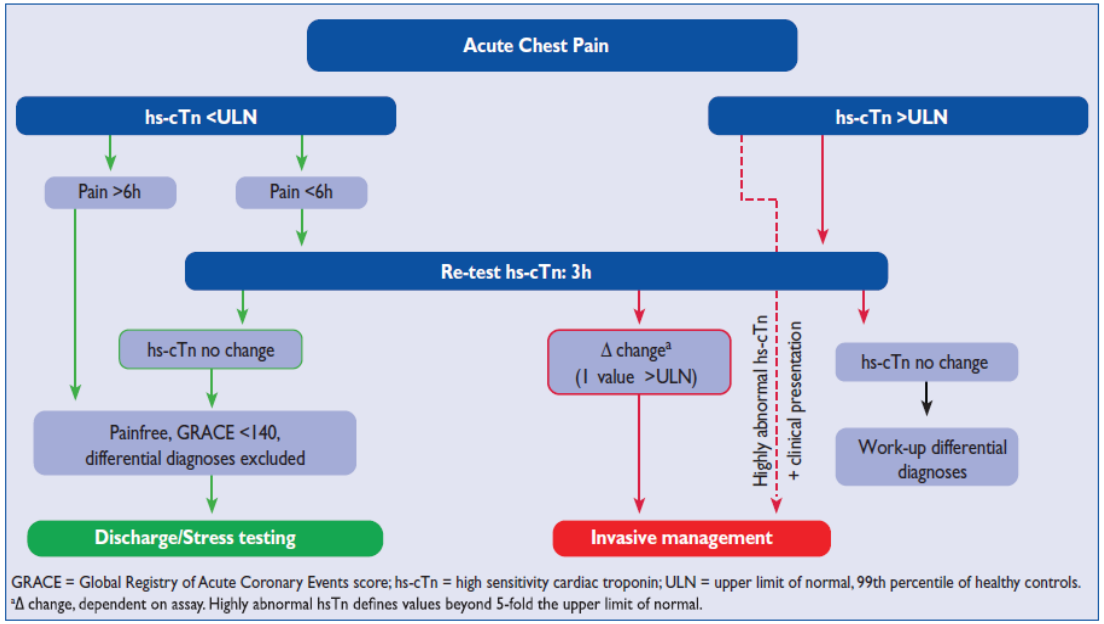

Figure 2 0 h/3 h rule-out algorithm of non-ST-elevation acute coronary syndromes using high-sensitivity cardiac troponin assays.

A causa della maggiore sensibilità e accuratezza diagnostica per la rilevazione di MI acuto, l'intervallo di tempo tra il primo e secondo dosaggio può essere ridotto con l'uso di test ad alta sensibilità. L'algoritmo a 0-3 ore attualmente risulta essere lo standard di riferimento,considerato tale dalle linee guida ESC 2015.

Naturalmente tali algoritmi dovrebbero sempre essere integrati con una dettagliata valutazione clinica ed è obbligatorio ripetere il prelievo di sangue in caso di dolore toracico in atto o ricorrente

European Heart Journal Advance Access published August 29, 2015
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2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

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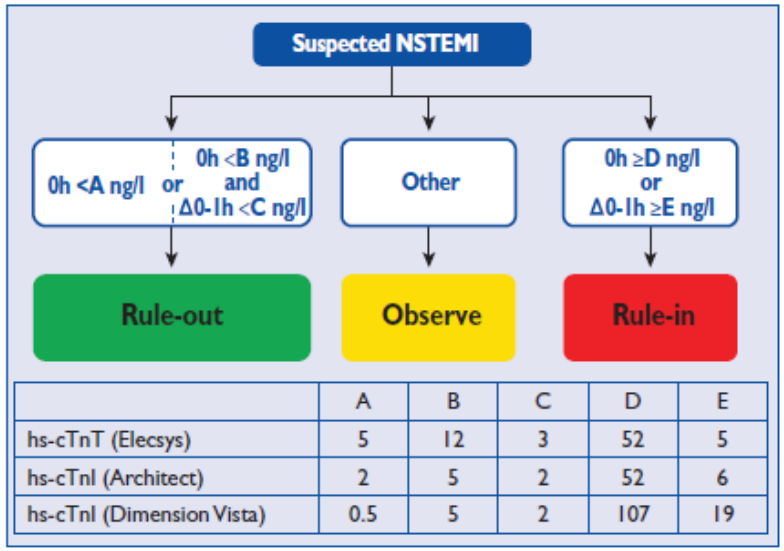

	A	B	C	D	E
hs-cTnT (Elecsys)	5	12	3	52	5
hs-cTnI (Architect)	2	5	2	52	6
hs-cTnI (Dimension Vista)	0.5	5	2	107	19

Figure 3 0 h/1 h rule-in and rule-out algorithms using high-sensitivity cardiac troponins (hs-cTn) assays in patients presenting with suspected non-ST-elevation myocardial infarction (NSTEMI) to the emergency department. 0 h and 1 h refer to the time from first blood test. NSTEMI can be ruled-out already at presentation, if the hs-cTn concentration is very low. NSTEMI can also be ruled-out by the combination of low baseline levels and the lack of a relevant increase within 1 h. Patients have a high likelihood for NSTEMI if the hs-cTn concentration at presentation is at least moderately elevated or hs-cTn concentrations show a clear rise within the first hour. Cut-off levels are assay-specific. Cut-off levels for other hs-cTn assays are in development.

Algoritmi a 0 h/1h per il rule-in e roule-out utilizzando test per la troponina cardiaca ad alta sensibilità (hs-cTn) nei pazienti che presentano sospetto infarto miocardico non-ST- (NSTEMI) al pronto soccorso.
NSTEMI può essere escluso già al momento della presentazione se la concentrazione hs-cTn è molto bassa. NSTEMI può essere altresì esclusa dalla combinazione di livelli basali bassi e la mancanza di un aumento rilevante entro 1 h.
I pazienti hanno un'alta probabilità di NSTEMI se la concentrazione di hs-cTn al momento della presentazione è almeno moderatamente elevato oppure se concentrazioni di hs-cTn mostrano un chiaro aumento entro la prima ora.

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NUOVA FLOW CHART SUGGERITA NEL 2017 DAL GRUPPO DI STUDIO DELL'ESC ACUTE CARDIOVASCULAR CARE ASSOCIATION

Martin Möckel, Evangelos Giannitsis, Christian Mueller, Kurt Huber, Allan S Jaffe, Johannes Mair, Mario Plebani, Kristian Thygesen and Bertil Lindahl

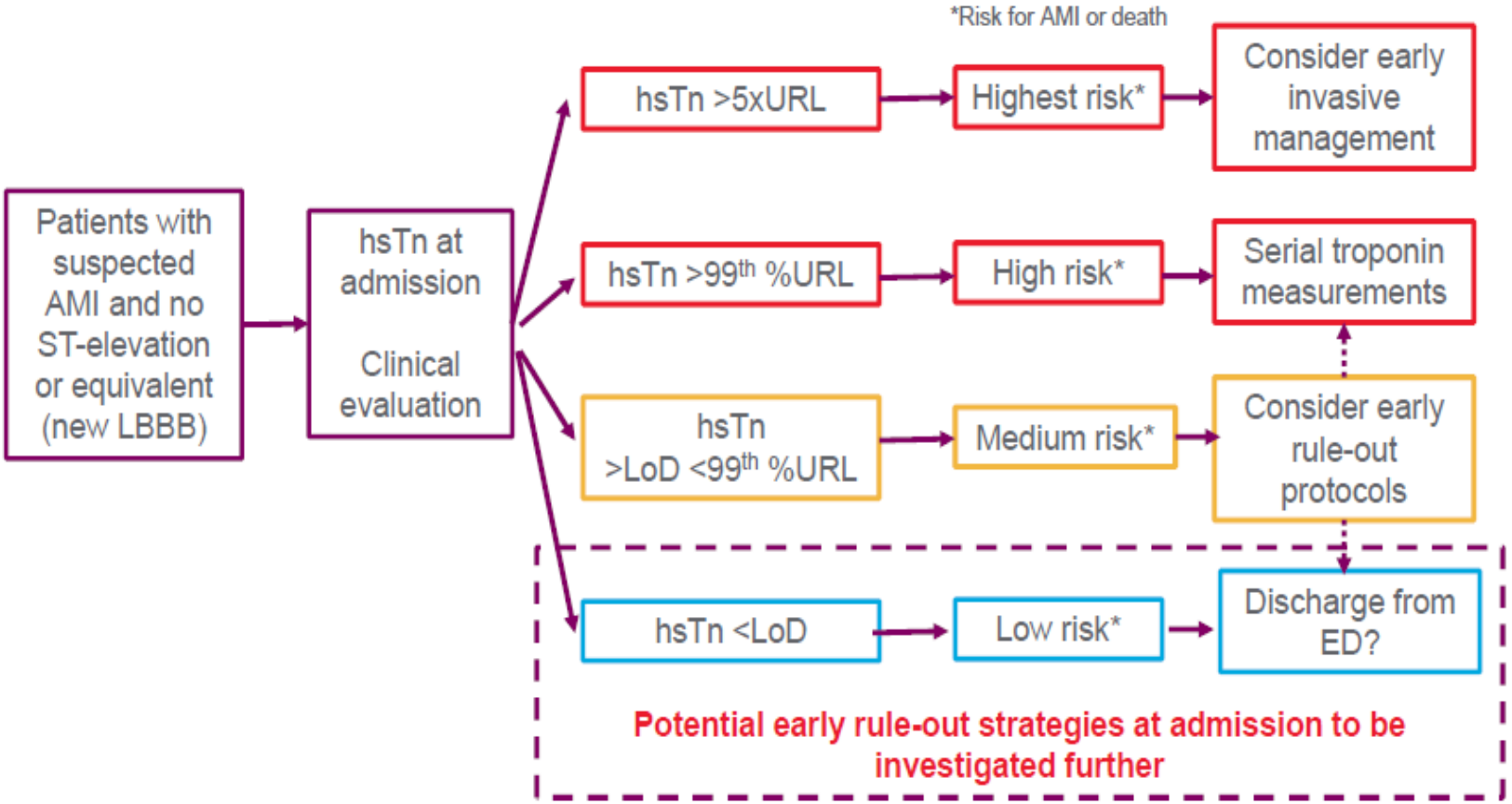


TABLE 2 Summary of Biomarker Strategies for Rapid Assessment of Patients With Potential ACS in the ED

	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

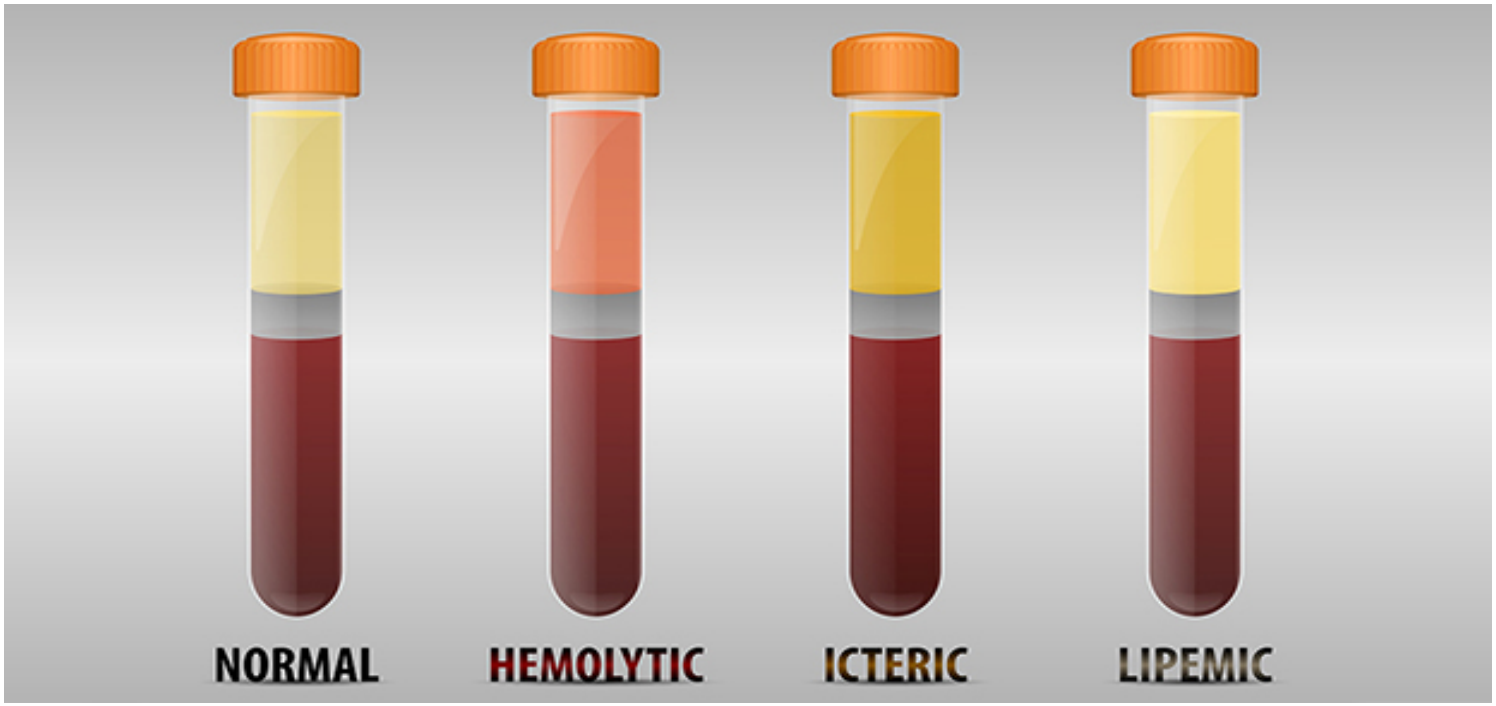
Twerenbold , JACC 2017

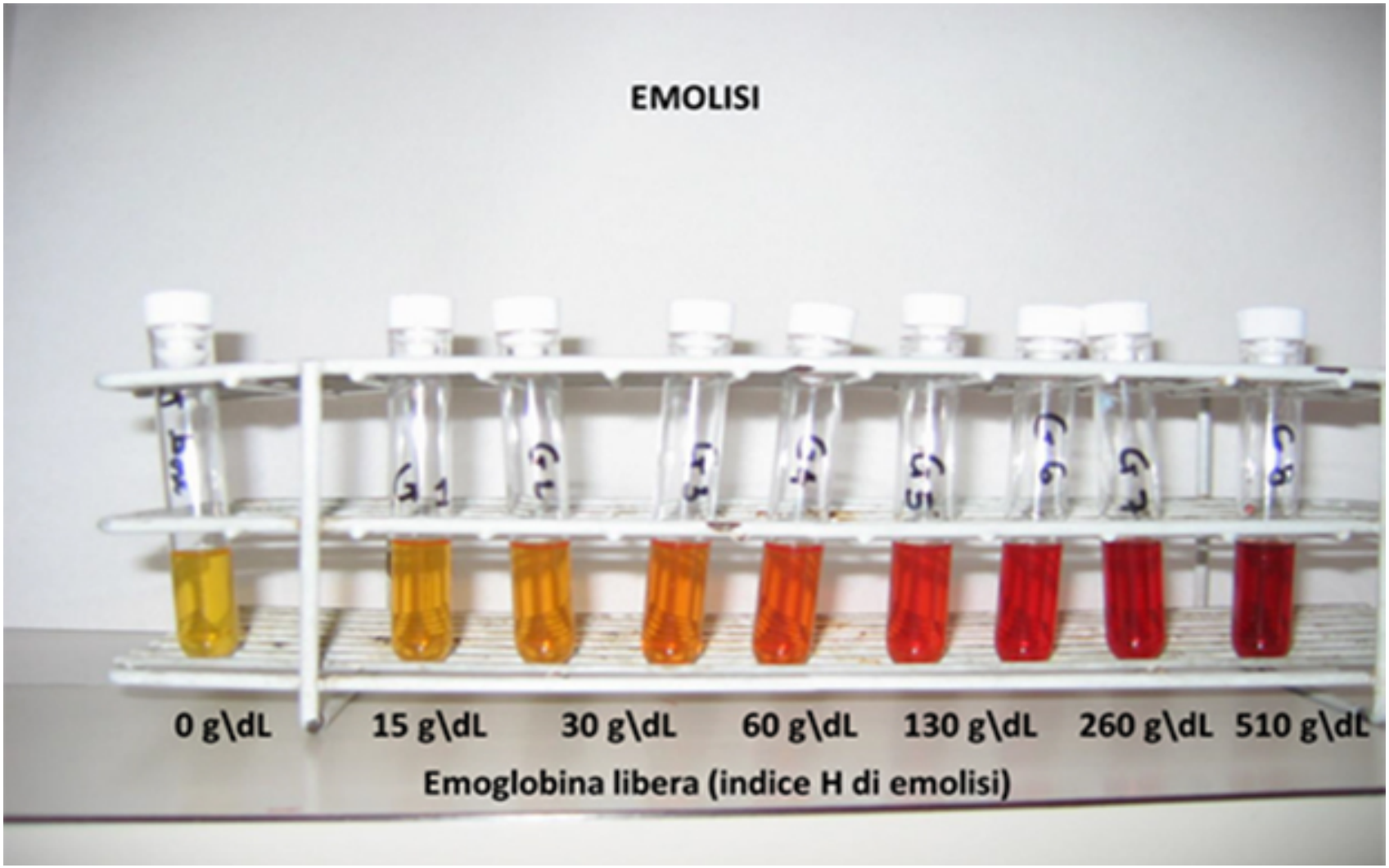
Interferenze

- **Preanalitiche**
- Paziente
  - ✓ Biotina
  - ✓ Digiuno/Lipemia
  - ✓ Iperfosfatasemia
  - ✓ Iperbilirubinemia
  - ✓ Emolisi in vivo
- Prelievo
  - ✓ Emolisi in vitro
  - ✓ Fibrina
  - ✓ Materiali
  - ✓ Matrice

- **Analitiche**
- Strumento
- Metodo
- Analita (stabilità)
- Campione
  - ➢ HA
  - ➢ HAMA
  - ➢ RF
  - ➢ Macrotroponina
  - ➢ Autoanticorpi anti-cTn

HIL




EMOLISI
0 g\dL
15 g\dL
30 g\dL
60 g\dL
130 g\dL
260 g\dL
510 g\dL
Emoglobina libera (indice H di emolisi)

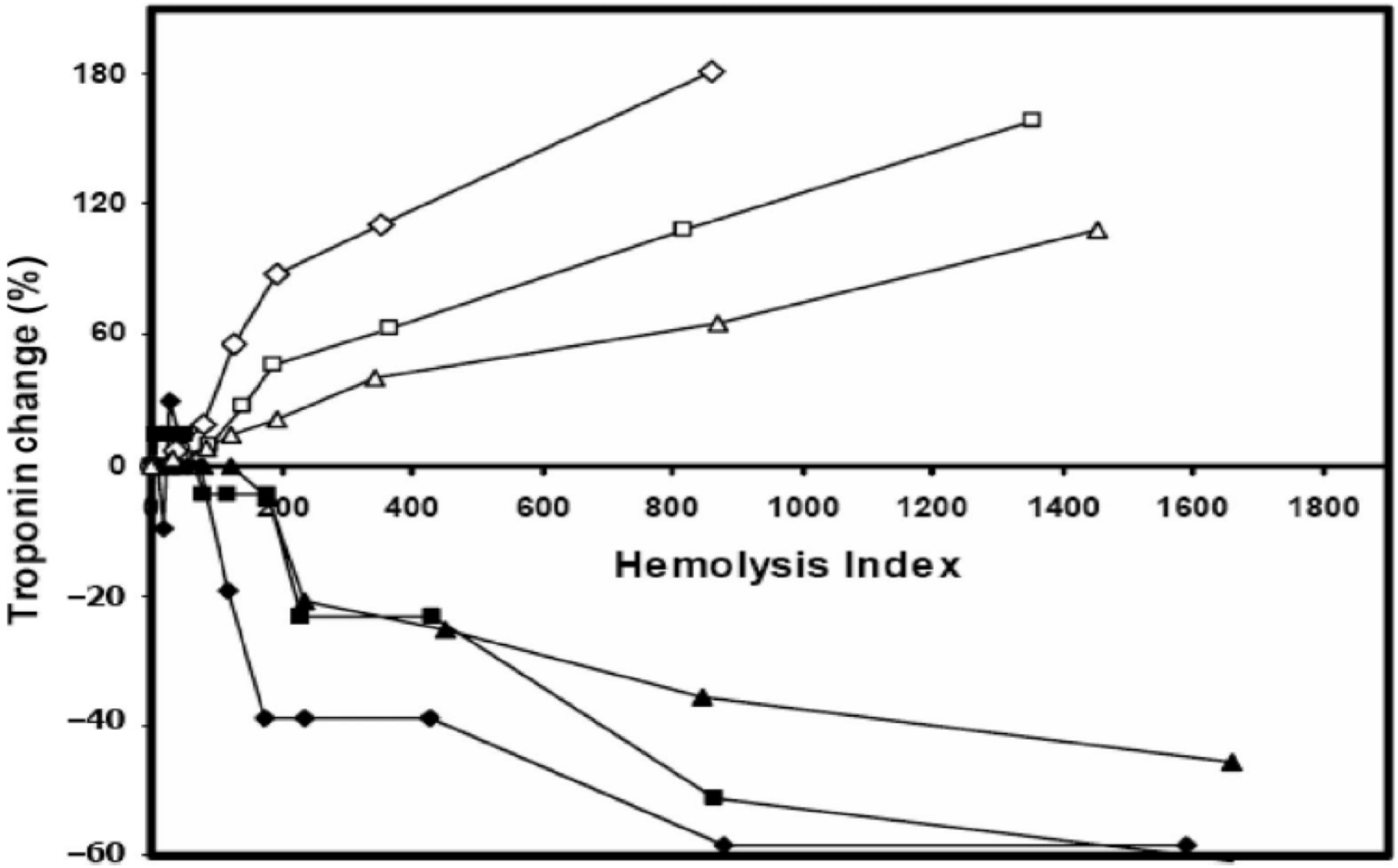


Fig. 1. Effect of increasing added hemolysis on the Ortho Clinical Diagnostics TnI ES assay (open symbols) and the Roche TnT hs assay (closed symbols).

A 20% change was considered clinically significant. The 3 cTnI concentrations were 24 ng/L (◇), 36 ng/L (□), and 49 ng/L (△), and the 3 cTnT concentrations were 6 ng/L (◆), 12 ng/L (■), and 23 ng/L (▲). (Note that the negative and positive scales are not equal.)

R Bias 2010

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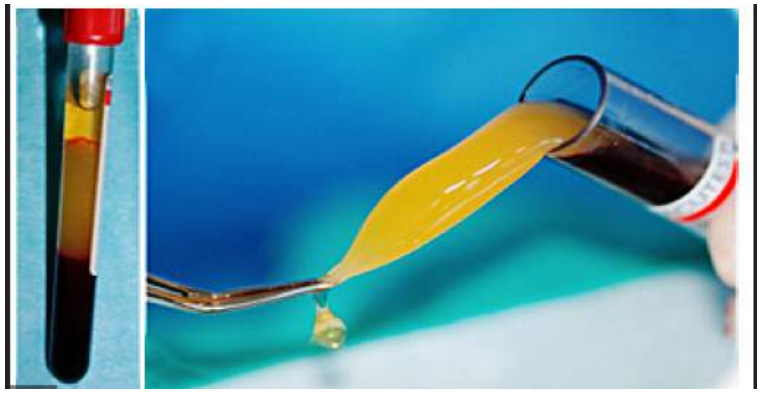
May 2010

GP44-A4

Procedures for the Handling and Processing of Blood Specimens for Common Laboratory Tests; Approved Guideline—Fourth Edition

This document includes criteria for preparing an optimal serum or plasma sample and for the devices used to process blood specimens.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.



5.3.4.1 Clot Release (Rimming the Tube)

The use of a wooden applicator stick or similar device for the release of a clot attached to the tube closure or the sides of the tube is not recommended. Rimming the tube is a potential source for laboratory-induced hemolysis.[109] Clot/cell hang-up has been virtually elim[illegible]ed by technical improvements in tube/closure design and manufacture.

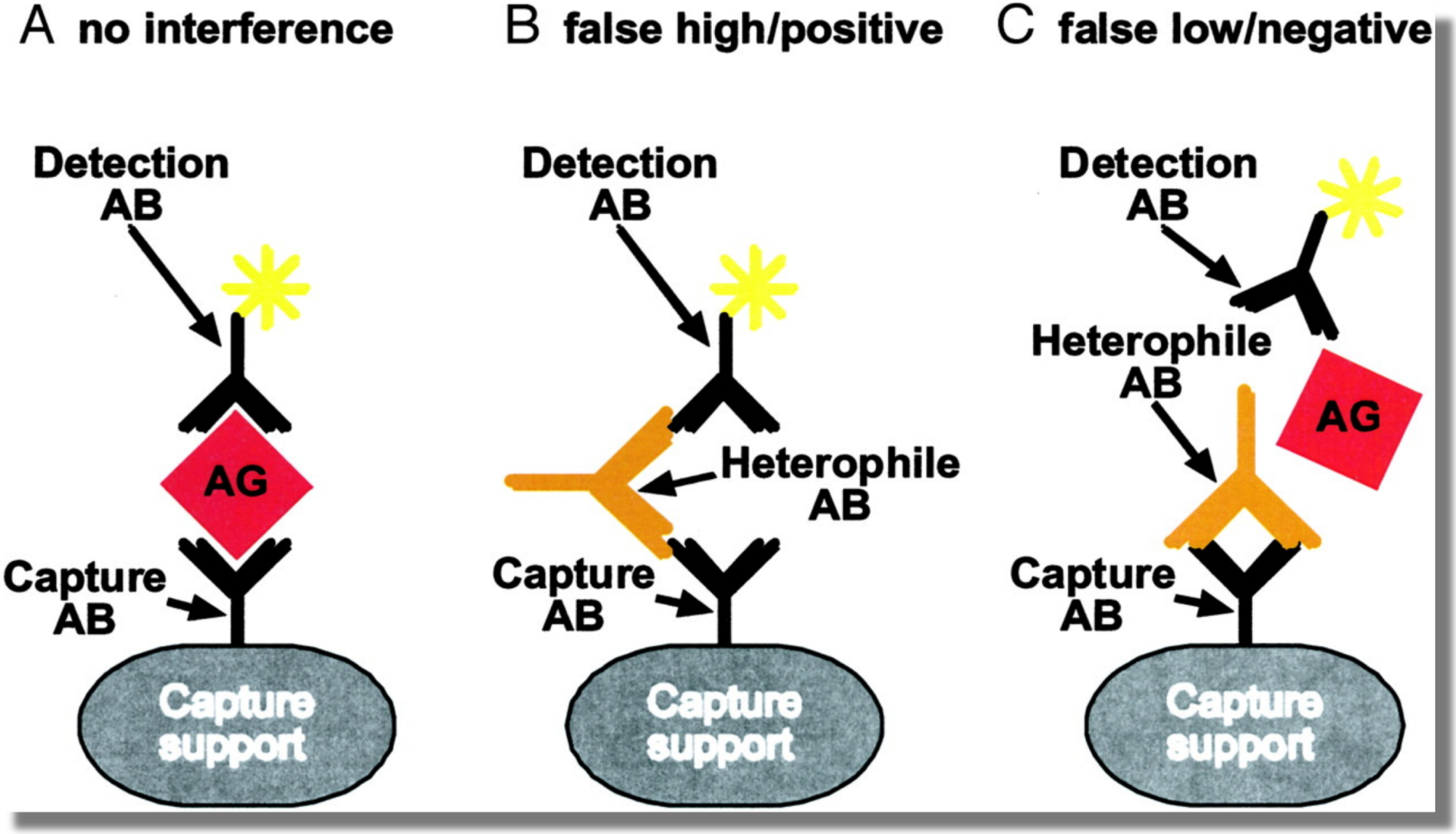
Residual fibrin, a possible interferent in the clinical lab[illegible]ry, may occur secondary to improper specimen handling during or after collection. Fibrin may [illegible]resent in the primary collection tube as a visible clot (described earlier) or as invisible microfibers or as strands.[110] These invisible fibrin strands may directly affect some assays, like troponin.[111,112] Fibrin interference usually is not reproducible and disappears with time as the fibrin settles out of the sample. Fibrin strands can be eliminated if the recommended times for blood clotting and subsequent centrifugation are employed.

Interferenze analitiche : Campione

Interferenze immunologiche

- Anticorpi eterofili
- HAMA
- Fattore reumatoide
- Macrotroponina
- Anticorpi anti reagenti (biotina, streptavidina) - rari
- Anticorpi anti troponina

FP e FN da HA/HAMA



Documento di consenso ANMCO SIMEU (2016)

Biomarcatori ***Executive summary***	
1.	È raccomandato l'uso della hs-cTn.
2.	L'algoritmo 0-3h è quello raccomandato con uso di hs-cTn validata specificamente.
3.	La troponina è lo standard diagnostico per l'infarto miocardico, ma occorre considerare che può essere elevata anche in altre condizioni cliniche e il suo isolato aumento non permette la diagnosi di infarto essendo considerato solo un marker di danno miocardico.
4.	Valori stabili o inconsistenti variazioni di troponina in assenza variazioni dinamiche della sua concentrazione plasmatica (ascesa/discesa con descrizione di una curva cinetica) non sono un marker di SCA.
5.	È indispensabile una collaborazione operativa con il proprio laboratorio d'analisi e la conoscenza del metodo diagnostico (assay) utilizzato.
6.	La cTn aumenta nell'insufficienza renale severa (più la cTnT che la cTnI). Usare un cut-off più elevato basato sui livelli di velocità di filtrazione glomerulare stimata per una più accurata diagnosi di infarto miocardico/ SCA-NSTE in pazienti con insufficienza renale terminale[72].

Conclusioni

I metodi ad alta sensibilità permettono di:

- Avere un alto VPN
- Ridurre l'intervallo di «troponin blind» per la diagnosi di MI
- Ridurre l'intervallo di tempo tra il primo e secondo dosaggio con diminuzione del ritardo nella diagnosi e dei tempi di permanenza in DE con conseguente riduzione dei costi.

Conclusioni

- Il dosaggio delle troponine cardiache I e T è cardio-specifico, ma non malattia-specifico

- Può fornire informazioni diagnostiche e prognostiche essenziali che però necessitano di essere interpretate alla luce del quadro clinico del paziente.

- I nuovi test ad alta sensibilità per le troponine richiedono quindi da parte degli esperti di medicina di laboratorio e soprattutto dei clinici una attenta riflessione riguardo al quesito diagnostico per cui il test viene richiesto.

Anno	Autori/giornale	Titolo	N° pz/validazione	Note
2013	Mahler SA, Miller CD, Hollander JE, et al, Int J Cardiol 168:795–802	Identifying patients for early discharge: performance of decision rules among patients with acute chest pain	1005 pz cTn 0–3 h con e senza score (NACPR, HEART) *rule out* 4.4%, 20%, 13% con sensibilità per ACS 100%, 99%, 95% rispettivamente	Combinazione cTn 0–3 h + score HEART migliore per dimissione rapida e sicura
2013	*Bahrmann P, Christ M, Bahrmann A et al, J Am Med Dir Assoc 14:409–416	A 3-hour diagnostic algorithm for non-ST-elevation myocardial infarction using high-sensitivity cardiac troponin T in unselected older patients presenting to the emergency department	306 pazienti anziani (età media 81 anni) cTn 0–3 h e delta assoluto *rule in* in 23% e *rule out* in 35%	L'algoritmo definisce in 3 h circa il 60% dei pazienti
2015	Storrow AB, Christenson RH, Nowak RM et al, Clin Biochem 48:254–259	Diagnostic performance of cardiac Troponin I for early rule-in and rule-out of acute myocardial infarction: Results of a prospective multicenter trial	1929 pazienti hs-cTnI 0–3 h: a 3 h NPV 99,5% e PPV 58%	Conferma protocollo 0–3 h; 6 h per pazienti ad alto rischio non diagnosticati prima
2015	Westwood M, van Asselt T, Ramaekers B et al, Health Technol Assess 19:1–234	High-sensitivity troponin assays for the early rule-out or diagnosis of acute myocardial infarction in people with acute chest pain: a systematic review and cost-effectiveness analysis	1000 pazienti teorici hs-cTnI < 3,4 ng/L *rule out* 29,1% (0% IMA) e a 3 h < 99° pc *rule out* un altro 48,6% (0,38% IMA). A 3 h *rule in* 98,2% IMA	Algoritmo a 3 step *rule out* 77,7% pazienti con 0,38% FN IMA
2016	Pickering JW, Greenslade JH, Cullen L et al, Heart 102:1270–1278	Validation of presentation and 3 h high-sensitivity troponin to rule-in and rule-out acute myocardial infarction	1061 pazienti hs-cTnI e 985 hs-cTnT PPV *rule in* IMA 83,5% e 72,0% IMA *rule in* 65,1% e 53,8% 99°pc *rule out* 93,2% e 94,8%	Algoritmo ESC *rule in* buon PPV con hs-cTnI e accettabile con hs-cTnT (*rule in* oltre 50% IMA). Sensibilità 99° pc per *rule out* IMA troppo bassa per l'uso clinico
2016	Wildi K, Nelles B, Twerenbold R et al, Am Heart J 181:16–25	Safety and efficacy of the 0 h/3 h protocol for rapid rule out of myocardial infarction	2727 pazienti protocollo 0–3 h con 4 hs-cTn e 3 cTn; a 3 h 40–60% *rule out* senza morti a 3 mesi; per i pazienti <6 h dall'esordio la performance a 3 h di hs è 99,9, 99,5, 100, 100% rispettivamente	L'algoritmo è valido e sicuro
2017	Chapman AR, Anand A, Boeddinghaus J et al, Circulation 135:1586–1596	Comparison of the Efficacy and Safety of Early Rule-Out Pathways for Acute Myocardial Infarction	1218 pazienti confrontati per algoritmi ESC e High STEAC (cTn < 5 ng/L o < 3 ng/L delta) a 0 e 3 h per *rule out* ed eventi	ESC *rule out* a 0 h 28,1% e a 3 h 78,9% con NPV 97,9% per eventi; High STEAC 40,7% e 7,2% con NPV 99,5%

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