Troponina HS nella pratica clinica

Topics in medicina di laboratorio

Bologna

30 novembre 2018

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High sensitivity Tn (hsTn) assays were proven

- to provide earlier detection of AMI [1], reduce the ‘troponin-blind’ interval in the first hours of an MI
- to have higher negative predictive value
- to improve overall diagnostic accuracy in patients with suspected ACS [2].

[1] E. Giannitsis, et al. High-sensitivity cardiac troponin T for early prediction of evolving non-ST-segment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin results on admission, Clin. Chem. 56 (2010) 642–650.
[2] N.L. Mills, Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome, JAMA 305 (2011) 1210

Update on high-sensitivity cardiac troponin in patients with suspected myocardial infarction

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European Heart Journal Supplements (2018) **20** (Supplement G), G2-G10
The Heart of the Matter
doi:10.1093/eurheartj/suy020

ESC
European Society of Cardiology

- *These improved assays are labelled 'sensitive' when able to detect cTn in 20–50% of healthy individuals and 'high-sensitivity' if they detect a cTn level in >50% of reference (apparently healthy) subjects, and if they have a coefficient of variation of <10% at the 99th percentile upper reference limit of the assay.*
- *Hs-cTnT and I are organ specific, but not disease-specific markers.*
- *They ought to be interpreted as quantitative variables and not in a binary fashion (negative/positive) like a pregnancy test.*
- *From a diagnostic perspective, it is highly inappropriate to label a patient as 'cTn-positive'*

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

EXPERT CONSENSUS DOCUMENT

Fourth universal definition of myocardial infarction (2018)

Criteria for type 1 MI

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and with at least one of the following:

- Symptoms of acute 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 including intracoronary imaging or by autopsy.[a]

MI caused by atherothrombotic coronary artery disease (CAD) and usually precipitated by atherosclerotic plaque disruption (rupture or erosion) is designated as a type 1 MI.

Plaque rupture/erosion with occlusive thrombus

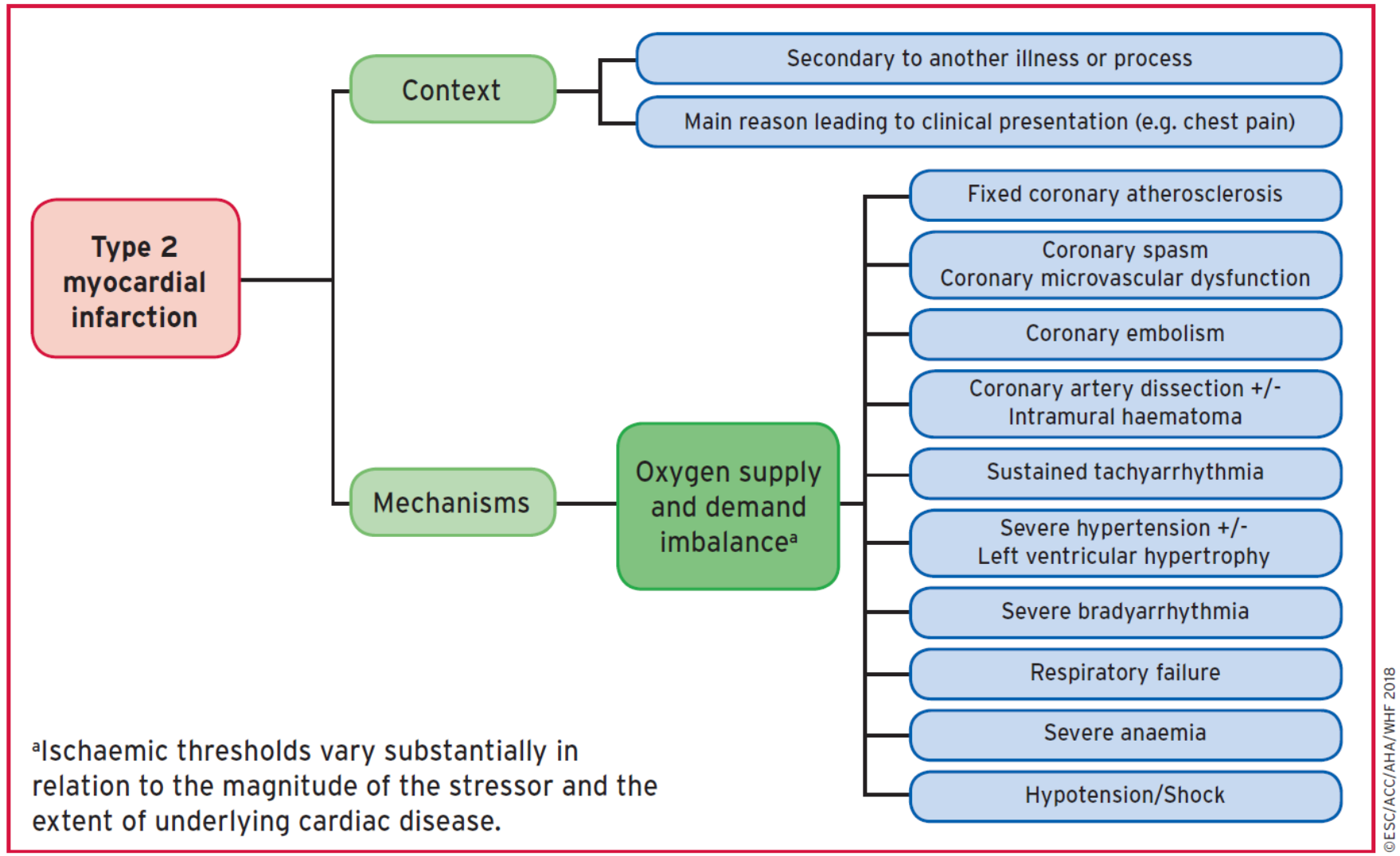
Plaque rupture/erosion with non-occlusive thrombus

“In the absence of overt myocardial ischemia, elevated cTn levels are often labelled as ‘false-positive’ hs-cTn results. This term should be avoided, as most of these unexpected hs-cTn elevations are ‘true positive’ for myocardial injury (rather than MI) and reflect previously undetected or underestimated cardiac disease”

Tweenbol R, European Heart Journal Supplements (2018) 20 (G), G2–G10

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.

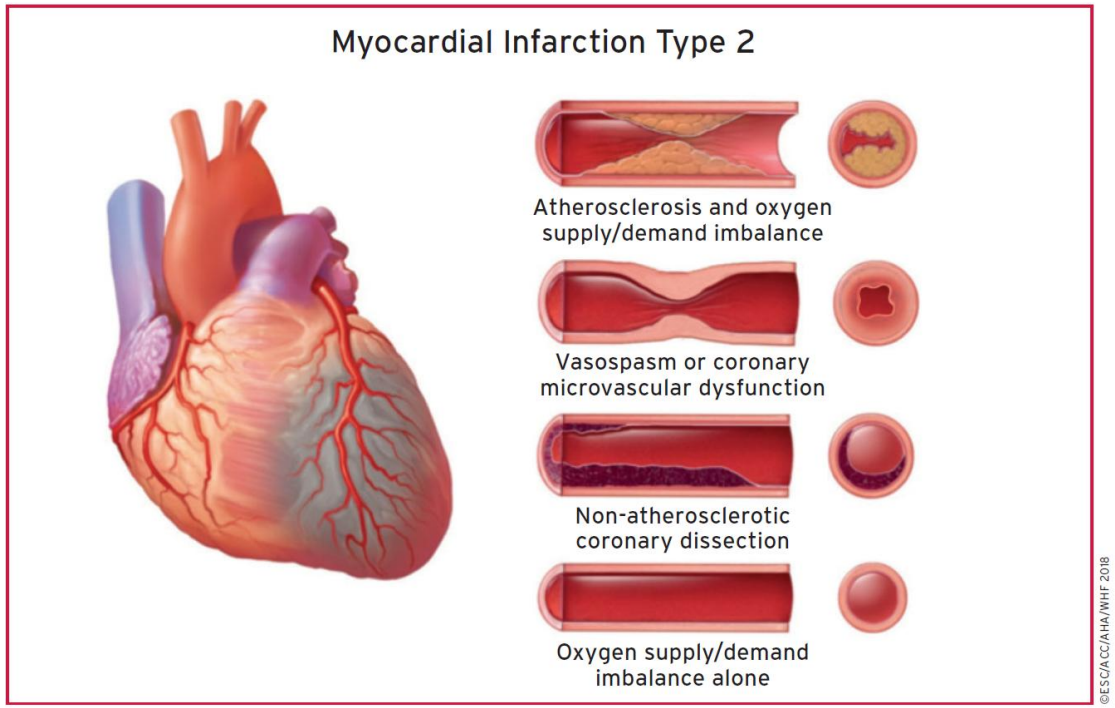


Eur Heart J. 2018 Aug 25

Criteria for type 2 MI

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following:

- Symptoms of acute 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.



Eur Heart J. 2018 Aug 25

Myocardial injury related to acute myocardial ischaemia because of oxygen supply/demand imbalance

Reduced myocardial perfusion, e.g.

- Coronary artery spasm, microvascular dysfunction
- Coronary embolism
- Coronary artery dissection
- Sustained bradyarrhythmia
- Hypotension or shock
- Respiratory failure
- Severe anaemia

Increased myocardial oxygen demand, e.g.

- Sustained tachyarrhythmia
- Severe hypertension with or without left ventricular hypertrophy

Other causes of myocardial injury

Cardiac conditions, e.g.

- Heart failure
- Myocarditis
- Cardiomyopathy (any type)
- Takotsubo syndrome
- Coronary revascularization procedure
- Cardiac procedure other than revascularization
- Catheter ablation
- Defibrillator shocks
- Cardiac contusion

Systemic conditions, e.g.

- Sepsis, infectious disease
- Chronic kidney disease
- Stroke, subarachnoid haemorrhage
- Pulmonary embolism, pulmonary hypertension
- Infiltrative diseases, e.g. amyloidosis, sarcoidosis
- Chemotherapeutic agents
- Critically ill patients
- Strenuous exercise

18 Myocardial injury or infarction associated with heart failure

Depending on the assay used, detectable to clearly elevated cTn values being indicative of myocardial injury may be seen in patients with heart failure (HF), both with reduced ejection fraction (EF) and with preserved EF.[88] Using hs-cTn assays, measurable hs-cTn concentrations may be present in nearly all patients with HF, with a significant percentage exceeding the 99th percentile URL, particularly in those patients with more severe HF syndromes, such as in acutely decompensated HF.[87]

Multiple mechanisms:

Type 2 MI may result from increased transmural pressure, small-vessel coronary obstruction, endothelial dysfunction, anaemia, hypotension.

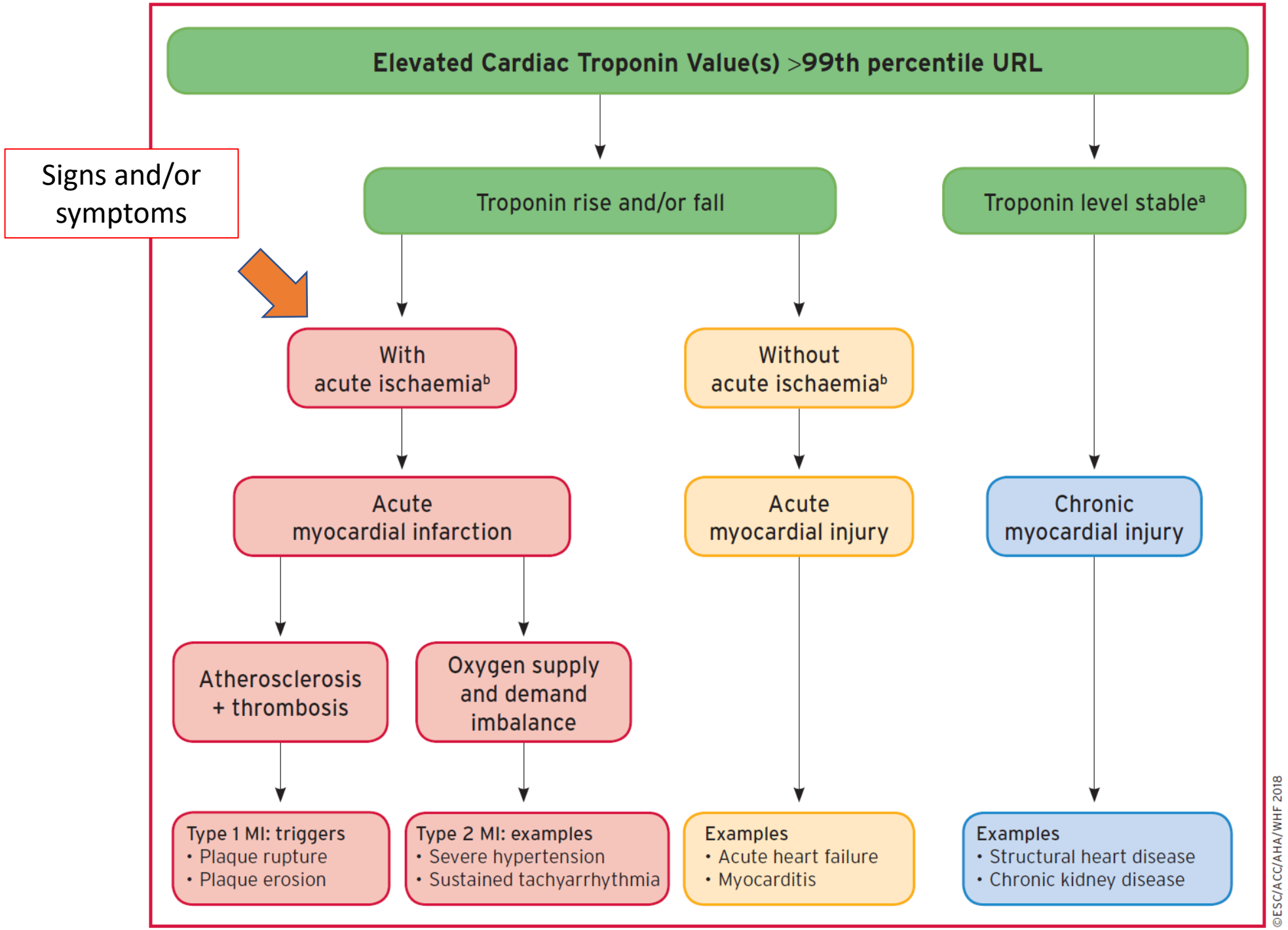
Besides type 1 MI or type 2 MI, cardiomyocyte apoptosis and autophagy due to wall stretch have been experimentally demonstrated. Direct cellular toxicity related to inflammation, circulating neurohormones, and infiltrative processes may present with HF and abnormal cTn measurements indicating myocardial injury. Finally, exocytosis of the early releasable cytosolic troponin pool into the blood stream from stressed cardiomyocytes has also been suggested as a cause of elevated cTn values

“First, they should be used only in conjunction with full clinical assessment, including a pre-test probability assessment to identify those patients at high risk who may not be suitable for early discharge.

Second, these strategies should be considered triage strategies rather than definite diagnostic strategies.

Third, the percentage of patients eligible for rule-out or rule-in varies widely from 9.8% to 77% depending on the underlying algorithm, the used cTn assay”

Tweenbol R, European Heart Journal Supplements (2018) 20 (G), G2–G10


Signs and/or symptoms
Elevated Cardiac Troponin Value(s) >99th percentile URL
Troponin rise and/or fall
Troponin level stable[a]
With acute ischaemia[b]
Without acute ischaemia[b]
Acute myocardial infarction
Acute myocardial injury
Chronic myocardial injury
Atherosclerosis + thrombosis
Oxygen supply and demand imbalance
Type 1 MI: triggers
• Plaque rupture
• Plaque erosion
Type 2 MI: examples
• Severe hypertension
• Sustained tachyarrhythmia
Examples
• Acute heart failure
• Myocarditis
Examples
• Structural heart disease
• Chronic kidney disease
©ESC/ACC/AHA/WHF 2018

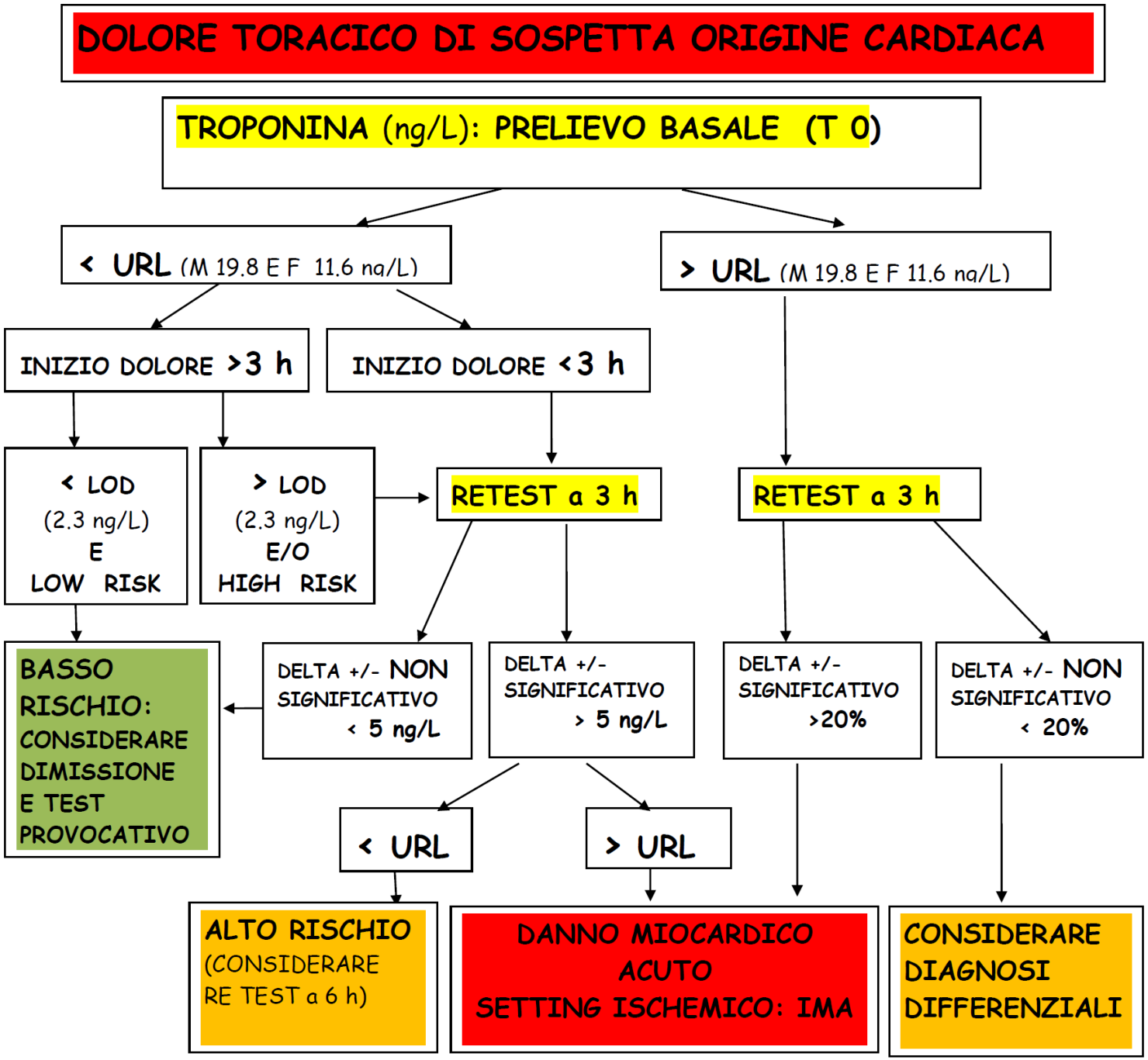
A partire dal giorno 5 settembre 2018 il sistema attuale di dosaggio della troponina ematica (*contemporary-sensitive AccuTnI, Beckman-Coulter*) sarà sospeso e sarà introdotto un sistema ad alta sensibilità (***hs-Tn I Access, Beckman–Coulter***).

a) La nuova hs-Tn prevede valori di cut-off (meglio definito come limite superiore di riferimento, o upper reference limit **[URL]**, al 99° percentile) differenziati tra femmine e maschi. Si avrà quindi un URL = **11.6 ng/L per le femmine** e = **19.8 ng/L per i maschi**. Entrambi i valori saranno riportati nel referto prodotto dal laboratorio.

a) Sarà inoltre introdotto il **LOD** (limit of detection, cioè il più basso valore quantificabile dal metodo), fino ad oggi non indicato. Il LOD del metodo usato in area metropolitana bolognese sarà di **2.3 ng/L** e sarà riportato nel referto prodotto dal Laboratorio.

b) In conseguenza di ciò sarà possibile definire un intervallo di riferimento di normalità, fino ad oggi non considerato. In pratica: valori compresi tra 2.3 e 11.6 ng/L (femmine), oppure tra 2.3 e 19.8 ng/L (maschi) dovranno essere considerati normali.

c) In considerazione di questo nuovo riferimento per la hs-TnI si potrà adottare un approccio da qualche tempo riportato in letteratura: un singolo valore di hs-TnI inferiore al LOD (2.3 ng/L), purché i sintomi siano iniziati da più di 3 ore e se associato a ECG normale e a bassa probabilità clinica, può **escludere** (rule-out) un infarto con probabilità molto vicina al 100% (tra 99.7 e 100% in diversi studi). Ciò potrebbe consentire di effettuare un solo prelievo in questa sottopopolazione di utenti e procedere ad un rapido rule-out del paziente a bassa probabilità clinica.



Algoritmo hs-TnI Settembre 2018

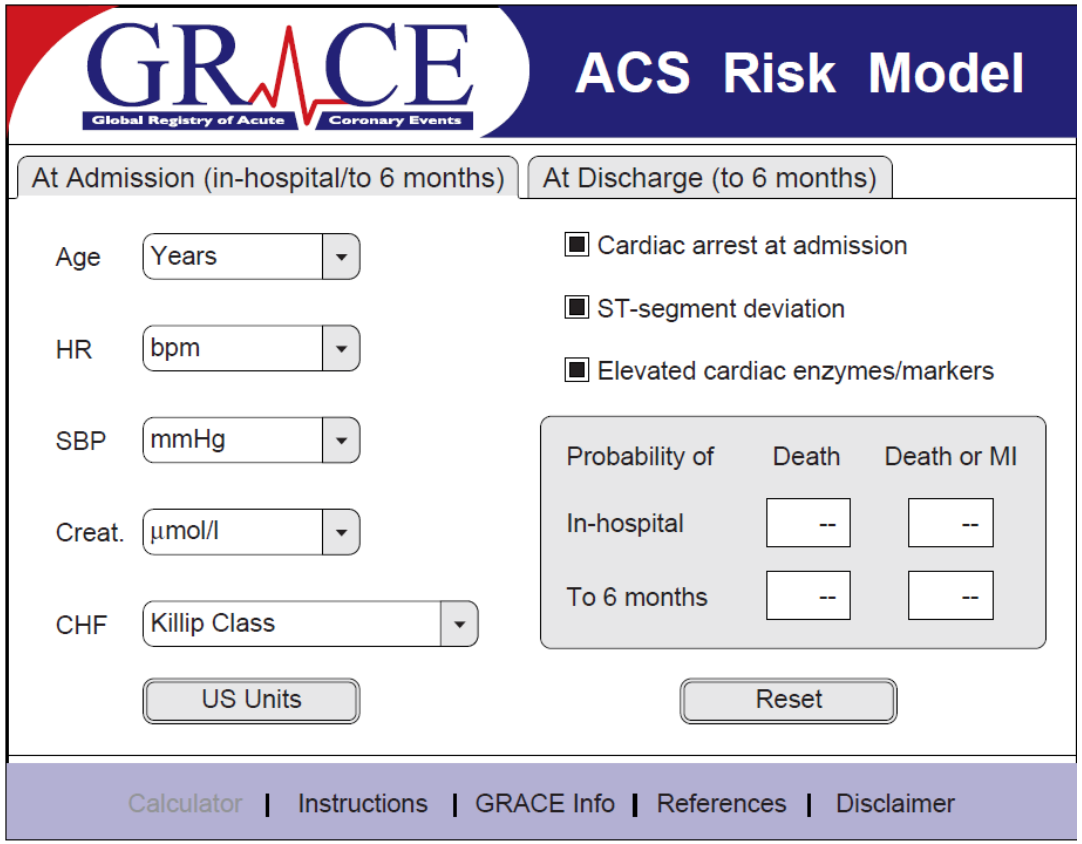
Valutazione clinica del dolore toracico

Tabella 2. Chest pain score.

	Punti
Localizzazione	
Restrosternale, precordiale	+3
Emitorace sinistro, collo, mandibola, epigastrio	+2
Apice	-1
Carattere	
Oppressivo, strappamento, morsa	+3
Pesantezza, restringimento	+2
Puntorio, pleuritico, pinzettante	-1
Irradiazione	
Braccia, spalla, posteriore, collo, mandibola	+1
Sintomi associati	
Dispnea, nausea, sudorazione	+2

Risultato: score <4 = dolore atipico, bassa probabilità di angina pectoris; score ≥4 = dolore tipico, intermedio-alta probabilità di angina.

Conti A, Paladini B, Toccafondi S, et al. Effectiveness of a multidisciplinary chest pain unit for the assessment of coronary syndromes and risk stratification in the Florence area. Am Heart J 2002; 144: 630-5



FACTS & FIGURES

Score interpretation:

Grace Score Range	Mortality Risk
0-87	0-2%
88-128	3-10%
129-149	10-20%
150-173	20-30%
174-182	40%
183-190	50%
191-199	60%
200-207	70%
208-218	80%
219-284	90%
≥ 285	99%

BMJ. 2006 Nov 25;333(7578):1091.
Am Heart J. 2009 Sep;158(3):392-9.

Table 1
The HEART score for chest pain patients at the emergency department.

History (=anamnesis)	Highly suspicious	2
	Moderately suspicious	1
	Slightly or non-suspicious	0
ECG	Significant ST-depression	2
	Nonspecific repolarization disturbance	1
	Normal	0
Age	≥65 years	2
	>45–<65 years	1
	≤45 years	0
Risk factors	≥3 risk factors, *or* history of atherosclerotic disease	2
	1 or 2 risk factors	1
	No risk factors known	0
Troponin	≥3× normal limit	2
	>1–<3× normal limit	1
	≤Normal limit	0
Total		

The HEART score is composed of 5 components: history, electrocardiogram (ECG), age, risk factors and troponin. For each component 0, 1 or 2 points is given (see methods for further details).

Low HEART scores (0–3), exclude short-term MACE with >98% certainty.

In patients with high HEART scores (7–10) the high risk of MACE may indicate more aggressive policies.

International Journal of Cardiology 168 (2013) 2153–2158

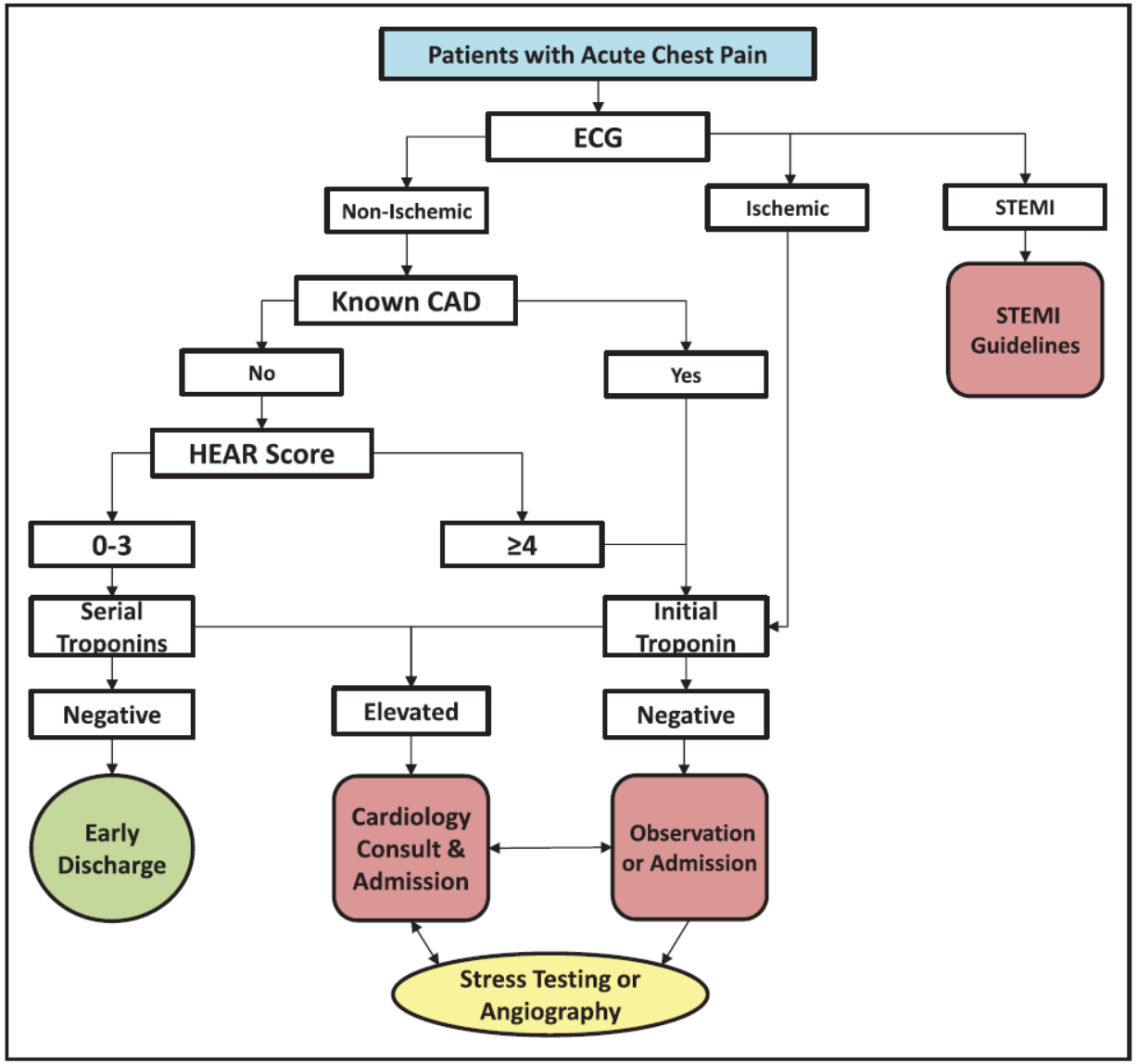
Circulation

ORIGINAL RESEARCH ARTICLE

Safely Identifying Emergency Department Patients With Acute Chest Pain for Early Discharge

HEART Pathway Accelerated Diagnostic Protocol

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio
HEART Pathway	98.3 (96.3–99.4)	39.9 (38.3–41.5)	13.5 (12.2–14.9)	99.6 (99.1–99.9)	1.64 (1.59–1.68)	0.04 (0.01–0.08)
HEAR score	83.6 (78.9–87.6)	43.0 (41.4–44.7)	11.0 (9.7–12.3)	96.9% (95.9–97.7)	1.47 (1.38–1.55)	0.38 (0.29–0.49)
Troponin	91.8 (88.4–94.5)	87.7 (86.6–88.8)	42.6 (39.0–46.2)	99.1 (98.7–99.4)	7.49 (6.81–8.23)	0.09 (0.07–0.13)



Circulation. 2018;138:2456–2468.

JIM Review

doi: 10.1111/joim.12779

Clinical implications of high-sensitivity cardiac troponins

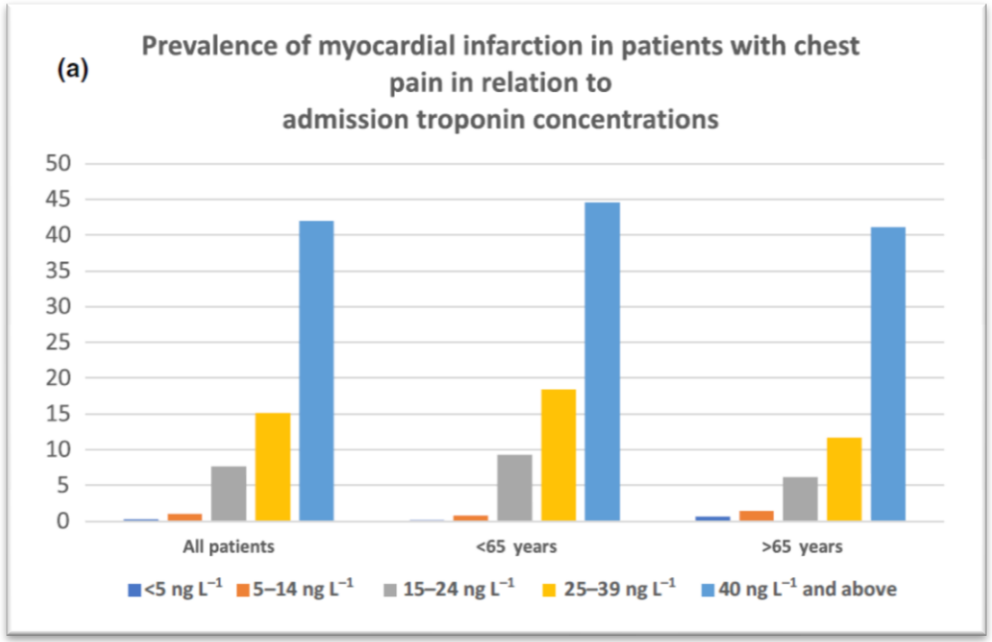
M. J. Holzmann[1,2]

[1]From the Department of Medicine, Karolinska Institutet, Solna; and [2]Functional area of Emergency Medicine, Karolinska University Hospital, Huddinge, Sweden

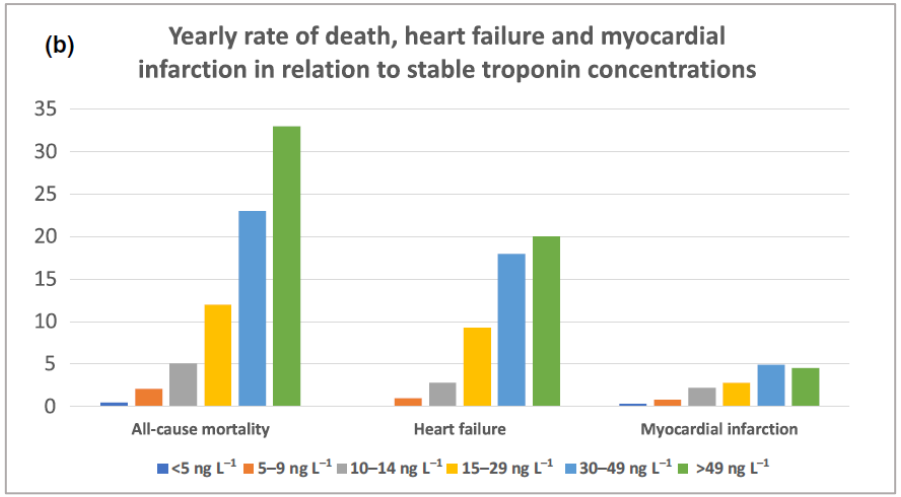
Journal of Internal Medicine, 2018, 284; 50–60

There were concerns expressed that the introduction of hs-cTn would lead to a sharp increase in the incidence of MI after an early report of a change from 18% to 22% in MI incidence after the transition to hs-cTn

cTn elevations universally portend a worse prognosis than otherwise similar patients without a cTn elevation, irrespective of the underlying disease.



21 503 patients with chest pain at the Sahlgrenska University Hospital, Gothenburg, Sweden



Biomarkers. 2018 Sep;23(6):551-557. doi: 10.1080/1354750X.2018.1460763. Epub 2018 Apr 18.

High-sensitivity cardiac troponin T for diagnosis of NSTEMI in the elderly emergency department patient: a clinical cohort study.

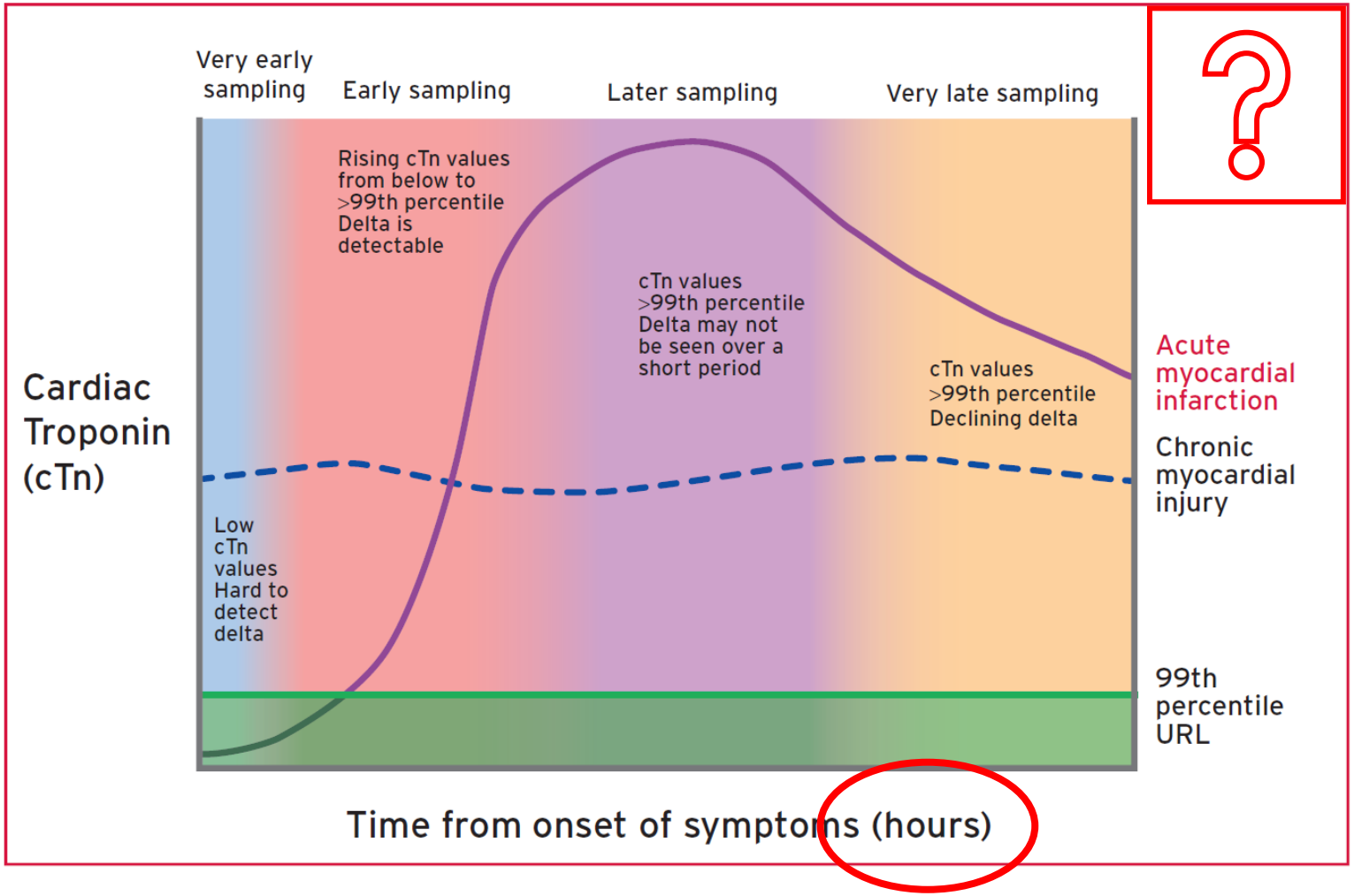
Riedlinger D[1], Möckel M[1], Müller C[1,2], Holert F[1,2], Searle J[1], von Recum J[1], Slagman A[1].

Author information

MATERIALS AND METHODS:
Data of 4118 consecutive emergency department (ED) patients who underwent a routine TnT measurement between 11 October 2012 and 30 November 2013 were analysed. Primary endpoint was a main hospital diagnosis of NSTEMI.

72.2% of all patients ≥75 years of age (583/808) without NSTEMI had hsTnT concentrations above the 99th percentile of a healthy reference population.

CONCLUSION: Patients' age needs to be considered **at least one influencing factor** on hsTnT concentrations at admission and should be included in the clinical interpretation of hsTnT concentrations for further clinical workup beneath other influencing factors like comorbidities and symptom onset time. The implementation of age-specific cut-off values could be considered for single troponin testing at admission but is associated with an increased risk of underdiagnosis of NSTEMI.



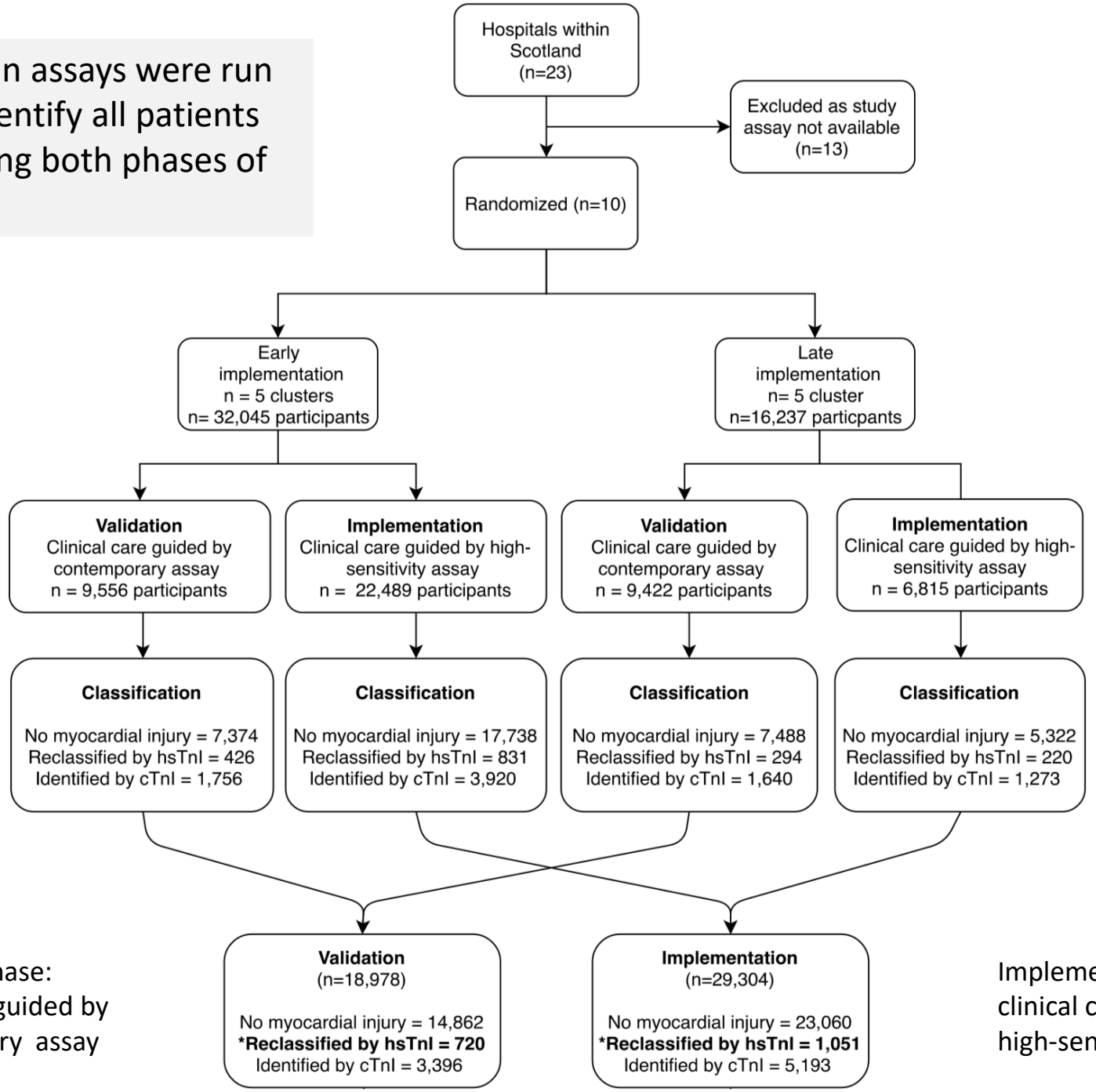
In most studies analytical and biological variation is in the range of 50 – 60%.
For that reason, this percentage has been suggested for use when initial baseline values are ≤ the 99th percentile URL.
However, for individuals with an initial value greater than the 99th percentile URL, a lesser degree of change during serial measurements is necessary to achieve improved clinical sensitivity (as compared with individuals with initial values ≤ 99th percentile URL).

Thus, an expert consensus group has recommended serial changes > 20% be used in this situation [1]

[1] Thygesen K, et al; Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J 2012;33:2252–2257.

Contemporary and high sensitivity troponin assays were run simultaneously in plasma, to accurately identify all patients reclassified by high-sensitivity testing during both phases of the trial

Diagram of the Trial and Populations



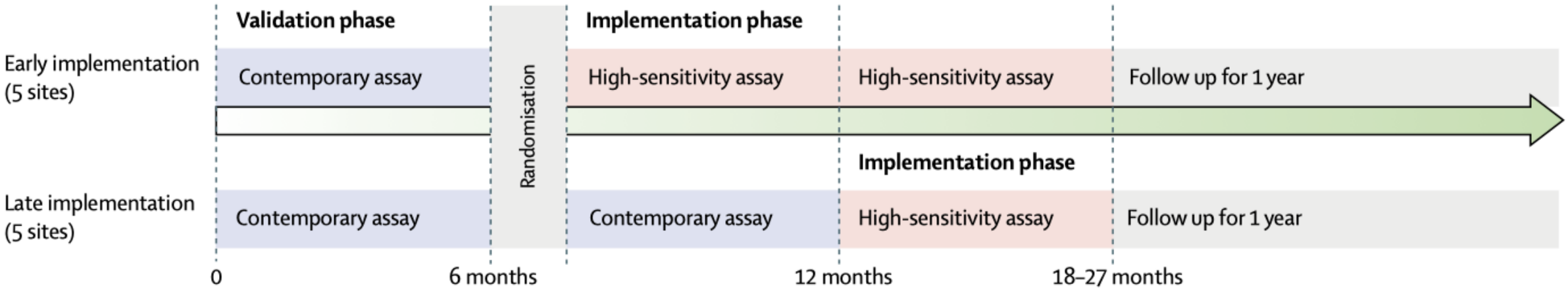
Validation phase: clinical care guided by contemporary assay

Implementation phase: clinical care guided by high-sensitivity assay

Diagram of the Trial and Populations

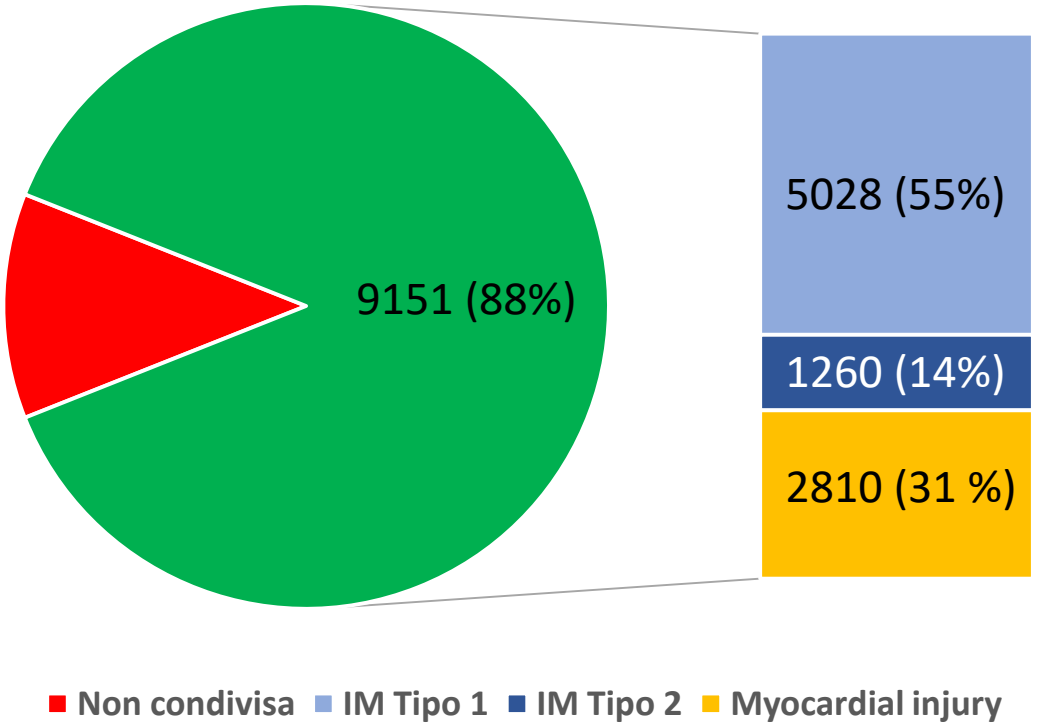
Validation phase: clinical care guided by contemporary assay

Implementation phase: clinical care guided by high-sensitivity assay

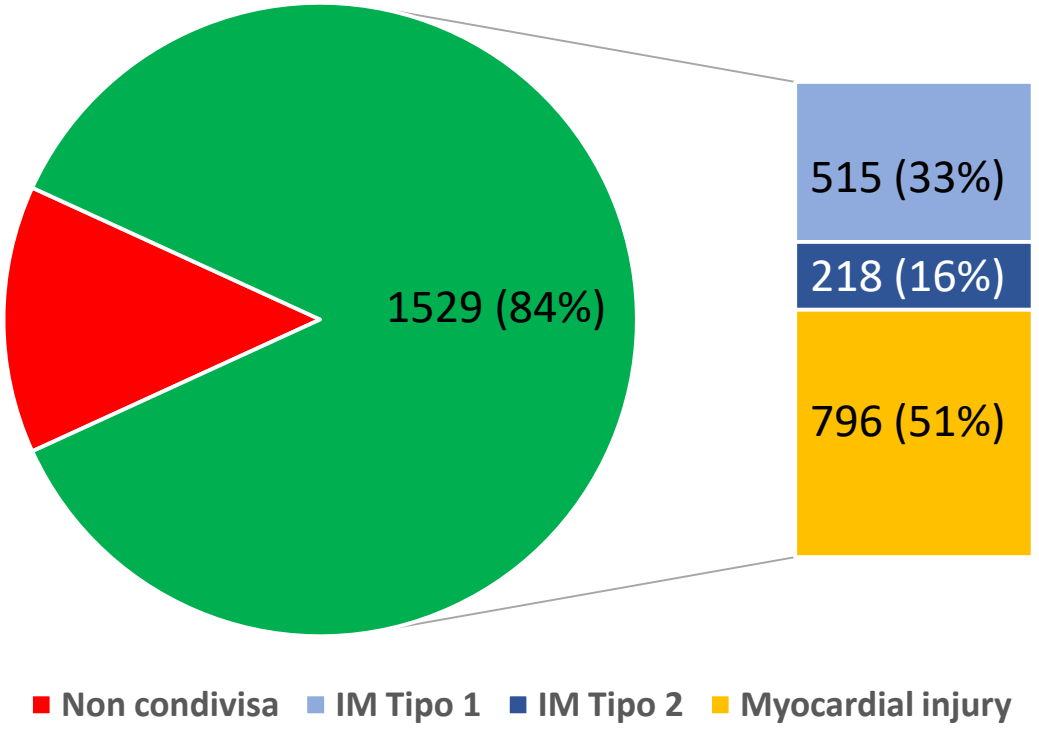


	All participants	No myocardial injury	Myocardial injury 10.360 diagnosticati con hs-cTnI	
			Reclassified by high-sensitivity cardiac troponin I assay	Identified by cardiac troponin I assay
Number of participants	48 282	37 922	1771	8589
Peak high-sensitivity cardiac troponin I, ng/L	4 (2–16)	3 (1–6)	26 (20–37)	297 (76–2600)

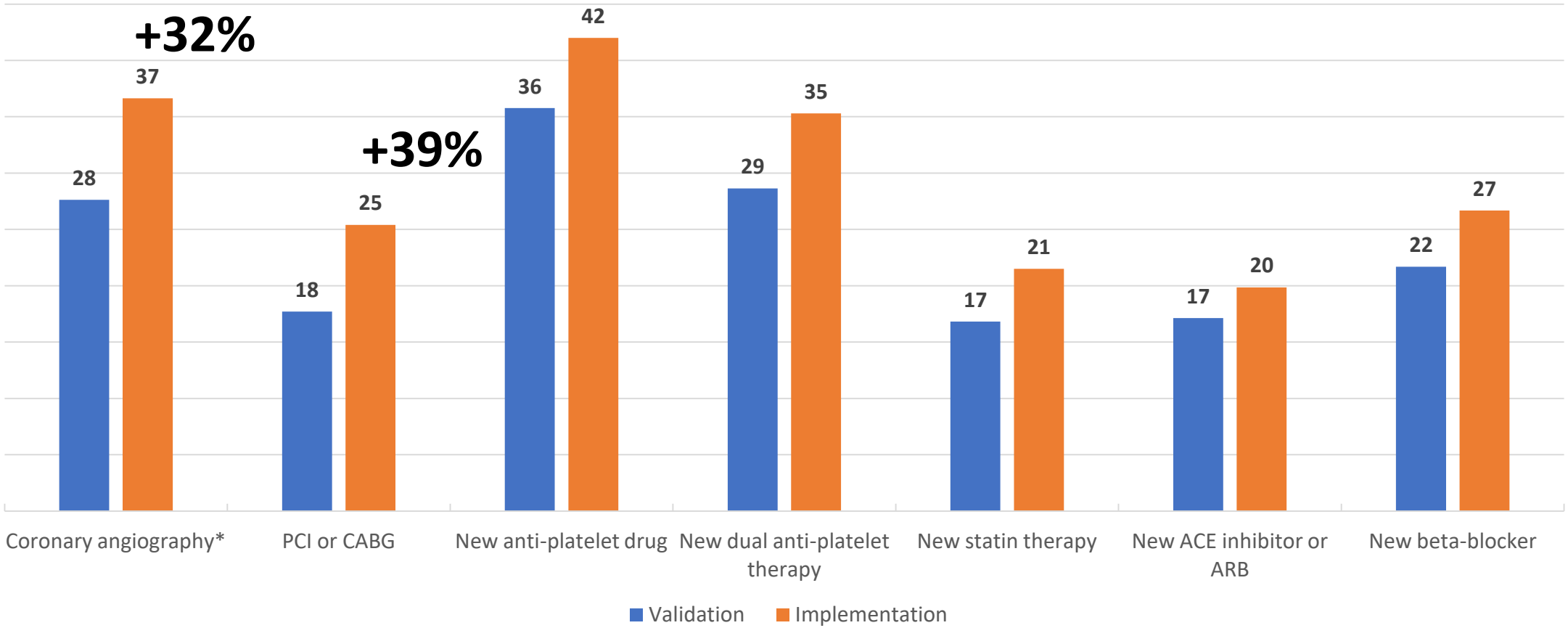
10.360 myocardial injury



Diagnosi riclassificati



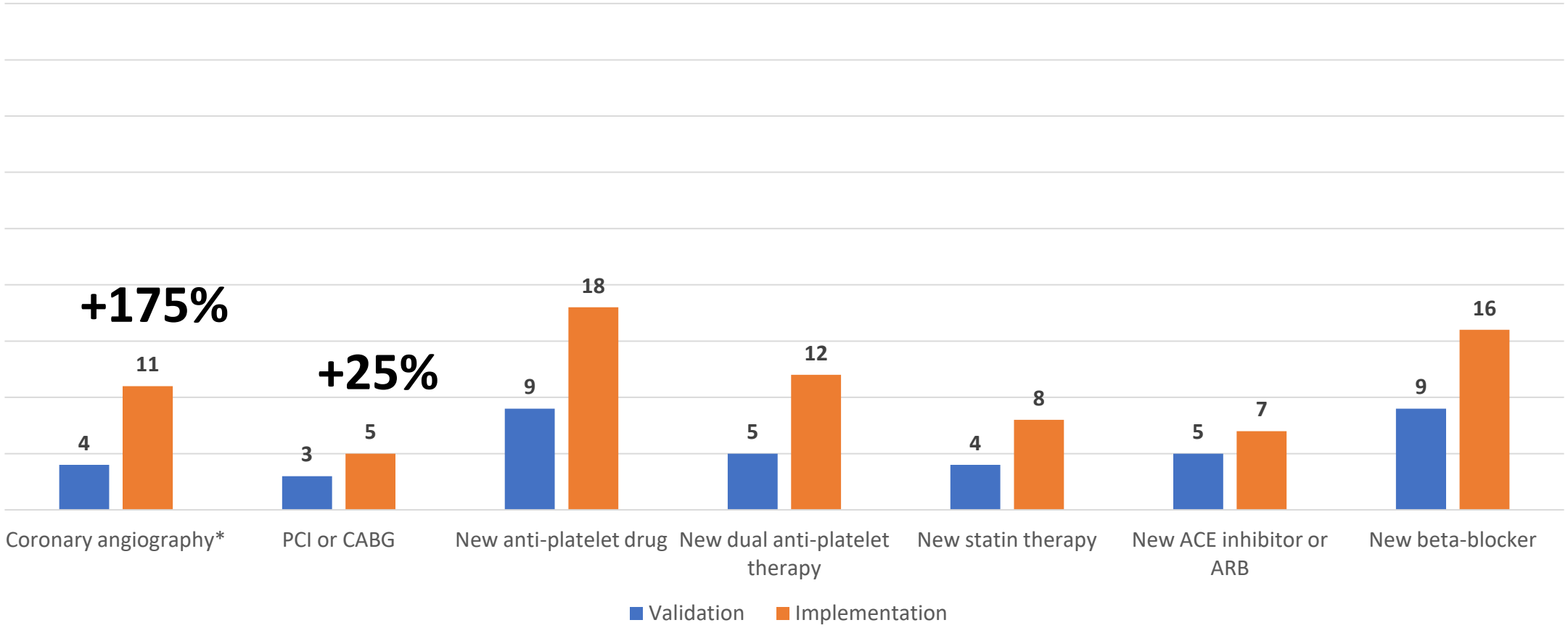
Procedure eseguite in funzione del tipo di troponina



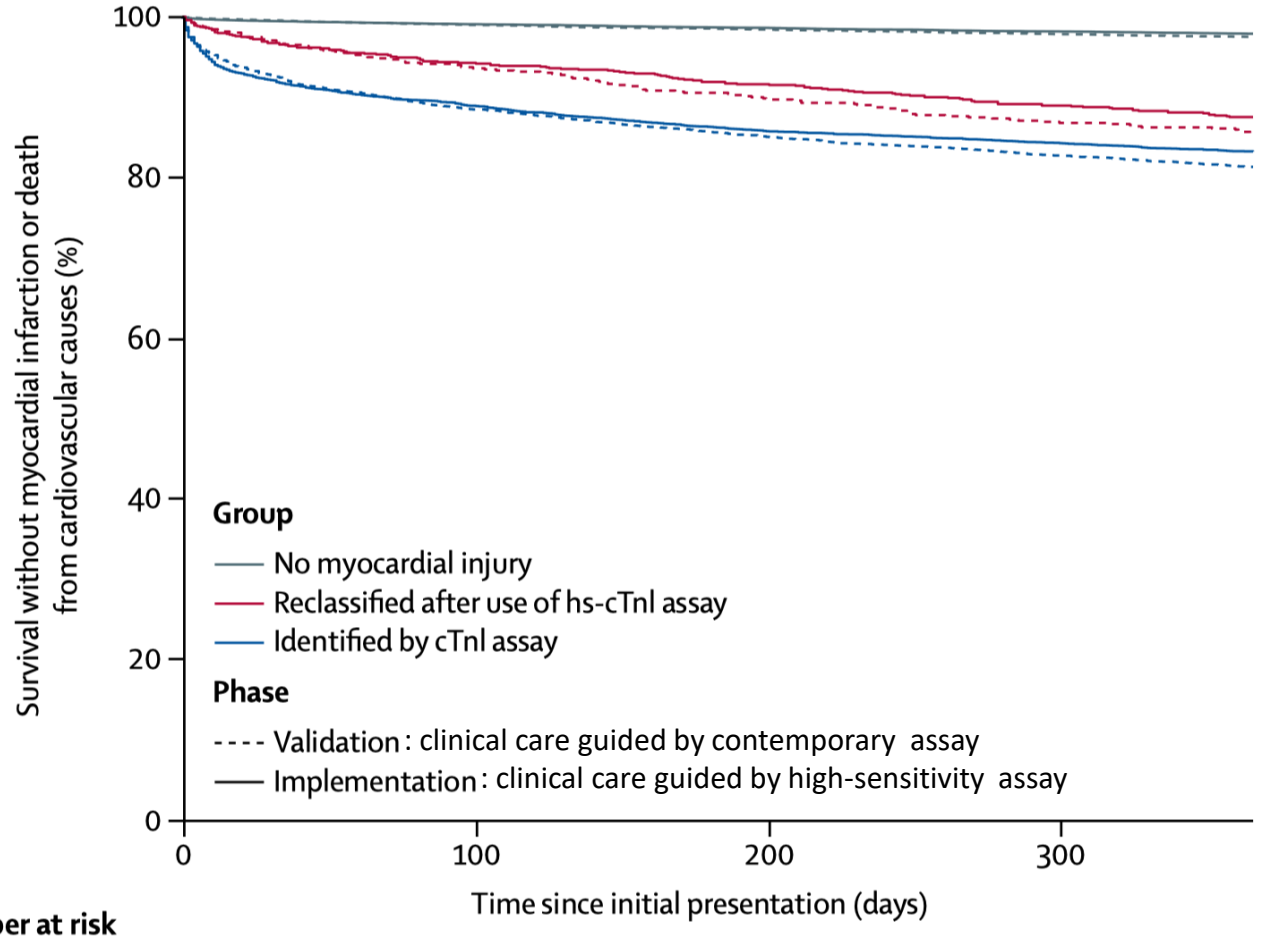
Reclassified by high-sensitivity cardiac troponin I assay (n=1771)

720 validation phase (clinical care guided by contemporary assay)

1051 implementation phase (clinical care guided by high-sensitivity assay)



Incidence of myocardial infarction or death from cardiovascular causes at 1 year, stratified by troponin concentration and phase



Number at risk				
Validation phase				
No myocardial injury	14862	14715	14631	14545
Reclassified by hs-TnI assay	720	674	646	625
Identified by cTnI assay	3396	3005	2889	2809
Implementation phase				
No myocardial injury	23060	22854	22750	22645
Reclassified by hs-TnI assay	1051	991	963	935
Identified by cTnI assay	5193	4619	4454	4377

8 Coronary procedure-related myocardial injury

Criteria for PCI-related MI ≤ 48 h after the index procedure (type 4a MI)

Coronary intervention-related MI is arbitrarily defined by an elevation of cTn values more than five times the 99th percentile URL in patients with normal baseline values. In patients with elevated pre-procedure cTn in whom the cTn level are stable (≤ 20% variation) or falling, the post-procedure cTn must rise by > 20%. However, the absolute post-procedural value must still be at least five times the 99th percentile URL. In addition, one of the following elements is required:

- New ischaemic ECG changes;
- Development of new pathological Q waves;[a]
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization.[b]

Criteria for cardiac procedural myocardial injury

Cardiac procedural myocardial injury is arbitrarily defined by increases of cTn values (> 99th percentile URL) in patients with normal baseline values (≤ 99th percentile URL) or a rise of cTn values > 20% of the baseline value when it is above the 99th percentile URL but it is stable or falling.

The use of hs-cTn assays to diagnose type 4a MI (and type 5 MI) is an area of active research. Many hs-cTn assays are available, which have wide dynamic ranges. Different criteria may be required for different assays. **However, it has recently been shown that the optimal hs-cTnT thresholds to predict cardiovascular events at 30 days and 1 year were very close to the five-fold increase** suggested by the Third Universal Definition of Myocardial infarction

8 Coronary procedure-related myocardial injury

- A large proportion of patients have abnormal values of cTn after PCI, ranging from 20 – 40% in stable CAD to 40 – 50% in MI.[1]
- Recent data corroborate the importance of elevated pre-procedure cTn values as a prognostic marker in patients that have values that rise after the procedure. [2]
- **The occurrence of procedural myocardial injury can be detected by the measurement of cTn before the procedure and repeated 3 – 6 h later**.
- Where the second value is rising, **further sampling should be performed to document the peak cTn** value. Increasing levels after the procedure can only be attributed with certainty to procedural myocardial injury when the pre-procedural cTn values are normal (<99th percentile URL), or if they are stable or falling.
- For patients that present with an ACS and undergo a prompt coronary revascularization procedure, the post-procedural increase should be attributed to the index event.

1. Tricoci P. Consensus or controversy?: Evolution of criteria for myocardial infarction after percutaneous coronary intervention. Clin Chem 2017;63:82–90
2. Ndrepepa G, et al. High-sensitivity troponin T and mortality after elective percutaneous coronary intervention. J Am Coll Cardiol 2016;68:2259–2268

- Per i pazienti con coronaropatia stabile nei quali si pensa che sia utile procedere ad angioplastica coronarica percutanea (PCI) o bypass aortocoronarico (CABG), è necessario effettuare un prelievo basale per la hs-TpnI, la mattina stessa prima della procedura.

- Si conferma che al ritorno dalla sala dopo PCI o dopo CABG occorre in tutti i casi dosare la troponina, da ripetere dopo 3 ore. Appena il risultato è disponibile deve essere mostrato al medico di reparto/di guardia per sapere se il paziente ha un **IMA periprocedurale**:

    - **Dopo PCI > 5 x URL** (M 19.8 E F 11.6 ng/L) se il basale è normale, **oppure incremento >20%** (ma in ogni caso deve essere > 5 x URL) se il basale è elevato e stabile o in riduzione.

    - **Dopo CABG > 10 X URL**.

- Si ribadisce che **l'incremento isolato della troponina non è un criterio sufficiente** per la diagnosi di infarto periprocedurale (i criteri diagnostici di infarto sono quelli dell'ultima linea guida ESC 2018).

10 Stent/scaffold thrombosis associated with percutaneous coronary intervention (type 4b myocardial infarction)

A subcategory of PCI-related MI is stent/scaffold thrombosis, type 4b MI, as documented by angiography or autopsy using the same criteria utilized for type 1 MI. It is important to indicate the time of the occurrence of the stent/scaffold thrombosis in relation to the timing of the PCI procedure.[68]

11 Restenosis associated with percutaneous coronary intervention (type 4c myocardial infarction)

Occasionally MI occurs and—at angiography, in-stent restenosis, or restenosis following balloon angioplasty in the infarct territory—is the only angiographic explanation since no other culprit lesion or thrombus can be identified. This PCI-related MI type is designated as type 4c MI, defined as focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL applying, the same criteria utilized for type 1 MI.

Criteria for CABG-related MI ≤ 48 h after the index procedure (type 5 MI)

CABG-related MI is arbitrarily defined as elevation of cTn values > 10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-procedure cTn in whom cTn levels are stable (≤ 20% variation) or falling, the post-procedure cTn must rise by > 20%. However, the absolute post-procedural value still must be > 10 times the 99th percentile URL. In addition, one of the following elements is required:

- Development of new pathological Q waves;[a]
- Angiographic documented new graft occlusion or new native coronary artery occlusion;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.

[a]Isolated development of new pathological Q waves meets the type 5 MI criteria if cTn values are elevated and rising but < 10 times the 99th percentile URL.