CORATA Belgique

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Impact of hs-troponin for the early diagnosis of acute Myocardial infarction

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Biomarkers applications	Drug Development	Disease management
Stratification markers	Select patient to increase likelihood of clinical trial success	Select the best treatment/drug for each patient
Efficacy biomarkers	Biomarkers as « early killers » or as approved surrogate markers	Improve patient compliance in the absence of early clinical improvement
Differentiation markers	Differentiate efficacy or safety of a drug within the same classv	Select the best treatment druf for each patient
Toxicity biomarkers	Biomarkers as « early killers » or used to exclude certain patient groups from clinical trials	Monitor and avoid potential toxic effects
Screening markers	Patient recruitment for clinical trials	Early disease detection, early treatment
Prognostic markers	Patient recruitment for clinical trials	Predict likely course of disease

IMPACT

IMPACT

Analytical validity

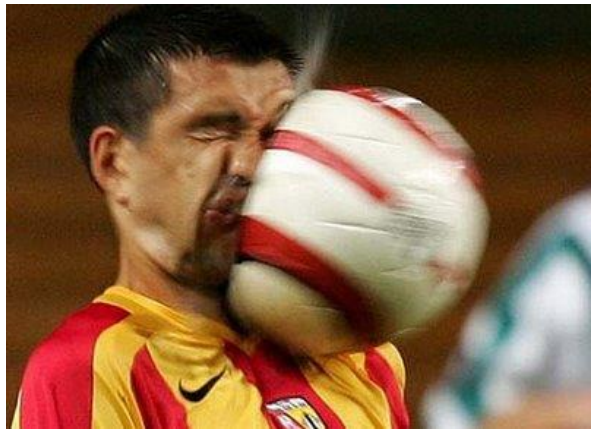
Clinical validity and utility

Practice change based on EBM

Ethical, legal and social implications

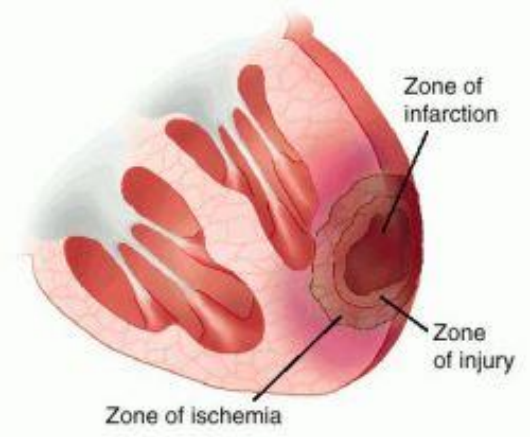
Cost-effectiveness

Optimization



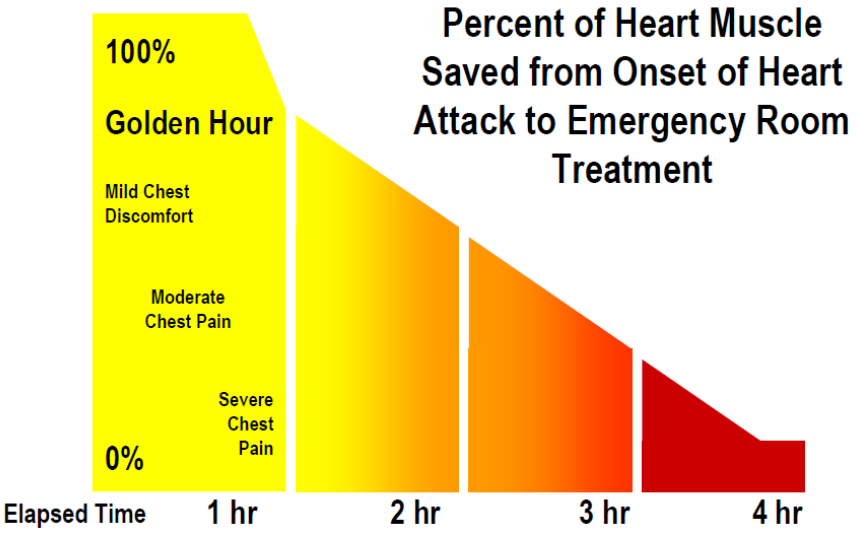
Clinical Utility

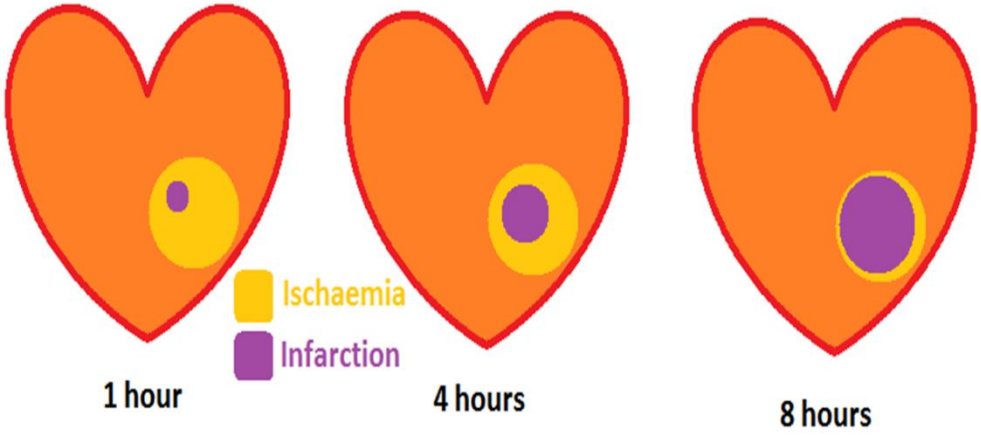
- ✓ **Patients with symptoms suggestive of acute myocardial infarction account for approximately 10% of all emergency department consultations.**
- ✓ **Electrocardiography (ECG) and cardiac troponin (cTn) assay form the diagnostic cornerstones and complement clinical assessment.**
- ✓ **Triage**



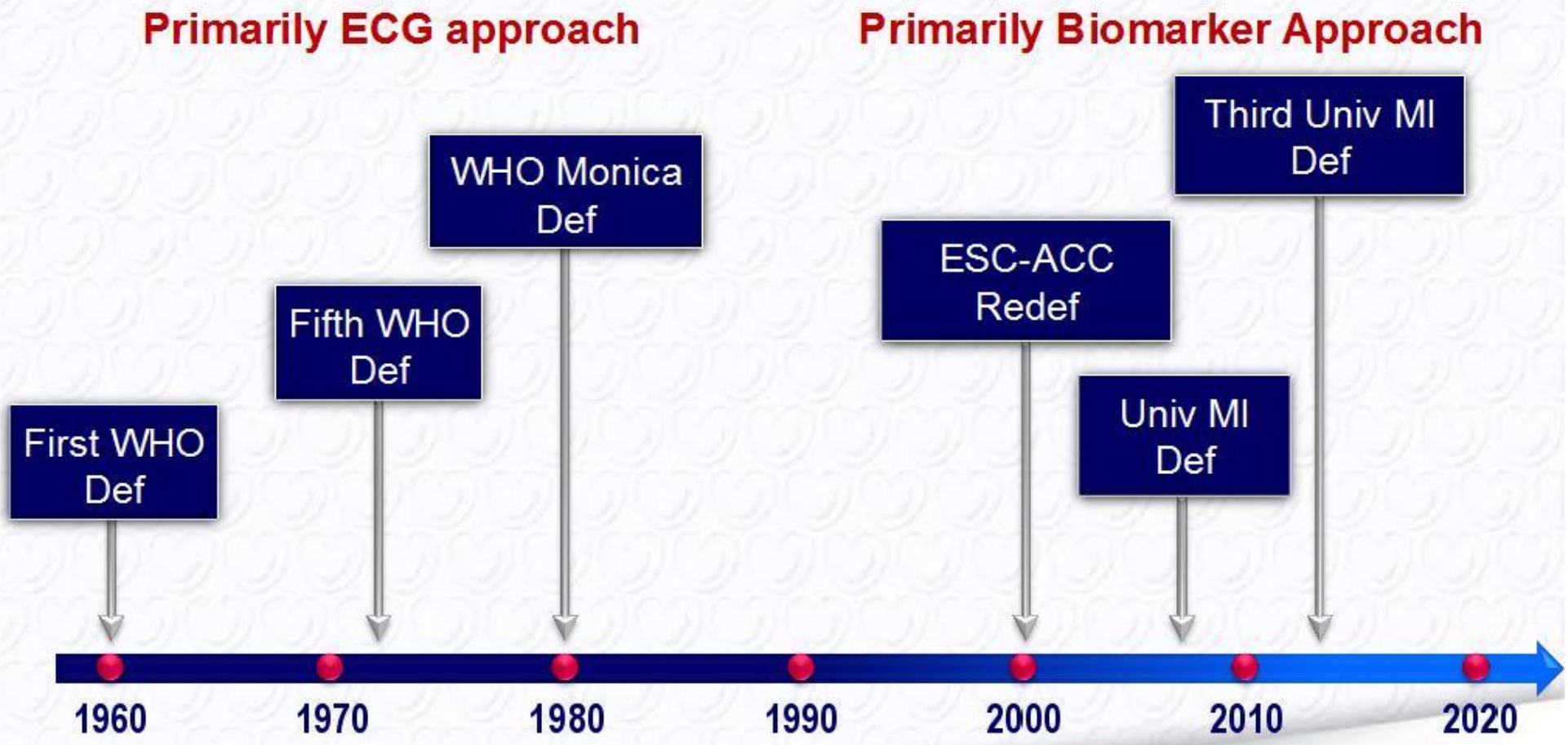
Clinical Utility

"Time is Myocardium"





Changing Criteria for Definition of Myocardial Infarction



www.escardio.org/guidelines

European Heart Journal (2012) 33: 2551–2567
doi:10.1093/eurheartj/ehs184

EUROPEAN SOCIETY OF CARDIOLOGY®

Universal New Definition of Myocardial Infarction

- Detection of a rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least and one of the following
  - Ischemic symptoms
  - ECG changes
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Joint ESC/ACC/AHA Task Force, Circulation 2007

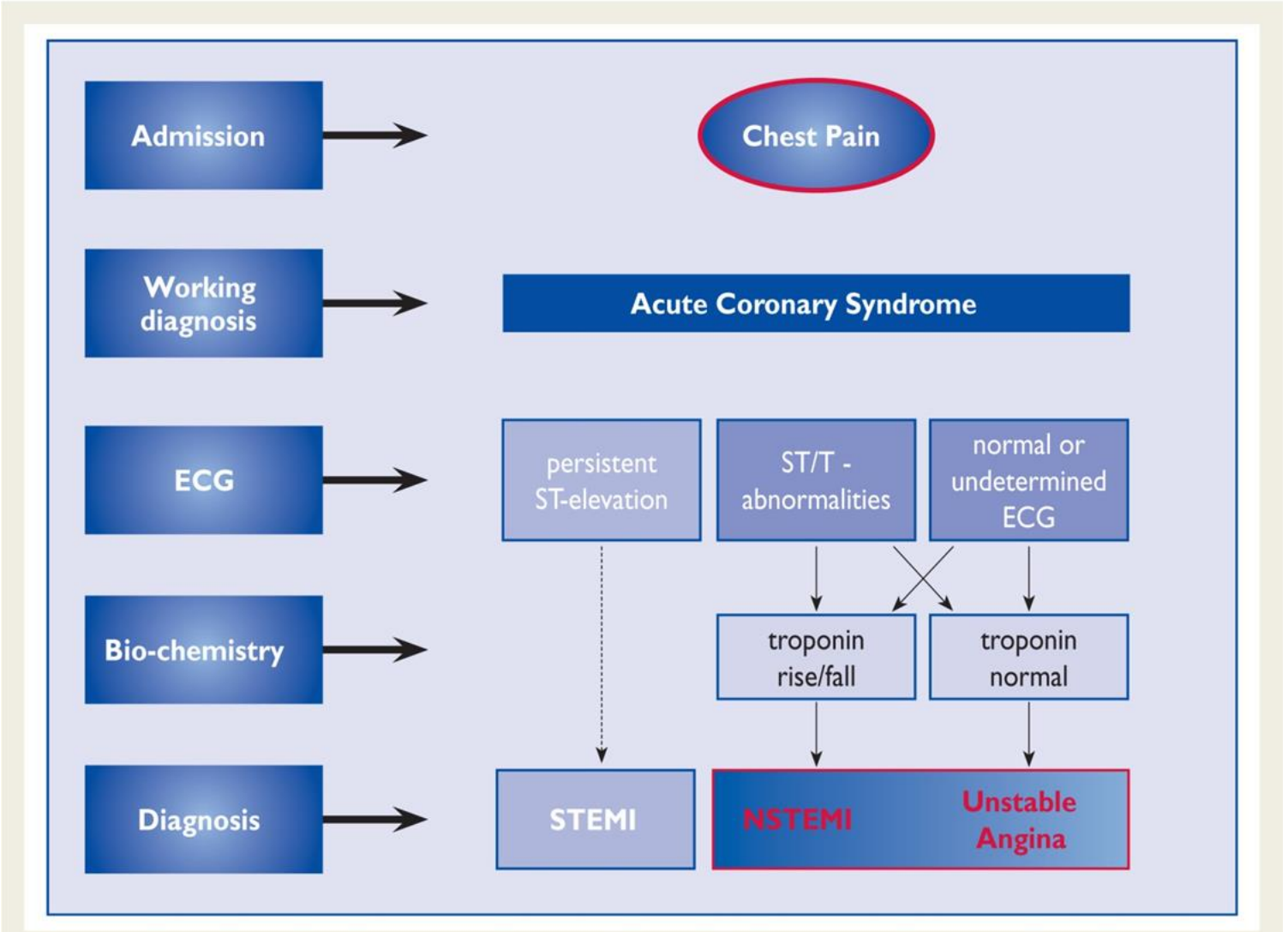
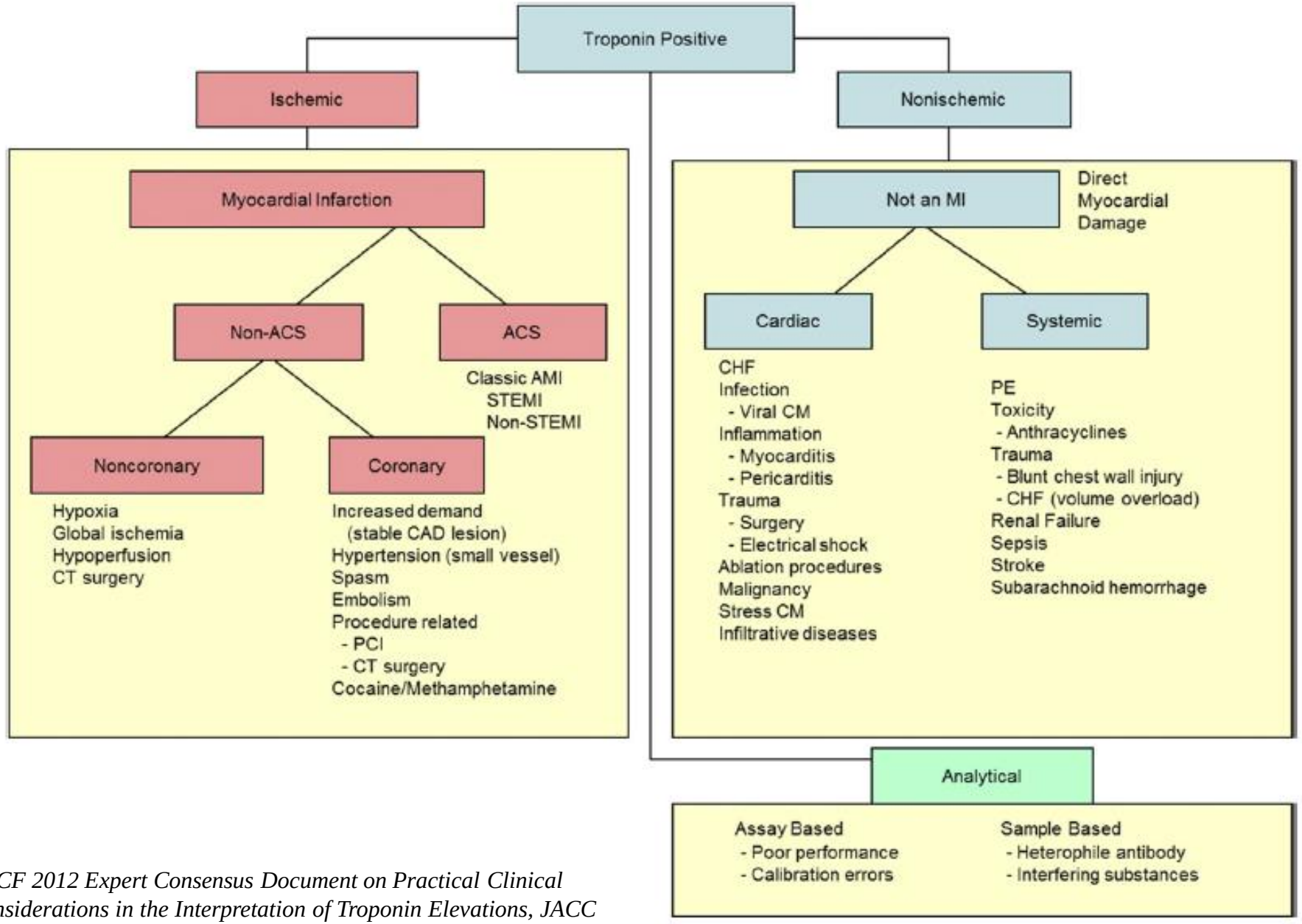


Figure 1 The spectrum of ACS. ECG = electrocardiogram; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction.

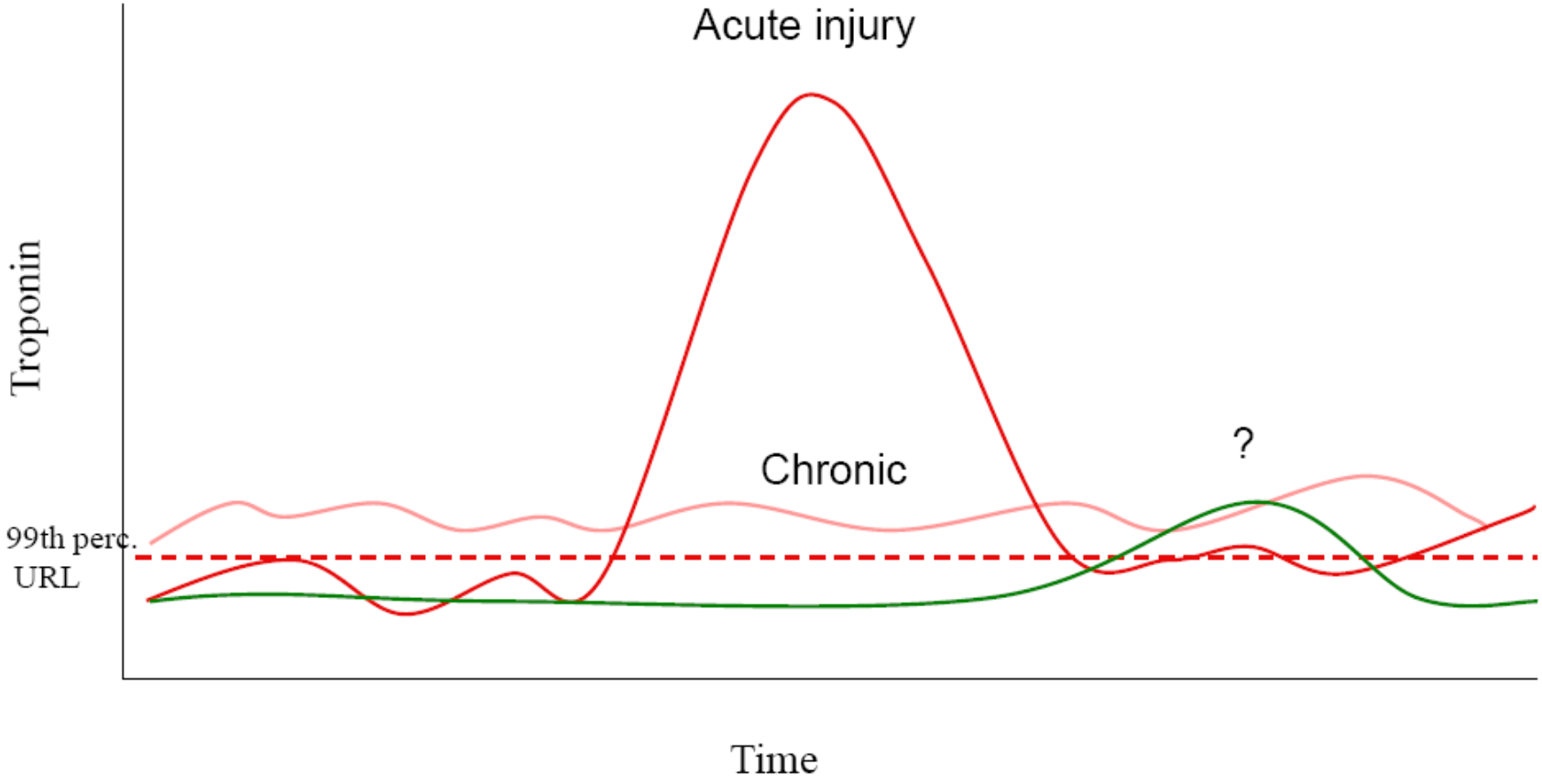
ESC guidelines for the management of ACS in patients presenting without persistent ST-segment elevation, Eur Heart J 2012

Interpretation of Troponin elevations

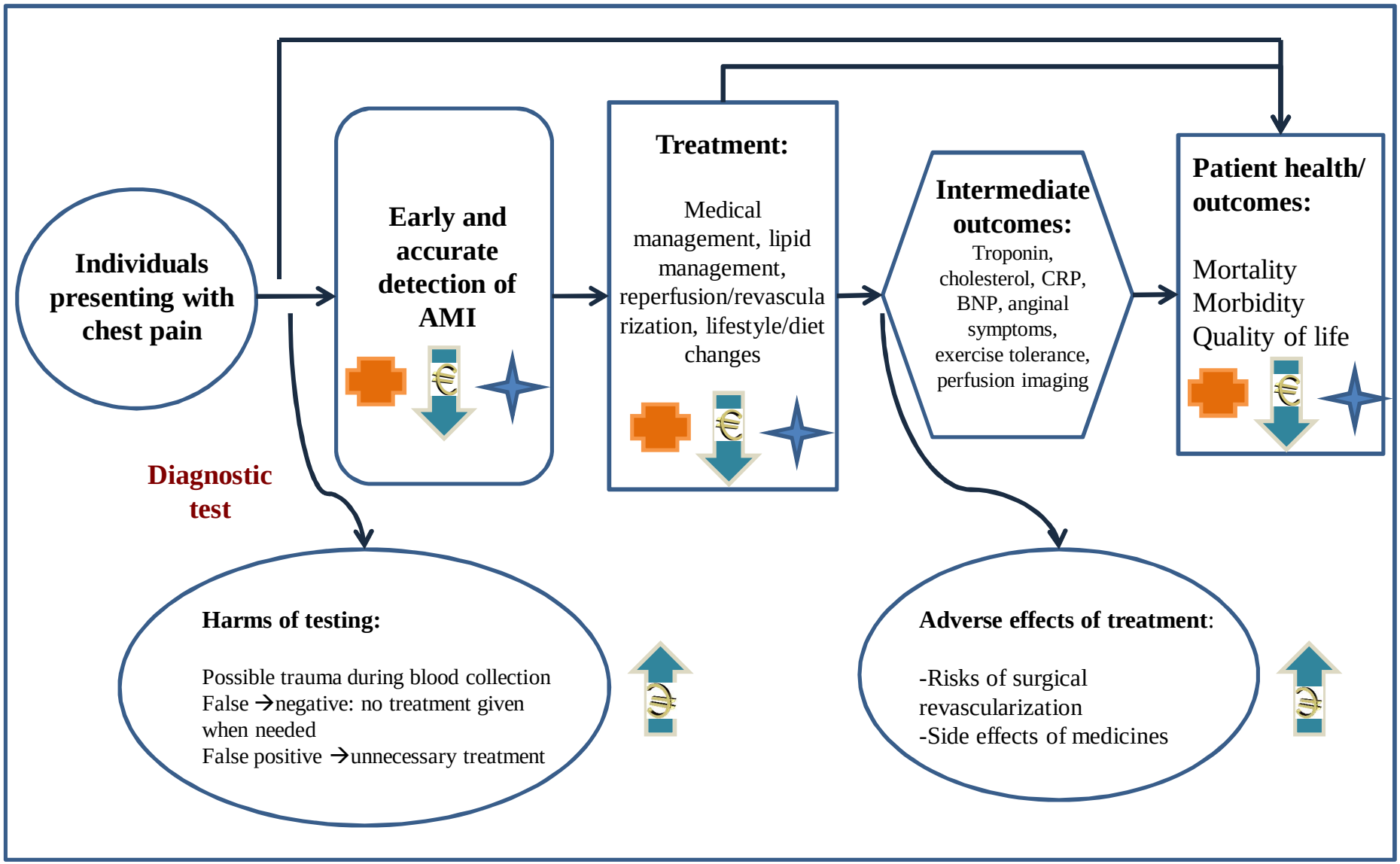


ACCF 2012 Expert Consensus Document on Practical Clinical Considerations in the Interpretation of Troponin Elevations, JACC November 2012

Importance of having serial measurement with Troponin



The scene é


Individuals presenting with chest pain
Early and accurate detection of AMI
Treatment:
Medical management, lipid management, reperfusion/revascularization, lifestyle/diet changes
Intermediate outcomes:
Troponin, cholesterol, CRP, BNP, anginal symptoms, exercise tolerance, perfusion imaging
Patient health/ outcomes:
Mortality
Morbidity
Quality of life
Diagnostic test
Harms of testing:
Possible trauma during blood collection
False →negative: no treatment given when needed
False positive →unnecessary treatment
Adverse effects of treatment:
-Risks of surgical revascularization
-Side effects of medicines

Analytical Utility

Troponin assays: a lack of standardization…

Assay	Epitopes								
Access	24-40	41-49							
Architect	24-40	41-49			87-91				
AxSYM 2nd generation	24-40	41-49			87-91				
i-STAT	27-39	41-49	69-86		88-91				
Immulite	24-40				80 - 110				
Liaison	27-39				80 - 110				
Ortho Clinical ECi	24-40	41-49			87-91				
Pathfast		41-49	71	-	116		163	-	209
Stratus	27-32	41-56							
TnI Ultra	27-40	41-49			87-91				
Tosoh AIA		41-49			87-91				
AQT90 FLEX		41-49				137-149		190-196	

Table 1. Analytical characteristics of contemporary sensitive and point-of-care cardiac troponin assays.

Company/platform/assay	Cardiac troponin concentration at: LoD,[a] μg/L	99th Percentile, μg/L (CV)[b]	10% CV concentration, μg/L	Amino acid residues of epitopes recognized by capture (C) and detection (D) MAbs
Abbott AxSYM ADV	0.02	0.04 (14%)	0.16	C: 87–91, 41–49; D: 24–40
Abbott ARCHITECT	0.009	0.028 (14%)	0.032	C: 87–91, 24–40; D: 41–49
Abbott i-STAT	0.02	0.08 (16.5%)	0.10	C: 41–49, 88–91; D: 28–39, 62–78
Alere Triage	0.05	<0.05 (NA)	NA	C: NA; D: 27–40
Alere Triage Cardio3[c]	0.01	0.02 (17%)	NA	C: 27–39; D: 83–93, 190–196
Beckman Access AccuTnI	0.01	0.04 (14%)	0.06	C: 41–49; D: 24–40
bioMérieux Vidas Ultra	0.01	0.01 (27.7%)	0.11	C: 41–49, 22–29; D: 87–91, MAb 7B9
Mitsubishi Pathfast	0.008	0.029 (5.0%)	0.014	C: 41–49; D: 71–116, 163–209
Ortho Vitros ECi ES	0.012	0.034 (10%)	0.034	C: 24–40, 41–49; D: 87–91
Radiometer AQT90 cTnI	0.009	0.023 (17.7%)	0.039	C: 41–49, 190–196; D: 137–149
Radiometer AQT90 cTnT	0.008	0.017 (15.2%)	0.026	C: 125–131; D: 136–147
Response RAMP	0.03	<0.01 (18.5% at 0.05)	0.21	C: 85–92; D: 26–38
Roche cobas h232 Cardiac T[c,d]	0.05	NA	NA	C: 125–131; D: 136–147
Roche Elecsys TnT Gen 4	0.01	<0.01	0.030	C: 136–147; D: 125–131
Roche Elecsys TnI	0.16	0.16 (10%)	0.30	C: 87–91, 190–196; D: 23–29, 27–43
Roche Cardiac Reader cTnT[e]	0.03	NA	NA	C: 125–131; D: 136–147
Siemens Centaur Ultra	0.006	0.04 (8.8%)	0.03	C: 41–49, 87–91; D: 27–40
Siemens Dimension RxL	0.04	0.07 (20%)	0.14	C: 27–32; D: 41–56
Siemens Immulite 2500	0.1	0.2 (NA)	0.42	C: 87–91; D: 27–40
Siemens Stratus CS	0.03	0.07 (10%)	0.06	C: 27–32; D: 41–56
Siemens Vista	0.015	0.045 (10%)	0.04	C: 27–32; D: 41–56
Tosoh AIA	0.06	<0.06 (NA)	0.09	C: 41–49; D: 87–91

Troponin assays: a new generation

2007

- **ESC-ACCF-AHA-WHF and IFCC Task Force recommends use of a high sensitivity troponin assay**

- **Requirements were detection of hs-Tn at the 99th percentile of an apparently healthy reference population with <10% variability**

Troponin assays: a new generation

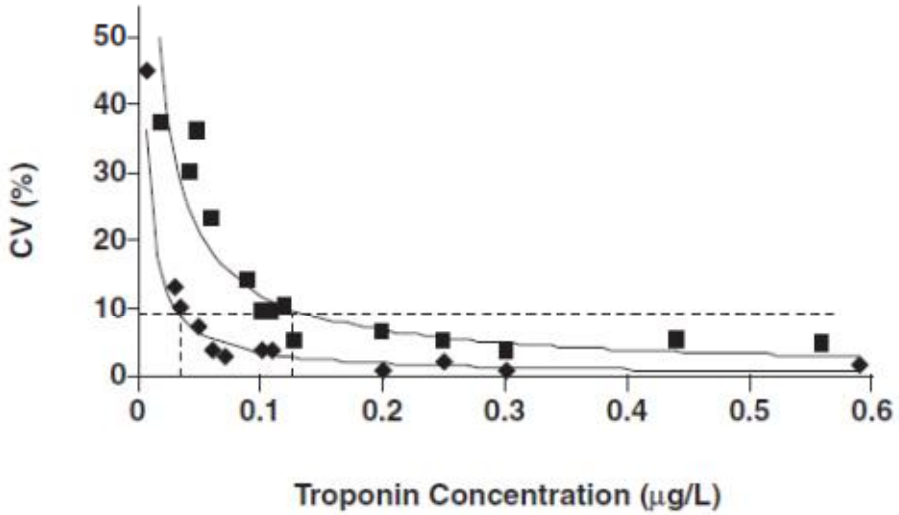
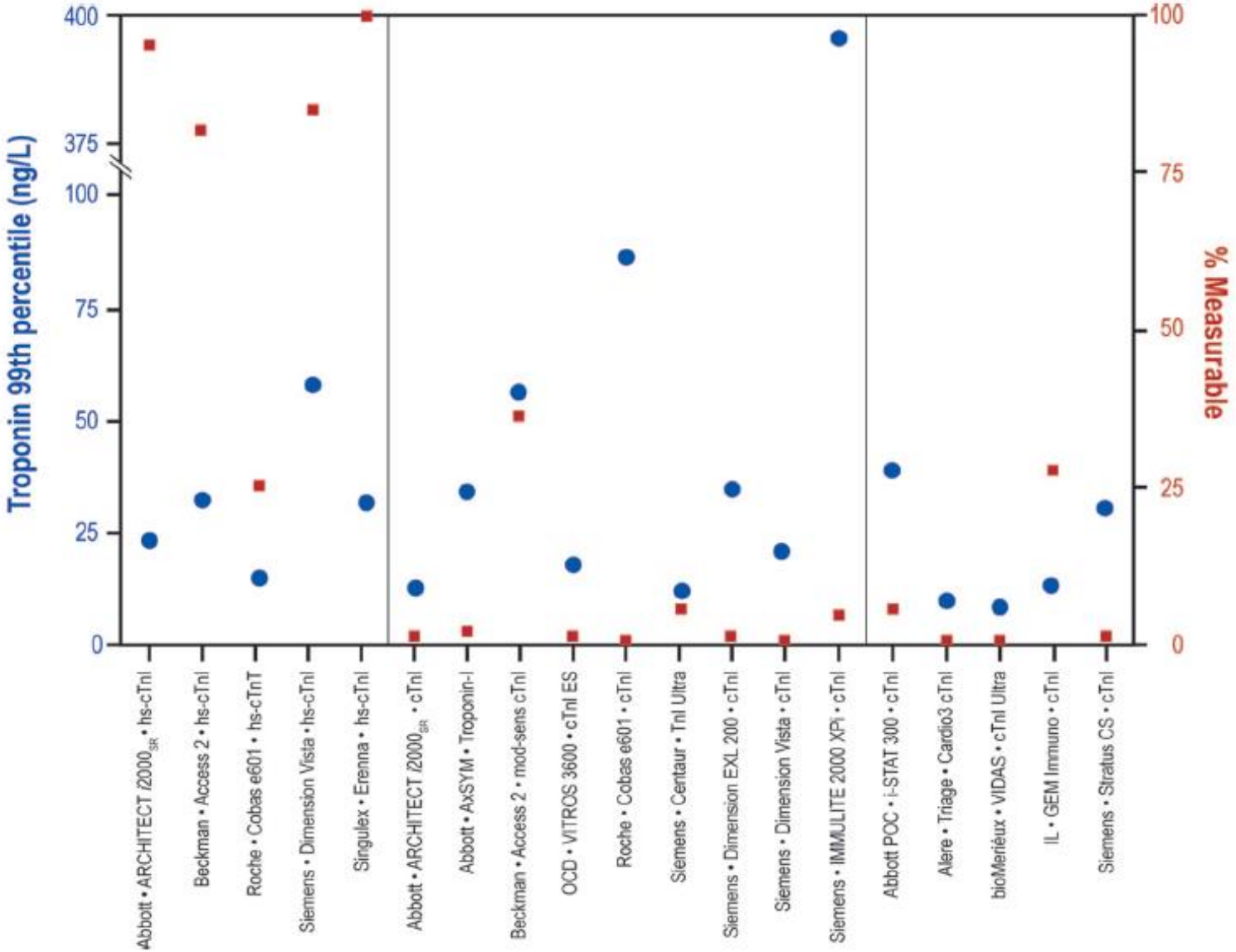


Table 2. Analytical characteristics of hs cardiac troponin assays.

Company/ platform/assay	Cardiac troponin concentration at: LoD,[a] ng/L	99th Percentile, ng/L (CV)[b]	10% CV concentration, ng/L	Amino acid residues of epitopes recognized by capture (C) and detection (D) MAbs
hs-cTnI				
Abbott ARCHITECT[c]	1.2	16 (5.6%)	3.0	C: 24–40; D: 41–49
Beckman Access[c]	2–3	8.6 (10%)	8.6	C: 41–49; D: 24–40
Nanosphere MTP[c]	0.2	2.8 (9.5%)	0.5	C: 136–147; D: MAb PA1010
Singulex Erenna[c]	0.09	10.1 (9.0%)	0.88	C: 41–49; D: 27–41
Siemens Vista[c]	0.5	9 (5.0%)	3	C: 30–35; D: 41–56, 171–190
hs-cTnT				
Roche Elecsys[d]	5.0	14 (8%)	13	C: 136–147; D: 125–131

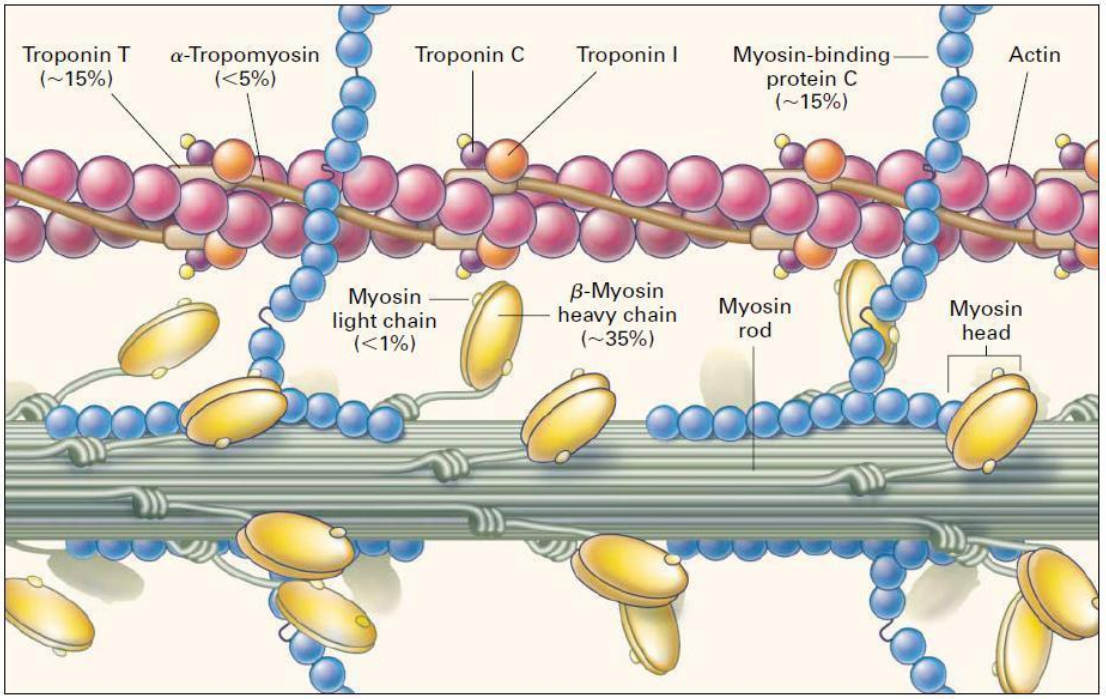
Troponin assays: a new generation



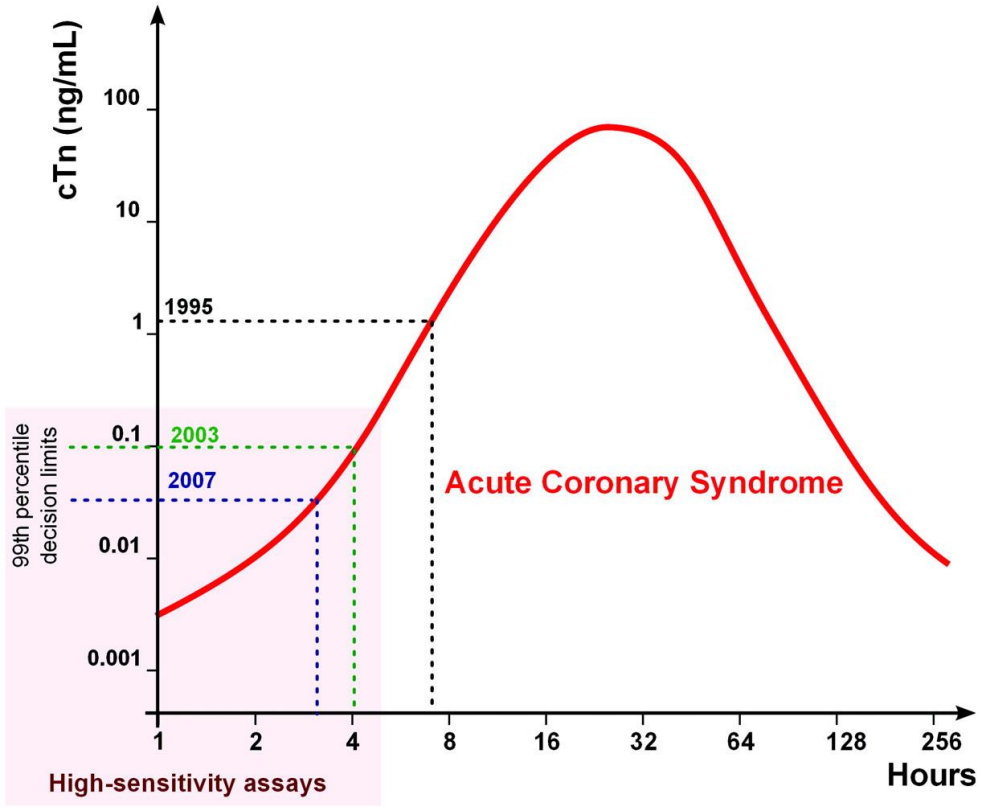
Troponin assays: a new generation

Manufacturer · analyzer · assay	No. of results	Male 99th percentile, ng/L	Female 99th percentile, ng/L
High sensitivity			
Abbott · ARCHITECT *i*2000$_{SR}$ STAT · hs-cTnI	524	36	15
Beckman · Access 2 · hs-cTnI	524	52	23
Roche · Cobas e601 · hs-cTnT	524	20	13
Siemens · Dimension Vista · hs-cTnI	503	81	42
Singulex · Erenna · hs-cTnI	524	36	30
Sensitive contemporary			
Abbott · ARCHITECT *i*2000$_{SR}$ STAT · cTnI	524	20	<9
Abbott · AxSYM · Troponin-I	459	38	29
Beckman · Access 2 · modified-sensitive cTnI	524	48	85
OCD · Vitros 3600 · cTnI ES	524	21	15
Roche · Cobas e 601 · cTnI	524	300	60
Siemens · Centaur · TnI Ultra	523	14	11
Siemens · Dimension EXL 200 · cTnI	524	39	22
Siemens · Dimension Vista · cTnI	523	30	<15
Siemens · Immulite 2000 XPi · cTnI	479	394	451
POC			
Abbott · i-STAT 300 · cTnI	524	37	41
Alere · Triage · Cardio3 cTnI	521	11	12
bioMeriéux · Vidas · cTnI Ultra	524	<10	<10
IL · GEM Immuno · cTnI	524	12	14
Siemens · Stratus CS · cTnI	498	40	<30

Hs-Tn: Clinical Validity



Evolution of the cardiac troponin (cTn) assays and their diagnostic cutoffs.



cTn Assay	Diagnostic cutoff	Implementation
TnI	≥ 1.5 ng/mL	1995
cTnI	> 0.10 ng/mL	2003
TnI-Ultra	> 0.04 ng/mL	2007

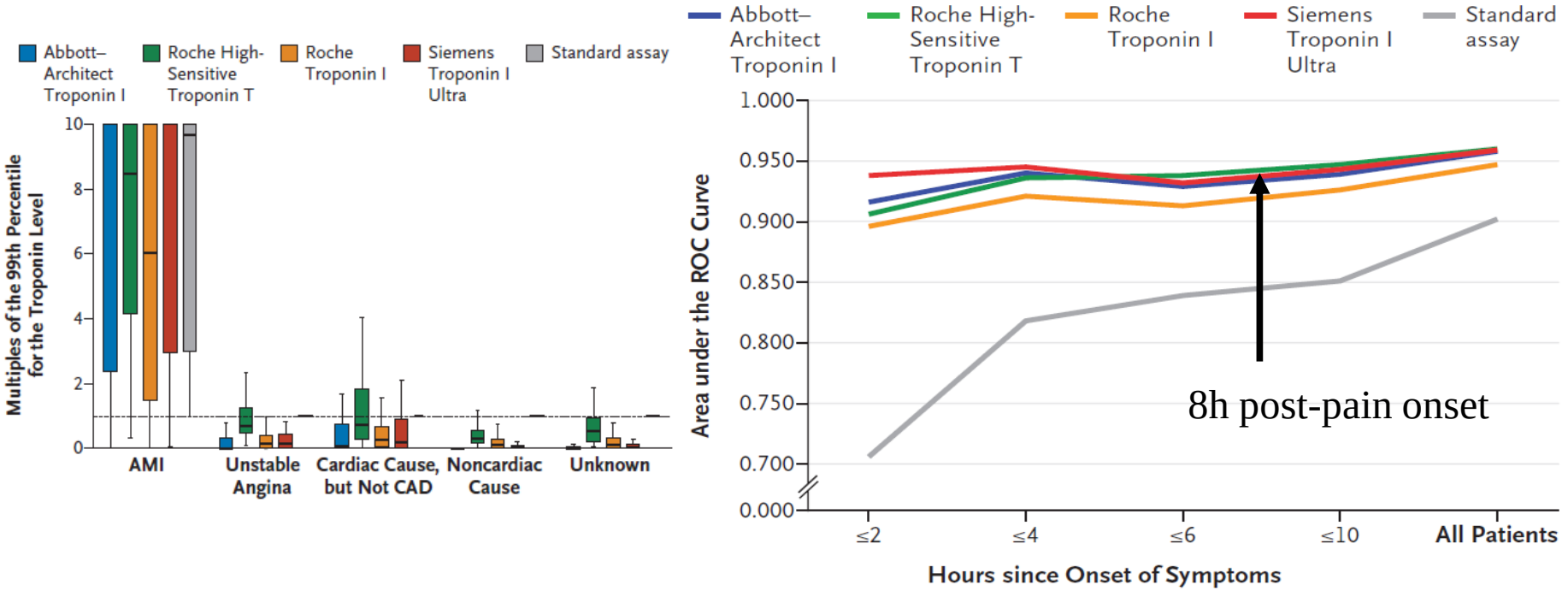
Mahajan V S , and Jarolim P Circulation 2011;124:2350-2354

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays

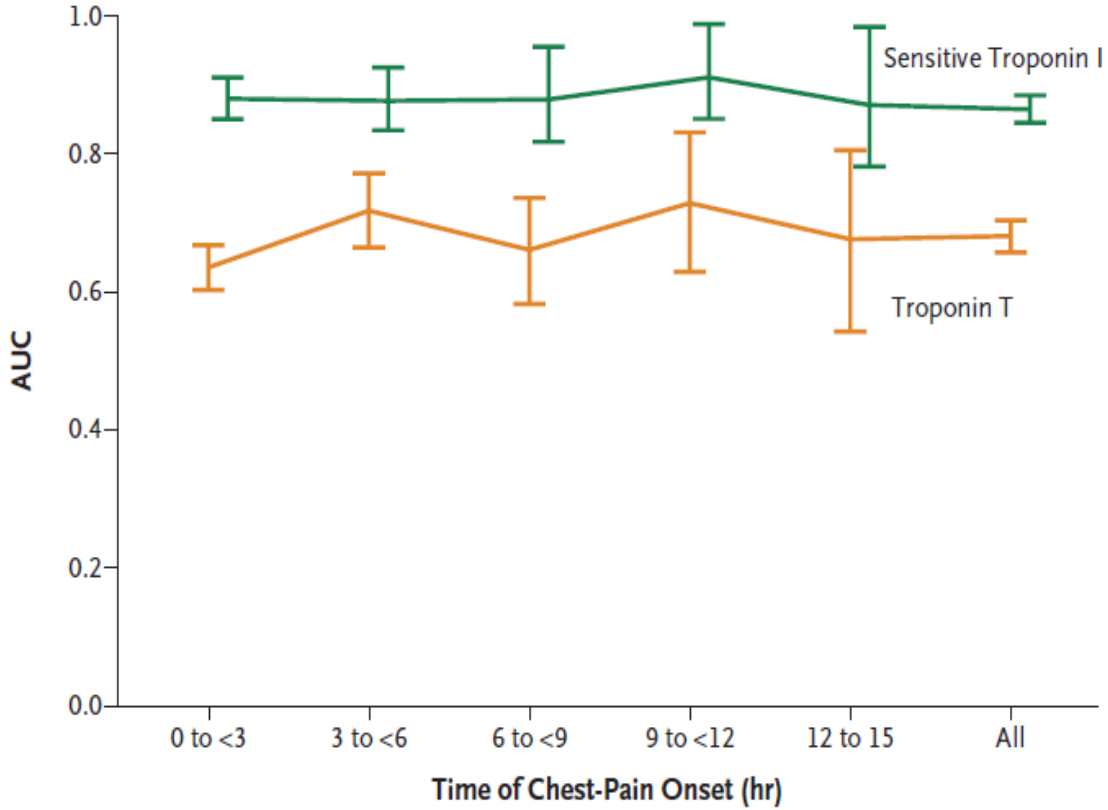
Samples obtained in the emergency department from 718 consecutive patients who presented with symptoms suggestive of acute myocardial infarction



The diagnostic performance of sensitive cardiac troponin assays is excellent, and these assays can substantially improve the early diagnosis of acute myocardial infarction, particularly in patients with a recent onset of chest pain

Reichlin et al. NEJM (2009) 361: 858

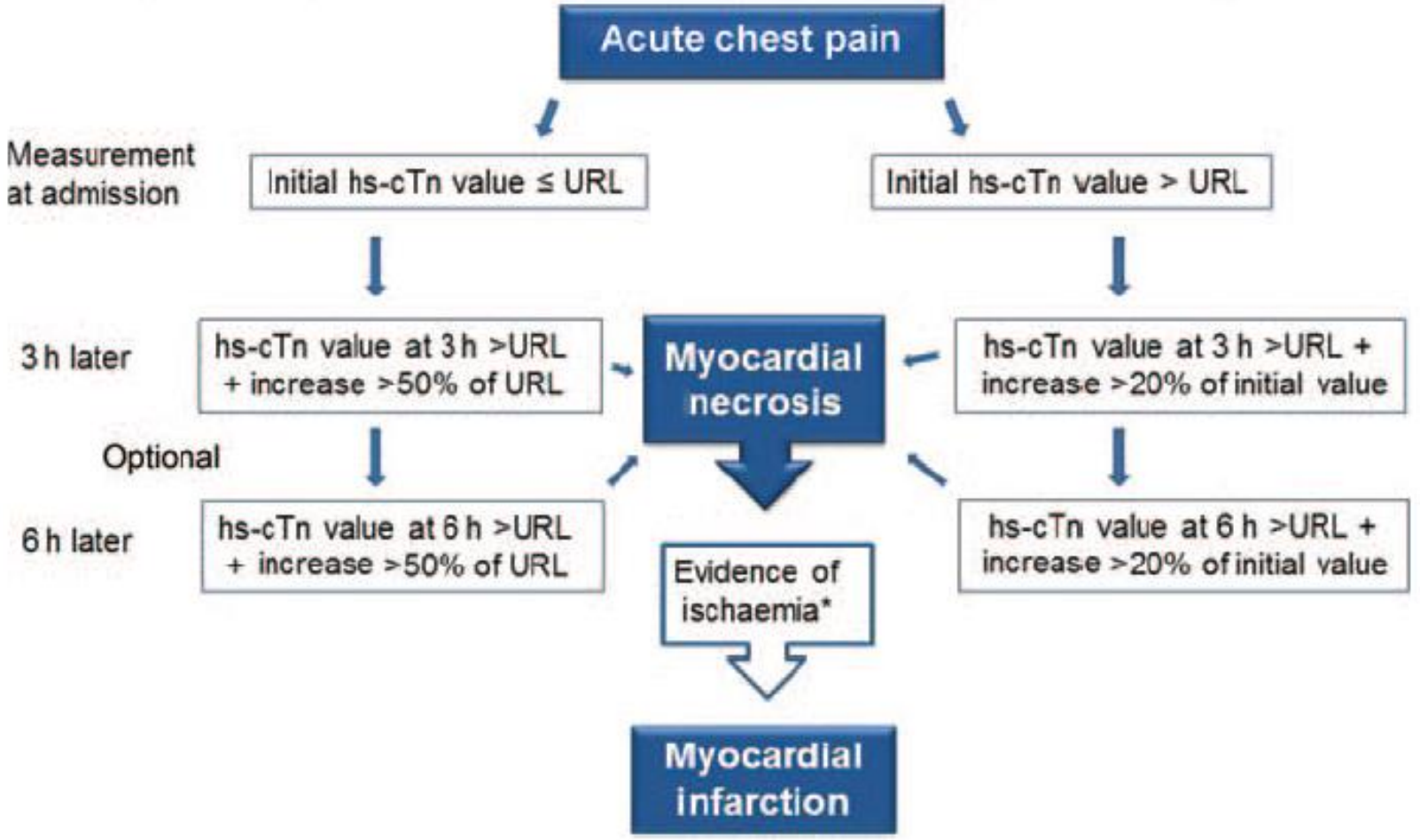
Diagnosis of acute MI (AMI) after pain onset
hs-Tn vs standard assay



Diagnosis of AMI (no.)	227	97	44	29	17	528
Single Determination (no.)						
Sensitive troponin I >0.04 ng/ml	184	100	38	32	25	534
Troponin T >0.03 ng/ml	81	56	19	21	12	305

Keller et al NEJM (2009) 361: 868-877

Rapid early rule-in of AMI with high-sensitivity cardiac troponin



Thygesen et al., 2012

Early Diagnosis of Myocardial Infarction Using Absolute and Relative Changes in Cardiac Troponin Concentrations

In a prospective, international multicenter study, high-sensitivity cardiac troponin (hs-cTn) was measured with 3 novel assays (hs-cTnT, Roche Diagnostics Corp, Indianapolis, Ind; hs-cTnI, Beckman Coulter Inc, Brea, Calif; hs-cTnI, Siemens, Munich, Germany) in a blinded fashion at presentation and after 1 and 2 hours in a blinded fashion in 830 unselected patients with suspected acute myocardial infarction.

Table 2 Area Under the Receiver Operating Characteristic Curves for the Diagnosis of Acute Myocardial Infarction for Absolute and Relative Changes in Cardiac Troponin 1 and 2 Hours After Presentation

		AUC (95% CI)	ROC-Derived Optimal Cutoff Values	Sensitivity	Specificity	PPV	NPV
hs-cTnT	1 h						
	Absolute change (Δ)	0.93 (0.91-0.95)	0.005	84	93	66	98
	Relative change (Δ%)	0.67 (0.64-0.70)	17	60	72	25	92
	Absolute and relative change	0.97 (0.95-0.98)		91	95	73	99
	2 h						
	Absolute change (Δ)	0.95 (0.93-0.97)	0.007	87	93	61	98
	Relative change (Δ%)	0.75 (0.71-0.78)	30	64	83	32	94
	Absolute and relative change	0.98 (0.96-0.99)		94	92	60	99
hs-cTnI Beckman Coulter Inc (Brea, Calif)	1 h						
	Absolute change (Δ)	0.93 (0.91-0.95)	0.005	91	88	54	99
	Relative change (Δ%)	0.65 (0.62-0.68)	27	63	66	22	92
	Absolute and relative change	0.95 (0.93-0.96)		92	90	58	99
	2 h						
	Absolute change (Δ)	0.97 (0.95-0.98)	0.01	94	92	60	99
	Relative change (Δ%)	0.75 (0.71-0.78)	88	60	89	43	95
	Absolute and relative change	0.97 (0.96-0.98)		96	92	58	99
hs-cTnI Siemens (Munich, Germany)	1 h						
	Absolute change (Δ)	0.95 (0.93-0.97)	0.005	94	88	54	99
	Relative change (Δ%)	0.67 (0.64- 0.70)	37	59	74	25	92
	Absolute and relative change	0.95 (0.94-0.97)		89	93	66	98
	2 h						
	Absolute change (Δ)	0.96 (0.94-0.97)	0.01	93	90	55	99
	Relative change (Δ%)	0.73 (0.70-0.77)	80	59	82	30	94
	Absolute and relative change	0.96 (0.94-0.98)		96	92	58	99

AUC = area under the curve; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; NPV = negative predictive value; PPV = positive predictive value; ROC = receiver operating characteristic.

Irfan et al., 2013

Ethical, legal and social implications?

- **Reevaluate potential sources of variation that have not been meaningful with present commercial assay (low-level nonspecific to other serum or plasma constituenté)**
- **Facing to an increase of patients diagnosed with MI.**
- **Societal implications for insurance and employment**
- **Assess the impact on the therapeutical implications**
- **Evaluate the need of hospitalization for those patients with a low clinical probability of ACS and positive hs Troponin**

Cost effectiveness é

- Transends across entire healthcare value chain:
  - Screening
  - Early diagnosis
  - Identification
  - Dosing and Monitoring of treatment
  - Surveillance

  } **Cost Saving Potential**

- Specific features: conception, development, introduction into medical practice, use over time

- Different type and level of evidence needed / available for regulatory approval and reimbursement decisions

Laffont, Brussels, June 2012

Is it Cost-Effective?

Systematic review, meta-analysis and economic modelling of diagnostic strategies for suspected acute coronary syndrome

Sensitivity and specificity (95% predictive interval) were:

77% (29-96%) and 93% (46-100%) for troponin I
80% (33-97%) and 91% (53-99%) for troponin T (99th percentile threshold),
81% (50-95%) and 80% (26-98%) for H-FABP
62% (35-83%) and 83% (35-98%) for myoglobin.

In most scenarios in the economic analysis presentation, high-sensitivity troponin measurement was the most effective strategy with an incremental cost-effectiveness ratio (ICER) of less than the £20,000-30,000/QALY threshold (ICER £7487-17,191/QALY).

Goodacre et al., 2012

Is it Cost-Effective?

Cost-effectiveness of presentation versus delayed troponin testing for acute myocardial infarction

Patients attending hospital with suspected myocardial infarction but a normal or non-diagnostic ECG and no major comorbidities requiring admission

- ✓**In all scenarios tested, presentation high-sensitivity troponin testing was the most effective strategy with an incremental cost-effectiveness ratio below the £20 000/QALY threshold.**

- ✓**Sensitivity analysis showed that including high-sensitivity troponin testing at presentation and 3 h in the analysis makes this the most cost-effective strategy**

Delayed troponin testing is unlikely to be cost-effective compared with high-sensitivity troponin testing at presentation in most scenarios

Thokala et al., 2012

Multi-tasks?

RESEARCH

Implications of lowering threshold of plasma troponin concentration in diagnosis of myocardial infarction: cohort study

2092 consecutive patients admitted with suspected acute coronary syndrome were stratified with a sensitive troponin I assay into three groups (<0.012, 0.012-0.049, and Ó0.050 ε g/L) based on the 99th centile for troponin concentration (0.012 ε g/L; coefficient of variation 20.8%) and the diagnostic threshold (0.050 ε g/L; 7.2%).

What this study adds

- Any increase in troponin concentration above the 99th centile predicts recurrent myocardial infarction and death in patients with suspected acute coronary syndrome
- Accepting greater assay imprecision to permit lowering the diagnostic threshold will identify patients at high risk of recurrent events but will increase the diagnosis of myocardial infarction by 47%
- Prospective trials are necessary to establish whether treatment for myocardial infarction in these patients will reduce risk and improve clinical outcomes

Mills et al., BMJ 2012

Prehospital Troponin T Testing in the Diagnosis and Triage of Patients With Suspected Acute Myocardial Infarction

Proportion of patients with positive prehospital biomarkers or first in-hospital biomarkers according to diagnosis

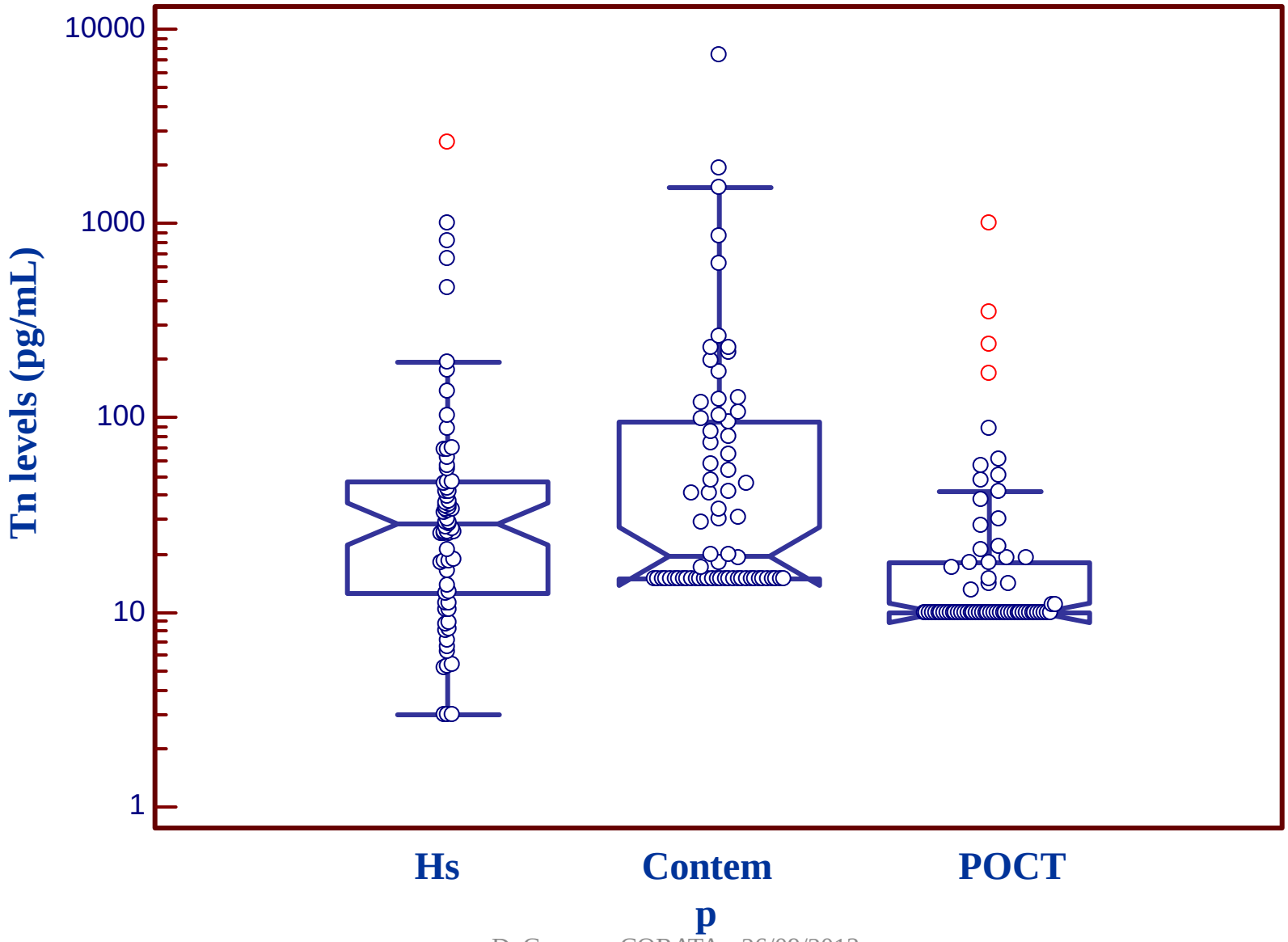
Variable	STEMI (n = 66)	Non-STEMI (n = 119)	BBBMI (n = 23)
Prehospital troponin T positive finding (≥0.10 ng/ml)	21/66 (32%)	36/119 (30%)	6/23 (26%)
First in-hospital troponin T ≥0.10 ng/ml	30/66 (45%)	56/119 (47%)	9/23 (39%)
First in-hospital troponin T ≥0.03 ng/ml	48/66 (73%)	98/119 (82%)	19/23 (83%)

Pre-hospital implementation of quantitative tests, with lower detection limits, could identify most patients with AMI irrespective of ECG changes.

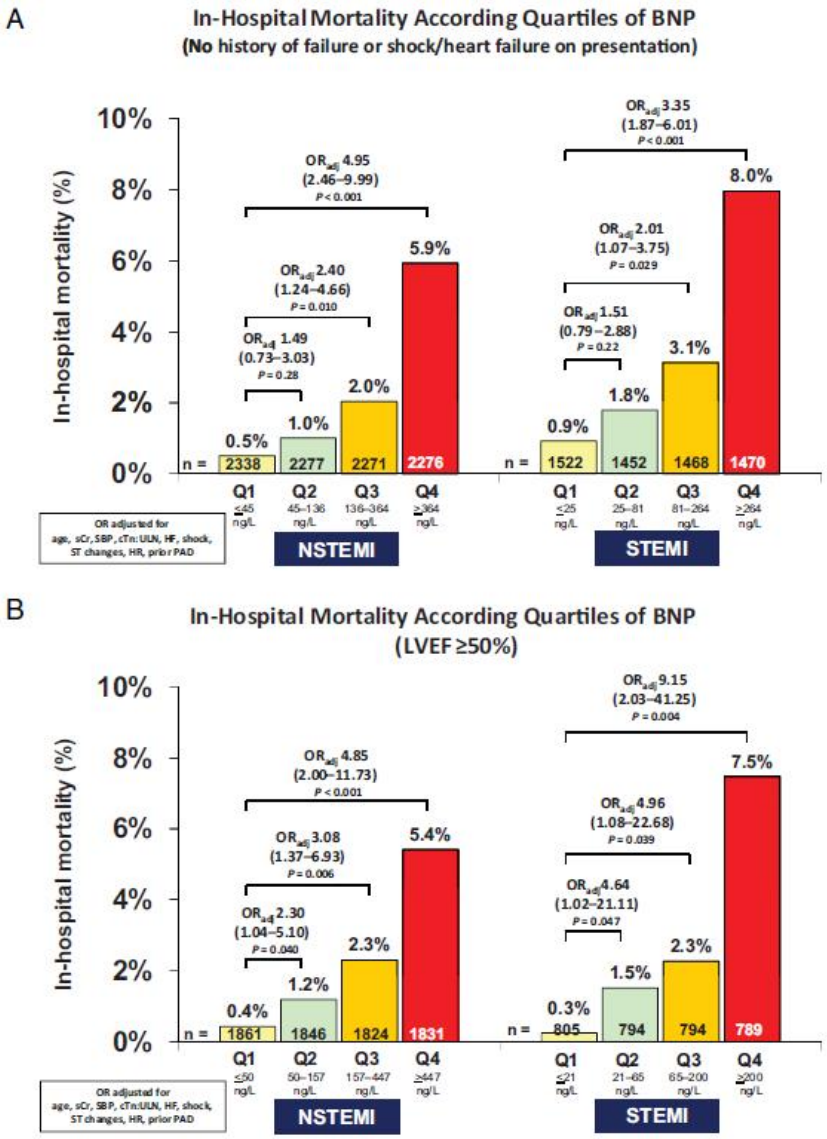
Pre- ? Post- ? Both?

Sorensen et al., 2011

Heart Failure



Association between Natriuretic Peptides and Mortality among Patients Admitted with Myocardial Infarction: A Report from the ACTION Registry®–GWTG™



Scirica et al. Clin Chem, 2013

CME

Prognostic Value of Biomarkers During and After Non–ST-Segment Elevation Acute Coronary Syndrome

Kai M. Eggers, MD, PhD,* Bo Lagerqvist, MD, PhD,* Per Venge, MD, PhD,†
Lars Wallentin, MD, PhD,* Bertil Lindahl, MD, PhD*

Uppsala, Sweden

Table 3 C-Statistics: Incremental Prognostic Value of Biochemical Markers Regarding the Composite of Death or Myocardial Infarction During 5-Year Follow-Up

			Calibration Hosmer-Lemeshow	
	C-Statistics	p Value	Chi-Square	p Value
6 weeks				
Clinical risk indicators	0.66 (0.63–0.72)		7.7	0.46
Clinical risk indicators + cTnI >0.01 μg/l	0.67 (0.62–0.71)	0.88	11.3	0.18
Clinical risk indicators + NT-proBNP (ln)	0.69 (0.65–0.73)	0.03	6.5	0.59
Clinical risk indicators + CRP (ln)	0.67 (0.63–0.72)	0.30	9.4	0.31
Clinical risk indicators + eGFR <75 ml/min/1.73 m^2	0.67 (0.62–0.71)	0.54	10.9	0.21
6 months				
Clinical risk indicators	0.65 (0.60–0.70)		18.3	0.02
Clinical risk indicators + cTnI >0.01 μg/l	0.66 (0.61–0.71)	0.48	10.2	0.25
Clinical risk indicators + NT-proBNP (ln)	0.68 (0.63–0.73)	0.07	10.0	0.26
Clinical risk indicators + CRP (ln)	0.67 (0.62–0.72)	0.16	4.7	0.79
Clinical risk indicators + eGFR <75 ml/min/1.73 m^2	0.65 (0.60–0.70)	0.59	13.0	0.11

Clinical risk indicators include age, sex, diabetes at the respective measurement instance, heart failure at the respective measurement instance, and previous AMI before the respective measurement instance. Abbreviations as in Table 1.

Thanks for your attention !