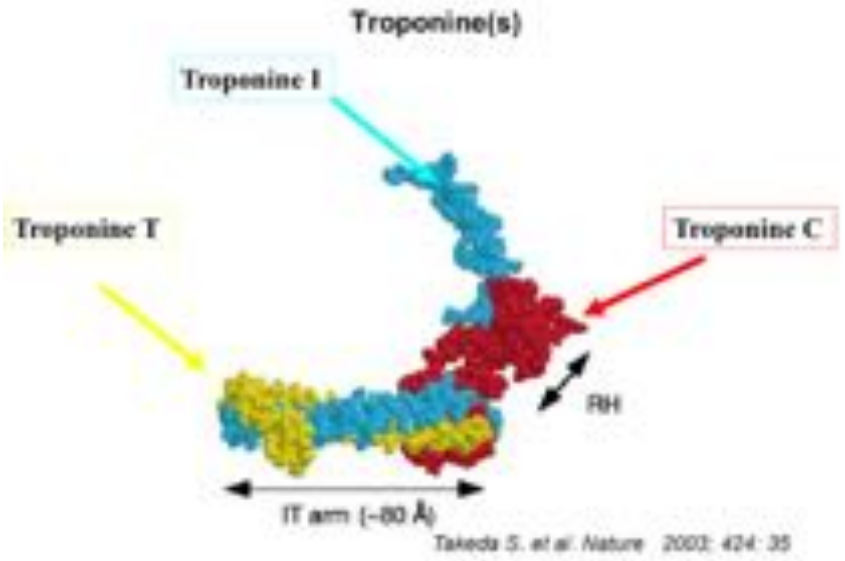
Journée Régionale CNBH IdF

Les Troponines



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DMU BioPhyGen, Hopital Cochin, APHP.Centre – Université de Paris

2 juin 2022

COLLÈGE NATIONAL DE BIOCHIMIE DES HÔPITAUX

Organisme de formation continue n° 82 07 00551 07

www.cnbh.fr

Journée Régionale Ile de France 2022 – 02/06/2022

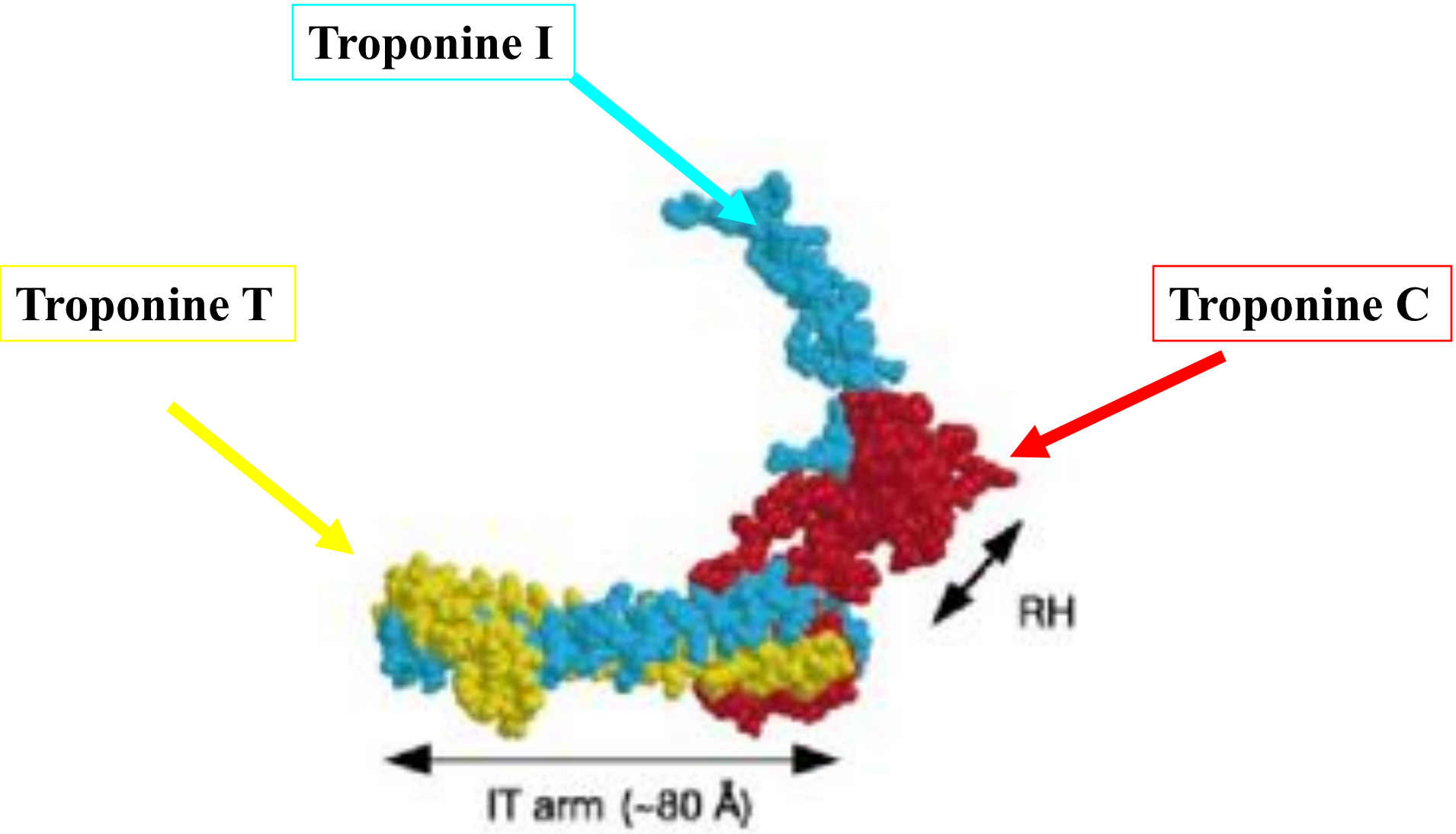
DECLARATION D'INTERET
DANS LE CADRE DE MISSIONS DE FORMATION
RÉALISÉES POUR LE CNBH

Dr Camille Chenevier-Gobeaux.
Exerçant à / au Hopital Cochin, Service de Diagnostic Biologique Automatisé
déclare sur l'honneur

Avoir des intérêts, direct ou indirect (financier), avec les entreprises du diagnostic susceptible de modifier mon jugement ou mes propos, **concernant le sujet et les DMDIV présentés** :

- **Radiometer SAS**
- **Siemens Healthineers**
- **Roche Diagnostics**

Troponine(s)

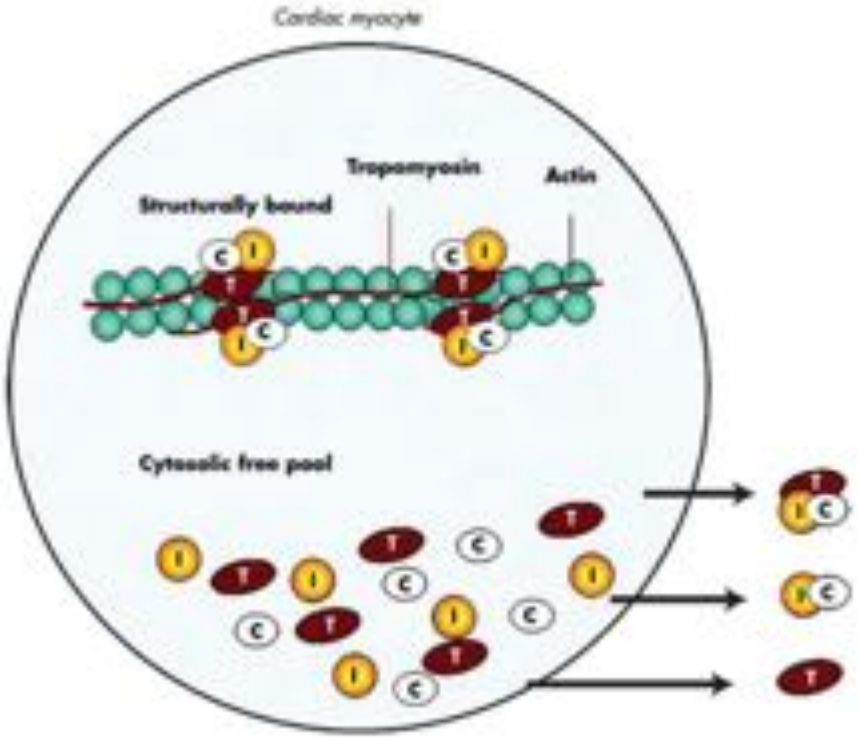


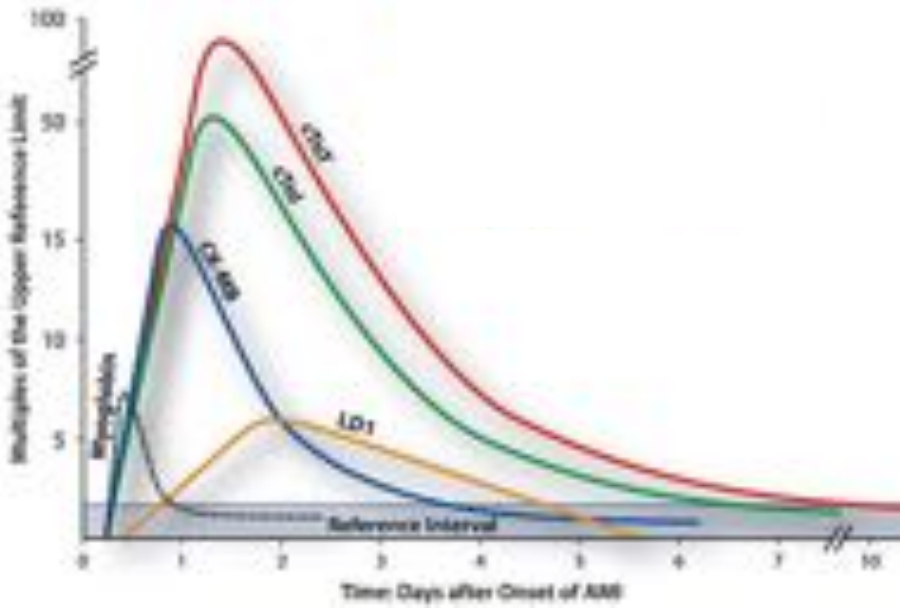
Takeda S. et al. Nature 2003; 424: 35

Qu'est-ce que la troponine ?

Une protéine de structure, pas une enzyme !

Complexe de myofibrille composé de troponine T (TnT), de troponine I (TnI) et de troponine C.





Marqueur de nécrose myocytaire

Agewall, Eur Heart J 2011

Quelques rappels

Deux Isoformes I et T cardiospécifiques

- **90% forme complexée**
- **10% forme libre cytoplasme**

En réponse à une ischémie myocardique:

Mort cellulaire myocardique	~20 minutes
Nécrose complète	2-4 heures
Persistance d'élévation de troponine	≥ 15 jours

Différentes méthodes de dosage, HS ou non, pas standardisés !

Les marqueurs cardiaques de nécrose
« Cahier des charges »

4 qualités :

- être totalement cardio-sélectif, c'est à dire permettre une sensibilité diagnostique optimale.

- être stable dans le sang circulant et ne pas évoluer biochimiquement selon les moments de la maladie.

- être en concentration intra myocardique suffisante pour permettre de détecter des nécroses minimes.

- être facile et rapide à doser, c'est à dire utilisable dans un contexte d'urgence.

Facteurs régulateurs de la cinétique des marqueurs de nécrose

Localisation cellulaire

Protéine cytosolique

passages transmembranaire

Protéines structurales

- **dissociation/dégradation**
- **passage transmembranaire**

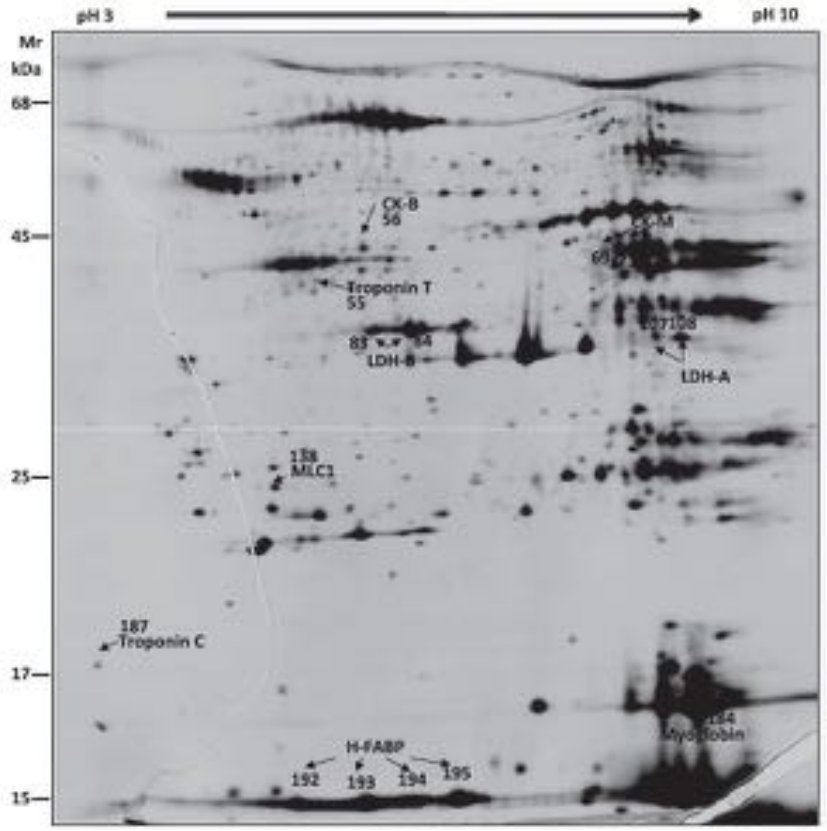
Masse moléculaire

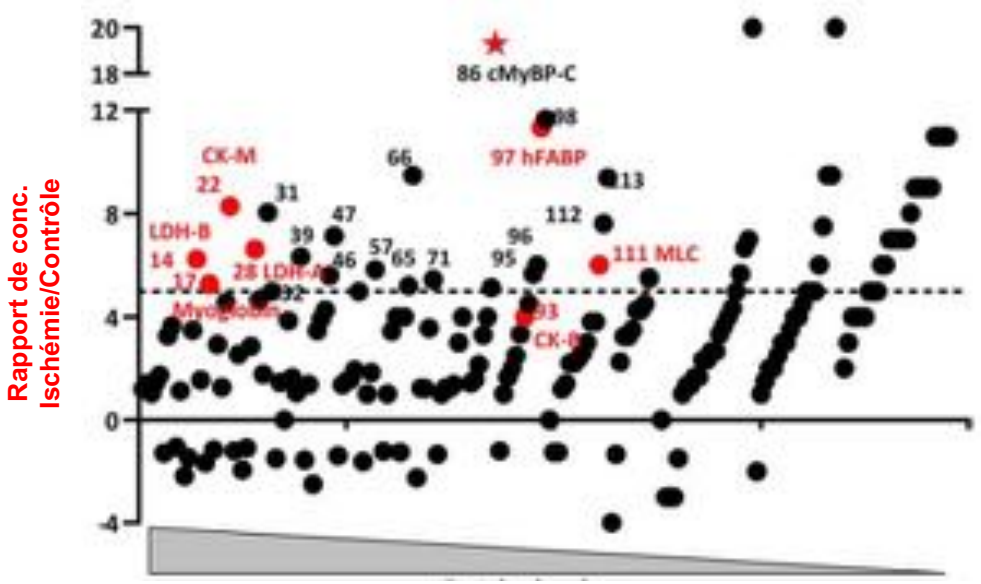
- **facteur minoritaire ne jouant que pour les marqueurs d'une même localisation cellulaire.**

Clairance sanguine

- **Différences des demi-vies : 1/2 vie CK = 10 - 15 h**
  1/2 vie LDH1 = 4 jours
- **catabolisme**
  - **marqueur MM élevée (LDH,CK, …) : foie, pancréas, rein, SRE**
  - **marqueur MM faible (Myoglobine, h-FAPB) : rein, urine +/-**

Protéines cardiaques retrouvées dans le sang coronaire après 5 minutes d'occlusion (modèle murin).

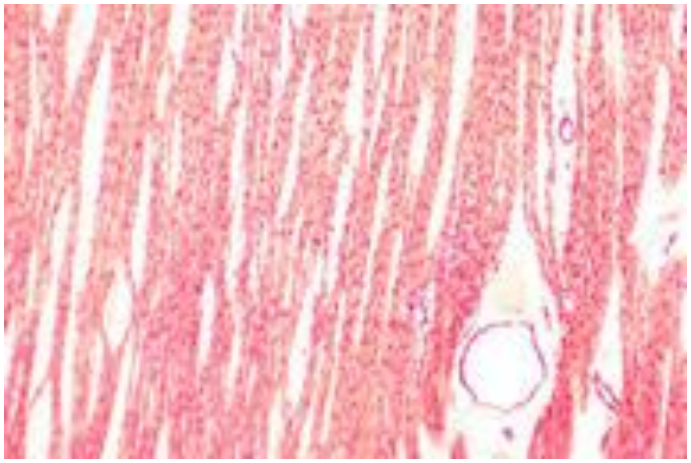




Spot identification	Protein name	Accession number	Molecular mass	Ischemia/control-fold
			kDa	
55	Troponin T	TNNT2_MOUSE	35	4.5
187	Troponin C	TNNC1_MOUSE	18	4.23
56	Creatine kinase B-type	KCRB_MOUSE	42	4.5
69	Creatine kinase M-type	KCRM_MOUSE	43	15.3
71	Creatine kinase M-type	KCRM_MOUSE	43	15.1
83	L-Lactate dehydrogenase B chain	LDHB_MOUSE	36	8.2
84	L-Lactate dehydrogenase B chain	LDHB_MOUSE	36	17.9
107	L-Lactate dehydrogenase A chain	LDHA_MOUSE	36	7.0
108	L-Lactate dehydrogenase A chain	LDHA_MOUSE	36	4.8
138	Myosin light polypeptide 3	MYL3_MOUSE	22	10.1
184	Myoglobin	MYG_MOUSE	17	20.7
185	Myoglobin	MYG_MOUSE	17	22.7
192	Fatty acid-binding protein, heart	FABPH_MOUSE	14	9.4
193	Fatty acid-binding protein, heart	FABPH_MOUSE	14	14.2
194	Fatty acid-binding protein, heart	FABPH_MOUSE	14	11.1
195	Fatty acid-binding protein, heart	FABPH_MOUSE	14	20.4

Myosine Chaine légère	x 111
hFABP	x 97
CKMB	x 93
Myoglobine	x 17
LDH	x 14

Jacquet et al. Mol. Cell Prot 2009; 8: 2687

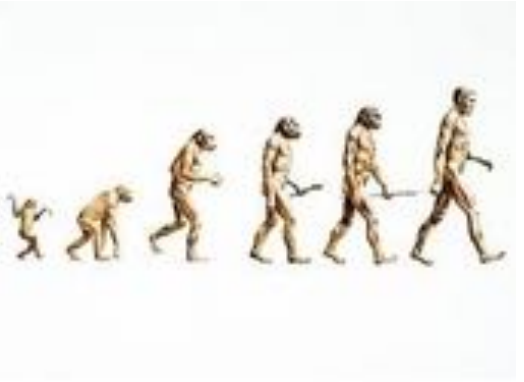


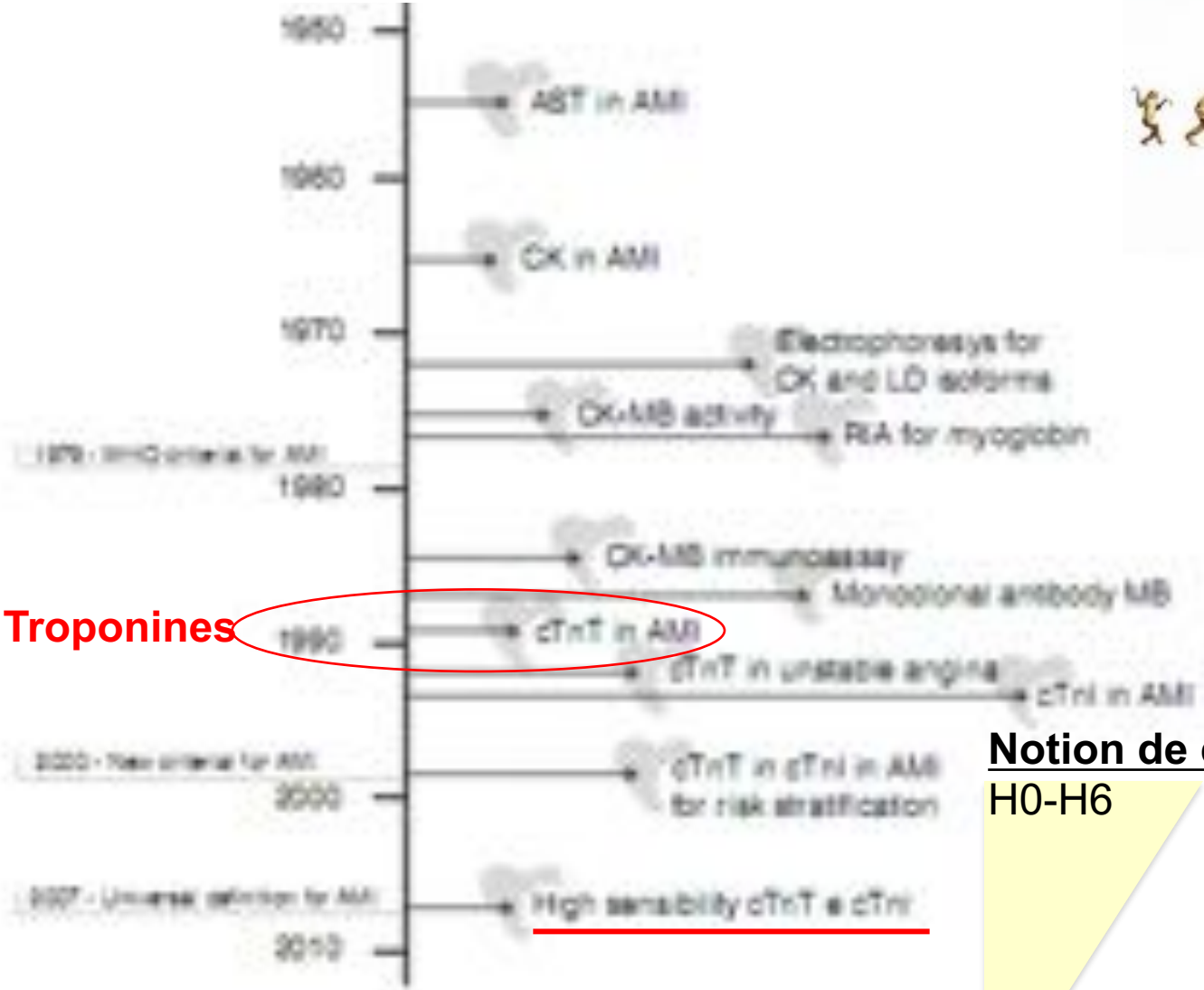
Localisation et concentrations intracellulaires des marqueurs cardiaques dosés en routine biochimique

	localisation		Conc.
	cytoplasme	App. contractile	intracardiaque
TnIc	3-4 %	96-97 %	5 mg/g
TnTc	6-8 %	92-94 %	11 mg/g
CKMB	100%	0 %	1 mg/g
Myoglobine	100%	0 %	24 mg/g

d'après Collinson 2001

Evolution des biomarqueurs du SCA





Troponines

Notion de cinétique :

H0-H6

Sept 2012	**ESC Guidelines**	**H0-H3**
Sept 2015	**ESC Guidelines**	**H0-H1 ?**
		H0 seul ?

+ copeptine ?

SEPT2018 : **injury ≠ infarction**

D'après Clerico A et al., 2009

ESC European Society of Cardiology
European Heart Journal (2020) 00, 1–79
doi:10.1093/eurheartj/ehaa575

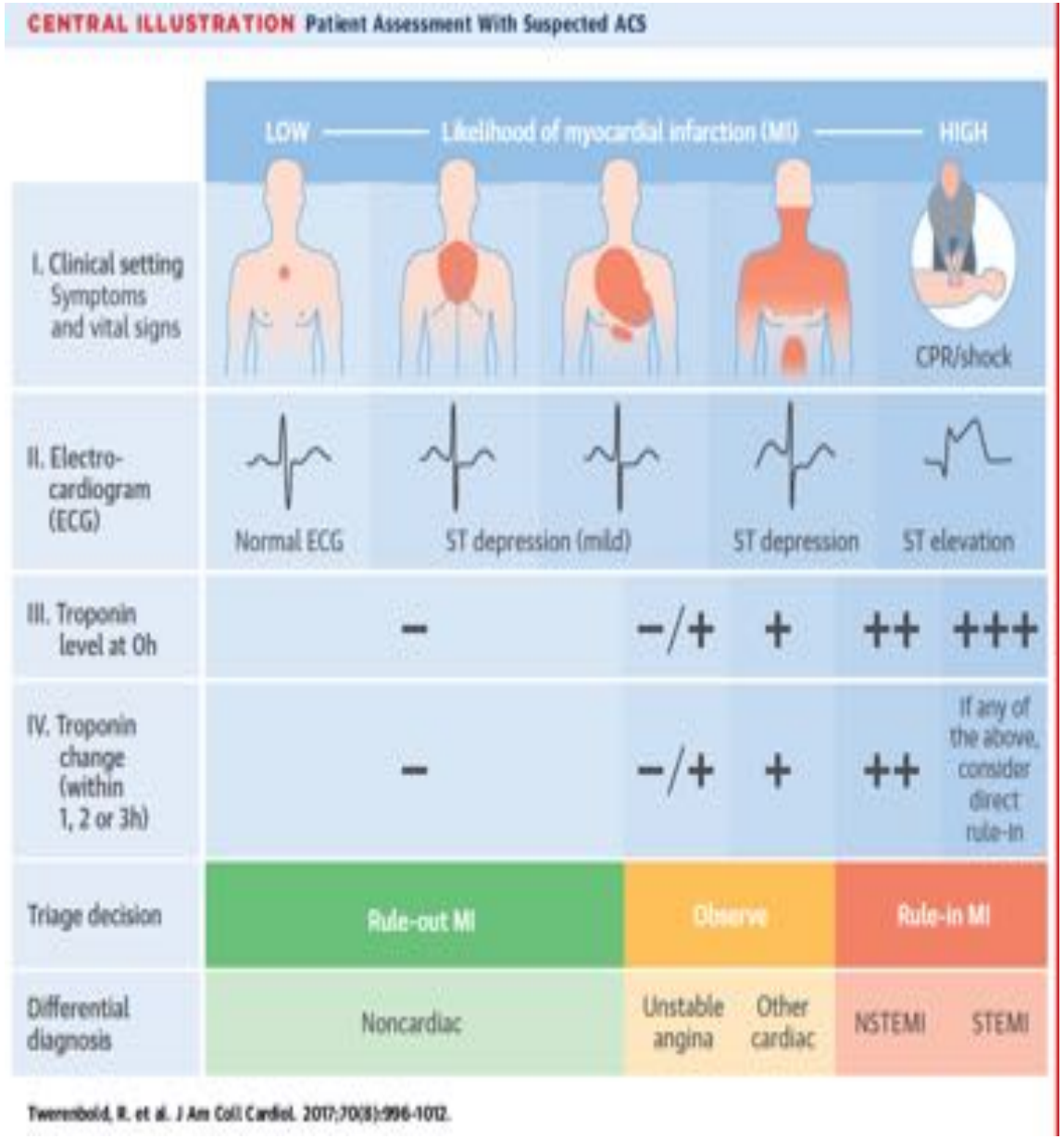
2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

Acute myocardial infarction (AMI) defines cardiomyocyte necrosis in a clinical setting consistent with acute myocardial ischaemia.[1,2] A combination of criteria is required to meet the diagnosis of AMI, namely the detection of an increase and/or decrease of a cardiac biomarker, preferably high-sensitivity cardiac troponin (hs-cTn) T or I, with at least one value above the 99th percentile of the upper reference limit and at least one of the following:

(1) Symptoms of myocardial ischaemia.
(2) New ischaemic ECG changes.
(3) Development of pathological Q waves on ECG.
(4) Imaging evidence of loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.
(5) Intracoronary thrombus detected on angiography or autopsy.

Relation clinique / biologie dans prise en charge du SCA



Définitions de l'IDM ESC 2018

IDM type 1

Rupture de plaque/érosion avec thrombus occlusif

Rupture de plaque/érosion avec thrombus non occlusif

IDM type 2

Athérosclérose et déséquilibre en fourniture ou demande en O_2

Vasospasme ou dysfonction microcirculatoire coronaire

Dissection coronaire non-athéroscléreuse

Déséquilibre isolé en fourniture ou demande en O_2

Pourquoi une 4e définition universelle ?

1. Augmentation du nombre de méthodes de dosages hyper-sensibles (HS)

2. Qui dit sensibilité augmentée dit :

Augmentation du nombre des circonstances où une atteinte myocardique existe comme une entité à part entière, en l'absence de pathologie cardiaque ischémique aigue.

ESC European Society of Cardiology
European Heart Journal (2019) 40, 226–235
doi:10.1093/eurheartj/ehy856

'Ten Commandments' for the Fourth Universal Definition of Myocardial Infarction 2018

ESC European Society of Cardiology
European Heart Journal (2018) 39, 3757–3765
doi:10.1093/eurheartj/ehy655

What's new in the Fourth Universal Definition of Myocardial infarction?

Myocardial injury
=
increase of cTn >99^{e} percentile

Acute
New detection of rise/fall pattern

\+
acute myocardial ischaemia
=
IDM

without
acute myocardial ischaemia

Chronic
Persistent elevation

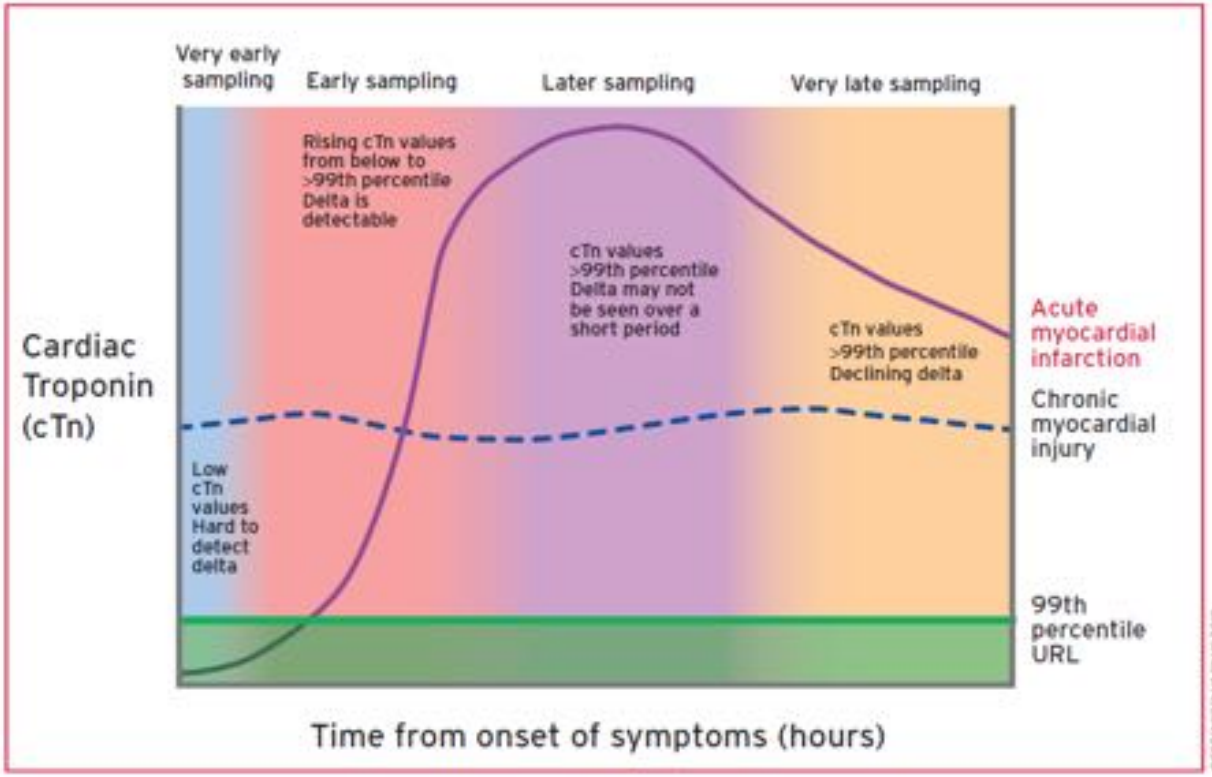
ESC European Society of Cardiology
European Heart Journal (2018) 00, 1–33
doi:10.1093/eurheartj/ehy462

EXPERT CONSENSUS DOCUMENT

Fourth universal definition of myocardial infarction (2018)

Cinétique de troponine +++

- Cardiac troponin: Analytical issues for cardiac troponins; *new Figure 7.*
- Emphasis on the benefits of high-sensitivity cardiac troponin assays.
- Considerations relevant to the use of rapid rule-out and rule-in protocols for myocardial injury and myocardial infarction.
- Issues related to specific diagnostic change ('delta') criteria for the use of cardiac troponins to detect or exclude acute myocardial injury.



Myocardial injury

- Cardiac troponin (cTn) values above 99th percentile of upper reference limit (URL).
- Acute or chronic.
- Different causes.
- Iatrogenic after PCI and CABG.
- Occurrence in the setting of acute myocardial ischaemia denotes myocardial infarction.

Cf diapo suivante

Myocardial infarction

- Type 1: reduced blood supply to myocardium due to coronary atherothrombotic obstruction to blood flow.
- Type 2: reduced oxygen supply or increased demand secondary to other causes unrelated to acute coronary atherothrombosis.
- Type 3: Cardiac event and death before biomarkers measured.
- Type 4a: PCI-related increases of cTn values >5 times the 99th percentile URL together with new myocardial ischaemia evidenced by ECG, imaging or complications leading to reduced coronary blood flow.
- Type 4b: stent/scaffold thrombosis.
- Type 4c: in-stent restenosis at angiography.
- Type 5: CABG-related increases of cTn values > 10 times 99th percentile URL together with new myocardial ischaemia or new loss of myocardial viability.

Table 4 Conditions other than acute type 1 myocardial infarction associated with cardiomyocyte injury (= cardiac troponin elevation)

Tachyarrhythmias
Heart failure
Hypertensive emergencies
Critical illness (e.g. shock/sepsis/burns)
Myocarditis*
Takotsubo syndrome
Valvular heart disease (e.g. aortic stenosis)
Aortic dissection
Pulmonary embolism, pulmonary hypertension
Renal dysfunction and associated cardiac disease
Acute neurological event (e.g. stroke or subarachnoid haemorrhage)
Cardiac contusion or cardiac procedures (CABG, PCI, ablation, pacing, cardioversion, or endomyocardial biopsy)
Hypo- and hyperthyroidism
Infiltrative diseases (e.g. amyloidosis, haemochromatosis, sarcoidosis, scleroderma)
Myocardial drug toxicity or poisoning (e.g. doxorubicin, 5-fluorouracil, herceptin, snake venoms)
Extreme endurance efforts
Rhabdomyolysis

Bold = most frequent conditions.
CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.
*Includes myocardial extension of endocarditis or pericarditis.

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European Heart Journal (2020) 00, 1–79
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The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

Troponine élevée ne veut pas dire coronaire bouchée !

ESC European Society of Cardiology
European Heart Journal (2020) 00, 1–79
doi:10.1093/eurheartj/ehaa575

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Table 3 Clinical implications of high-sensitivity cardiac troponin assays

Compared with standard cardiac troponin assays, hs-cTn assays:
• Have higher NPV for AMI.
• Reduce the 'troponin-blind' interval leading to earlier detection of AMI.
• Result in ~4% absolute and ~20% relative increases 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 hs-cTn 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%) PPV for acute type 1 MI.
• Elevations up to 3-fold the upper reference limit have only limited (50–60%) PPV for AMI 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 (as in MI) from chronic cardiomyocyte damage (the more pronounced the change, the higher the likelihood of AMI).

AMI = acute myocardial infarction; hs-cTn = high-sensitivity cardiac troponin; MI = myocardial infarction; NPV = negative predictive value; PPV = positive predictive value.

Ce qu'on sait déjà sur les troponines :

- **Immunodosages :**
  - **Troponine I, troponine T**
  - **Non standardisés**

  ⇒ Dosages non équivalents, non interchangeables

  ⇒ Valeurs seuils non transposables

Limite

- **Existence récente de méthodes de dosage plus sensibles :**
  - **Détection de faibles concentrations (~ng/L)**
  - **Meilleure précision analytique**

  ⇒ Meilleure sensibilité diagnostique

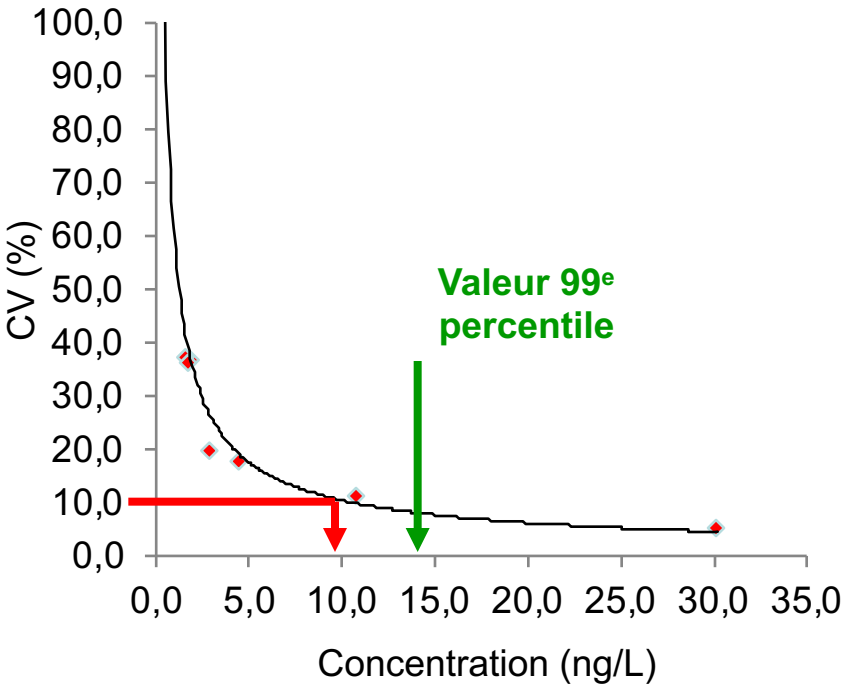
Intérêt

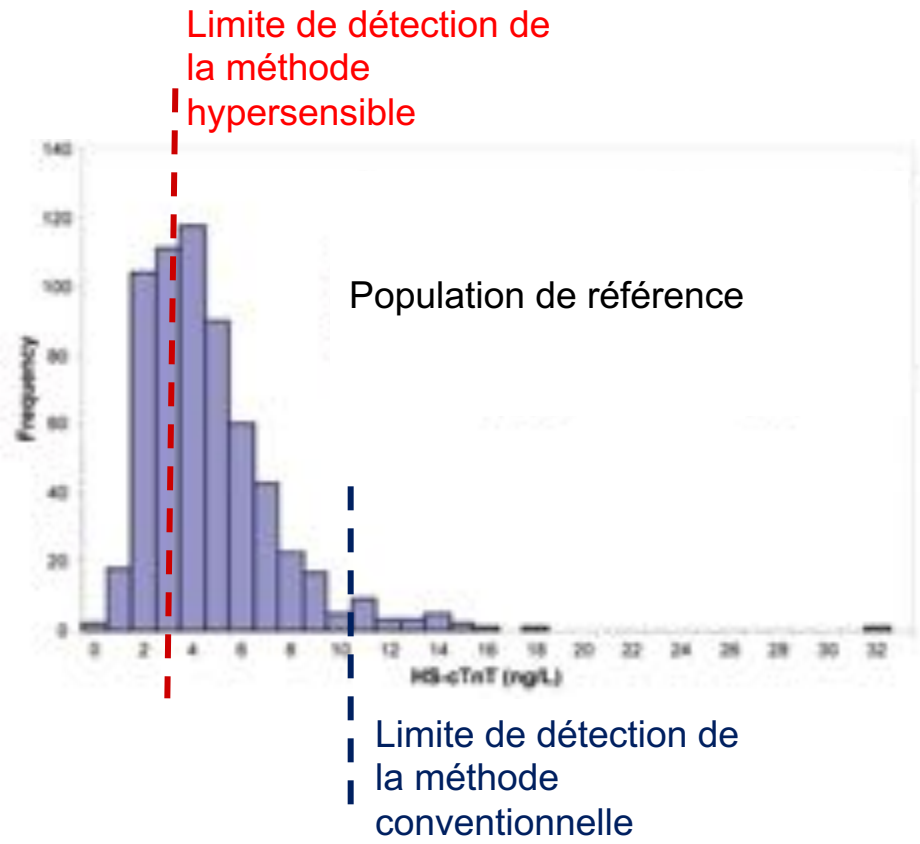
Une méthode hypersensible, c'est :

Précision analytique (CV<10%) au 99e percentile

+

>Plus de 50% population témoin détectable





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The Task Force for the manage
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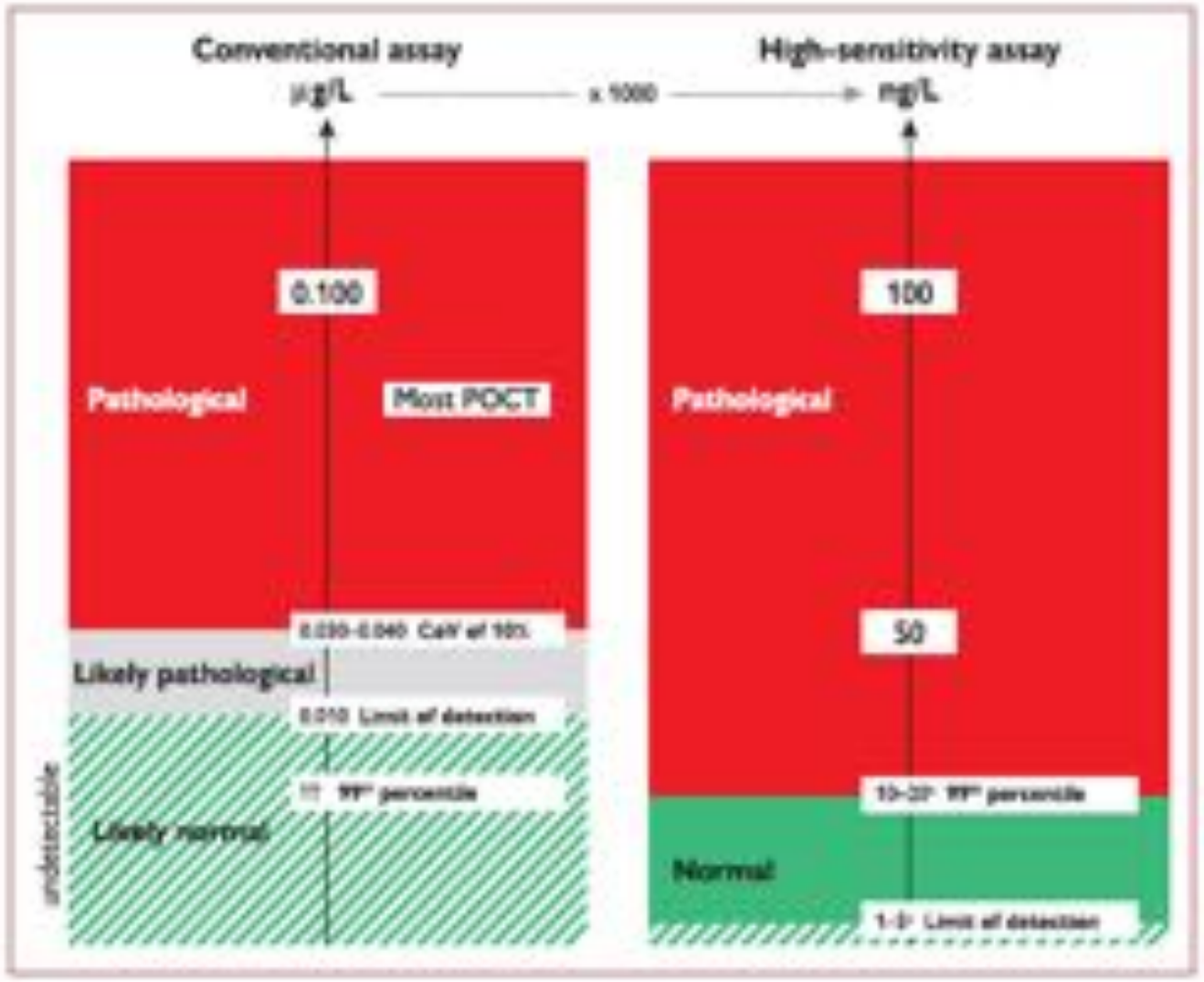

Méthodes de dosages de Troponines

Apple FS & Collinson O., Clin Chem 2012

Absence de standardisation

Conventionnels

Company/platform/assay	LoD,* µg/L	99th Percentile, µg/L (CV)†	10% CV, µg/L
Abbott AxSYM ADV	0.02		
Abbott ARCHITECT	0.009	0.028 (14%)	
Abbott i-STAT	0.02		
Alere Triage	0.05		
Alere Triage Cardio3	0.01		
Beckman Access AccuTnI	0.01	0.04 (1	
bioMérieux Vidas Ultra	0.01		
Mitsubishi PathFast	0.008	0.029 (5.0%)	
Ortho Vitros ECi ES	0.012	0.034 (10%)	0.034
Radiometer AQT90 cTnI	0.009	0.023 (17.7%)	0.039
Radiometer AQT90 cTnT	0.008	0.017 (15.2%)	0.026
Response RAMP	0.03	<0.01 (18.5% at 0.05)	0.21
Roche Cobas h 232 cTnT‡,§	0.05	NA	NA
Roche Elecsys TnT Gen 4	0.01	<0.01	0.030
Roche Elecsys TnI	0.16	0.16 (10%)	0.30
Roche Cardiac Reader cTnT‖	0.03	NA	NA
Siemens Centaur Ultra	0.006	0.04 (8.8%)	0.03
Siemens Dimension RxL	0.04	0.07 (20%)	0.14
Siemens Immulite 2500	0.1	0.2 (NA)	0.42
Siemens Status CS	0.03	0.07 (10%)	0.06
Siemens Vista	0.015	0.045 (10%)	0.04
Tosoh AIA	0.06	<0.06 (NA)	0.09

Temps analytique
~20 minutes

Hyper-sensibles

	Cardiac troponin concentration at:		
	LoD,* ng/L	99th Percentile, ng/L (CV)†	10% CV, ng/L
	1.2	16 (5.6%)	3.0
	2–3	8.6 (10%)	8.6
		2.8 (9.5%)	0.5
Singulex Erenna‡	0.09	10.1 (9.0%)	0.88
Siemens Vista‡	0.5	9 (5.0%)	3
hs-cTnT			
Roche Elecsys‖	5.0	14 (13%)	13

Détection de faibles concentrations (~ng/L)
+
Meilleure précision analytique
=
Meilleure sensibilité diagnostique

Quelques rappels

Nombreuses méthodes de dosage :

- **méthodes HS : n~20**
- **méthodes POCT : n~10**

(liste IFCC, sept 2021)

Méthodes de dosage non standardisées

Table 4 Conditions other than acute type 1 myocardial infarction associated with cardiomyocyte injury (= cardiac troponin elevation)

Tachyarrhythmias
Heart failure
Hypertensive emergencies
Critical illness (e.g. shock/sepsis/burns)
Myocarditis*
Takotsubo syndrome
Valvular heart disease (e.g. aortic stenosis)
Aortic dissection
Pulmonary embolism, pulmonary hypertension
Renal dysfunction and associated cardiac disease
Acute neurological event (e.g. stroke or subarachnoid haemorrhage)
Cardiac contusion or cardiac procedures (CABG, PCI, ablation, pacing, cardioversion, or endomyocardial biopsy)
Hypo- and hyperthyroidism
Infiltrative diseases (e.g. amyloidosis, haemochromatosis, sarcoidosis, scleroderma)
Myocardial drug toxicity or poisoning (e.g. doxorubicin, 5-fluorouracil, herceptin, snake venoms)
Extreme endurance efforts
Rhabdomyolysis

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ESC GUIDELINES

High-Sensitivity* Cardiac Troponin I and T Assay Analytical Characteristics Designated by Manufacturer

IFCC Committee on Clinical Applications of Cardiac Bio-Markers (C-CB) v092021

Company/ Platform/ Assay	LoB (ng/L)	LoD (ng/L)	% CV at 99th Percentile	Conc at 20% CV (ng/L)	Conc at 10% CV (ng/L)	Reference Population N, Ages, Sex	99th Percentile Overall M / F (ng/L)	Specimen Type	Percent Normals Measured ≥ LoD Overall M / F	Statistic Used to Calc 99th Percentile	% RCV	Epitopes Recognized by Antibodies	Country of Package Insert: Version Date
Abbott/Alinity i systems/ Alinity i STAT High Sensitive Troponin-I; commercial-OUS	1.0	1.6	Overall: 4.0% F: 5.3% M: 3.5%	1.3	4.7	Overall n =1531 21-75y F: n=764 21-75y M: n=766 21-73y	Overall: 26.2 F: 15.6 M: 34.2	Lithium heparin (with/without separator), K2 EDTA, K3 EDTA, serum (with/without separator), serum with thrombin-based clot activator	Overall: 85% F: 78% M: 92%	Robust	NP	NP	OUS Only G71275R02 January 2017
Abbott/ ARCHITECT i systems/ ARCHITECT STAT High Sensitive Troponin-I; commercial-US	0.9	1.7	Overall: 4.3% F: 5.0% M: 4.1%	2.3	4.6	Overall n =1531 21-75y F: n=764 21-75y M: n=766 21-73y	Overall: 28 F: 17 M: 35	K2 EDTA	Overall: 85% F: 78% M: 92%	Robust	NP	NP	US FDA 510k September 2019
Abbott/ ARCHITECT i systems/ ARCHITECT STAT High Sensitive Troponin-I; commercial	0.7 to 1.3	1.1	Overall: 4.0% F: 5.3% M: 3.5%	1.3	4.7	Overall n =1531 21-75y F: n=764 21-75y M: n=766 21-73y	Overall: 26.2 F: 15.6 M: 34.2	Lithium heparin (with/without separator), K2 EDTA, K3 EDTA, serum (with/without separator), serum with thrombin-based clot activator	Overall: 85% F: 78% M: 92%	Robust	NP	NP	OUS only: G5-6634/R01 April 2015
Beckman Coulter/ Access 2, DxI/Access hsTnI; commercial – OUS	0.0 to 1.7	1.0 to 2.3	Overall: 3.7% F: 4.2% M: 3.6%	1.0 to 2.3	5.6	Overall n=1089 21-99y F: n=595 M: n=494	Overall: 17.5 F: 11.6 M: 19.8	Heparin plasma	> 50%	Non-Parametric	NP	NP	OUS B52699/ C11140 Sept 2017
Beckman Coulter/ Access 2, /Access hsTnI; commercial – U.S.; LiHep plasma	0.0 to 0.8	1.0 to 2.0	Overall: 3.7% F: 4.2% M: 3.6%	0.9 to 2.3	4.1	Overall n=1089 21-99y F: 595 M: 494	Overall: 17.5 F: 11.6 M: 19.8	Heparin plasma	> 50%	Non-Parametric	NP	NP	US B52699/ C09449 June 2018

Company/ Platform/ Assay	LoB (ng/L)	LoD (ng/L)	% CV at 99th Percentile	Conc at 20% CV (ng/L)	Conc at 10% CV (ng/L)	Reference Population N, Ages, Sex	99th Percentile Overall M / F (ng/L)	Specimen Type	Percent Normals Measured ≥ LoD Overall M / F	Statistic Used to Calc 99th Percentile	% BCV	Epitopes Recognized by Antibodies	Country of Package Insert: Version Date
Beckman Coulter/ Access 2, (Access hsTnI; commercial – U.S.: Serum	0.0 to 0.8	1.0 to 2.0	Overall: 6.0% F: 6.9% M: 5.8%	0.9 to 2.3	4.1	Overall n=1088 21-99y F: 595 M: 493	Overall: 18.2 F: 11.8 M: 19.7	Serum	> 50%	Non-Parametric	NP	NP	US B52699/ C09449 June 2018
Beckman Coulter/ Dxl, Access hsTnI; commercial – U.S.: LiHep plasma	0.0 to 1.7	1.5 to 2.3	Overall: 5.2% F: 5.6% M: 5.0%	1.2 to 2.3	5.6	Overall n=1088 21-99y F: 593 M: 495	Overall: 17.9 F: 14.9 M: 19.8	Heparin plasma	> 50%	Non-Parametric	NP	NP	US B52699/ C09446 June 2018
Beckman Coulter/ Dxl, Access hsTnI; commercial – U.S.: Serum	0.0 to 1.7	1.5 to 2.3	Overall: 6.2% F: 6.5% M: 6.1%	1.2 to 2.3	5.6	Overall n=1085 21-99y F: 592 M: 493	Overall: 18.1 F: 13.6 M: 19.8	Serum	> 50%	Non-Parametric	NP	NP	US B52699/ C09446 June 2018
bioMérieux VIDAS High Sensitive Troponin I; commercial	1.9	3.2	7.0%	4.9	NP	Overall n = 815 41-80y F: 368 41-80y M: 447 41-80y	Overall: 19 F: 11 M: 25	Serum or heparin plasma	NP	NP	NP	C: 41-49, 24-40 D: 87-95	France Dec 23rd 2015
ET Healthcare Pylon hsTnI assay; China FDA approved	0.8	1.2 – 1.4	10%	2	10	Overall n =863 15-91y F: 438 M: 425 (AACC Universal Sample Bank)	Overall: 27 F: 21 M: 27	EDTA plasma, EDTA whole blood, serum	Overall: 91% F: 89% M: 94%	Non-Parametric	NP	C: 27-40 D: 41-49	China, 2018

Company/ Platform/ Assay	LoB (ng/L)	LoD (ng/L)	% CV at 99th Percentile	Conc at 20% CV (ng/L)	Conc at 10% CV (ng/L)	Reference Population N, Ages, Sex	99th Percentile Overall M / F (ng/L)	Specimen Type	Percent Normals Measured ≥ LoD Overall M / F	Statistic Used to Calc 99th Percentile	% RCV	Epitopes Recognized by Antibodies	Country of Package Insert: Version Date
ET Healthcare Pylon hsTnT; research	0.4	0.8	4%	1	4	Overall n=863 15-91y F: 438 M: 425 (AACC Universal Sample Bank)	Overall: 13 F: 13 M: 14	EDTA whole blood, EDTA plasma, serum	Overall: 94% F: 93% M: 97%	Non-Parametric	NP	C: 119-136, D: 132-151	China, 2018
Fujirebio Lumipulse G G1200 and G600II hsTnI	1.2	2.1	44.6%	NP	7.3	Overall n=1018, 18-90 years F: 428 M: 590	Overall: 28.6 F: 22.4 M: 32.9 Serum Overall: 26.9 F: 21.4 M: 29.4 Li-Hep plasma Overall: 29.6 F: 27.8 M: 32.6	Red top serum, serum separator tube, rapid clotting tubes; Disodium EDTA*, Dipotassium EDTA*, Lithium heparin, Sodium heparin, Sodium Citrate, PST with lithium heparin	Overall: 68.3% Serum: 68.1% Li Heparin Plasma: 65.0%	Robust	NP	NP	English IFI60030, Feb 2017 Ver.01
LSI Medience (formerly Mitsubishi) PATHFAST cTnI, commercial	NP	1	< 6%	2	3.1	Overall n =474 18-86y F: 236 M: 238	Overall: 15.48 M: 16.91 F: 11.46	Heparin-Na, heparin-Li or EDTA whole blood or plasma	Overall: 76.3%	Non-Parametric	NP	C: 41-49 D: 71-116, 163-209	WW except US & Japan; Ver.5, Apr.2014
LSI Medience (formerly Mitsubishi) PATHFAST hs-cTnI /PATHFAST cTnI-II	1.23	2.33	6.1%	4	15	Overall n=734 Age >18 F: 352 M: 382	Overall: 27.9 F: 20.3 M: 29.7	Heparin-Na, heparin-Li or EDTA whole blood or plasma	Total: 66.3% F: 52.8% M: 78.8%	Non-Parametric	ND	C:41-49 D: 71-116, 163-209	hs-cTnI : WW except US Ver.1, May 2018

Company/ Platform/ Assay	LoB (ng/L)	LoD (ng/L)	% CV at 99th Percentile	Conc at 20% CV (ng/L)	Conc at 10% CV (ng/L)	Reference Population N, Ages, Sex	99th Percentile Overall M / F (ng/L)	Specimen Type	Percent Normals Measured ≥ LoD Overall M / F	Statistic Used to Calc 99th Percentile	% RCV	Epitopes Recognized by Antibodies	Country of Package Insert: Version Date
Ortho/ VITROS/ hsTroponin I; commercial	0.14 to 0.51	0.39 to 0.66	<10%	1.23	1.99	Overall n =952 22-91y F: 466 M: 466	Serum Overall: 11 F: 9 M: 12 LiHep Plasma Overall: 11 F: 9 M: 13	Serum; Lithium Heparin Plasma	>50%	Non-Parametric	NP	C: 87-91 D: 24-40, 41-49	CE Mark; March 2019
Quidel/Alere TriageTrue hs-cTnI	0.4 (plasma) 0.5-0.8 (whole blood)	0.7 – 1.6 (plasma) 1.5-1.9 (whole blood)	5.0 – 5.9% at 21 ng/L (plasma) 5.9 – 6.5% at 22 ng/L (whole blood)	2.1 – 3.6 (plasma) 2.8 (whole blood)	4.4 – 8.4 (plasma) 5.8 – 6.2 (whole blood)	Overall n = 789 F: 391 M: 398	Overall: 20.5 F: 14.4 M: 25.7	EDTA whole blood or plasma	Overall: ≥ 50%	NP	NP	NP	hs-cTnI: WW except US April 2020
Roche/ cobas e601, e602, e411/cTnT-hs 18-min; commercial	2.53; (1.58 for e411)	3.16; (2.54 for e411)	<10%	1.72 (4.01 for e411)	3.94 (7.45 for e411)	Overall n=533 20-71y F: 49.7%	Overall:14 F: 9 M:16	Serum, plasma: EDTA, heparin	Overall: 71.5%	NP	NP	C: 125-131 D: 136-147	EU (Product number 09315322190)
Roche/ cobas e601, e602, e411/ cTnT-hs STAT; commercial	2.36; 2.14 for e411	2.85; 3.25 for e411	<10%	1.21 (2.88 for e411)	2.92 (6.74 for e411)	Overall n =533 20-71y F: 49.7%	Overall: 14 F: 9 M: 16	Serum, plasma: EDTA, heparin	Overall: 58.9%	NP	NP	C: 125-131 D: 136-147	EU (Product number 09315349190)
Roche/ cobas e601/ e402 cTnT-hs 18-min and STAT; commercial	18 min: 2.21 9 min: 1.91	18 min: 2.97 9 min: 2.72	<10%	18 min: 2.30 9 min: 1.00	18 min: 5.40 9 min: 3.22	Overall n =533 20-71y F: 49.7%	Overall: 14 F: 9 M: 16	Serum, plasma: EDTA, heparin	Overall: 57.4%	NP	NP	C: 125-131 D: 136-147	EU (Product number 09315357190)
Roche/ cobas e601, e602, E17D/ TnT Gen 5 STAT *specified value; **including e411 data; commercial	2.6*; 3 for e411	3*; 5 for e411	<10%	6**	11**	Overall n =1301 21-89y F: 50.4%	Overall: 19 F: 14 M: 22	Plasma heparin	Overall: 55.1%	NP	NP	C: 125-131 D: 136-147	USA, v1

Company/ Platform/ Assay	LoB (ng/L)	LoD (ng/L)	% CV at 99th Percentile	Conc at 20% CV (ng/L)	Conc at 10% CV (ng/L)	Reference Population N, Ages, Sex	99th Percentile Overall M / F (ng/L)	Specimen Type	Percent Normals Measured ≥ LoD Overall M / F	Statistic Used to Calc 99th Percentile	% RCV	Epitopes Recognized by Antibodies	Country of Package Insert: Version Date
Siemens ATELLICA High-Sensitivity TnI (TnIH), US & OUS; commercial	0.50	1.6	<4.0%	2.50	<6.0	Overall n = 2001 22-91y F: 1007 M: 994	Overall: 45.4 F: 38.6 M: 53.5	Li Hep Serum	Overall: 75% F: 62% M: 89%	Non-Parametric	NP	C: 41-50, 171-190 D: 29-34	CE-marked March 2017 FDA 510k July 2018
Siemens ATELLICA VTLi hs-cTnI	0.55	1.2 (plasma) 1.6 (whole blood)	6.5% (plasma) 6.1% (whole blood)	2.1 (plasma) 3.7 (whole blood)	6.7 (plasma) 8.9 (whole blood)	Overall n = 694 18-91y F: 331 M: 363	Overall: 22.9 F: 16.5 M: 27.1	Li Hep whole blood and plasma, capillary blood	Overall: 84% F: 80% M: 87%	Non-Parametric	NP	C: 41-49 D: 2 Abs in range 20-100 cTnC Ab	CE-marked March 2021
Siemens ADVIA Centaur XPr XPT/CP* High-Sensitivity TnI (TNIH), US & OUS; commercial	0.50	1.6	<4.9%	2.50	<6.0	Overall n = 1990 22-91y F: 1006 M: 984	Overall: 46.5 F: 39.6 M: 58.0	Li Hep Serum	Overall: 72% F: 57% M: 86%	Non-Parametric	NP	C: 41-50, 171-190 D: 29-34	CE-marked March 2017 / *March 2021 FDA 510k July 2018
Siemens Dimension VISTA High Sensitivity TnI (TNIH), OUS; commercial	1.0	2.0	<5.0%	3.0	10.0	Overall n = 2021 22-91y F: 1017 M: 1004	Overall: 58.9 F: 53.7 M: 78.5	Li Hep Serum (OUS only)	Overall: 81.8% F: NP M: NP	Non-Parametric	NP	D: 41-50 171-190 C: 29-34	CE-marked 2017 FDA 510k March 2019
Siemens Dimension Exl, High Sensitivity TnI (TNIH), OUS; commercial	1.1	2.7	<5.0%	4.0	12.0	Overall n = 2020 22-91y F: 1017 M: 1003	Overall: 60.4 F: 51.4 M: 76.2	Li Hep Serum (OUS only)	Overall: 51.5% F: NP M: NP	Non-Parametric	NP	D: 41-50 171-190 C: 29-34	CE-marked 2017 FDA 510k May 2019
Tosoh CL AIA-PACK cTnI; commercial	NP	1.61	NP	2.3	5.6	Overall n = 328 Asian/Caucasian	Overall: ≤ 24 (Asian) ≤ 31 (Caucasian)	Li Hep, EDTA Serum	NP	NP	NP	NP	CE-marked EU CL-cTnI-020/118 For use in Europe and Asia

LoB, limit of blank; LoD, limit of detection; NP, not provided; C, capture antibody; D, detection antibody; M, male; F, female; Conc, concentration; WW, worldwide; OUS, outside United States; RCV, reference change value. All data have been listed as provided by the manufacturer. *Please note manufacturers may have submitted assays they claim to be 'high sensitivity' that do not meet the IFCC requirements of: a) ≤10% CV at the 99th percentile and b) ≥ 50% measurable concentrations ≥ LoD for both males AND females.

Dosage de la troponine au laboratoire

- Hautement robotisée
- Méthodes HS de + en + déployées

Efficacité pour un délai de rendu <1h ???

Immuno-Dosages
Hors du laboratoire

«Savonnettes »
Near Patient Testing

- Immunochromatographie
- Sang total

Semi-qualitatif

Quantitatif

Automate délocalisé
Point-of-Care Testing

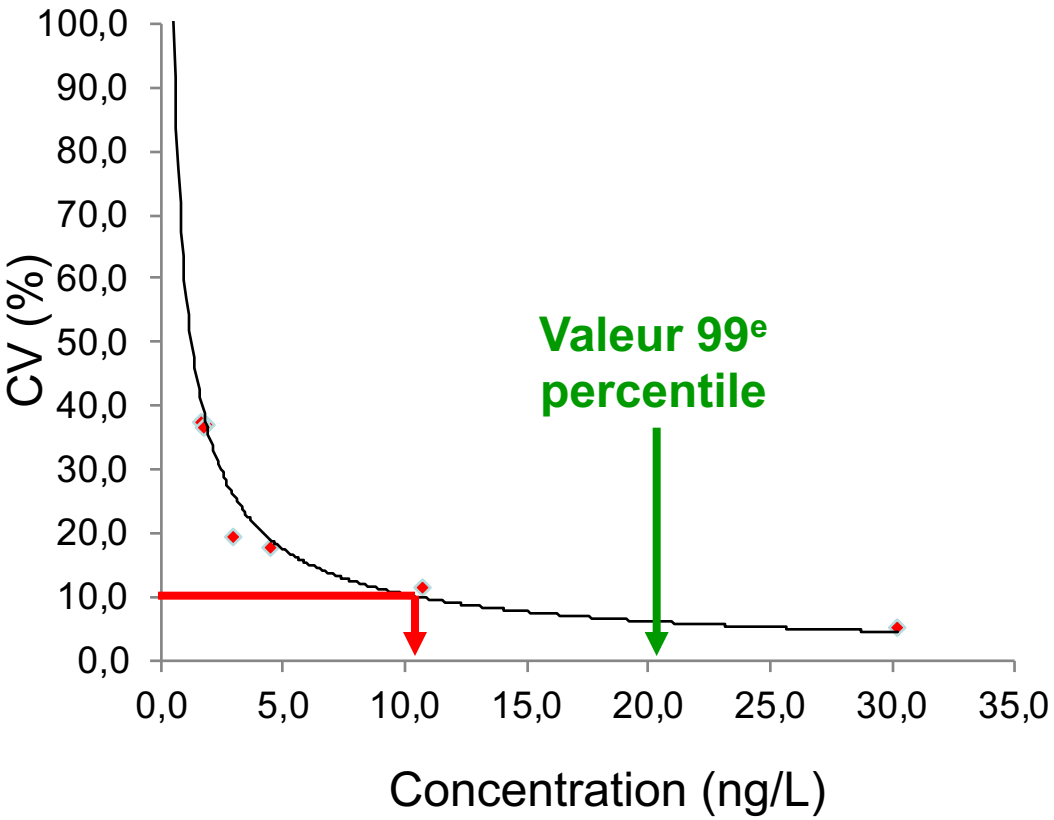
- Immuno-dosage
- Sang total

Biologie délocalisée : hypersensible ou pas ?

- TriageMeter®

- Pathfast™

- Atellica® VTLi



⇒ Rapidité

⇒ Maitrise de l'étape pré-analytique ?

Pathfast™ :

- ✓ **Sang total**
- ✓ **14 minutes**
- ✓ **Précision au 99e percentile**
- ✓ **>50% population détectable**

Etudes de validation ?
Seuils ?

Précision au 99ème percentile: La courbe établie à partir des dilutions de HS-cTnI a permis d'établir la valeur du CV10% à 10,6 ng/L (Figure 2). Cette valeur est inférieure à la valeur du 99ème percentile annoncée par le fabricant. La précision obtenue au 99ème percentile (20,5 ng/L) est retrouvée à 6,1%.

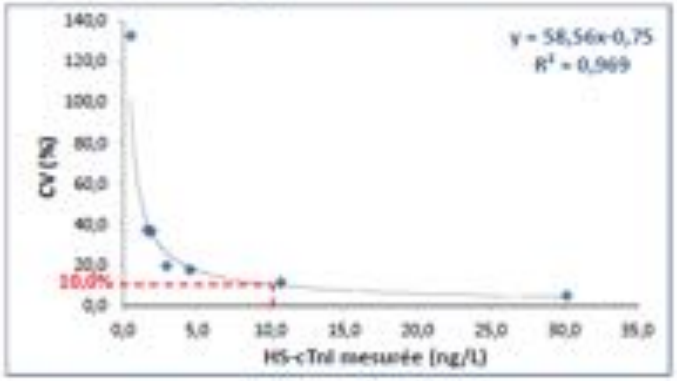
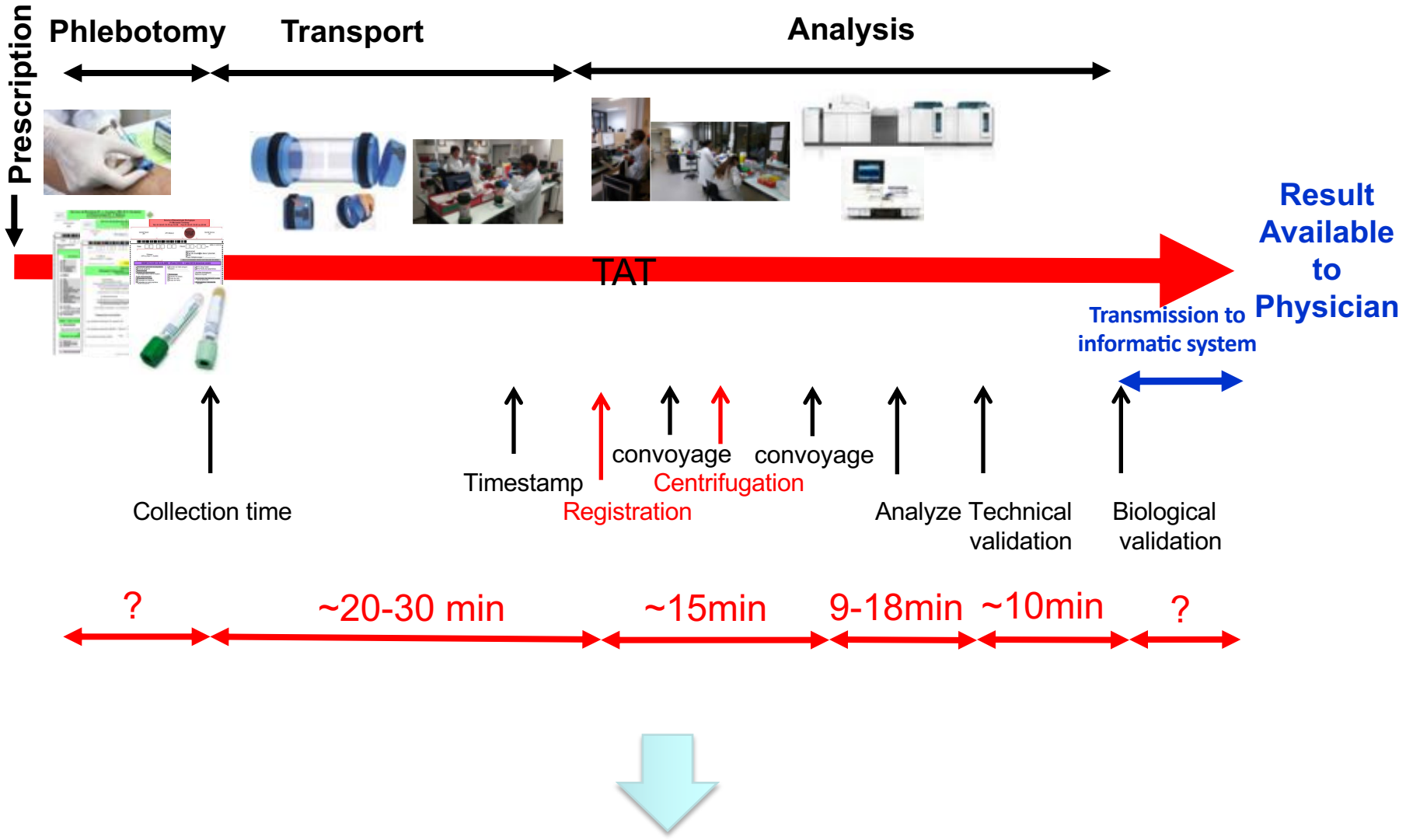


***Figure 2** : Courbe de precision de la HS-cTnI Triage Meter*

Triage ® :

- ✓ **Sang total**
- ✓ **Précision au 99e percentile**

Critères HS ?
Etudes de validation ?
Seuils ?



Difficile de rendre un résultat en moins d'une heure

La biologie format POC

- POC = *point of care (testing)*
  = biologie en dehors du laboratoire central
  = biologie au lit du malade / au poste de soin
  = biologie délocalisée
- C'est le personnel soignant qui réalise l'examen de biologie
- C'est le laboratoire qui supervise :
- Comité d'encadrement
- Justification +++ :
  - Urgence vitales
  - Eloignement géographique du labo
  - Epargne sanguine
  - Organisationnelle

« Les procédures d'analyse biologique au lit du patient représentent un complément limité et non une substitution des procédures classiques. Les laboratoires centraux demeurent la référence en matière d'exécution d'analyses biologiques. »

Biologie délocalisée vs centralisée

Avantages :	Inconvénients :
- Rapidité - Orientation - Traitement - Economie de soin	- Surcout du budget labo - Glissement de tâche - Entretien de l'analyseur - panel d'analyses restreint - Précision - troponines : méthodes non HS
- Qualité / Sécurité - Prix - Précision - Cadence	- Temps d'acheminement - TAT - Disponibilité 24h/24 ?

AP-HP. Centre Université de Paris

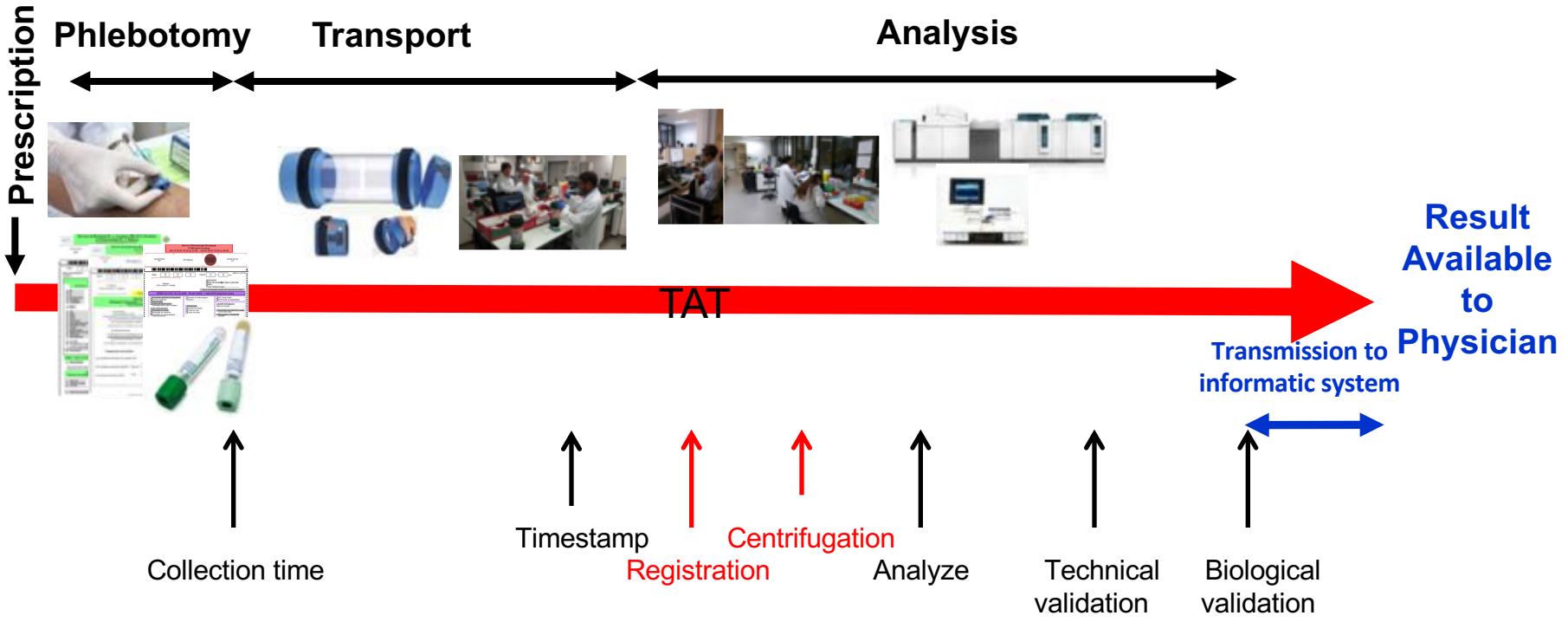
Point-of-care testing with high-sensitivity cardiac troponin assays: the challenges and opportunities

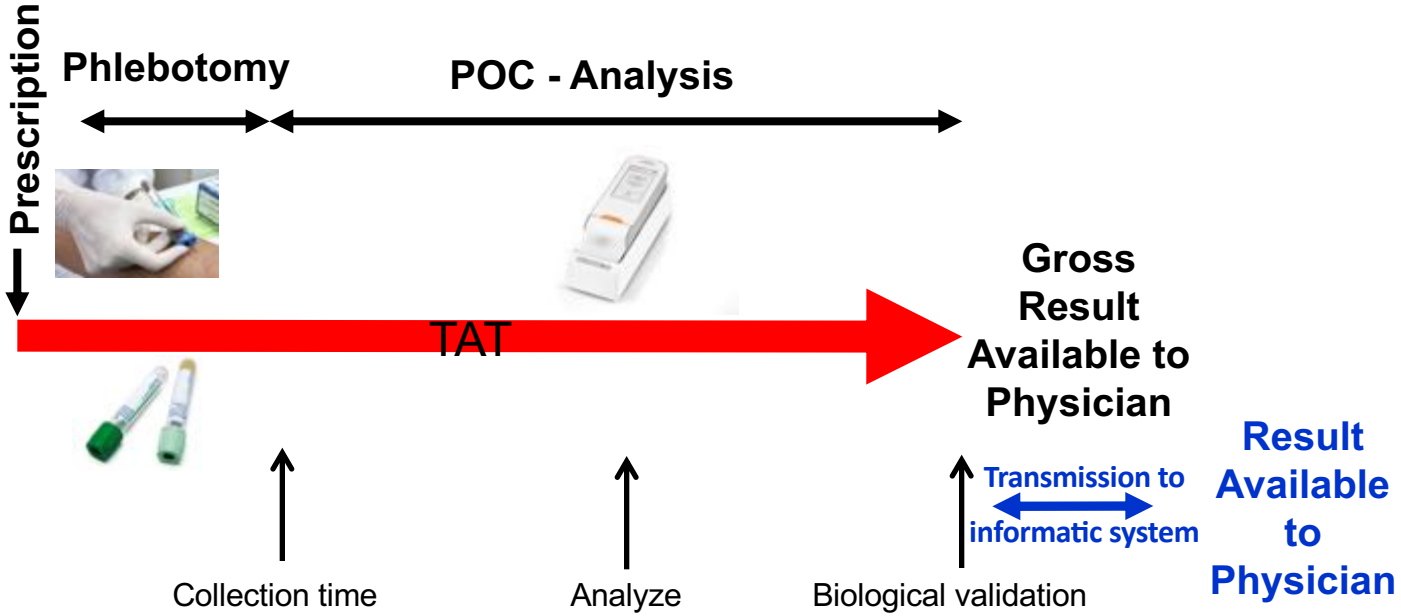
Louise Cullen ,[1] Paul O Collinson ,[2] Evangelos Giannitsis[3]

Table 1 Performance characteristics of POCT troponin assays[8 % 18]

Assay	Platform	Company	Concentration at 10% CV	Specimen type	99th percentile	Per cent normals measured ≥LoD	Assay type/ device
hs-cTnI	Atellica VTLi	Siemens	6,7 ng/L (plasma) 8,9 ng/L (sang total)	Li-heparin plasma	Overall: 23 ng/L F: 18 ng/L M: 27 ng/L	Overall: 83.7% F: 79.7% M: 87.3%	hs; cds
hs-cTnI/cTnI-II	PATHFAST	LSI Medience (formerly Mitsubishi)	15 ng/L	Heparin-Na, heparin-Li or EDTA whole blood or plasma	Overall: 27.9 ng/L F: 20.3 ng/L M: 29.7 ng/L	Overall: 66.3% F: 52.8% M: 78.8%	hs; cds
hs-cTnI	TriageTrue	Quidel/Alere	4.4–8.4 ng/L (plasma) 5.8–6.2 ng/L (whole blood)	EDTA whole blood or plasma	Overall: 20.5 ng/L F: 14.4 ng/L M: 25.7 ng/L	Overall: ≥50%	hs; bls
cTnI test pack	STRATUS CS Acute Care	Siemens	0.06 µg/L	Whole blood (Li or NP heparin) or plasma Li or Na heparin	Overall: 0.07 µg/L		cs; bls
TnI	AQT90 FLEX	Radiometer	0.027 µg/L	EDTA and heparinised whole blood and plasma	Overall: 0.023 µg/L		cs; bls
TnT	AQT90 FLEX	Radiometer	0.026 µg/L	EDTA and heparinised whole blood and plasma	Overall: 0.017 µg/L		cs; bls
Troponin I	RAMP	Response Biomedical	0.21 µg/L	Only EDTA whole blood	Overall: <0.10 µg/L		Non-hs/cs; bls
cTnI	i-STAT	Abbott	0.1 µg/L	Na and Li heparinised whole blood and plasma	Overall: 0.08 µg/L		Non-hs/cs; cds
Cardiac POC troponin T	Cobas h 232	Roche	9.3% between 0.04 and 0.2 µg/L	Heparinised whole blood	NP		Non-hs/cs; cds

Adapted from the International Federation of Clinical Chemistry and Laboratory Medicine—Clinical Applications of Cardiac Bio-Markers Updated tables (https://www.ifcc.org/media/407653/point-of-care-cardiac-troponin-i-and-t-assay-analytical-characteristics-designated-by-manufacturer-v012019.pdf).


Prescription
Phlebotomy
Transport
Analysis
TAT
Result Available to Physician
Transmission to informatic system
Collection time
Timestamp
Registration
Centrifugation
Analyze
Technical validation
Biological validation


Prescription
Phlebotomy
POC - Analysis
TAT
Gross Result Available to Physician
Transmission to informatic system
Result Available to Physician
Collection time
Analyze
Biological validation

ESC European Society of Cardiology
European Heart Journal (2020) 00, 1–79
doi:10.1093/eurheartj/ehaa575

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

2.3 What is new?

New key recommendation

Diagnosis

Risk stratification

⇒ **Nouvel Algorithme H0-H2**

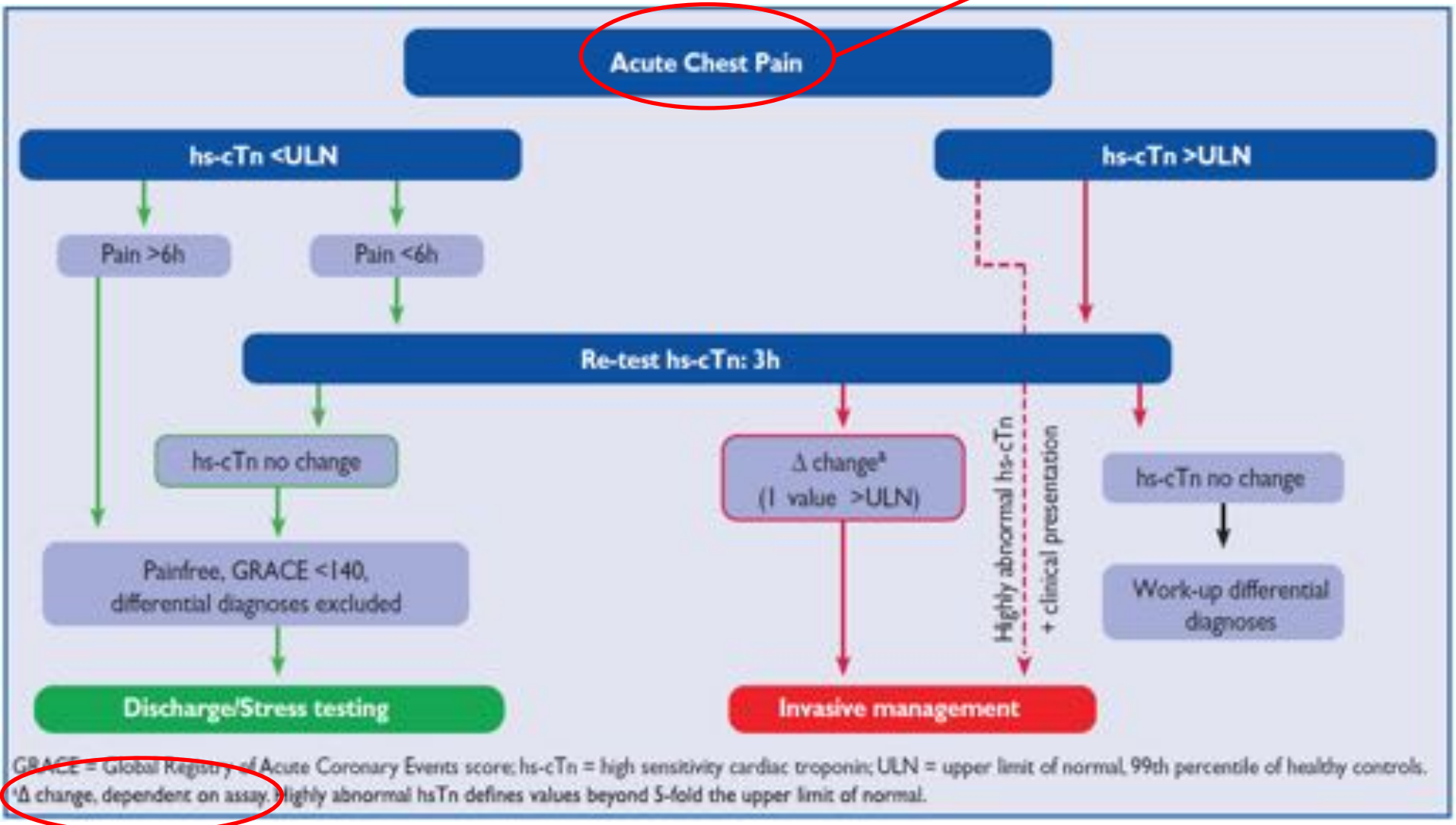
⇒ **Place de la troponine HS renforcée**

In Algorithm we trust ?

- H0-H6 : avant 2012
- H0-H3 : le classique 2012
- H0-H1 : le rapide d’exclusion
- H0-H2 : le nouveau

1. H0-H3

Equivalent chez le sujet âgé ?



ESC 2015

2. H0-H1

Uniquement si douleur thoracique >3 heures

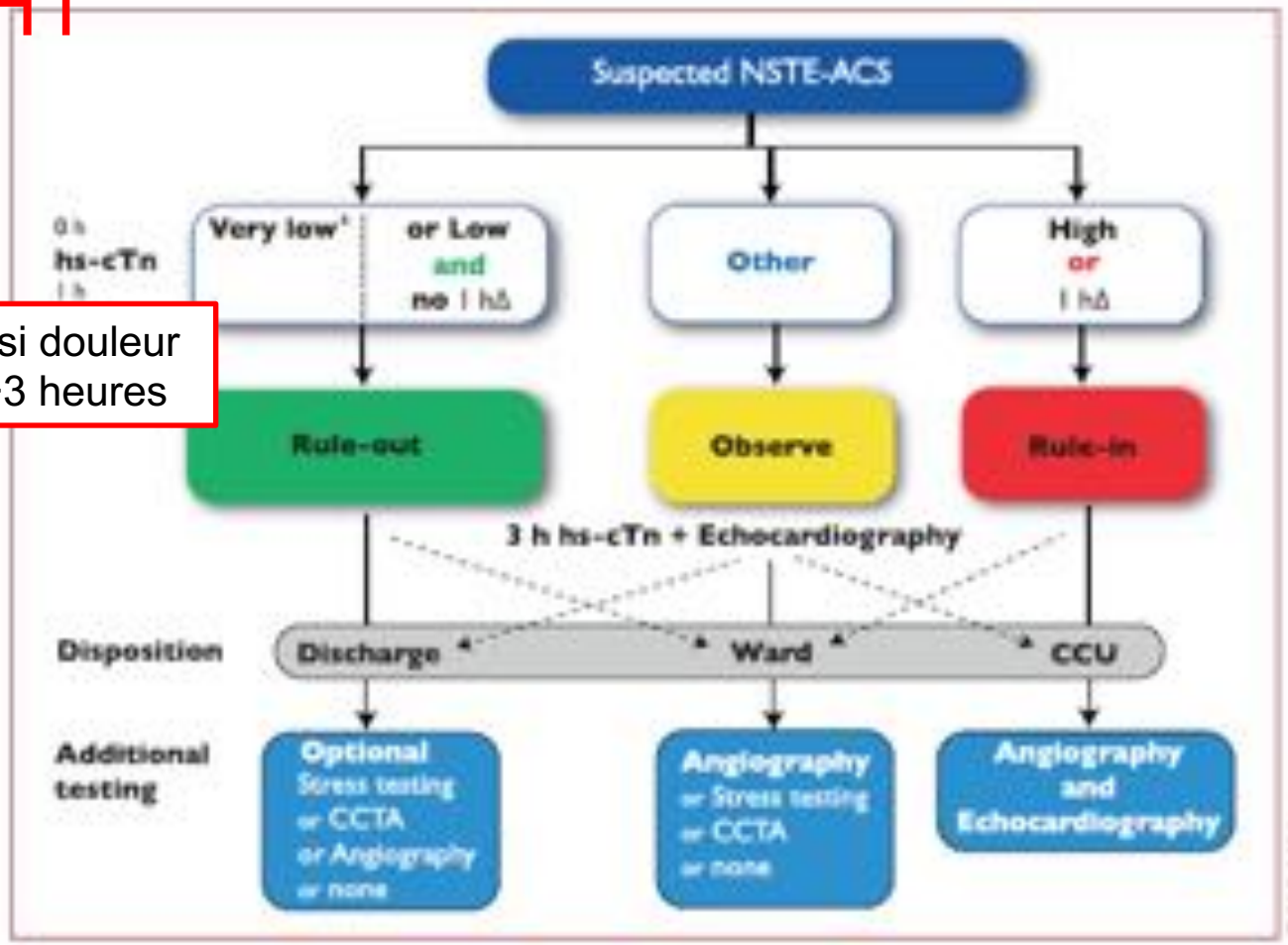


Figure 3 0 h/1 h rule-out and rule-in algorithm using high-sensitivity cardiac troponin assays in haemodynamically stable patients presenting with suspected non-ST-segment elevation acute coronary syndrome to the emergency department. 0 h and 1 h refer to the time from first blood test. NSTEMI can be ruled out 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 (no 1hΔ). Patients have a high likelihood of 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 (1hΔ).[1A–B,10–11,29–31,33] Cut-offs are assay specific (see Table 3) and derived to meet predefined criteria for sensitivity and specificity for NSTEMI. CCU = coronary care unit; CCTA = coronary computed tomography angiography; CPO = chest pain onset; hs-cTn = high-sensitivity cardiac troponin; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction. *Only applicable if CPO >3 h. *Listen to the audio guide of this figure online.*

Principal intérêt du dosage de la troponine aux urgences :

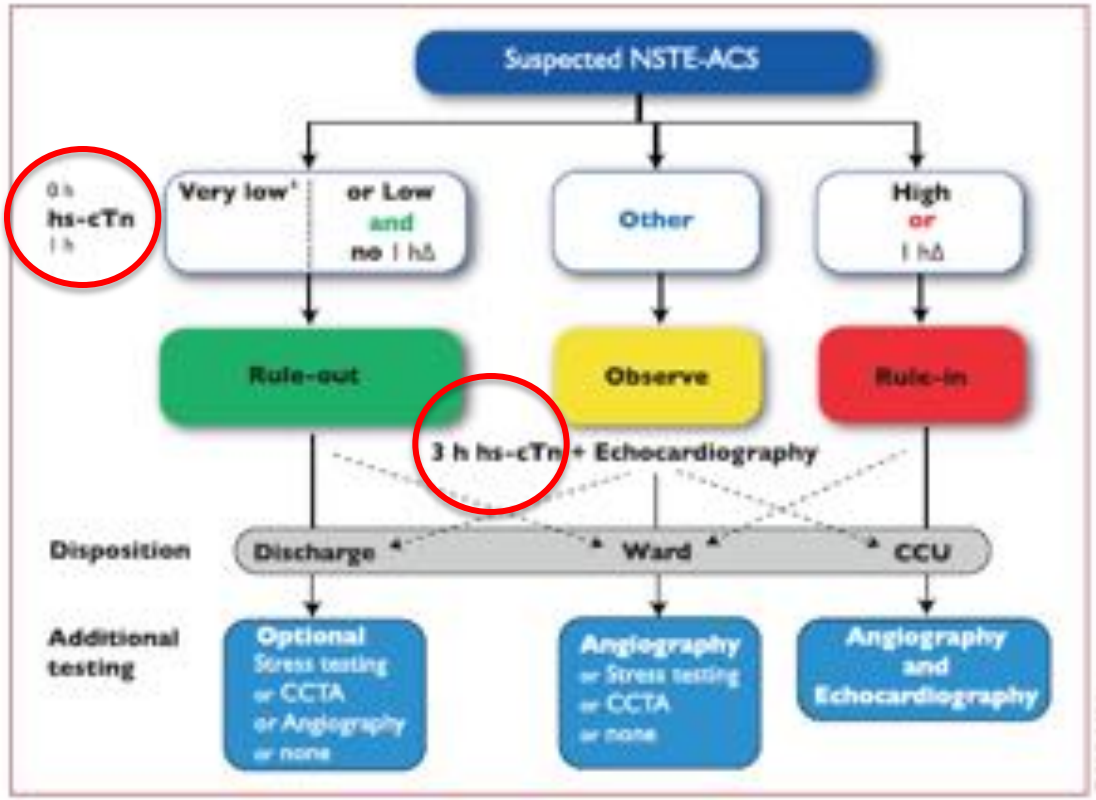


Figure 3 0 h/1 h rule-out and rule-in algorithm using high-sensitivity cardiac troponin assays in haemodynamically stable patients presenting with suspected non-ST-segment elevation acute coronary syndrome to the emergency department. 0 h and 1 h refer to the time from first blood test. NSTEMI can be ruled out 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 (no 1hΔ). Patients have a high likelihood of NSTEMI if the hs-cTn concentration at presentation is at least moderately elevated. Patients with hs-cTn concentrations show a clear rise within the first hour (1hΔ).[5A–8,10–13,29–33] Cut-offs are assay specific (see Table 3) and derived to maximize predefined criteria for sensitivity and specificity for NSTEMI. CCU = coronary care unit; CCTA = coronary computed tomography angiography; CPO = chest pain onset; hs-cTn = high-sensitivity cardiac troponin; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction. *Only applicable if CPO >3 h. *Listen to the audio guide of this figure online.*

Table 2 Overview on the performance of fast rule-out strategies based on single and serial blood draw at 0 hour/1 hour

	Test principle	Company	Meta-analysis cohorts	Troponin (ng/L)	Sensitivity (pooled)	NPV (pooled)	Proportion eligible for rule-out	Event rate after rule-out		
								MACE	Death	MI
0-hour rule-out: single hs-cTNT <LoD (SMS)										
Pickering, et al[23]	hs-cTnT		11 cohorts 9241 patients	<LoD (<5 ng/L)	98.7% (96.6 to 99.5)	99.3% (97.3 to 99.8)	30-60%	21/8059	1.30%	148/8059
ESC 0/1 hour: either very low 0 hour <LoD or low hs-cTn and small δ between 0 and 1 hour										
Chiang, et al[25] 15 cohorts: 11 014 patients	hs-cTnI	Abbott	4 cohorts	Either very low 0 hour (<2 ng/L), or low hs-cTnI (<5 ng/L) and small δ (<2 ng/L) between 0 and 1 hour	98.1% (94.6 to 99.3)	99% (96.0 to 100)	50.00%	NA	0.10%	NA
	hs-cTnI	Siemens	4 cohorts	Either very low 0 hour (<0.5 ng/L), or low hs-cTnI (<5 ng/L) and small δ (<2 ng/L) between 0 and 1 hour	98.7% (97.3 to 99.3)	100% (99 to 100)	53.00%	NA	0.10%	NA
	hs-cTnT	Roche	7 cohorts 7744 patients	Either very low 0 hour (<5 ng/L), or low hs-cTnT (<12 ng/L) and small δ (<3 ng/L) between 0 and 1 hour	98.4% (96.1 to 99.5)	99.6% (99.0 to 99.9)	55.00%	NA	0.10%	NA

ESC, European Society of Cardiology; hs-cTnI, high-sensitivity cardiac troponin I; LoD, limit of detection; MACE, major adverse cardiac events; MI, myocardial infarction; NA, not available; NPV, negative predictive value; SMS, single marker strategy.

RESEARCH ARTICLE

Economic evaluation of the one-hour rule-out and rule-in algorithm for acute myocardial infarction using the high-sensitivity cardiac troponin T assay in the emergency department

⇒ **DMS : 4,3h (vs 6,5h)**

⇒ **Réduction cout estimée :**

2480 £ (vs 4561£)

PLOS ONE | https://doi.org/10.1371/journal.pone.0187662 November 9, 2017

Exclure un SCA non ST+ en <1h, c'est bien, mais…

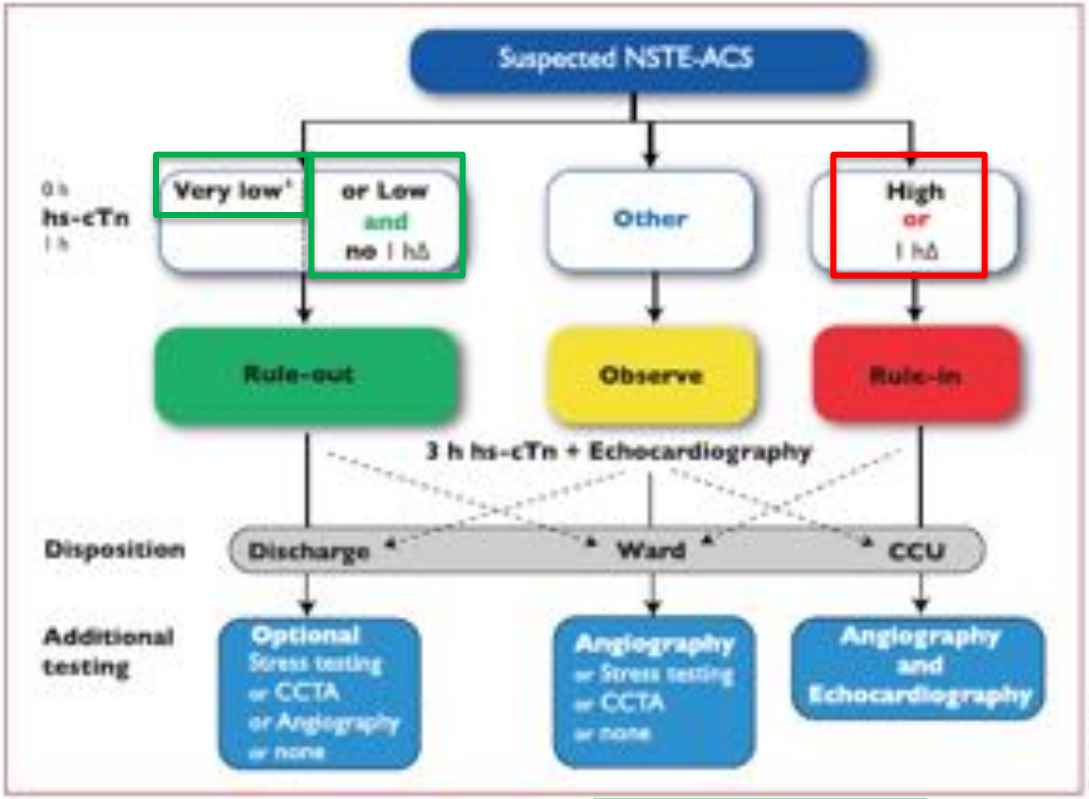
Encore faut il avoir :

- La certitude que la DT >3h

!! Jusqu'à 30% des patients ont une DT <2h !!

- Un dosage de troponine avec une méthode hypersensible (troponine HS)
- Un résultat de troponine HS en moins d'une heure
- Les bons seuils d'interprétation

Du bon usage des valeurs seuils…



0 h/1 h algorithm	Very low	Low	No 1hΔ	High	1hΔ
hs-cTn T (Elecsys; Roche)	<5	<12	<3	≥52	≥5
hs-cTn I (Architect; Abbott)	<4	<5	<2	≥64	≥6
hs-cTn I (Centaur; Siemens)	<3	<6	<3	≥120	≥12
hs-cTn I (Access; Beckman Coulter)	<4	<5	<4	≥50	≥15
hs-cTn I (Clarity; Singulex)	<1	<2	<1	≥30	≥6
hs-cTn I (Vitros; Clinical Diagnostics)	<1	<2	<1	≥40	≥4
hs-cTn I (Pathfast; LSI Medience)	<3	<4	<3	≥90	≥20
hs-cTn I (TriageTrue; Quidel)	<4	<5	<3	≥60	≥8

Hs-cTn I Atellica ?

Limites de cet algorithme rapide (1/2)

Ex. cTnT HS Roche (LoD= 5 ng/L) :

- **Précision analytique à 5 ng/L >10%**
  - **4,5 ng/L ⇔ 5,5 ng/L**

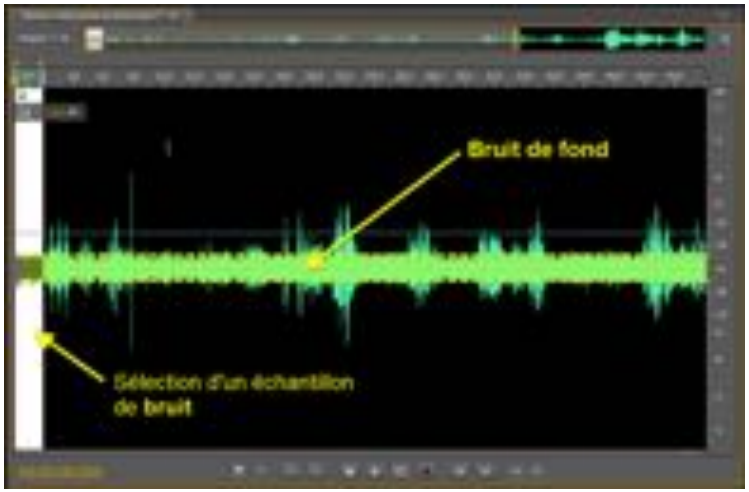
- **Précision diagnostique à 5 ng/L ?**
  - **Body et al. Clin Chem 2015 : Se 98,7% [95%CI: 87,5-98,6%]**
  - **Meta-analyse (Zhelev et al., BMJ, 2015) : Se 97,4% [95%CI:94,9-98,7%]**
  - **Chenevier-Gobeaux et al, 2016 : Se 97.8% [95%CI: 86.8-99.9]**
  - **On rate des NSTEMI !**
    - **Early presenters**
    - **Quid si on ne peut pas dater le début de la douleur ??**

Limites de cet algorithme rapide (2/2)

- **Deltas entre H0 et H1 : peut être aussi petit que 3 ng/L :**

  Valeur << Taux de Changement Critique de la méthode de dosage :

Alors Comment distinguer la variation pathologique de la variation analytique ??



Why new algorithm using high-sensitivity cardiac troponins for the rapid rule-out of NSTEMI is not adapted to routine practice.

Chenevier Gobeaux et al. SFBC, SFC, SFMU CCLM 2016

Critiques sur l'utilisation des seuils bas ou des variations H0->H1:

1°) LoD différentes selon les tests et imprécision à la LoD toujours > 10%:
augmentation des erreurs de classification?

2°) pas de résultats rendus en Tnhs si conc. < LoQ (soit CV10%):
messages ambivalents aux services cliniques?

3°) Problèmes analytiques:

- variations inter réactifs (erreur totale) entraine des biais qui augmentent l'incertitude des résultats dans les valeurs basses en Tn.
- Pas de contrôles biologiques au niveau LoD et difficiles vers 99eme percentile

4°) une sensibilité diagnostique pas à 100% peut entrainer des erreurs diagnostics

3. H0-H2

Table 5 Assay specific cut-off levels in ng/l within the 0 h/1 h and 0 h/2 h algorithms

0 h/1 h algorithm	Very low	Low	Rule-out	High	Rule-in
hs-cTn T (Elecsys; Roche)	<5	<12	<3	≥52	≥5
hs-cTn I (Architect; Abbott)	<4	<5	<2	≥64	≥6
hs-cTn I (Centaur; Siemens)	<3	<6	<3	≥120	≥12
hs-cTn I (Access; Beckman Coulter)	<4	<5	<4	≥50	≥15
hs-cTn I (Clarity; Singulex)	<1	<2	<1	≥30	≥6
hs-cTn I (Vitros; Clinical Diagnostics)	<1	<2	<1	≥40	≥4
hs-cTn I (Pathfast; LSI Medience)	<3	<4	<3	≥90	≥20
hs-cTn I (TriageTrue; Quidel)	<4	<5	<3	≥60	≥8
0 h/2 h algorithm	**Very low**	**Low**	**Rule-out**	**High**	**Rule-in**
hs-cTn T (Elecsys; Roche)	<5	<14	<4	≥52	≥10
hs-cTn I (Architect; Abbott)	<4	<6	<2	≥64	≥15
hs-cTn I (Centaur; Siemens)	<3	<8	<7	≥120	≥20
hs-cTn I (Access; Beckman Coulter)	<4	<5	<5	≥50	≥20
hs-cTn I (Clarity; Singulex)	<1	TBD	TBD	≥30	TBD
hs-cTn I (Vitros; Clinical Diagnostics)	<1	TBD	TBD	≥40	TBD
hs-cTn I (Pathfast; LSI Medience)	<3	TBD	TBD	≥90	TBD
hs-cTn I (TriageTrue; Quidel)	<4	TBD	TBD	≥60	TBD

These cut-offs apply irrespective of age and renal function. Optimized cut-offs for patients above 75 years of age and patients with renal dysfunction have been evaluated, but not consistently shown to provide better balance between safety and efficacy as compared to these universal cut-offs.[32,34,69] The algorithms for additional assays are in development.

hs-cTn = high-sensitivity cardiac troponin; TBD = to be determined.[30–32,37,39,40,68,69,71–84]

Et les « very early presenters » ?

= Douleur thoracique datant de <2 h ou 3h avant la présentation aux urgences

Assez peu étudiés à part entière. Et pourtant… 25-35% des patients selon les études !

BMJ Open, 2019: n=160 avec une CPO<2h

- **NSTEMI non diagnostiqués sont tous des « very early presenters »**
- **Performances diagnostiques diminuées si DT <2 ou 3h**

Age	Chest pain since	CPO category	cTnI	HS-cTnT	Copeptin
89	1 hour 15 min	<2 hours (very early presenters)	0.04 µg/L (40 ng/L)	44.9 ng/L	208.7 pmol/L
86	30 min		0.06 µg/L (60 ng/L)	11.3 ng/L	77.2 pmol/L
35	50 min		0.01 µg/L (10 ng/L)	<3 ng/L	54.7 pmol/L
44	45 min		0.01 µg/L (10 ng/L)	<3 ng/L	10.7 pmol/L
74	3 hours	2–4 hours	0.04 µg/L (40 ng/L)	8.8 ng/L	10.7 pmol/L
34.2	2 hours 35 min		0.04 µg/L (40 ng/L)	<3 ng/L	23.5 pmol/L
55	3 hours 50 min		0.02 µg/L (20 ng/L)	6 ng/L	25.9 pmol/L
34	3 hours 15 min		0.01 µg/L (10 ng/L)	4 ng/L	52.4 pmol/L
61	3 hours		0.03 µg/L (30 ng/L)	18.7 ng/L	27.2 pmol/L
59	2 hours 45 min		0.04 µg/L (40 ng/L)	16.1 ng/L	241.8 pmol/L

Table 3 AUC values according to CPO category

	Biomarker	AUC	95% CI
CPO <2 hours (very early presenters)	cTnI	0.841	0.775 to 0.894
	cTnI+copeptin	0.880	0.819 to 0.926
	HS-cTnT	0.853	0.789 to 0.904
	HS-cTnT+copeptin	0.897	0.840 to 0.940
CPO 2–4 hours	cTnI	0.886	0.823 to 0.933
	cTnI+copeptin	0.915	0.857 to 0.955
	HS-cTnT	0.869	0.802 to 0.919
	HS-cTnT+copeptin	0.891	0.829 to 0.937
CPO >4 hours	cTnI	0.956	0.905 to 1.000
	cTnI+copeptin	0.979	0.940 to 0.995
	HS-cTnT	0.980	0.942 to 0.996
	HS-cTnT+copeptin	0.953	0.906 to 0.981

AUC, area under the ROC curve; CPO, chest pain onset; cTnI, cardiac troponin I; HS-cTnT, high-sensitivity cardiac troponin T.

La problématique du patient âgé

Atypie clinique de la maladie coronaire aiguë

L'essentiel de la dynamique de recherche des biomarqueurs est tournée vers l'exclusion du SCA: pas « la » problématique des patients âgés

Comprendre l'augmentation de troponine avec la multiplication des étiologies

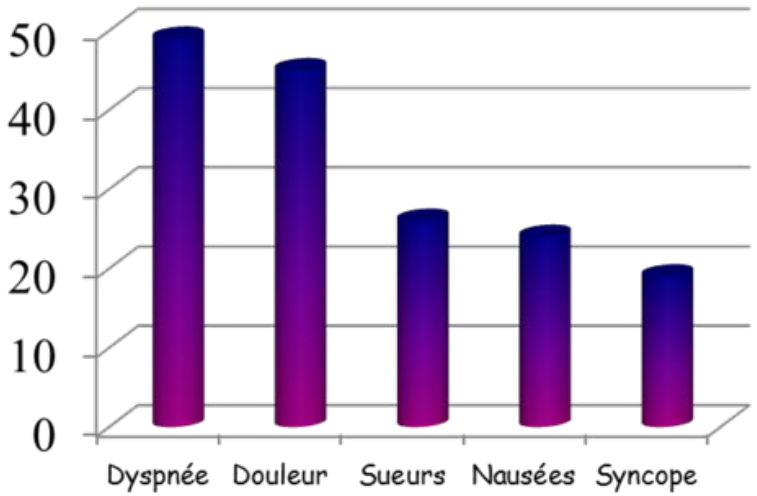
Sémiologie atypique du patient âgé

Cognitivement intacts 40 %

Naughton, Ann emerg Med 1995
Naughton, Acad emerg Med, 1997

Présentation SCA

IdM silencieux: 60 % des IdM > 85 ans



Fréquence des signes d'ins. cardiaque

Alexander, Circulation 2007
Brieger, Chest 2004
Kannel, NEJM 1984

Sémiologie atypique

+

Anomalies ECG base

- 60 %
- Risque x3 entre 65 et 85 ans

Molaschi, Recent Prog Med 1995
Campbell, Br Heart J 1974

Grande est la tentation de doser la troponine

Interprétation ?????

Vieillissement cardiovasculaire et ses conséquences

Vieillissement vasculaire

- Glycation
- Fibrose
- Modif. Elastine
- Modif. collagène
- Dysfonction endothéliale
- (↓ régénération, NO)

⇓

- Epaississement intima/media
- ↑ contraintes mécaniques

⇔

Vieillissement Cardiaque

- ↓prolifération et survie myocyte
- ↓Cellules souches
- ↑ Fibrose myocardique
- Perte cellulaire

⇓

- anomalies diastolique
- Hypertrophie VG
- Susceptibilité à l'ischémie

Insuffisance coronaire — **Insuffisance cardiaque** — **Fibrillation auriculaire** — **AVC**

G. Lefevre, JIB 2011

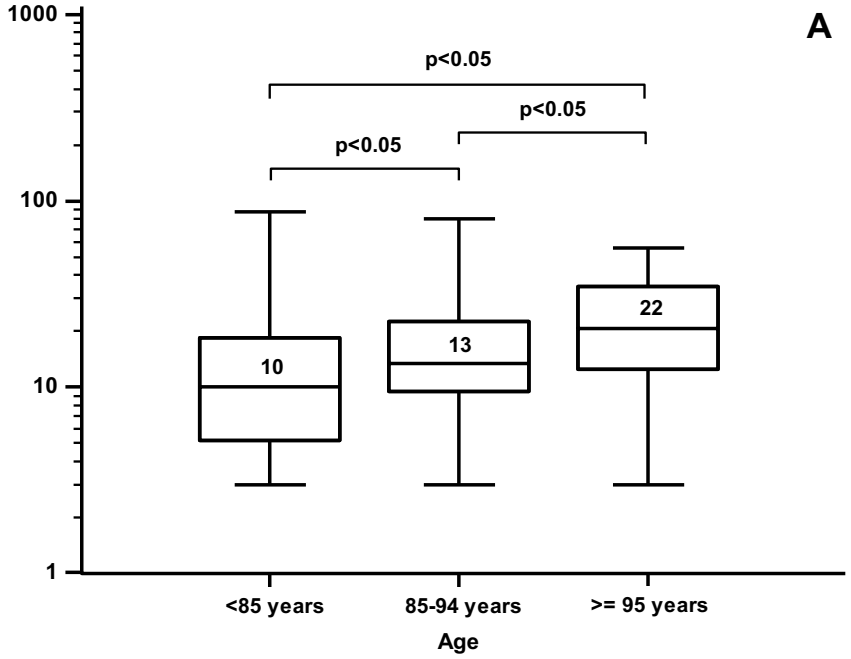
Reference range values of troponin measured by sensitive assays in elderly patients without any cardiac signs/symptoms.

n=326, >75 ans

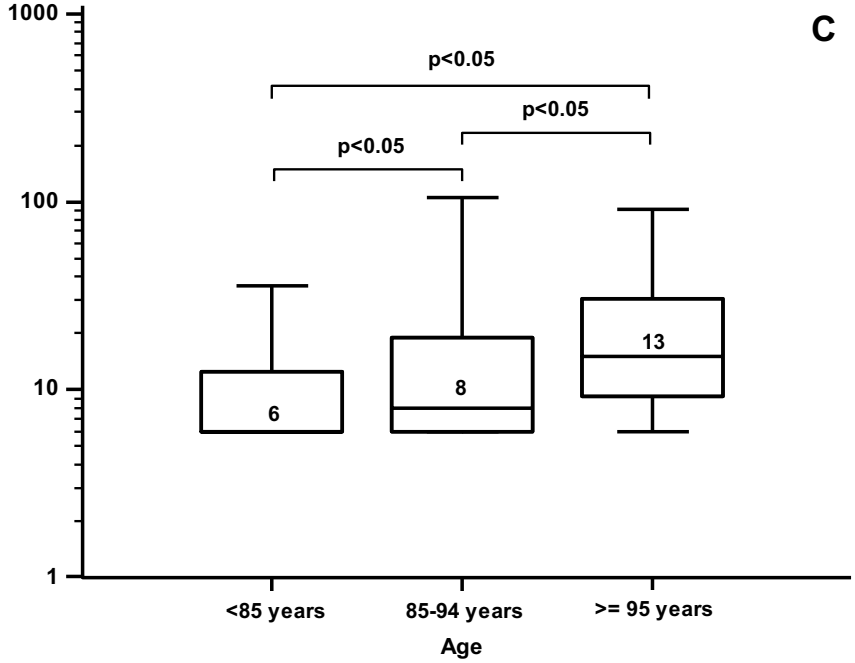
Table 1: Repartition of cTn values of the studied elderly population

	hs-cTnT	cTnI Architect	cTnI Centaur	cTnI Vitta-LOCI
Median cTn values (ng/L)	12 (10-21)	10 (10-19)	7 (6-16)	0 (0-7)
Patients with cTn values :				
above the LoD, n (%)	295 (81)	185 (51)	203 (56)	53 (15)
above the LoQ (n, %)	174 (48)	40 (11)	40 (11)	22 (6)
above the 99th percentile value [a]	157 (43)	45 (12)	31 (9)	20 (5)
Elderly studied population:				
99th Percentile value [b] (ng/L)	92 [66-124]	116 [91-175]	148 [91-220]	150 [108-198]

Menacer S. et al, Clin Chim Acta, accepted Nov 2012



n=326
>75 ans (âge médian 84 ans)



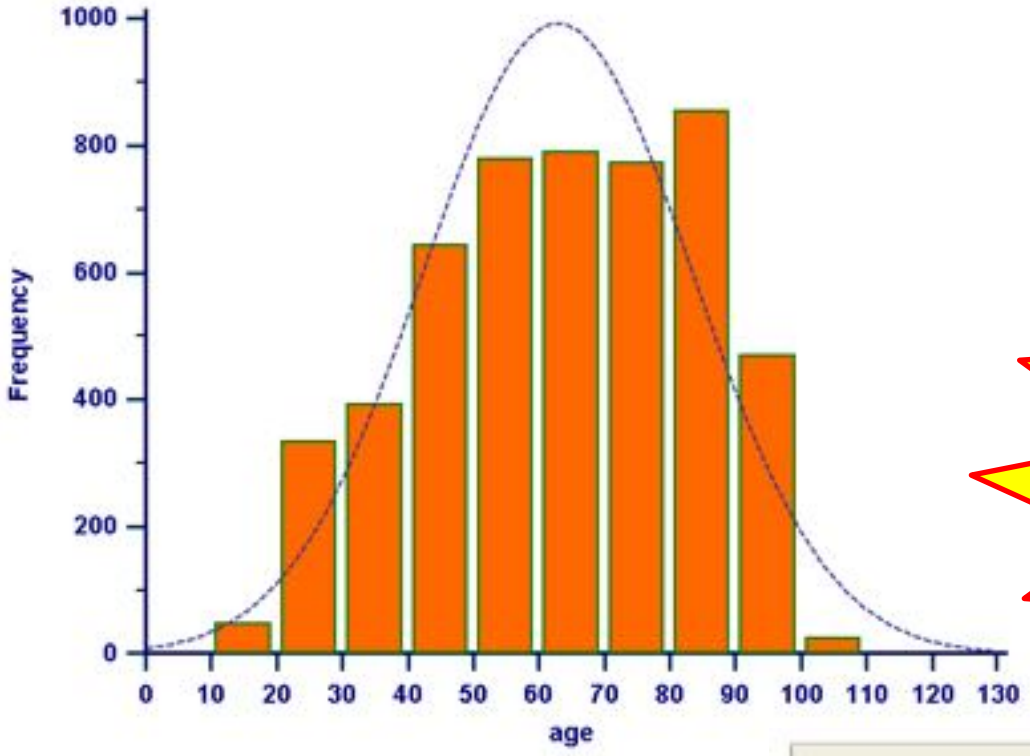
33% patients eGFR<60 ml/min

58% : chute +/- trauma

Co-morbidités :
- HTA (53%)
- ATCD CV (37%)

Menacer S. et al, Clin Chim Acta, 2013

5103 dosages de troponine T HS entre 1er janvier et le 4 décembre 2017



80% des sujets >75 ans ont une TnT HS >14 ng/L

Troponine T HS	Age <75 ans	>75 ans	
<14 ng/L	2524	349	2873
>14 ng/L	825	1405	2230
	3349	1754	5103

Chi-square	1437,278
DF	1
Significance level	P < 0,0001

(75%)

Chez qui ne pas doser la troponine :

SCA ST+ (STEMI) +++++++

Pathologie n’ayant rien à voir avec un problème coronarien

Patient chez qui le résultat ne modifiera pas le traitement (ex: traitement médical maximal et n’aura pas de coronarographie)

Chez qui doser la troponine :

- SCA non ST+ (non STEMI)

- Troubles de la repolarisation mal expliqués

- Patient chez qui on veut préciser le pronostic

Aussi, chez le sujet âgé :

- Ai-je vraiment besoin d'un dosage de troponine ?
- Pas d'algorithme rapide
- Privilégier le H0-H2/3
  - Ne pas oublier la variation biologique aux faibles valeurs
  - Considérer un delta d'environ 20-50% comme significatif pour définir une variation en lien avec une ischémie aigue ?

Le « challenge » analytique du dosage des troponine HS

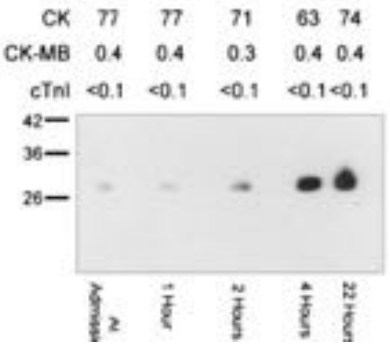
Concentrations sanguines relatives chez sujet normal

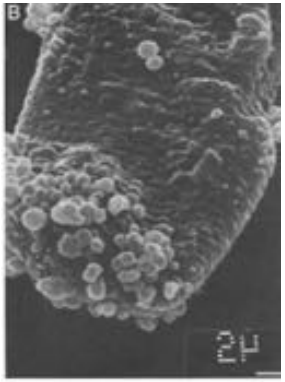
Glucose	1g/l	5,5 mmol/l	$14 .10^{9}$
Créatinine	10 mg/l	90 µmol/l	$230 . 10^{6}$
Bilirubine totale	10 mg/l	17 µmol/l	48.10^{6}
Facteur Natriurétique B	50 ng/l	14 pmol/l	40
Troponine cardiaque	13 ng/l	350 fmol/l	1

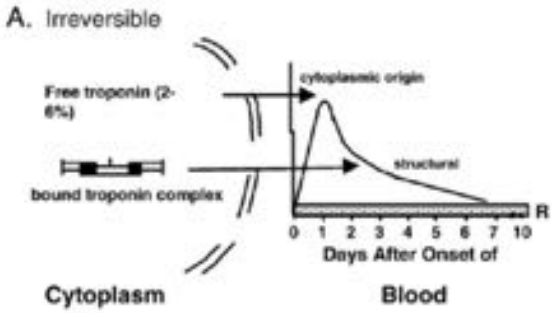
Classification des mécanismes d'augmentation de la troponine dans le sang

Type 1	Nécrose myocytaire
Type 2	Apoptose
Type 3	Renouvellement myocytaire normal
Type 4	Libération cellulaire de produits de dégradation issus de la protéolyse de la troponine
Type 5	Augmentation de la perméabilité de la membrane cellulaire
Type 6	Formation et libération de vésicules membranaires

=> Multiplicité des mécanismes

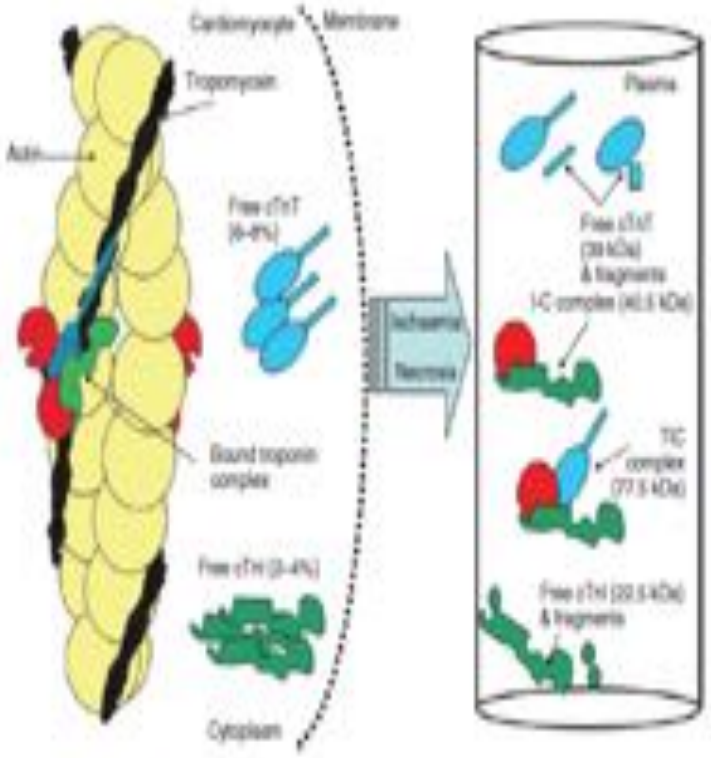


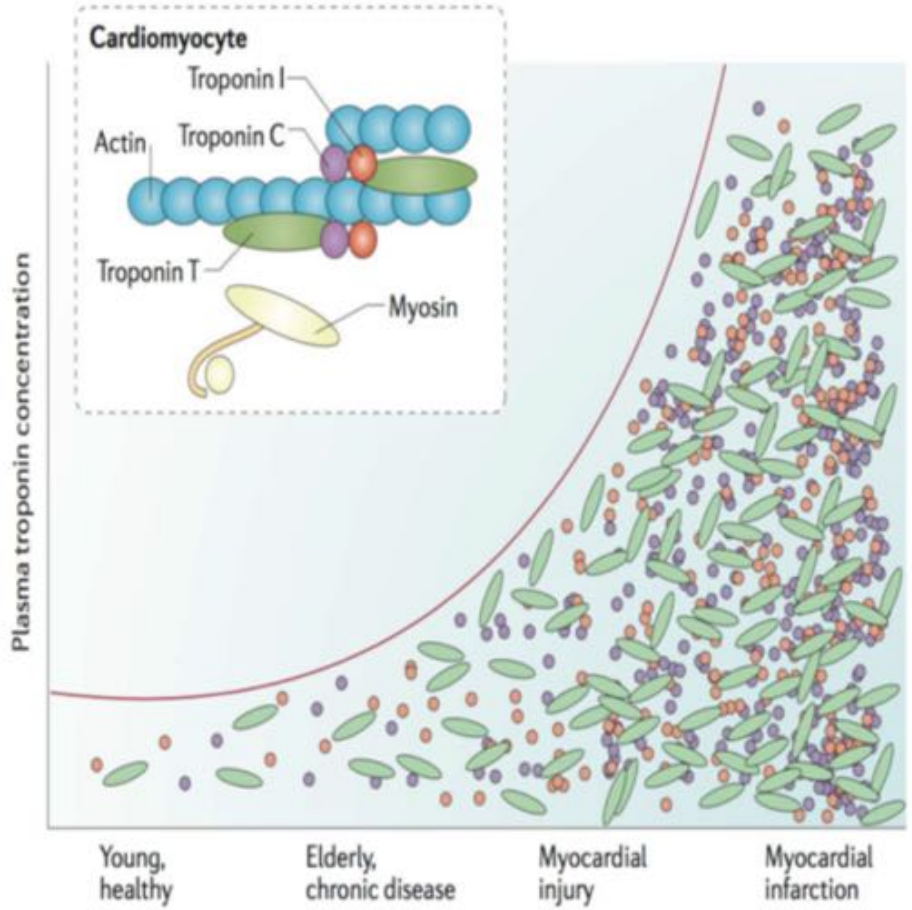




White JACC 2011

Les formes circulantes de Troponine





Variations qualitatives

Gaze 2014

Variations quantitatives

Westermann 2017

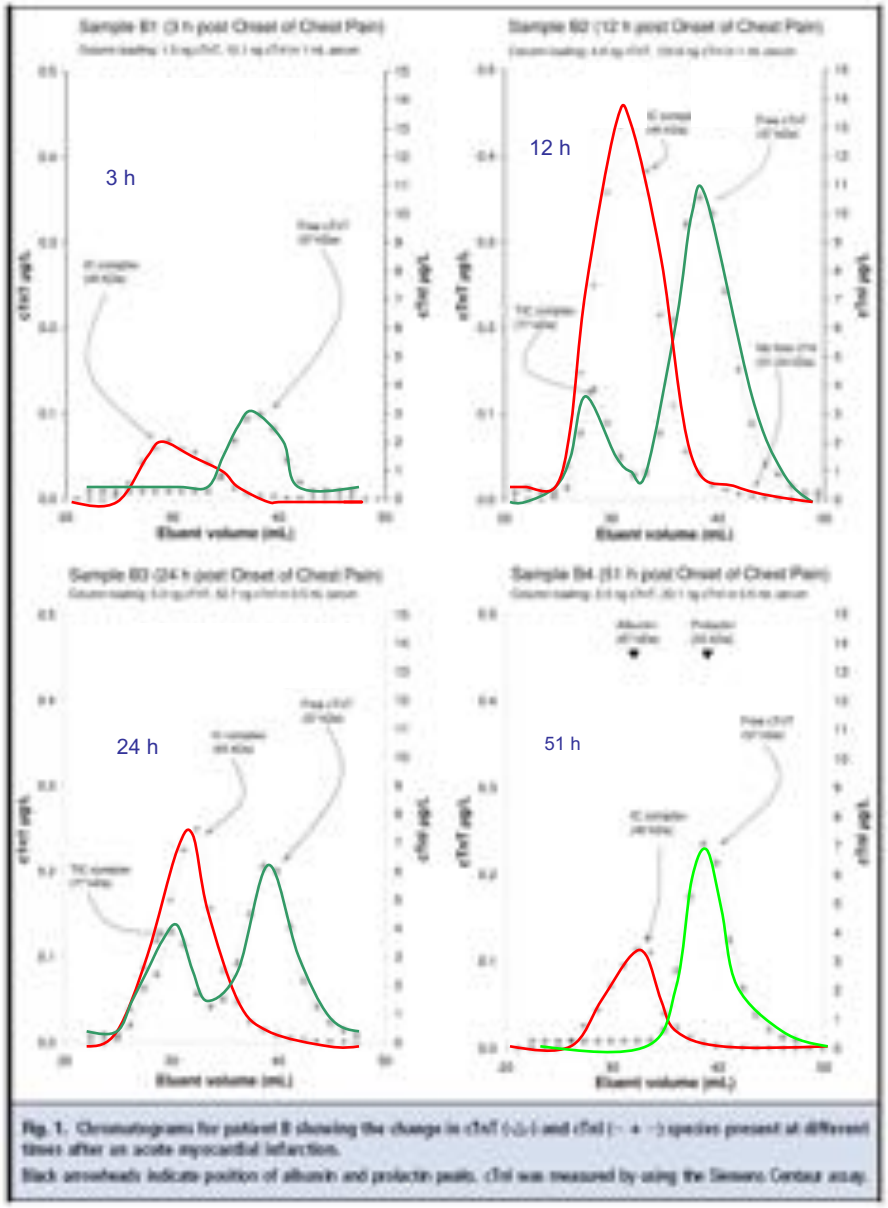


Fig. 1. Chromatograms for patient 8 showing the change in cTnT (-△-) and cTnI (— ● —) species present at different times after an acute myocardial infarction.
Black arrowheads indicate position of albumin and prolactin peaks. cTnI was measured by using the Siemens Centaur assay.

Troponines circulantes post IDM

Formes prédominantes

3h	TnT libre	I-C	
12h	TnT libre	I-C	ITC
24h	TnT libre	I-C	ITC
51h	TnT libre	I-C	

Bates et al. Clin Chem 2010

Clinical Chemistry 65:7
882-892 (2019)

Full-Size and Partially Truncated Cardiac Troponin Complexes in the Blood of Patients with Acute Myocardial Infarction

Alexandra V. Vylegzhanina,[1*] Alexander E. Kogan,[1,3] Ivan A. Katrukha,[1,2] Ekaterina V. Koshkina,[4] Anastasia V. Bereznikova,[1,3] Vladimir L. Filatov,[1,3] Marina N. Bloshchitsyna,[1,3] Agnessa P. Bogomolova,[2] and Alexey G. Katrukha[1,2]

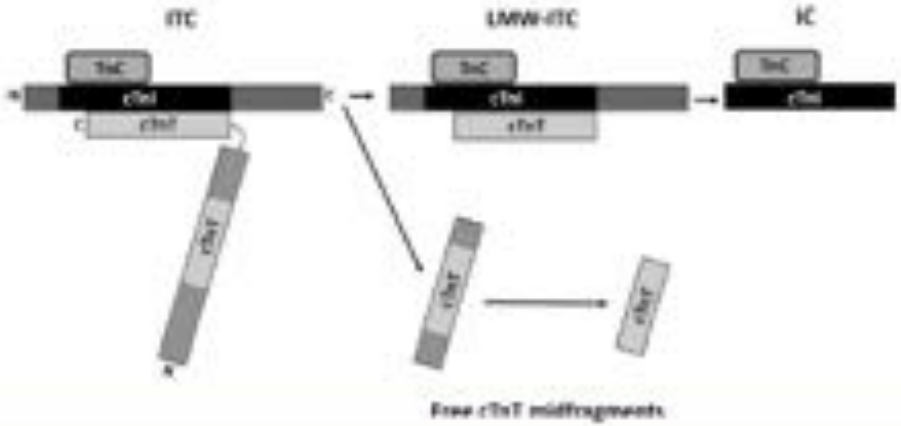


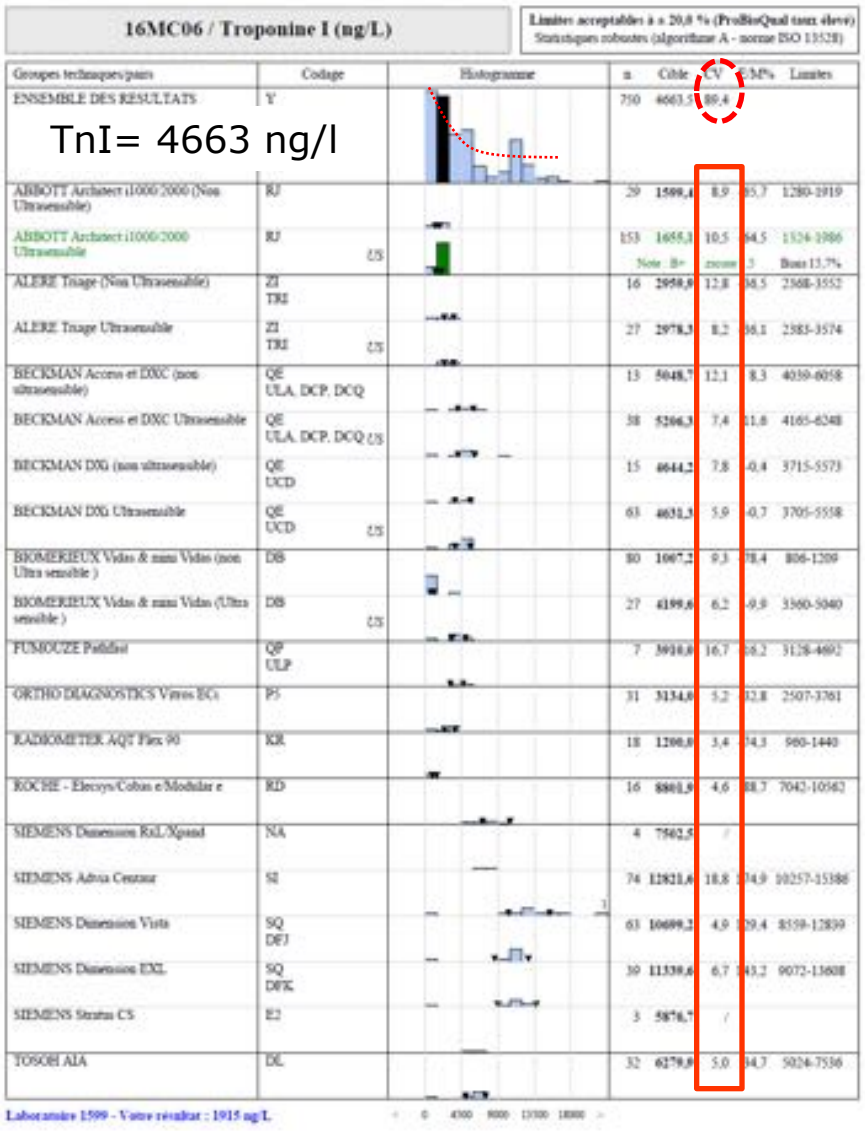
Fig. 6. Predicted scheme of troponin transformation from a full-size molecule to low molecular weight forms.

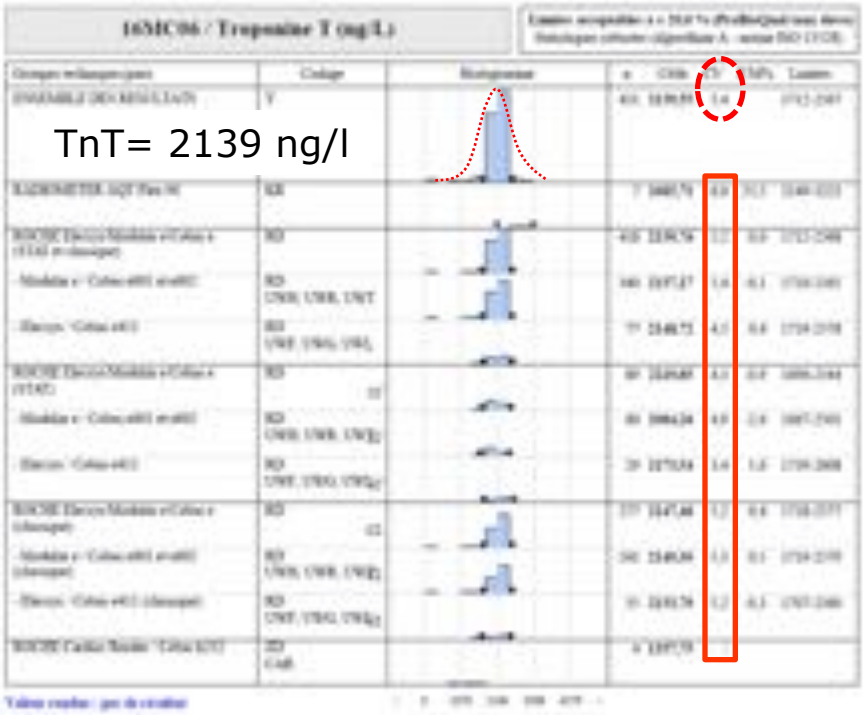
"Un complexe protéine ternaire TnI-TnT-TnC existe sous 2 formes dans le sang du patient avec IDM. Le complexe primaire est ensuite protéolysé (TnI)

Un complexe binaire I-C et les formes libres de TnT sont également présentes post IDM.
Les formes libres TnThs sont également protéolysées.

Origine des différences des résultats de troponine entre les méthodes

- Reconnaissance différente des formes circulantes
- Transformations post-traductionnelles
- Différences entre les épitopes reconnus
- Calibrateurs variables
- Nature des prélèvements
- Interférences
- Théoriquement différences moins importantes entre dosages de Troponine T (< 4ème génération)





Le même échantillon, dosé avec 20 trousses de TnI et 8 de TnTc

TnI : variabilité facteur 1 à ≈ 12

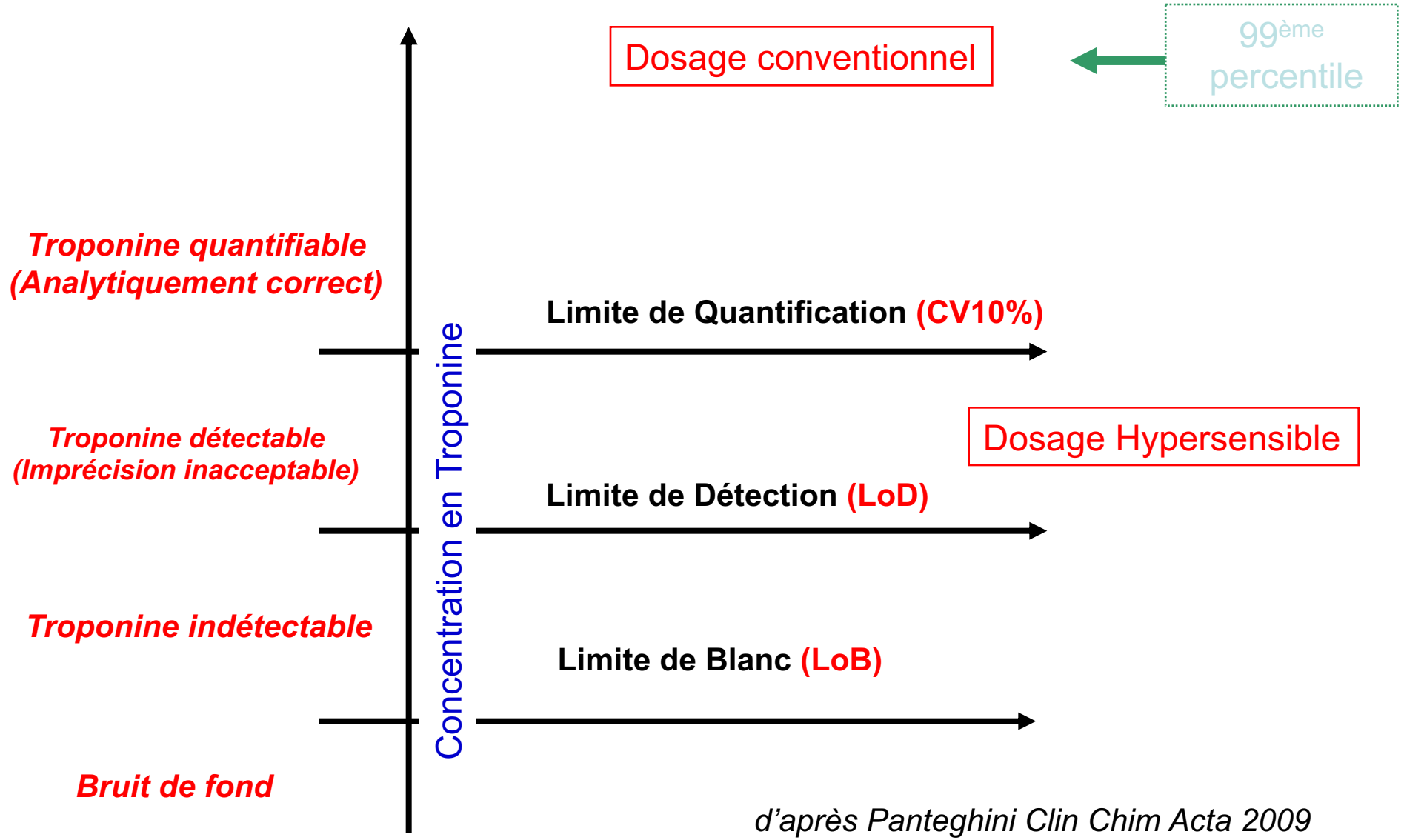
CV pairs entre 3,4 et 18,8%

TnT : variabilité facteur 1 à ≈ 2

CV pairs entre 3,4 et 6,6 %

Comparaison avec pairs seule licite …

Les paramètres des Troponines….



d'après Panteghini Clin Chim Acta 2009

Troponines Hypersensibles (Tnhs)

Caractéristiques analytiques (données fabricants)

Dosage Troponine		CV 10 %	99e perc. (ng/l) ♀/♂/Tous	CV au 99e pct (en %)	% sujets mesurés (% > LdD)	Agréments
Abbott	Architect	4,7	16/34/26	4	85	ME sauf USA
Beckman	Access II	5,6	12/20/17	3,7	> 50	ME sauf USA
BioMérieux	Vidas	NP	11/25/19	7	NP	France
Fujirebio	Lumipulse	7,3	28/32/29	< 5	68	UK
Mitsubishi	Pathfast	15	20/29/28	6	66	ME sauf USA
Ortho	Vitros	2	9/12/11*	< 10	> 50	CE
Roche	Cobas e801	6	9/16/14	< 10	57	CE
Siemens	Atellica	< 6	38/58/46	< 5	75	CE 2018
Siemens	Centaur	< 6	40/58/46	< 5	63	CE 2017
Siemens	Vista	10	54/78/59	< 5	82	CE 2017
Siemens	Dimension	12	51/76/60	< 5	52	CE 2017
Singulex	Clarity	0,5	9/9/9**	2	99	CE
Tosoh	AIA	5,6	ND/ND/31	NP	NP	CE

NP : non précisé

LdD : Limite de Détection

* Plasma Hep uniquement

** Plasma EDTA uniquement

ME : monde entier

UK: Royaume Uni

Source Task Force Cardiac Markers IFCC (M à J: 19 Avril 2021)

http://www.ifcc.org/ifcc-education-division/emd-committees/committee-on-clinical-applications-of-cardiac-bio-markers-c-cb/

Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine

Alan H.B. Wu,[1*] Robert H. Christenson,[2] Dina N. Greene,[3] Allan S. Jaffe,[4] Peter A. Kavsak,[5] Jordi Ordonez-Llanos,[6] and Fred S. Apple[7]

Contrôle de Qualité Interne et Troponine Hs

❖ **3 niveaux de CQ Troponine Ihs ou Ths (avec une précision d'une décimale)**

- **1 concentration basse** de troponine hs entre la LoD et 99ème percentile le plus bas (99ème perct. femmes) :

ex:	TnIhs Abbot Architect	entre 1,1 et 16,0 ng/l
	TnIhs Siemens Atellica	entre 1,6 et 39,0 ng/l
	TnT Cobas Roche	entre 3,0 et 9,0 ng/l

- **1 concentration intermédiaire** correspondant au 99ème percentile le plus élevé (99ème perct. hommes) ± 20%

ex :	Abbott Architect	34,2 ng/l ± 20% = 27,4 à 41,0 ng/l
	TnIhs Siemens Atellica	53,5 ng/l ± 20% = 42,8 à 64,2 ng/l
	TnT Cobas Roche	16,0 ng/l ± 20% = 13,0 à 19,0 ng/l

- **1 concentration élevée** pour les IDM post procéduraux (post angioplastie type 4a ou 5) correspondant à 4 ou 5 fois le 99ème percentile soit

ex:	Abbott Architect	104 à 170 ng/l
	TnIhs Siemens Atellica	181 à 222 ng/l
	TnT Cobas Roche	56 à 70 ng/l

❖ **objectifs analytiques**

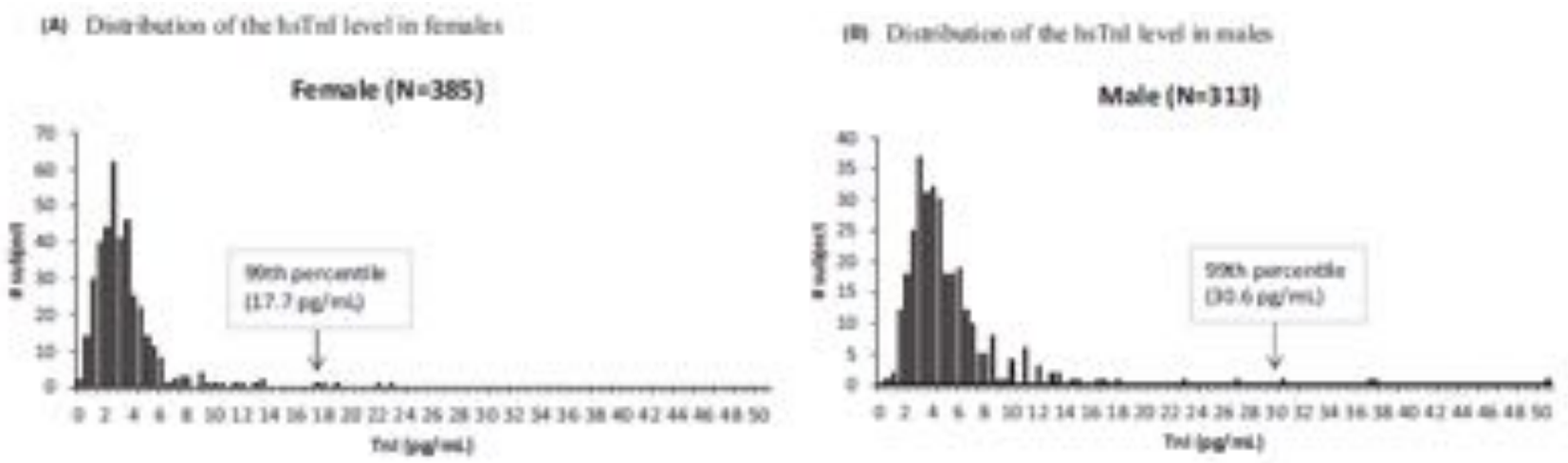
- **erreur tolérable de 3,5 ng/ l pour les CQI < 10 ng/l**

Commentaires:

suivi des concentrations très basses (~LoD) et basses (< 99ème percentile)
Erreur total 35% pour valeurs proches du 99ème percentile
Objectifs de concentrations très variables selon les techniques

Influence du genre dans le calcul des valeurs usuelles de la troponine I (Abbott Architect)

- Effectif> 300 sujets par genre
- valeurs ♂ > valeurs ♀



Distribution of cardiac troponin I in the Japanese general population and factors influencing its concentrations

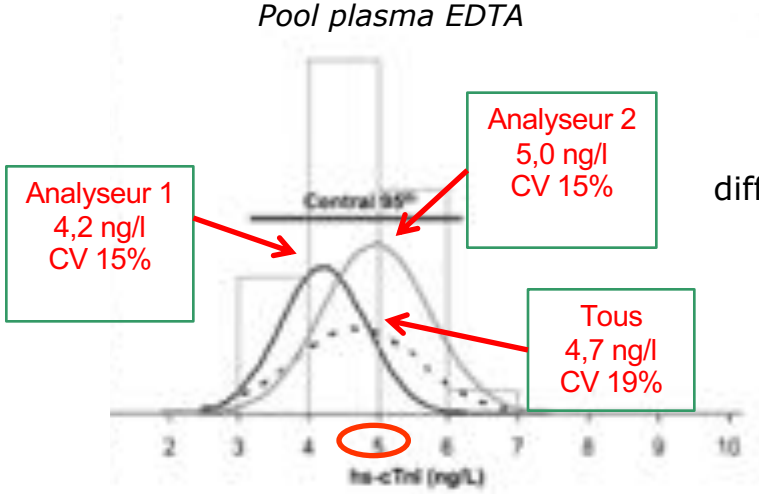
NB: peu d'effet de l'ethnie sur valeurs TnI us (voir diapo suivante)

How to cite this article: Abe N, Tomita K, Teshima M, et al. Distribution of cardiac troponin I in the Japanese general population and factors influencing its concentrations. *J Clin Lab Anal*. 2018;32:e22294. https://doi.org/10.1002/jcla.22294

Variation analytique
et seuils décisionnels bas des Troponine I hs

TnIhs Architect (Fournisseur)
LoB: 1,3 ng/l
LoD : 1,9 ng/l
CV 10%: 4,7 ng/l
99ème percentile : 26 ng/l

Pool plasma EDTA



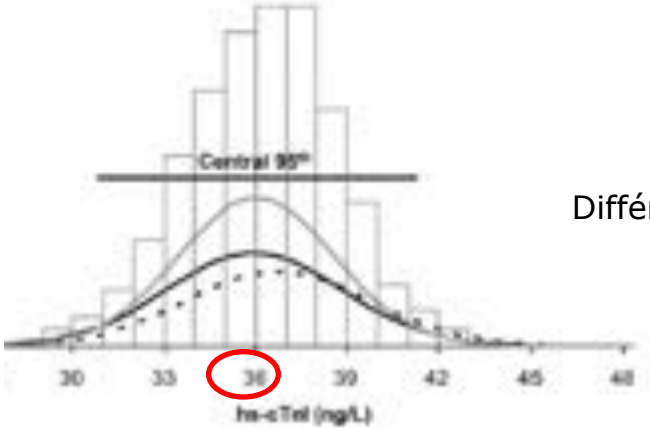
A 5 ng/L
différences inter-analyseur
significatives

Exemple Architect Abbott:
Analyseur 1
M = 4,2 CV 15% => E.T= 0,63 ng/l
95% des résultats entre 2,9 et 5,5 ng/l
Analyseur 2
M = 5,0 CV 15% => E.T= 0,75 ng/l
95% des résultats entre 3,5 et 6,5 ng/l

Différence des extrêmes: 3,6 ng/l

Mais ….
Dans le protocole d'exclusion de l'IDM T0-T2h, la variation décisionnelle proposée est de **2 ng/L**

c.a.d.< différences inter-analyseur du test…



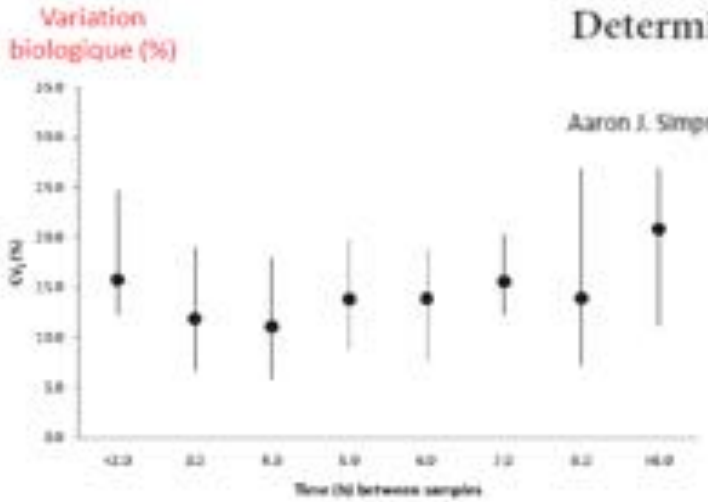
A 36 ng/l,
Différences inter-analyseur
non significatives

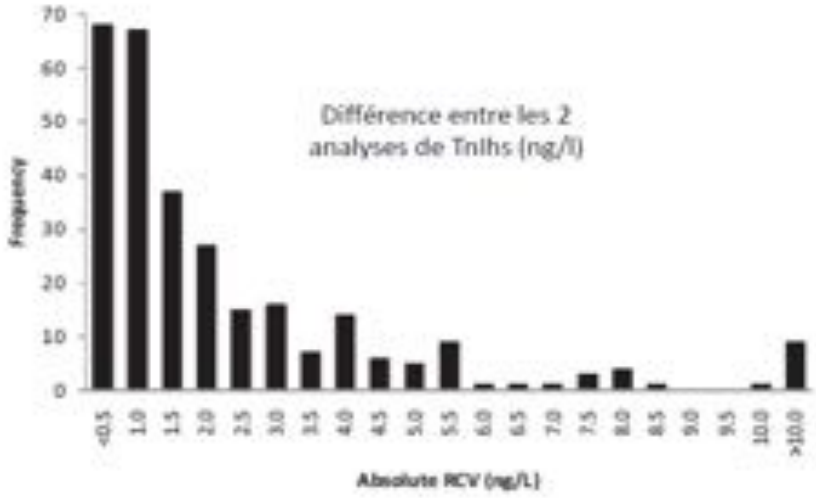
Kavsak et al. Clin Chem 2016

Variation biologique de la troponine I chez le sujet « normal »

Use of Observed Within-Person Variation of Cardiac Troponin in Emergency Department Patients for Determination of Biological Variation and Percentage and Absolute Reference Change Values

Aaron J. Simpson,[1] Julia M. Potter,[1,2] Gus Koerbin,[1,3] Carmen Oakman,[1] Louise Cullen,[4,5] Garry J. Wilkes,[6] Samuel L. Scanlan,[7] William Parsonage,[5,8] and Peter E. Hickman[1,2*]



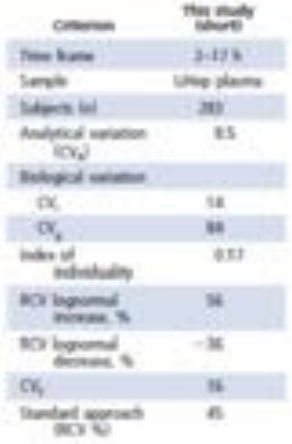


N =283 patients non cardiaques

97% variation TnIhs < 10 ng/l
72% variation < 2 ng/l

CVi # 15% (TnIhs < 40 ng/l)
Indépendant du délai (entre 2 et 8h)
CVa = 8,5 %

RCV TnIhs = 45%



Points forts / points faibles Troponine I et T

	Troponine I	Troponine T
Fournisseur	multiples	unique
Standardisation	Non	Non
Anticoagulants	LiHep, sérum	EDTA, sérum, LiHep
Seuils	variables	unique
Chaîne automatisée	+/-	oui
Délocalisation	oui	oui
Temps analyse	15-18 min	7-15 min
Cardiospécificité	oui	oui
Production extracardiaque	non	oui mais non dosée
Diagnostic IDM	oui	oui
Pouvoir prédictif complications CV	oui	oui