La troponine en pratique, mais au fait à quoi ça sert ? Du bon usage clinique et biologique

BIO-RAD

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- Service de Biochimie, Hôpital Cochin,
- AP-HP. Centre – Université Paris Cité

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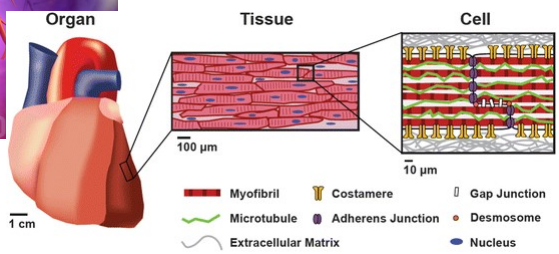
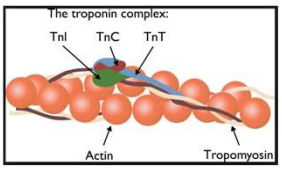
Conflits d'intérêts

- Roche Diagnostics
- Siemens Healthineers
- Radiometer
- Quidel Ortho
- Nephrotek /AAZ

3





troponine = Une protéine de structure, pas une enzyme !

= Marqueur d'atteinte du cardiomyocyte

90-95% forme complexée

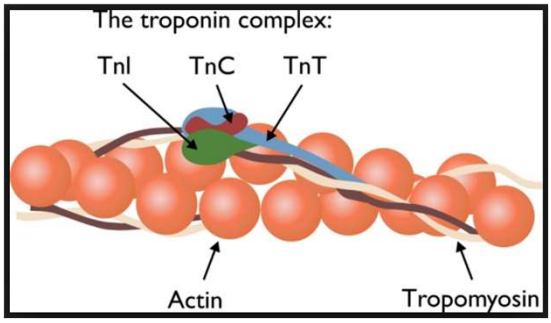
5-10% forme libre cytoplasme

4

4

Le complexe Troponine : complexe hétérotrimérique

- Troponine C : fixation du Calcium
- Troponine I : Inhibition de la liaison actine-myosine – 3 isoformes :
  - Isoforme spécifique du muscle squelettique à contraction rapide
  - Isoforme spécifique du muscle squelettique à contraction lente
  - Isoforme spécifique du cœur : cTnI ou TnIc
- Troponine T : liaison avec la Tropomyosine – nombreuses isoformes :
  - Isoformes squelettiques
  - Isoformes spécifiques du cœur : cTnT ou TnTc



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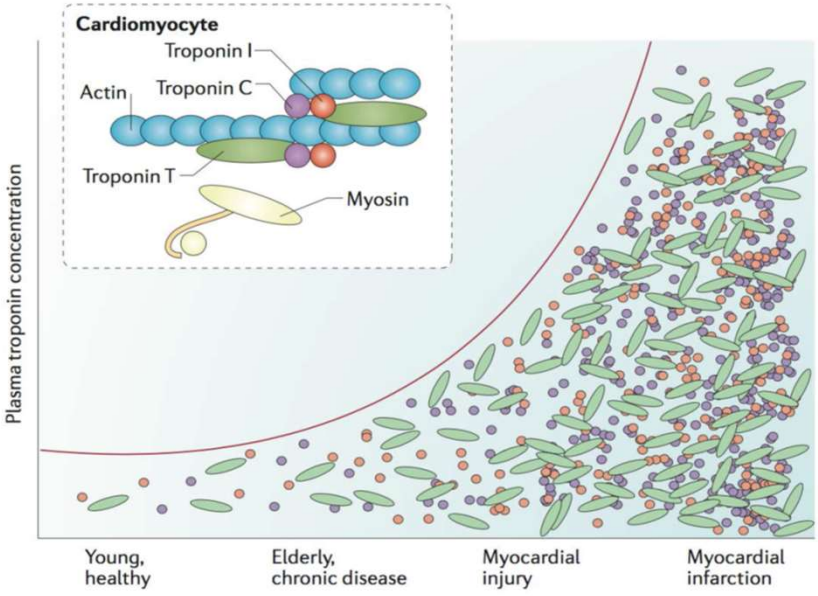
Les formes circulantes de Troponine



Westermann 2017

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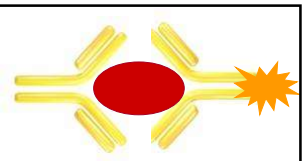
Dosages HS cTn en 2024

« Designated by manufacturers endorsed by IFCC»



- 30 dosages hypersensibles lités par IFCC
  - Biomarkers Reference Tables – IFCC
  - 4 dosages validés sur sang total

- Hétérogénéité des techniques sandwich (TnI)
- Absence de standardisation

  => pas de « transfert » des résultats inter-technique

https://ifcc.org/ifcc-education-division/emd-committees/committee-on-clinical-applications-of-cardiac-bio-markers-c-cb/biomarkers-reference-tables/

version Juin 2024

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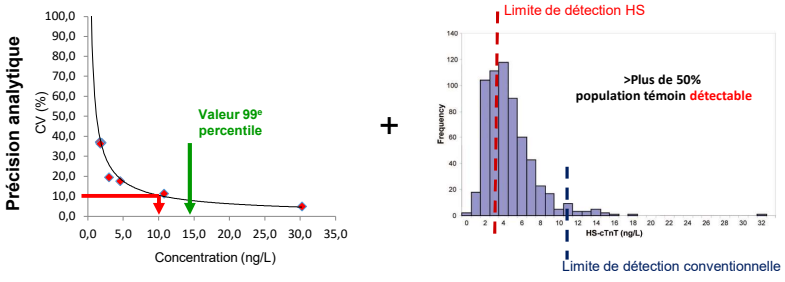
méthode de dosage hyper-sensible :



Deux critères ont été retenus par Apple et Collinson pour définir « l'hypersensibilité » d'un dosage de cTn (Apple et al., 2012) :

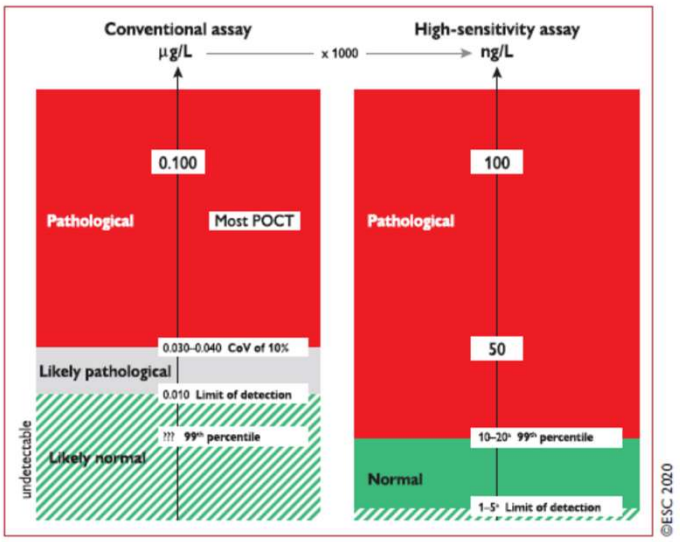
- sa précision au seuil du 99e percentile d'une population de référence, qui doit être ≤ 10%
- la proportion de sujets sains détectables (sujets dont la concentration de cTn est supérieure à la limite de détection de la méthode), qui doit être d'au moins 50 % des sujets sains analysés

8

ESC GUIDELINES

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

The Task Force for the manage
in patients presenting without
the European Society of Cardic



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Cardiospécificité

+

Hyper-sensibilité analytique

=

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

Table S3 Conditions other than acute Type 1 myocardial infarction associated with cardiomyocyte injury (i.e. cardiac troponin elevation)

Myocardial injury related to acute myocardial ischaemia because of oxygen supply/demand imbalance (Type 2 MI)
Reduced myocardial perfusion, e.g.:
• Coronary artery spasm, microvascular dysfunction
• Coronary embolism
• Non-atherosclerotic 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 ventri

Other causes of myocardial injury
Cardiac conditions:
• Heart failure
• Myocarditis[a]
• Cardiomyopathy (any type)
• Takotsubo syndrome
• Cardiac contusion or cardiac procedures (CABG, PCI, valvular interventions, ablation, pacing, cardioversion, or endomyocardial biopsy)
Systemic conditions:
• Sepsis, infectious disease
• Chronic kidney disease
• Stroke, subarachnoid haemorrhage
• Pulmonary embolism, pulmonary hypertension
• Infiltrative diseases (e.g. amyloidosis, sarcoidosis, haemochromatosis, scleroderma)
• Myocardial drug toxicity or poisoning (e.g. doxorubicin, 5-fluorouracil, trastuzumab, snake venoms)
• Critically ill patients
• Hypo- and hyper-thyroidism
• Strenuous exercise
• Rhabdomyolysis

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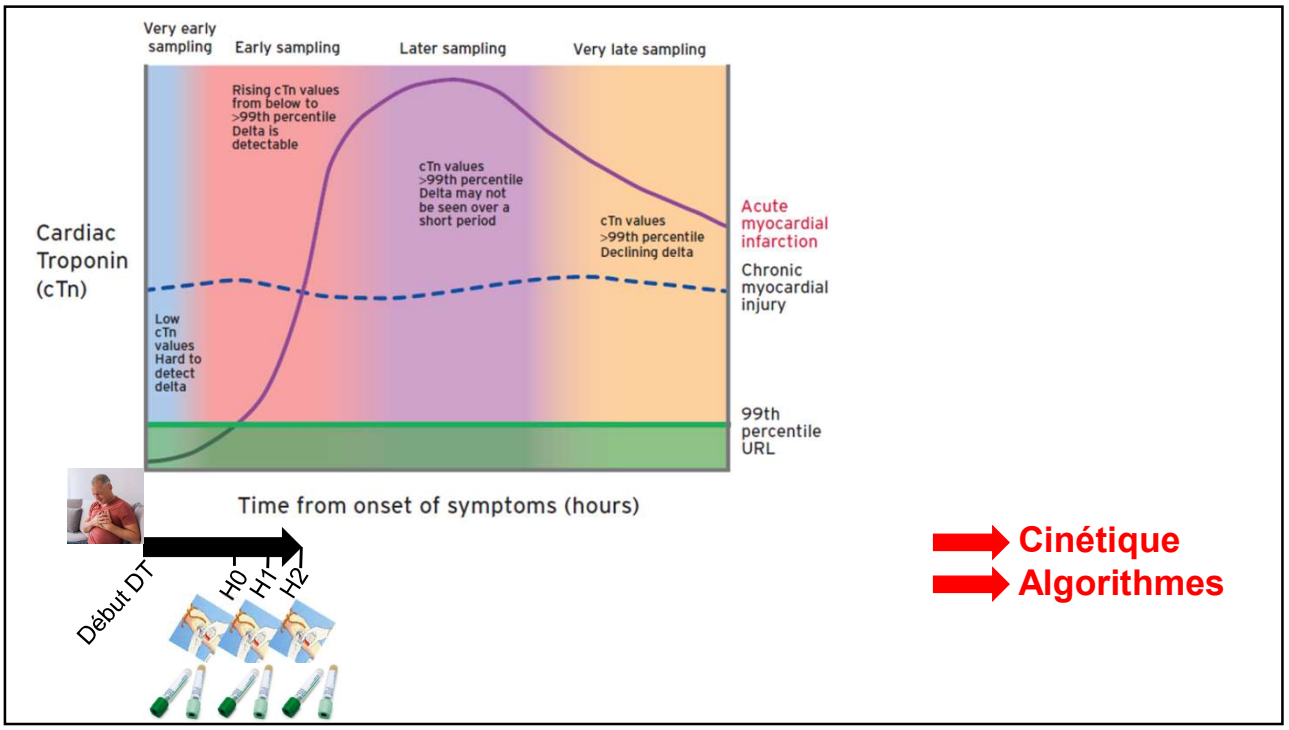

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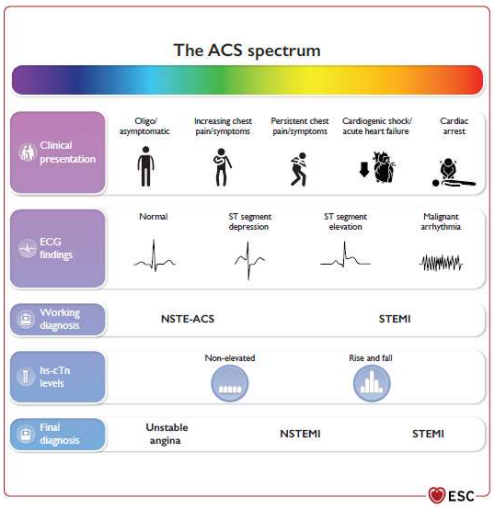
ESC European Society of Cardiology
European Heart Journal (2023) 00, 1–107
https://doi.org/10.1093/eurheartj/ehad191

ESC GUIDELINES

2023 ESC Guidelines for the management of acute coronary syndromes

Developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC)

Measurement of a biomarker of cardiomyocyte injury, preferably high-sensitivity cardiac troponin (hs-cTn), is recommended in all patients with suspected ACS.[15,17,25–27,53,54] If the clinical presentation is compatible with myocardial ischaemia, then a rise and/or fall in cTn above the 99th percentile of healthy individuals points to a diagnosis of MI as per the criteria in the fourth universal definition of MI.[1] In patients



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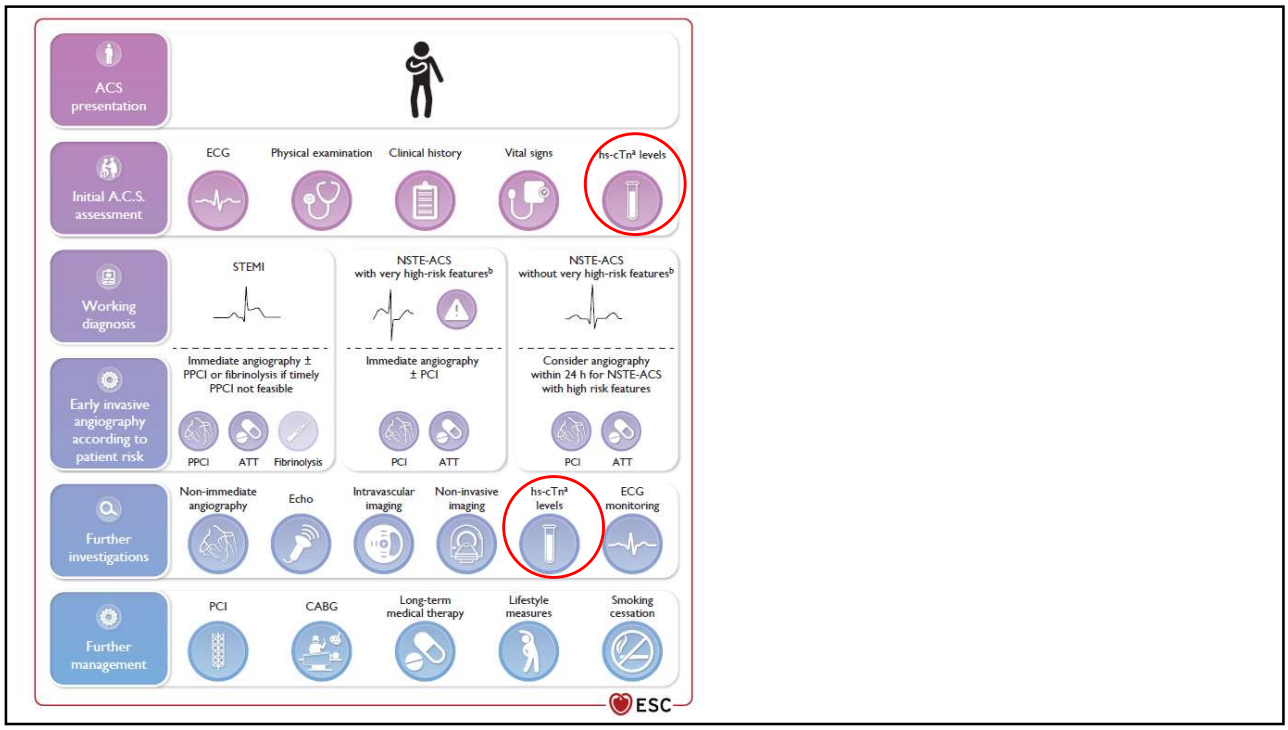

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ESC GUIDELINES

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3.3.4. Rapid 'rule-in' and 'rule-out' algorithms

Due to their higher sensitivity and diagnostic accuracy for the detection of MI at presentation, the time interval to the second cTn assessment can be shortened with the use of hs-cTn assays. This substantially reduces the delay to diagnosis, translating into shorter stays in the ED, lower costs, and less diagnostic uncertainty for patients.[15,83–88] It is recommended to use the 0 h/1 h algorithm (best option) or the 0 h/2 h algorithm (second-best option) (*Figure 6*). These algorithms have been derived and validated in large multicentre diagnostic studies using central adjudication of the final diagnosis for all currently available hs-cTn assays.[27–39,62,70,73,82,89–93] Optimal thresholds for rule-out were selected to allow a sensitivity and NPV of at least 99%. Optimal thresholds for rule-in were selected to allow a positive predictive value (PPV) of at least 70%. These algorithms were developed from large derivation cohorts and then validated in large independent validation cohorts. The previous ESC 0 h/3 h algorithm was considered as an alternative,[40,56] but three recent large diagnostic studies suggested that the ESC 0 h/3 h algorithm appears to balance efficacy and safety less well than more rapid protocols using lower rule-out concentrations, including the ESC 0 h/1 h algorithm.[41–43] The very high safety and high efficacy of applying the ESC 0 h/1 h algorithm was recently confirmed in three real-life implementation studies, including one randomized controlled trial (RCT).[44,94,95] Therefore, the ESC 0 h/3 h algorithm is an alternative for cases where the ESC 0 h/1 h or 0 h/2 h algorithms are not available. Of note, patients assigned to the 'rule-out' pathway using the ESC 0 h/1 h or 0 h/2 h algorithms have a very low rate of clinical events through to 30 days.[95,96]

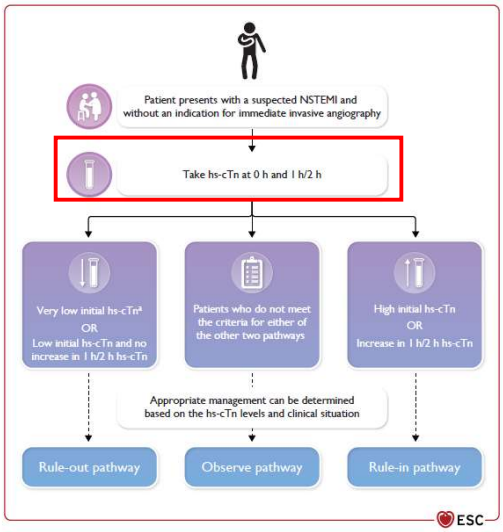

Figure 6 The 0 h/1 h or 0 h/2 h rule-out and rule-in algorithms using high-sensitivity cardiac troponin assays in patients presenting to the emergency department with suspected NSTEMI and without an indication for immediate invasive angiography. hs-cTn, high-sensitivity cardiac troponin; NSTEMI, non-ST-elevation myocardial infarction. Patients are classified into one of three pathways as per the results of their hs-cTn values at 0 h (time of initial blood test) and 1 h or 2 h later. Patients with a very low initial hs-cTn value or patients with a low initial value and no 1 h/2 h change in hs-cTn are assigned to the 'rule-out' pathway. Patients with a high initial hs-cTn value or a 1 h/2 h change in hs-cTn are assigned to the 'rule-in' pathway. Patients who do not meet the criteria for the rule-out or rule-in strategies are assigned to the 'observe' pathway, and these patients should have hs-cTn levels checked at 3 h ± echocardiography in order to decide on further management. Cut-offs are assay specific (see Supplementary material online, *Table S4*) and derived to meet pre-defined criteria for sensitivity and specificity for NSTEMI. Potential management and testing options for each of the three strategies are provided in the relevant sections of the main text.[12–15,24,27,53,55–58,100,101] [a]Only applicable if the chest pain onset was >3 h prior to the 0 h hs-cTn measurement.

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Table S4 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	No 1 hΔ	High	1 hΔ
hs-cTnT (Elecsys; Roche)	<5	<12	<3	≥52	≥5
hs-cTnI (Architect; Abbott)	<4	<5	<2	≥64	≥6
hs-cTnI (Centaur; Siemens)	<3	<6	<3	≥120	≥12
hs-cTnI (Access; Beckman Coulter)	<4	<5	<4	≥50	≥15
hs-cTnI (Clarity; Singulex)	<1	<2	<1	≥30	≥6
hs-cTnI (Vitros; Clinical Diagnostics)	<1	<2	<1	≥40	≥4
hs-cTnI (Pathfast; LSI Medience)	<3	<4	<3	≥90	≥20
hs-cTnI (TriageTrue; Quidel)	<4	<5	<3	≥60	≥8
hs-cTnI (Dimension EXL; Siemens)	<9	<9	<5	≥160	≥100
0 h/2 h algorithm	**Very low**	**Low**	**No 2 hΔ**	**High**	**2 hΔ**
hs-cTnT (Elecsys; Roche)	<5	<14	<4	≥52	≥10
hs-cTnI (Architect; Abbott)	<4	<6	<2	≥64	≥15
hs-cTnI (Centaur; Siemens)	<3	<8	<7	≥120	≥20
hs-cTnI (Access; Beckman Coulter)	<4	<5	<5	≥50	≥20
hs-cTnI (Clarity; Singulex)	<1	TBD	TBD	≥30	TBD
hs-cTnI (Vitros; Clinical Diagnostics)	<1	TBD	TBD	≥40	TBD
hs-cTnI (Pathfast; LSI Medience)	<3	TBD	TBD	≥90	TBD
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The cut-offs apply irrespective of age, sex, 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 with these universal cut-offs.[30,31] The algorithms for additional assays are in development: hs-cTn T on Elecsys (Roche), hs-cTn I on Architect (Abbott), hs-cTn I on Centaur (Siemens), hs-cTn I on Access (Beckman Coulter), hs-cTn I on Clarity (Singulex), hs-cTn I on Vitros (Clinical Diagnostics), hs-cTn I on Pathfast (LSI Medience), and hs-cTn I on TriageTrue (Quidel).
hs-cTn, high-sensitivity cardiac troponin; TBD, to be determined.[30,31,67–88]

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Faire des cinétiques H0- H1/2 : challenges

Time to decision = time of blood draw + turnaround time. The use of the ESC 0 h/1 h algorithms is irrespective of the local turnaround time (time from blood draw to blood results); 0 h and 1 h refer to the time points at which blood is taken. The second blood draw may need to be taken before the result from the first one is available (although the results should be available in most cases within 60 min of blood sampling), but this does not affect the interpretation of the algorithms. The clinical and economic benefit of the ESC 0 h/1 h algorithm compared with other algorithms where the second blood draw is later than 1 h is therefore independent of the local turnaround time.[98]

- Méthode de dosage HS pour la Troponine
- Demander systématiquement la datation de la DT ?
- Contractualiser avec le service prescripteur
- Recours à la biologie délocalisée ?
- Faire H1 sans avoir le résultat de H0 ??

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Du bon usage clinique

- Le bon usage clinique des cTn reposera sur plusieurs éléments :
- Une prescription justifiée
- Une prescription documentée :
  - datation de la douleur thoracique,
  - seuils d'interprétation

+ connaitre les causes d'élévation hors SCA

+ connaitre la valeur ajoutée de la cTn dans la prise en charge du patient.

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Du bon usage clinique des dosages de troponine

- Mieux encadrer l'usage du dosage de troponine ?
  - Ex du sujet âgé :

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

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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

Du bon usage biologique

- Le bon usage biologique sera assuré par :
  - une maitrise de la qualité analytique des dosages :
    - suivi de l'imprécision dans les faibles valeurs du domaine de mesure

  - une maitrise des délais de rendus compatibles avec la prise en charge du patient
  - l'exploration des éventuels faux positifs analytiques.

Pourquoi maitriser l'imprécision de la méthode de dosage dans les faibles valeurs du domaine de mesure ?

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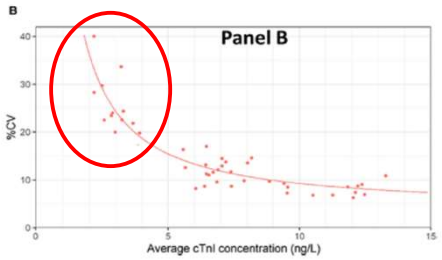

Ziwen Li*, Yong Yong Tew, Peter A. Kavsak, Kristin M. Aakre, Allan S. Jaffe, Fred S. Apple, Paul O. Collinson and Nicholas L. Mills, on behalf of the High-STEACS Trial Investigators

Impact of high-sensitivity cardiac troponin I assay imprecision on the safety of a single-sample rule-out approach for myocardial infarction

Table 1: Estimated proportion of patients with suspected acute coronary syndrome misclassified due to hs-cTnI assay imprecision (coefficient of variation (CV) from 10 to 50 %) at the rule-out threshold of <5 ng/L and the proportion of all patients evaluated (n=47,357) with missed MI or myocardial injury due to imprecision.

CV	Measured hs-cTnI concentration, ng/L	Proportion misclassified as low risk by imprecision % (95 %CI)	Likelihood of MI in those reclassified % (95 %CI)	Proportion of all patients with missed MI due to imprecision % (95 %CI)	Likelihood of myocardial injury in those reclassified % (95 %CI)	Proportion of all patients with missed myocardial injury due to imprecision % (95 %CI)
10 %	5	15.9 (14.4–17.5)	0.3 (0.1–0.5)	0.01 (0.01–0.03)	0.5 (0.2–0.8)	0.02 (0.01–0.04)
	6	0.1 (0–0.4)	0 (0–0.2)		0 (0–0.2)	
20 %	5	31.1 (29.2–33.1)	0.5 (0.3–0.9)	0.03 (0.02–0.05)	0.9 (0.6–1.4)	0.05 (0.03–0.07)
	6	6.7 (5.5–8)	0.2 (0–0.5)		0.3 (0.1–0.6)	
	7	0.6 (0.3–1.2)	0 (0–0.2)		0 (0–0.3)	
30 %	5	36.9 (34.9–39)	0.7 (0.4–1.1)	0.05 (0.03–0.07)	1.1 (0.8–1.7)	0.08 (0.06–0.11)
	6	15.9 (14.2–17.7)	0.4 (0.2–0.8)		0.7 (0.3–1.2)	
	7	4.7 (3.6–5.9)	0.1 (0–0.5)		0.3 (0.1–0.7)	
	8	1 (0.5–1.7)	0 (0–0.3)		0.1 (0–0.4)	
	9	0.1 (0–0.6)	0 (0–0.3)		0 (0–0.3)	
40 %	5	40.1 (38–42.2)	0.7 (0.4–1.1)	0.06 (0.04–0.09)	1.2 (0.8–1.8)	0.11 (0.08–0.14)
	6	22.6 (20.6–24.7)	0.6 (0.3–1.1)		0.9 (0.5–1.5)	
	7	10.6 (9–12.5)	0.3 (0.1–0.7)		0.7 (0.3–1.2)	
	8	4 (3–5.3)	0.1 (0–0.4)		0.2 (0.1–0.7)	
	9	1.2 (0.6–2.1)	0 (0–0.4)		0.1 (0–0.5)	
	10	0.3 (0.1–0.9)	0 (0–0.4)		0 (0–0.4)	
	11	0.1 (0–0.6)	0 (0–0.4)		0 (0–0.4)	
50 %	5	42.1 (40–44.3)	0.7 (0.4–1.1)	0.08 (0.05–0.1)	1.3 (0.9–1.8)	0.14 (0.11–0.18)
	6	27.3 (25.1–29.5)	0.7 (0.4–1.2)		1.2 (0.7–1.8)	
	7	15.8 (13.9–17.9)	0.4 (0.2–0.9)		1 (0.5–1.7)	
	8	8.1 (6.6–9.8)	0.2 (0.1–0.6)		0.5 (0.2–1)	
	9	3.4 (2.4–4.8)	0.2 (0–0.6)		0.3 (0.1–0.9)	
	10	1.4 (0.7–2.5)	0.1 (0–0.5)		0.1 (0–0.7)	
	11	0.4 (0.1–1.1)	0 (0–0.4)		0 (0–0.5)	
	12	0.2 (0–0.8)	0 (0–0.5)		0 (0–0.5)	

- 48,282 consecutive patients with suspected acute coronary syndrome
- hs-cTnI assay (ARCHITECTSTAT, Abbott Laboratories)
- HighSTEACS trial,
- simulated the effect of imprecision for a range of CVs at the rule-out threshold

Clin Chem Lab Med 2024

23

Clinical Chemistry 64:4
645-655 (2018)

Special Report

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]

Recommandation :

- **3 niveaux de concentrations** différentes en QC avec **passage quotidien [..].**
- Chaque niveau validé avec les **limites d'imprécision indiquées par le fournisseur**
- Résultats des CQ en ng/L exprimés avec 1 décimale

(1) Concentration 1: concentration entre la **LoD et le 99ème percentile ♀.**

(2) Concentration 2 : concentration supérieure mais proche **(limite + 20%) du 99ème percentile ♂.**

(3) Concentration 3: concentration très élevée (évaluation de la limite de linéarité) des Tn

Ex: 10 x 99ème percentile si patients avec intervention cardiaque .

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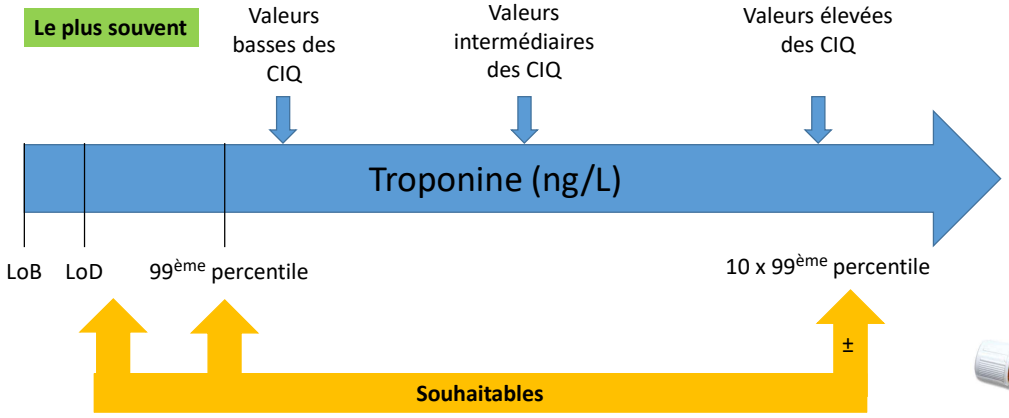
Contrôles de qualité et dosage de Troponine



Produit de contrôle complet et multi-analytes optimisé pour le dosage de la troponine haute sensibilité près de la limite de détection

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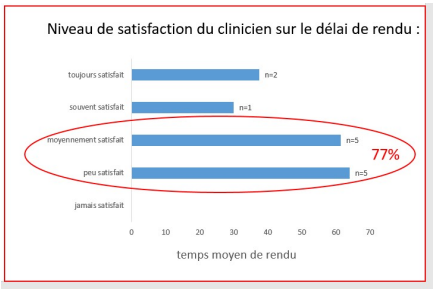
Combien de temps pour le résultat de troponine ?

Enquête « Entroprise » SFBC SFMU
28 centres participants

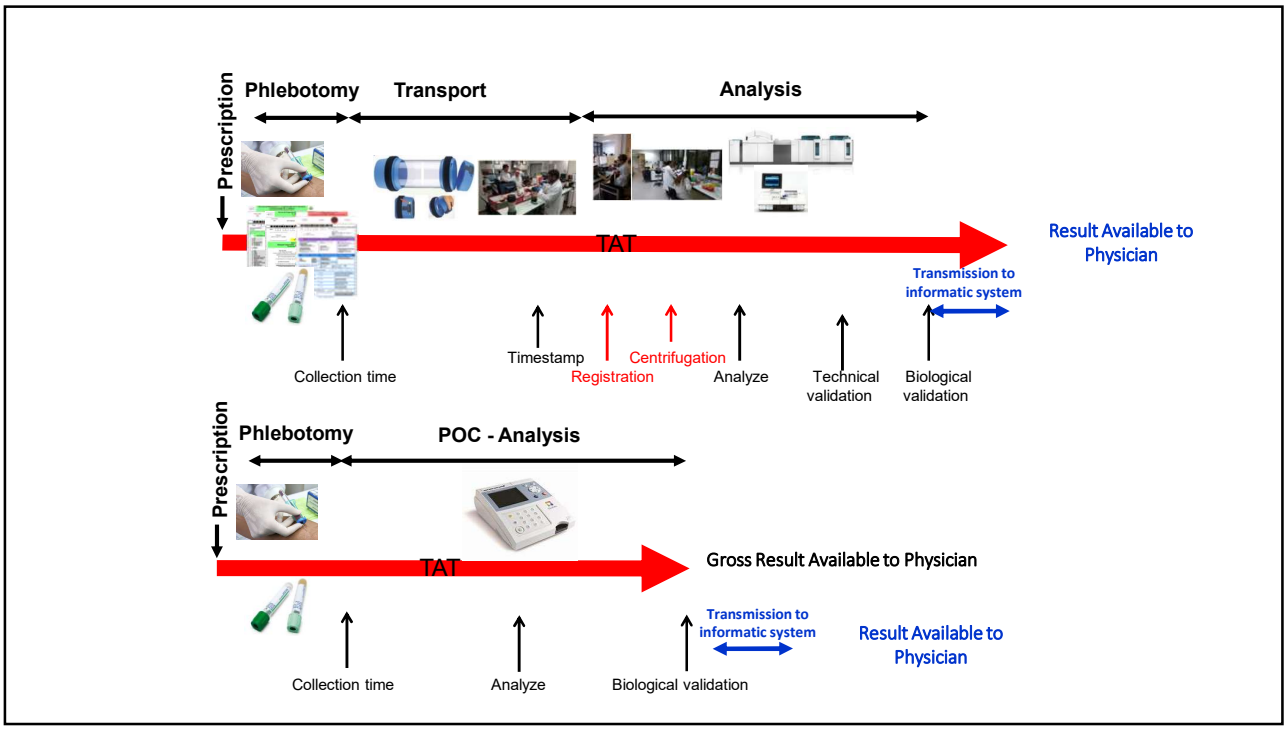


87 410 dossiers demandes de troponine étudiées :

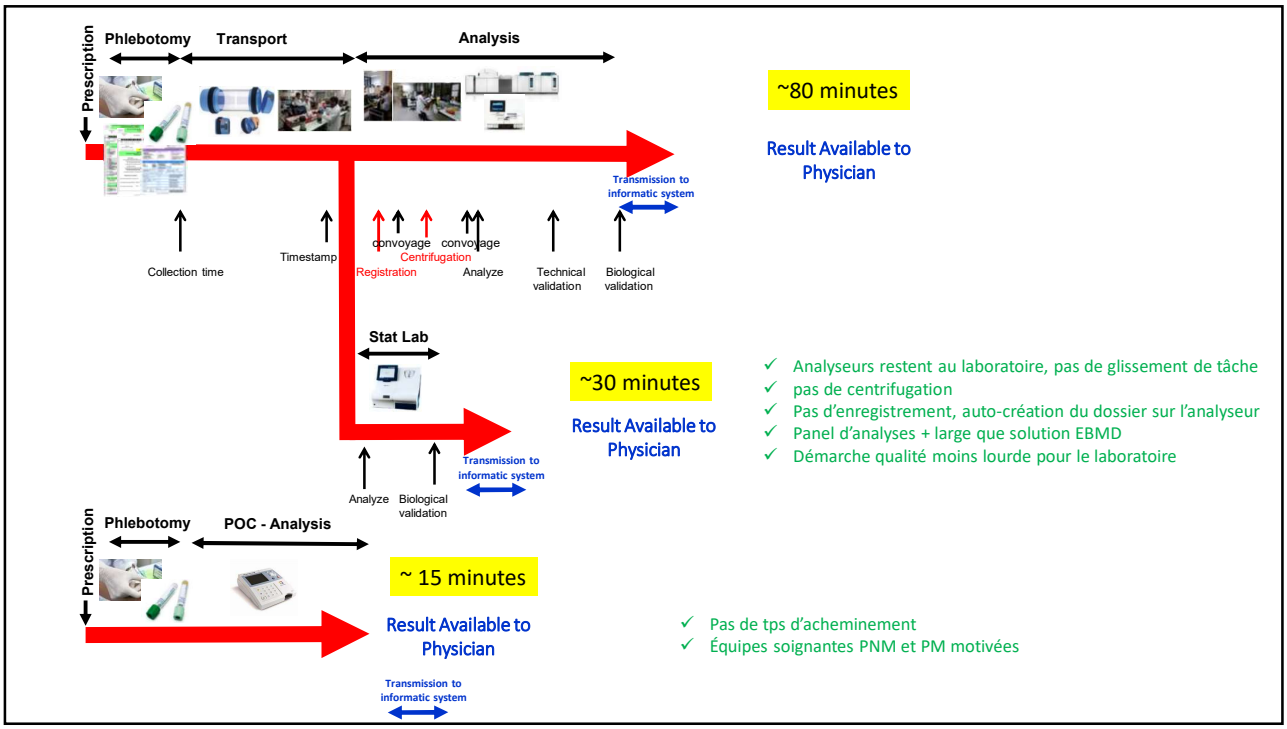
Délai médian de rendu global
= 81 minutes

Résultat rendu

26


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

27


Prescription
Phlebotomy
Transport
Analysis
~80 minutes
Result Available to Physician
Transmission to informatic system
Collection time
Timestamp
convoyage
convoyage
Centrifugation
Registration
Analyze
Technical validation
Biological validation
Stat Lab
~30 minutes
Result Available to Physician
Transmission to informatic system
Analyze
Biological validation
Prescription
Phlebotomy
POC - Analysis
~ 15 minutes
Result Available to Physician
Transmission to informatic system
✓ Analyseurs restent au laboratoire, pas de glissement de tâche
✓ pas de centrifugation
✓ Pas d'enregistrement, auto-création du dossier sur l'analyseur
✓ Panel d'analyses + large que solution EBMD
✓ Démarche qualité moins lourde pour le laboratoire
✓ Pas de tps d'acheminement
✓ Équipes soignantes PNM et PM motivées

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Dosage de troponine : faux négatifs, faux positifs ?

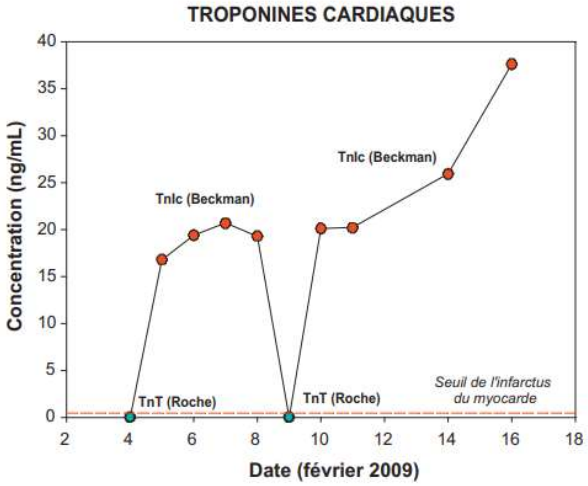

Figure 1 Évolution des résultats du dosage de la troponine chez le patient.

Immuno-analyse et biologie spécialisée (2010) **25**, 272–275

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Substances interférentes

While the overall prevalence of false positive cTnT and cTnI is unknown, false positive troponin I elevations of up to 3.1% have been reported in reference populations.[w44] [w45] Antibodies with varying epitope specificities used in different cTnI assays have been suggested as an important cause of discrepant test results. Post-translational modifications such as proteolytic degradation and phosphorylation of cTnI may lead to changed cTnI epitopes.[w46] [w47] Such modifications are less likely

Box 2 Possible causes of false positive troponin results

- Heterophile antibodies
- Human anti-mouse antibodies
- Autoantibodies
- Rheumatoid factor
- Haemolysis
- Fibrin clots
- Microparticles in specimen
- Interference by endogenous components in blood (bilirubin, haemoglobin, lipaemia)
- High concentration of alkaline phosphatase
- Immunocomplex formation
- Analyser malfunction

Modified from Lum *et al*[11] with permission of the American Society for Clinical Pathology.

Excess fibrin has also been described as a cause of false positive cTnI results due to non-specific antibody binding, or to trapped indicator enzyme in the separation matrix in incompletely clotted serum samples.[w31]

Positive interference may also occur due to high concentrations of alkaline phosphatase in some cTnI assays using alkaline phosphatase as a substrate, or to the presence of a macro immunocomplex involving cTnI and IgG.[w32] [w33]

Vafaie M, *et al*. *Heart* 2014;**100**:508–514. doi:10.1136/heartjnl-2012-303202

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Box 3 Algorithm for assumed false positive troponin result due to discrepancy between clinical presentation and laboratory value

Suspected false positive troponin result

↓

Same test result in repeated blood draw? Haemolysis?

↓

Rule out true cardiac pathology (1)

Check for non-acute coronary syndrome related causes of elevated troponin (echocardiography, further laboratory testing, etc)

↓

Consider analytically false positive result

Test sample with different troponin assay (if available)

Directly communicate with laboratory to: (1) consider adding endogenous immunoglobulin-free serum samples or using blocking agents; (2) check analyser to rule out instrument malfunction; (3) examine specimen tube for microparticles or clots to rule out fibrin interference (centrifuge again if necessary); (4) refer further testing to reference laboratory or manufacturer

↓

Rule out true cardiac pathology (2)

Consider further cardiac testing using more sensitive methods (cardiac MRI, coronary CT angiography, coronary angiography, myocardial biopsy)

Vafaie M, *et al*. *Heart* 2014;**100**:508–514. doi:10.1136/heartjnl-2012-303202

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Retenir l'essentiel

- La troponine cardiaque (cTn) : I ou T, c'est un **marqueur d'atteinte du tissu myocardique**
- Nombreuses méthodes de dosage de troponine, non standardisées. Méthodes hypersensibles (HS) = permettent de **mesurer avec précision de faibles concentrations circulantes de cTn**, y compris dans les populations de référence
- Une variation de concentration circulante de cTn au-dessus des valeurs usuelles (soit >99^{e} percentile d'une population de référence) signe une **atteinte du tissu myocardique**
- La cTnHS un excellent biomarqueur d'atteinte du tissu myocardique, et permet de détecter de **nombreuses circonstances où une atteinte myocardique existe** comme une entité à part entière, y compris en l'absence de pathologie cardiaque ischémique aigue.
- **Dosages répétés** sur des prélèvements différents => caractère aigu ou chronique de l'élévation
- Douleur thoracique suspecte du SCA : les sociétés savantes proposent des **algorithmes** d'interprétation sur des prélèvements séquentiels dont les délais sont raccourcis à **1 ou 2 heures**, permettant d'optimiser la prise en charge des patients.
- **Le bon usage clinique =**
  - **prescription justifiée,**
  - **Prescription documentée (datation de la douleur thoracique, seuils d'interprétation)**
- **Le bon usage biologique =**
  - **maitrise de la qualité analytique des dosages aux seuils décisionnels,**
  - **maitrise des délais de rendus compatibles avec la prise en charge du patient,**
  - **exploration des éventuels faux positifs analytiques.**

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