IFCC Task Force on Clinical Applications of Cardiac Biomarkers (TF-CB)

Report to the General Conference 2016

Madrid

CREATED

By the EB in 2011, following to the

Committee on Standardization of Cardiac Markers Damage (C-SCMD)

COMPOSITION

50% clinical laboratory + 50% ED physicians/cardiologists +

company (9) representatives

AIM

Integrate clinical and laboratory information to develop educational materials for the best use of cardiac biomarkers in daily practice

TERMS OF REFERENCE

- Education: Established and novel biomarkers
- Biochemistry: Physiology
- Laboratory: Quality specifications
- Clinical use: Diagnostics, reference values (p99th), serial (delta) values, biological variation, risk stratification, therapy

WEB SITE

http://www.ifcc.org/ifcc-executive-board-and-council/eb-task-forces/task-force-on-clinical-applications-of-cardiac-bio-markers-tf-cb

FIRST EDUCATIONAL ACTIVITY
focused on

High sensitivity cardiac troponin assays

Sensitive Troponin I Assay in Early Diagnosis of Acute Myocardial Infarction
Till Keller, et al.
One hs-Troponin I
N Engl J Med 2009;361:868-77.

Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays
Tobias Reichlin, et al.
Two hs-Troponin I, one hs-TroponinT
N Engl J Med 2009;361:858-67.

Analytical Characteristics of High-Sensitivity Cardiac Troponin Assays

Fred S. Apple, Paul O. Collinson and
For the IFCC Task Force on Clinical Applications of Cardiac Biomarkers
Clin Chem 2012; 58:54-61.

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

[a] LoD, limit of detection; [illegible]P, microtiter plate.
[b] CV at the 99th percen[illegible]
[c] Under development an[illegible]t available for commercial use.
[d] Available for use worl[illegible]e but not cleared by the US Food and Drug Administration for use in the US.

c Under development and not available for commercial use.

How does an assay become designated hs?
How to define healthy (normal) reference populations for determining the 99th percentile?
What is the biological variation of these analytes?
What assay imprecision are acceptable?
Will standardization of cTn assays be attainable?

Table 3. Short-term analytical and biological variation by hs-cTnI assays.

	Abbott[a]	Beckman[a]	Roche (E170)[b]	Siemens[a]	Singulex[c]
CV-A,[d] %	13.8	14.5	7.8	13.0	8.3
CV-I, %	15.2	6.1	15.0	12.9	9.7
CV-G, %	70.5	34.8	NA	12.3	57
Index of individuality	0.22	0.46	NA	0.11	0.21
RCV, %[e]	NA	NA	47.0	NA	NA
RCV increase, %[f]	69.3	63.8	NA	57.5	46.0
RCV decrease, %[f]	−40.9	−38.9	NA	−36.5	−32
Within-individual mean, ng/L	3.5	4.9	NA	5.5	2.8

[a] Apple et al. *(38)*.
[b] Vasile et al. *(36)*.
[c] Wu et al. *(35)*.
[d] CV-A, analytical CV; CV-I, within-individual CV; CV-G, between-individual CV; NA, not available; RCV, relative change value.
[e] RCV percentage applies to the parametric data.
[f] RCV increase and decrease percentages refer to nonparametric data and are log-transformed.

Clinical Biochemistry 48 (2015) 201–203

Contents lists available at ScienceDirect

Clinical Biochemistry

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

Position Statement

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

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on behalf of the International Federation of Clinical Chemistry (IFCC) Task Force on Clinical Applications of Cardiac Bio-Markers

Educational documents posted on the IFCC website
http://www.ifcc.org/ifcc-news/2014-07-22-tf-cbdocuments

99th Percentile URL

Universally endorsed as the cut-off to aid in the diagnosis of acute myocardial infarction

- should be determined in a healthy population
- values form peer-reviewed literature or manufacturers' product considered acceptable
- measured with an analytical imprecision of ≤10% (% CV; coefficient of variation)
- hs assays should measure cTn above the limit of detection in ≥50% of healthy subjects
- values reported as whole numbers only (ng/L)

Factors influencing the 99th percentile

- age, increase with increasing age, especially >60-y
- gender, men higher values
- assay, 99th percentile for each assay
- specimen, 99th percentile may vary for serum, plasma and/or whole blood
- values or with appropriate statistical power, minimum of:
  - established in 300 male and 300 female
  - confirmed in 20 subjects each gender
- using an appropriate 1-tailed nonparametric statistical method

Pocket-size documents

Hs-TROPONINS. CLINICAL USE

Pocket-size documents

Changing values suggest acute myocardial injury. However, acute myocardial injury is not always an Acute Myocardial Infarction (AMI)[1]

Distinguishing acute from chronic c-Tn elevations using high sensitivity assays requires serial measurements to detect significant changes.

Key components for detecting rising and/or falling values are:

Obtain samples for cTn on admission and as clinically indicated. At present 3 hour intervals seems most reasonable.[2]

A change in values (delta) can be reported as a percentage or absolute concentrations between serial measurements.

Deltas must be calculated with values from the same cTn assay.[3]

Key considerations for interpreting deltas:

The larger the delta, the higher the specificity (i.e., the lower the sensitivity) for acute cardiac injury, including AMI.[4]

The lower the delta, the higher the sensitivity (i.e., the lower the specificity) for acute cardiac injury, including AMI.[4]

Delta values are dependent on the cTn assay used and the timing interval used.

All groups involved in the clinical care of patients should decide conjointly about what criteria should be used and possible exceptions to their use.

AMI diagnosis

AMI is an appropriate diagnosis if there is a change in cTn values measured with high sensitivity assays of a magnitude appropriate for the assay being used with at least one result exceeding the 99th percentile in the appropriate clinical situation.[1]

Practical tips

Correlate the cTn values with the clinical characteristics of the patient.

Recent reports suggest that an absolute delta (in ng/L) may be superior to a relative (percent) delta.[5,6]

Patients who present late after AMI may not manifest a change in values.[7]

When in doubt, obtain additional data including further serial hs-cTn results, as appriopriate.

At present, it appears that in some patients, clinical judgement will be necessary to modify and/or augment the results of delta calcuations.[3-7]

To date, there is no expert consensus guidance on a procedure for establishing or confirming delta values. Until this is available, institutions should agree on a delta value based on available data (peer-reviewed journals, manufacturer's documentation), for individual cTnI and cTnT high sensitivity assays and then modify based on experience and feedback.

USING HIGH SENSITIVITY CARDIAC TROPONIN ASSAYS IN PRACTICE

TASK FORCE ON CLINICAL APPLICATIONS OF CARDIAC BIO-MARKERS

ifcc International Federation of Clinical Chemistry and Laboratory Medicine

CURRENT ACTIVITIES

UNDER DEVELOPMENT

Contemporary cTn Assays

At present contemporary cTnI and cTnT assays are not standardized. Therefore, cTn results from different assays should not be used for the evaluation and management of a patient.

Contemporary cTn assays have higher analytical limits of detection (LoD) than hs-cTn assays. For this reason, both the majority of reference subjects as well as patients with diverse myocardial pathologies with minor myocardial injury and AMI patients who present within 6 hours of their initial clinical presentation may manifest undetectable (<LoD) cTn concentrations at presentation.

Optimal clinical specificity and negative predictive values (NPV) are found at $\geq$ 6 hours after presentation.

The likelihood of a future adverse event is higher in a patient found with an increased cTn above the 99th percentile independent of the clinical diagnosis.

Increased and changing (delta) cTn values can occur with acute myocardial injury, including any type of AMI.

For contemporary assays, delta cTn values expressed as a relative, percent change assists in optimizing diagnosis specificity and NPV; i.e. acute myocardial injury (including type 1 and type 2 AMI) from chronic myocardial injury.

cTn increases due to chronic renal disease (hemodialysis patients) are more common with cTnT than cTnI, but both assays are associated with an increased mortality risk. This is also true for hs-assays.

Patients with increased cTn values during an acute hospitalization are at great risk of adverse events, but appropriate interventions are often unclear. A cardiovascular follow-up evaluation of these patients after discharge is warranted to assess appropriate management.

High Sensitivity-cTn assays

At present there is not an evidence-based definition for a 'hs-cTn' assay. The IFCC TF-CB, a multi-disciplined group, comprised of laboratory medicine, cardiology and emergency medicine biomarker experts, has recommended that to be designated a 'high sensitivity' assay, 2 criteria need to be meet:

cTn assays need to measure $\geq$ 50% of reference (apparently healthy) subjects above the assay's LoD,

cTn assays must have a %CV of $\leq$ 10% at the 99th percentile URL of the assay.

Improved analytical imprecision around the 99th percentile decreases the noise around the URL and substantially few false positives are found.

High sensitivity assays concentration reporting are distinguished from contemporary assays (µg/L) through reporting on value as whole number in ng/L

High-sensitivity assays should be interpreted based on sex derived 99th percentile URLs, as men have statistically higher values compared to women.

Growing evidence points towards improved detection of myocardial injury and AMI in women that were missed with a single combined, gender 99th percentile.

While a larger number of patients will be found with a minor cTn increases, the rate of AMI has not significantly increased with the use of hs-assays.

The evidenced-based literature suggests that deltas for hs-assays be defined based on an absolute concentration value, not a percentage change, to optimize clinical specificity

The ability to determine the biological variability (BV) of hs-cTn in healthy subjects needs to be considered when evaluating serial (delta) changes for ruling out AMI.

Optimal clinical specificity and negative predictive values (rule out) are found at $\geq$2 to 3 hours after presentation; a substantial improvement to the contemporary assays.

The likelihood of a future adverse event is higher in patients found with cTn values both: 1) at the higher end of the reference interval, and 2) above the 99th percentile independent of the clinical diagnosis.

CONTEMPORARY cTn ASSAYS MERIT SOME ROOM

- Planning to develop a review dealing with contemporary cTn assays, including POCT ones, and hs-cTn to update the current knowledge

ADAPTING THE MESSAGES TO THE NEW TECHNOLOGIES

- Papers on journals are useful for education, but not always accessible everywhere
- But everybody has a cellphone or a laptop
- Will develop an app (if approved by the IFCC) to maximally distribute the educational messages