GENERAL CONFERENCE
November 2012, Kuala Lumpur

TASK FORCE ON CLINICAL APPLICATIONS
OF CARDIAC BIOMARKERS
(TF CB)
BACKGROUND

IFCC Committee on Standardization of Markers of Cardiac Damage (C-SMCD)
Standardise Myoglobin, CK-MB, Troponin I, natriuretic peptides &
Development lab and clinical recommendations about markers use
Ended activities in December 2009

NEED TO STANDARDIZE METHODS
IFCC Working Group on cardiac TnI Standardization

NEED TO EDUCATE ON THE DAILY USE
IFCC Task Force on Clinical Applications
GENERAL OBJECTIVES

In accordance with the IFCC objectives:

“To ensure that standardization and research activities are more oriented towards the patient and towards the health of the individual”

“To develop and maintain IFCC communications, to promote publications and products from IFCC, etc”.

The TF aims:

• To develop an educational initiative for the field of cardiovascular biomarkers.

• To create a forum in which clinicians and laboratory professionals produce educational materials to communicate the correct use of cardiovascular biomarkers to laboratories, clinicians and regulatory agencies.
MEMBERS

• Clinicians
  – Allan Jaffe. Cardiovascular Division, Mayo Clinic. Rochester, MN. USA
  – Bertil Lindahl. Dpt. Medical Sciences, Cardiology & Uppsala Clinical Research Center, University of Uppsala, Sweden
  – Martin Than. Christchurch Hospital Emergency Dpt. Christchurch. New Zealand

• Clinical Laboratory
  – Fred Apple. Clinical Laboratories, Hennepin County Medical Center. Minneapolis, MN. USA
  – Michael HM Chan. Chemical Pathology Dpt.. Prince of Wales Hospital. Hong-Kong, China
  – Paul O Collinson. Chemical Pathology & Cardiology Depts. St George's Hospital. London, UK
  – Mario Plebani. Laboratory Medicine Dpt., University-Hospital, Padova, Italy
MEMBERS

• IFCC
  – Ian Young. Scientific Division (Liaison)
  – Robert Christenson. Committee on Evidence-based Laboratory Medicine (C-EBLM)
  – Ellis Jacobs. Communication and Publications Division
• Corporate members
  – Abbott Diagnostics
  – Alere
  – Beckman-Coulter
  – Radiometer
  – Randox
  – Roche Diagnostics
  – Siemens Medical Solutions
  – ThermoFisher

*The corporate members are not only supporters of the TF activities, but their scientific contribution to TF is remarkable.*
(Most of the biomarkers/methods have been developed in the R&D departments of these companies)
SPECIFIC OBJECTIVES & ACTION PLAN

Defined priority
EDUCATE ON THE USE OF HIGH SENSITIVE TROPONIN ASSAYS

• Review current analytical and clinical evidence about:
  – Limits for differential diagnosis of acute coronary syndromes (ACS)
  – Critical changes for diagnosing myocardial infarction
  – Role of high-sensitive troponin in pathologies other than ACS

Action plan

• Development of short (one-page documents) as basis for educational materials
• Search of partnerships with:
  – Scientific organizations. Other organizations (both clinically and laboratory oriented) who might wish to share the materials produced
  – Industry. Companies producing assays for measuring cardiac markers which would require of educational materials for their best use
• Support from educational experts
FIRST ACTIVITY
Review and co-authoring of a mini-review produced by 2 members

Clinical Chemistry 58:1
54–61 (2012)

Mini-Reviews

Analytical Characteristics of High-Sensitivity
Cardiac Troponin Assays

Fred S. Apple¹,²* and Paul O. Collinson,³
for the IFCC Task Force on Clinical Applications of Cardiac Biomarkers†

BACKGROUND: Cardiac troponins I (cTnI) and T (cTnT) have received international endorsement as the standard biomarkers for detection of myocardial injury, for risk stratification in patients suspected of acute coronary syndrome, and for the diagnosis of myocardial infarction. An evidence-based clinical database is growing rapidly for high-sensitivity (hs) troponin assays. Thus, clarifications of the analytical principles for the immunoassays used in clinical practice are important.

CONTENT: The purpose of this mini-review is (a) to provide a background for the biochemistry of cTnT and cTnI and (b) to address the following analytical questions for both hs cTnI and cTnT assays: (i) How does an assay become designated hs? (ii) How does one realistically define healthy (normal) reference populations for determining the 99th percentile? (iii) What is the usual biological variation of these analytes? (iv) What assay imprecision characteristics are acceptable? (v) Will standardization of cardiac troponin assays be attainable?

SUMMARY: This review raises important points regarding cTnI and cTnT assays and their reference limits and specifically addresses hs assays used to measure low concentrations (nanograms per liter or picograms per milliliter). Recommendations are made to help clarify the nomenclature. The review also identifies further challenges for the evolving science of cardiac troponin measurement. It is hoped that with the introduction of these concepts, both laboratories and clinicians can develop a more unified view of how these assays are used worldwide in clinical practice.

¹ Task Force members include: Jordi Ordonez (Chair, Spain), Fred Apple (US), H.M. Chan (China), Paul Collinson (UK), Judd Hollander (US), Allan Jaffe (US), Bertil Lindahl (Sweden), Martin Möckel (Germany), Mario Plebani (Italy), and Martin Than (New Zealand).

© 2011 American Association for Clinical Chemistry
“ONE-PAGE” DOCUMENTS

The basis for summarizing in short sentences the messages to be included in educational materials

CURRENT STATUS
Drafts redacted, but still under internal discussion. After been completed (end of the year), circulated inside the IFCC bodies for open discussion
SOME EXAMPLES OF THE ONE-PAGE DOCUMENTS

Topics are

- What is a high-sensitive assay for cardiac troponin (hs-cTn)?
- How to calculate (and use) the 99th reference percentile?
- How to calculate (and use) a significant serial change?
- What is the role of point-of-care systems in the era of hs-cTn?

The documents are structured in three levels

1st level. The educational statement. All professionals regardless their specialty should know; should be included in any educational material produced

2nd level. Additional issues. All professionals should know, but their inclusion in the educational materials is not mandatory

3rd level. Any other relevant/very specific additional issue that most professionals should know
How to calculate (and use) the 99\textsuperscript{th} reference percentile?

EDUCATIONAL STATEMENT

Is the recommended decision cutoff for detecting myocardial infarction

HOW SHOULD IT BE OBTAINED?

- In a population of healthy individuals without known cardiovascular disease
- Considering ethnic diversity and as many age decades as possible
- Independently for both men and women
- In a statistically powered manner enabling analysis by a 1-tailed nonparametric method.

ADDITIONAL ISSUES

- Needs to be independently validated for specimen type
- Should be reported as whole numbers in ng/L
- Values from manufacturers or peer-reviewed literature should be adopted when an own 99\textsuperscript{th} percentile cannot be determined
What is a high-sensitive assay for cardiac troponin (hs-cTn)?

**EDUCATIONAL STATEMENT**

A cTn assay could be considered as of **high sensitivity** if its total imprecision at the 99th percentile is \( \leq 10\% \) as CV and can **detect cTn (\( >\text{LoD} \))** in \( \geq 50\% \) of the reference population.

**IMPRECISION ISSUES**

- **Imprecision** at the 99\(^{th}\) percentile is basic for choice of a cTn assay for clinical practice.
- **Recommendable total imprecision** at the 99\(^{th}\) percentile should be:
  - Ideally \( \leq 10\% \)
  - Clinically acceptable when between 10\% and \( \leq 20\% \)

\( \text{LoD}= \text{Limit of Detection} \)
How to calculate (and use) a significant serial change?

EDUCATIONAL STATEMENT
Serial changes are an extremely valuable way to differentiate between patients with any acute cardiac injury, including acute myocardial infarction (AMI and patients with chronic elevations, most likely related to structural heart disease

ISSUES ABOUT SERIAL CHANGES
What is the current gold standard for their calculation?
What is the optimal timing for sampling?
How should serial changes be calculated?
Do they exist unspecific serial changes?
What is the role of point-of-care systems in the era of hs-cTn?

EDUCATIONAL STATEMENT

POC methods should be considered if the laboratory lacks an alternative, more sensitive methodology or turnaround times (TAT) do not meet clinical needs.

ADDITIONAL ISSUES

What TAT do not meet clinical needs?

How the TAT should be calculated?

How are POC devices used in the diagnosis of AMI?
PARTNERSHIPS
SIMILAR ACTIVITIES OF OTHER SCIENTIFIC ORGANIZATIONS

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

A Report of the American College of Cardiology Foundation Task Force on
Clinical Expert Consensus Documents

Writing Committee Members

L. Kristin Newby, MD, MHS, FACCC, FAHA, Co-Chair
Robert L. Jesse, MD, PhD, FACC, FAHA, Co-Chair
Joseph D. Babb, MD, FACC, FSCAI‡
Robert H. Christenson, PhD, DABCC, FACC
Thomas M. DeFer, MD, FACP§
George A. Diamond, MD, FACC,*
Francis M. Fessman, MD, FACP¶
Stephen A. Geraci, MD, FACC, FCCP, FAHA, FACP¶
Benjamin J. Gersh, MB, ChB, DPhil, FACC*
Greg C. Larson, MD, FACC*
Sanjay Kaul, MBBS, FACC, FAHA#
Charles R. McKay, MD, FACC*
George J. Philippides, MD, FACC*
William S. Weintraub, MD, FACC, FAHA**

*American College of Cardiology Foundation Representative; Society for Cardiovascular Angiography and Interventions Representative; American Association for Clinical Chemistry Representative; American College of Physicians Representative; American College of Emergency Physicians Representative; American College of Chest Physicians Representative; FACC Task Force on Clinical Expert Consensus Documents Representative; American Heart Association Representative.

ESC/ACCF/AHA/WHF Expert Consensus Document

Third Universal Definition of Myocardial Infarction

Kristian Thygesen, Joseph S. Alpert, Allan S. Jaffe, Maarten L. Simoons, Bernard R. Chaitman and
Harvey D. White: the writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the

AUTHORS/TASK FORCE MEMBERS CHAIRPERSONS

Kristian Thygesen (Denmark),§ Joseph S. Alpert (USA),* Harvey D. White (New Zealand),# Biomarker Subcommittee: Allan S. Jaffe (USA), Hugo A. Katus (Germany), Fred S. Apple (USA), Bertil Lindahl (Sweden), David A. Morrow (USA),

How to use high-sensitivity cardiac troponins in acute cardiac care†

Kristian Thygesen, Johannes Mair, Evangelos Giannitsis, Christian Mueller,
Bertil Lindahl, Stefan Blankenberg, Kurt Huber, Mario Plebani, Luigi M. Biasucci,
Marco Tubaro, Paul Collinson, Per Venge, Yonathan Hasin, Marcello Galvani,
Wolfgang Koenig, Christian Hamm, Joseph S. Alpert, Hugo Katus, and Allan S. Jaffe,
the Study Group on Biomarkers in Cardiology of the ESC Working Group
on Acute Cardiac Care

CURRENT OPINION

European Heart Journal (2011) 32, 2252–2257
doi:10.1093/eurheartj/ehn154
AACC Division of Biomarkers of Acute Cardiovascular Diseases (starting date: January 2013)

R. Christenson (member & AACC President)
F. Apple
A. Jaffe
J. Ordonez-Llanos
M. Plebani
EDUCATIONAL SUPPORT

During a meeting held at the 2012 Meeting of the European Society Cardiology, we were advised by an educational expert

Ms. Connie Mardis, RN, M.Ed.

Director, Global Marketing Education
at Siemens Healthcare Diagnostics

about the “best format” for the educational materials
### RATIONALE

- Except in Japan, readers first scan from upper left across top, and down right margin.

**Call to action in lower right**

- Color draws attention
  - ‘Eye catcher’ is a highlight color

- Rely on ‘over-learned’ knowledge
  - Red is critical/stop, green is go

- Adults only hold 5-7 items in short-term memory, so employ mnemonic devices:
  - Songs or rhymes (alphabet song)
  - Acronyms (SCUBA)
  - Chunking into sections

- Use consistent format

---

**Example of the best format for an educational material**

---

**Troponin Guidelines:**

*Use the 99th Percentile Cut Point for early detection of myocardial injury*

---

**Definitive Cut Point for Myocardial Injury**

---

**Analytical Characteristics**

- The 99th percentile value of cardiac troponin (cTnI or cTnT) is the universally endorsed medical decision cutoff for detection of myocardial infarction.
- A cTn assay is considered to be a high sensitivity assay if the assay meets the 10%CV criteria at the 99th percentile as well as can measure concentrations (greater than or equal to the limit of detection) in 90% of the reference population subjects used to determined the 99th percentile.
- Choosing a cTn for clinical practice should be based on the impression characteristics.
- The ideal total imprecision of a cTn assay at the 99th percentile value is recommended to be at ≤ 10%CV, clinically acceptable at ≤ 20%CV.

---

**Clinical utility highlights:**

- Diagnose MI in less than 3 hrs
- Initiate most appropriate treatment faster to improve outcomes
- Reliable, early detection of acute cardiac damage
- Endorsed by IFCC, NACB, ISOLACC, WHF Global Task Force

---

**99th Percentile Cut Point for early detection of cardiac damage**

---

**cTn assays should not be used in clinical practice if the %CV at the 99th percentile is > 20%.”**

---

**99th Percentile Basics:**

- cTn 99th percentile values should be reported as whole numbers in ng/ml concentration units.
- Validate independently for specimen type regarding whole blood, serum or plasma.
- The reference population should include an ethnic diversity across as many age decades as possible.
- The reference population should be powered appropriately to enable statistical analysis by a 1-tailed nonparametric method.
SUMMARY

• TF-CB is a forum where laboratorians, clinicians and companies work together for a common objective, i.e. producing educational materials for the best use of clinical biomarkers

• Several one-page documents are drafted; they will be the basis for future educational materials

• TF-CB will require the support of other IFCC committees and groups for the critical review of our documents and materials

• The partnership for sharing educational materials with other scientific bodies is desirable and would be possible

• Next year 2013 will be critical for achieving the TF-CB objectives
DISCUSSION (GB)

- Do you have any comments on the approach being taken by the Task Force?
- Who do you think needs to receive advice on the use and interpretation of cardiac biomarkers?
- Where and how should the outcomes of the TF be published?
- What opportunities exist in your country for collaboration with cardiologists, emergency department doctors?
- Are there other cardiac biomarkers that the TF should consider? If so, in which clinical context?