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GUIDELINES ON INSTRUCTION FOR USE OF TROPONIN I/T CARDIAC MARKER DEVICES

Version issue : October 3rd 2006

**Document related to
the guidelines on evaluation
of Troponin I/T cardiac
marker devices**

Purpose:

Taking account :

- the many false positive results issued from vigilance reports,
- the new definition of the acute coronary syndromes : American (ACC) and European (ESC) international organizations,
- the national (SFBC), European (ESC), International (IFCC) and American (NACB, ACC) organization's orientations and recommendations.

Directive 98/79/EC :

Essential Requirements Annex I, section A. and B.8 and particularly :

Annex I A 3. "...taking account of the generally acknowledged state of the art...The traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order."

References :

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- Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000; 36: 959-69. Validation of NACB and IFCC guidelines for the use of cardiac markers for early diagnosis and risk assessment in patients with acute coronary syndromes.
- Panteghini M, Gerhardt W, Apple FS, Dati F, Ravkilde J, Wu AH. Quality specifications for cardiac troponin assays. *Clin Chem Lab Med* 2001; 39: 175-9.
- Mockel M, Gerhardt W, Heller G Jr, Klefisch F, Danne O, Maske J, Muller C, Stork T, Frei U, Wu AH. Validation of NACB and IFCC guidelines for the use of cardiac markers for early diagnosis and risk assessment in patients with acute coronary syndromes. *Clin Chim Acta*; 303 :167-79.
- Alpert JS, Thygesen K, Antman E, Bassand JP Myocardial infarction redefined-a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol*. 2000 ;36:959-69.
- Special issue on reference values and reference intervals Petersen PH, Kazmierczak SC *Clin Chem Lab Med* 2004; 42 (7): 685-876.
- Groupe de travail mixte SFBC – CNBH « Troponines » (responsable : C. Morin). B. Capolaghi, B. Charbonnier, M. Dumontet, B. Hennache, J. Henninot, T. Laperche, A. Lavoinne, G. Lefèvre, C. Morin, D. Pateron, Recommandations sur la prescription, le dosage et l'interprétation des troponines cardiaques. *Ann Biol Clin* 2005 ; 63(3) :245-61.
- G.Lefèvre, C.Morin, pour le groupe de travail mixte SFBC-CNBH « Troponines », Utilisation des marqueurs cardiaques et de la troponine en France *Spectra Biologie* 2005 ; 145 :35-48.

Abbreviations :

NACB : National Academy of Clinical Biochemistry – www.nacb.org
ACC : American College of Cardiology – www.acc.org
IFCC : International Federation of Clinical Chemistry
ESC : European Society of Cardiology – www.escardio.org
SFBC : Société Française de Biologie Clinique – www.sfbc.asso.fr

Experts :

Dr Christine Morin (Drouais hospital)
Dr Monique Dehoux (AP-HP Bichat hospital)
Dr Guillaume Lefèvre (AP-HP Tenon hospital)

Endorsement :

In bold type writing are the characteristics of the studied parameter : troponin I or T
In normal type writing are general requirements of the Directive 98/79/EC.

Guidelines on the instruction for use :

These guidelines mention where appropriate, the essential requirements of troponin I/T cardiac marker devices instruction for use.

- 1) The instruction for use must be in French (for devices placed on the French market),
- 2) The name or trade name and address of the manufacturer and of the authorised representative,
- 3) Identification and intended purpose of the device :
 - **mention Tnl or TnT tested,**
 - **if applicable, indication of the possibility to use the device into quantitative or semi-quantitative testing.**
- 4) The medical interest of testing, reference to :
 - **the possibility to use the device as an aid to the diagnosis of acute coronary syndrome, (acute myocardial infarction, angina),**
 - **and/or the risk stratification ,**
 - **and/or the diagnosis or the prediction of myocardial disease other than acute coronary syndrome.**
- 5) If applicable, following mentions : “STERILE”, “infectious”, “dangerous chemical material”...
- 6) A statement indicating the *in vitro* use of the device.
- 7) The composition of the reagent (nature and amount or concentration of all the active ingredient, concentration of the dangerous substances), reference made to :
 - **antibody : mention its nature, origin, monoclonal or polyclonal , the recognized epitops localization, free or complex forms and nature of the complex,**
 - **calibrator composition : TnT or Tnl ; its composition : free, binary or ternary forms, molecular balance and traceability toward the international standard (SRM 2921).**
- 8) The storage conditions and stability **before opening or reconstitution.**
- 9) The storage conditions and stability **after opening or reconstitution.**
- 10) An indication of any special equipment required including information necessary for the identification of that special equipment for proper use.
- 11) The specimen :
 - Type of specimen to be used:
 - **mention the proved forbidden type of specimen and recommended ones,**
 - **mention, when appropriate, differences between anticoagulants.**
 - Mention the special conditions of collection, pre-treatment and storage conditions of the specimens :
 - **necessity to use plugged specimen receptacles,**
 - **the storage delays for several temperatures.**
 - **coagulation conditions (complete for sera),**
 - **centrifugation conditions in order to avoid fibrin and/or cellular material interferences.**

- 12) The measurement procedure to followed with the device including as appropriate :
- a. The principle of the method,
 - b. The details of any further procedure or handling needed before the device can be used,
 - c. A detailed description of the procedure to be followed in using the device,
 - d. The specific analytical performance characteristics :
- Functional sensitivity
 - **the Tn values referring to a CV of 10% and referring to the detection threshold (IFCC) by a precision profile in low concentrations toward the analyte in an environment as close as a physiological environment ; the precision profile must take into account the concentrations and not the analytical signals.**
 - Analytical specificity, mention :
 - **the possible equimolarity between free and complexed forms (binary, ternary) of troponin,**
 - **the cross-reactivity toward non cardiac isoforms of TnI and TnT, or toward cardiac TnC**
 - Diagnostic sensitivity, mention :
 - **the interpretation thresholds needed for diagnosis and/or for risk stratification :**
 - **the 99th percentile of a reference population Tn value with % CV of 10 and lower**
 - **the lowest measured Tn value for % CV of 10 and lower.**
 - Diagnostic specificity :
 - **if necessary, mention the results of any clinical trials dealing with Tn increases without cardiac injury, or with muscular injury, rheumatoid arthritis etc ...**
 - **if necessary, furnish the results of any sensitivity and clinical specificity studies for several thresholds values with the assistance of the curve « Receiver Operator Characteristic » (ROC).**
 - Correlation study, mention:
 - **the principle of the method of comparison,**
 - **the number of tested samples,**
 - **the measurement range,**
 - **the correlation toward the method of comparison, the comparison technique, the gradient and ordinate to the origin.**
 - Repeatability and reproductibility :
 - **furnish the results for 3 concentration levels, one must be close from the interpretation threshold.**
 - Lower limit of detection:
 - **mention the lower limit of detection using a troponin-free media, for example : zero calibrator or a matrix close from human serum.**
 - Measurement range :
 - **mention the modality for the dilution in case of high Tn concentration, the linearity limit, the highest dilution and the suitable medium for dilution.**

- Interferences and method limits, furnish the results of the interference studies for :
 - **drugs, haemoglobin, bilirubin, triglycerids, indicating the first interfering concentration,**
 - **immunological specificity to : rheumatoid factor, HAMA,**
 - **the highest Tn concentration without hook effect.**
 - Calibration frequency.
- e. the indication whether any particular training is required; for example for point of care testing.
- 13) The mathematical approach upon which the calculation of the analytical result is made,
 - 14) The results expression (international units).
 - 15) The measures to be taken in the event of changes in the analytical performance of the device,
 - 16) The information concerning the internal quality control, traceability of the calibration towards reference materials :
the values of the controls must be included in the sub normality zone.
 - 17) The reference intervals for the analyte to be tested,
mention the results of the study reference population : number of subject tested (a minimum of 120 would be desirable), 99th percentile Tn value ; describe the reference population : gender ratio and age, inclusion and exclusion criteria.
 - 18) If the device must be used in combination : sufficient details to identify the correct device to use in order to obtain a safe and proper combination.
 - 19) The precaution to be taken against any special, unusual risks related to the use or disposal of the device including special protective measures (ionising radiation, substances of human or animal origin, chemical hazard)
 - 20) Specifications for devices for self-testing :
 - Clear mention to the self-testing intended purpose of the device,
 - the results need to be expressed and presented in a way that is readily understood by a lay person ; information needs to be provided with advice to the user on action to be taken (in case of positive, negative or intermediate result) and on the possibility of false positive or false negative result,
 - the information supplied by the manufacturer is sufficient to enable the user to use the device and to understand the result(s) produced by the device,
 - the information provided must include a statement clearly directing that the user should not take any decision of medical relevance without first consulting his or her medical practitioner.
 - 21) Bibliography.
 - 22) Date of issue or latest revision of the instructions for use.
 - 23) CE Marking of conformity,
 - 24) The CE marking shall be accompanied by the identification number of the notified body for self-testing devices.