

11th November 2010

**Roche hs-cTnT:
A Consensus View - Ireland.**

Venue: The Heritage Hotel, Portlaoise, Ireland.

Delegates:

Professor Evangelos Giannitsis, Cardiologist, University Hospital Heidelberg, Germany

Paula O'Shea, Consultant Clinical Biochemist, Galway University Hospitals, Galway

Dr Maria Fitzgibbon, Consultant Clinical Biochemist, Mater University Hospital, Dublin.

Dr Edward Barrett, Consultant Clinical Biochemist, Mid-Western Regional Hospital, Dooradoyle, Limerick.

Dr Derek McKillop, Consultant Clinical Biochemist, Craigavon Area Hospital, Armagh.

Mr Peter Auld, Consultant Clinical Biochemist, Belfast Trust, Royal Group Hospitals, Co. Antrim.

Dr John O'Mullane, Consultant Clinical Biochemist, Cork University Hospital, Cork.

Dr Sean Cunningham, Consultant Clinical Biochemist, St Vincent's University Hospital, Dublin

Ellie Duly, Consultant Clinical Biochemist, Ulster Hospital, Belfast, Co. Antrim

Dr Michael Ryan, Consultant Chemical Pathologist, Antrim Area Hospital, Antrim, Co. Antrim.

Dr Ophelia Blake, Principal Clinical Biochemist, St James's Hospital, Dublin and

Dr Ingrid Borovickova, Specialist Registrar Chemical Pathology, St James's Hospital, Dublin, (for Dr Vivion Crowley).

Jane Fogarty, Senior Medical Scientist, Adelaide and Meath Hospital, Dublin, Incorporating the National Children's Hospital, (for Dr Gerard Boran).

The purpose of this meeting was to reach consensus regarding the use and application of the new hs-cTnT Roche (guideline acceptable) ¹ assay in the evaluation of a patient with chest pain throughout Ireland. The decisions reached were based on current best evidence. This report outlines the consensus view of the group. However, we acknowledge that as new evidence becomes available this protocol will have to be modified accordingly.

Units:

1. It was agreed that the reporting units for hs-cTnT should be ng/L and that results should be reported as whole numbers.
Concerns were raised regarding the Cardiac Reader Point Of Care Test device. Users need be made aware that troponin results from these devices are reported in $\mu\text{g/L}$ and that the assay system is less sensitive than the current 4th generation contemporary cTnT assay. Roche representatives gave assurances that these matters were actively being addressed.

Reporting Limits:

2. The consensus view was that results should be reported down to the limit of the blank (LOB) that is 3ng/L.
There was much debate regarding this issue as it was felt by some that the limit of detection (LOD, 5ng/L) ought to be employed as the lower reporting limit. It was decided that reporting down to 3ng/L might provide useful information²⁻⁴ but that this decision should be reviewed as new evidence becomes available.
3. It was agreed that 14ng/L, the 99th percentile of hs-cTnT in healthy individuals³ should be employed as the upper reference limit (URL).
There was considerable discussion over the characteristics of the reference population in respect of age, sex and ethnicity and the potential impact of these differences on the determination of the 99th percentile, 14ng/L (95% CI 12.7–24.9ng/L). Professor Giannitsis informed those present that the reference population study included 616 apparently healthy volunteers and blood donors aged between 20 and 71 years. Exclusion criteria applied to the healthy volunteers were diabetes, renal impairment, coronary arterial disease, and cardiac structural abnormalities (Echocardiogram assessed). He also stated that when similar studies⁵ were carried out using less stringent criteria the 99th percentile was broadly in accord.

Clinical Significance

4. It was agreed that this new hs-cTnT assay will enable more rapid diagnosis of MI⁶ but will also increase the detection frequency of cardiac troponin elevations not due to an acute coronary syndrome (ACS). Therefore close adherence to the Universal Definition of MI (UDMI)⁷ is mandatory to discriminate ischemic from non-ischemic causes of cardiac troponin elevation. The diagnosis of AMI currently requires the rise and/or fall of biomarkers (e.g. cTnT) with at least one value above the 99th percentile, alongside one of: symptoms of ischemia, appropriate ECG changes, and/or imaging evidence of new wall motion abnormality; or the loss of viable myocardium. *The fact that troponin is only one variable in the diagnostic armamentarium of a patient presenting with suspected ACS was emphasised. Risk stratification of patients requires robust clinical assessment aided by the use of bedside risk prediction tools e.g. the Global Registry of Acute Coronary Events (GRACE) Risk Score.*^{8,9}

Serial Measurements

5. It was agreed that at least two measurements of hs-cTnT are essential to satisfy the UDMI. The first sample to be collected on presentation and the second, 6 hours later. *There was debate of the evidence to support the rule out of AMI using a sampling protocol for hs-cTnT at presentation and 3hrs post presentation¹⁰. Although it was felt that this strategy would likely identify the majority of individuals with MI, it could not be recommended because current evidence is inadequate.*

Delta Change Value

6. *It was agreed that:-*
In an evolving MI, hs-cTnT would be expected to rise above the 99th percentile (>14ng/L) within the first 6 hrs after presentation with a delta change of at least 100% over that same period.

A delta change of 20-100% within a 6 hr period indicates a significant rise in hs-cTnT and requires further testing to distinguish between acute and chronic causes of elevation in hs-cTnT.

A delta change of <20% within 6 hrs was not consistent with an acute event.

In addition, after exclusion of AMI, the reason for the observed hs-cTnT elevation should be pursued actively to identify the possible causes of myocardial injury.

7. Diagnostic Criteria for MI post PCI and CABG

The advice from Professor Giannitsis was that troponin after PCI is sensitive to pre-procedural concentrations. To avoid false positive MI diagnoses, troponin should be measured before as well as after the procedures and then only actual increases should be regarded as indicating procedure-related MI. The UDMI⁷ states that, "in the setting of PCI, the balloon inflation during a procedure almost always results in ischemia whether or not accompanied by ST-T changes. Elevations of biomarkers above the 99th percentile URL after PCI, assuming a normal baseline troponin value, are indicative of post-procedural myocardial necrosis. There is currently no solid scientific basis for defining a biomarker threshold for the diagnosis of peri-procedural myocardial infarction. Pending further data, and by arbitrary convention, it is suggested to designate increases more than three times the 99th percentile URL as PCI-related myocardial infarction".

Scant literature exists concerning the use of biomarkers for defining myocardial infarction in the setting of CABG. According to the UDMI, "increases in cardiac troponin more than five times the 99th percentile URL during the first 72 hr following CABG, when associated with the appearance of new pathological Q-waves or new left bundle branch block (LBBB), or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium, should be considered as diagnostic of a CABG-related myocardial infarction." It was agreed that evidence regarding the application of the UDMI criteria in the setting of PCI and CABG is not at present available for the new hs-cTnT assay.

Report Comments

8. It was suggested that interpretative comments that accompany hs-cTnT results should be harmonised. Time constraints did not allow consensus to be reached

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References

1. Apple F.S. A New Season for cardiac Troponin Assays: It's Time to Keep a Scorecard. *Clin Chem* 2009; 55:1303-1306
2. Morrow D.A. and Antman E.A. Evaluation of High-Sensitivity Assays for Cardiac Troponin. *Clin Chem*. 2009; 55:5-8
3. Giannitsis E. *et al.* Analytical Validation of a High-Sensitivity Cardiac Troponin T Assay. *Clin Chem*. 2010; 56: 254-261
4. Latini R. *et al.* Prognostic Value of Very Low Plasma Concentrations of Troponin T in Patients with Stable Chronic Heart Failure. *Circulation*. 2007; 116: 1242-1249
5. Mingels A. *et al.* Reference population and Marathon Runner Sera Assessed by Highly sensitive Cardiac Troponin T and Commercial Cardiac Troponin T and I Assays. *Clin Chem*. 2009; 55:101-108
6. Reichlin T. *et al.* Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays. *NEJM*. 2009; 361:858-867
7. Thygesen K., Alpert J.S., White H.D.: Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. *Circulation*. 2007; 116: 2634-53
8. Stracke S. *et al.* GRACE risk score as predictor of in-hospital mortality in patients with chest pain. *Clin Res Cardiol*. 2010; 99:627-631
9. Tang E.W., Wang C.K., and Herbison P. Global Registry of Acute Coronary Events (GRACE) Hospital Discharge Risk Score Accurately Predicts Long-Term Mortality Post Acute Coronary Syndrome. *Am Heart J*. 2007; 153:29-35
10. Giannitsis E. *et al.* High-Sensitivity Cardiac Troponin T for Early Prediction of Evolving Non-ST-Segment Elevation Myocardial Infarction in Patients with Suspected Acute Coronary Syndrome and Negative Troponin Results on Admission. *Clin Chem*. 2010; 56:642-650.