CONSENSUS STATEMENT

Consensus statement on the use of high sensitivity cardiac troponins

SA Heart Association

Task force

R.M. Jardine, FCP(SA)*; A.J. Dalby, FCP(SA), FACC, FESC#; E.Q. Klug, MMed FCP(SA)†; W.H. Vermaak, MMed(Chem Path)‡; H.D. White, DSc, FRACP, FACC, FESC, FAHA, FHKCC(Hon), FCS(ANZ), FRSNZ◊; J.C.W. Badenhorst, MMed(Int)+; L.B. Osrin MMed(Int)~; M. du Plessis, MMed(Chem Path), FCPath(SA)§; T.J. Naicker, MFGP FCPath(SA), MMed(Chem Path)Δ; P.D. Rambau FFPath(SA)ƒ; E.S. Hitchcock MMed(Chem Path)»

*Linmed Hospital, Benoni; #Milpark Hospital, Johannesburg; †Sunninghill Hospital, Sandton; ‡Vermaak laboratory, Pretoria; ◊Auckland City Hospital, New Zealand; +Unitas Hospital, Pretoria; ~Zuid-Afrikaanse Hospital, Pretoria; §Ampath laboratory, Centurion; ΔNational Health Laboratory Services, Johannesburg; ƒLancet laboratories, Johannesburg; »Pathcare laboratories, Cape Town.

Corresponding author

Dr R.M. Jardine (jardinerm@gmail.com)

ABSTRACT **The increased sensitivity of high sensitivity cardiac troponin assays comes at a cost of decreased specificity, and "false positive" diagnosis of acute coronary syndromes has made clinicians wary of their use, fearing unnecessary hospitalisations, angiography and revascularisation. The Ethics and Guidelines Standing Committee of SA Heart Association convened a meeting of cardiologists, chemical pathologists, emergency medicine specialists and industry representatives to discuss the role of high sensitivity troponin (hsTn) testing. An international expert provided guidance, and this Consensus Statement is the product of that meeting. It is recommended that hsTn assays be widely adopted as the preferred biomarker for diagnosis of myocardial infarction. Pathology laboratories will standardise the units of measurement and the reporting of results. Rules for interpretation of results and algorithms for their application are provided. Separate algorithms apply to troponin T and troponin I, and the several troponin I assays on the market each have different numerical values. Use of high sensitivity troponin assays will result in earlier diagnosis of myocardial infarction, more reliable ruling out of myocardial infarction, and shortening of chest pain triage (to 4 hours), compared to former assays.** SAHeart 2012; 9:210-215

INTRODUCTION

Troponins I, T and C are structural proteins bound to the thin filaments (actin) in striated muscle. A small amount (5 - 8%) of troponin (Tn) exists free in the cytosol. In cardiac myocytes, cardiac troponins T and I (cTnT and cTnI) are isoforms distinct from those in skeletal myocytes, and monoclonal antibody techniques enable measurement of serum levels of cTnI and cTnT with high specificity and sensitivity for cardiomyocyte injury. Consequently, since their introduction in 1999, serum Tn levels have assumed a pivotal role in the diagnosis, prognosis and strategy selection for acute coronary syndromes (ACS) other than ST-elevation myocardial infarction (STEMI).[1,2]

Early Tn assays had only moderate sensitivity for cardiomyocyte injury. Successive generations of assays have increased sensitivities progressively to the point where a number of assays now comply with the recommendation of the Joint ESC/ACCF/AHA/WHF panel which redefined myocardial infarction (MI) in 2000, stating that the co-efficient of variation (imprecision) for the measurement of troponin should be ≤10% at or below the upper limit of normal, which is the 99th percentile of a reference control group. This is essentially what defines "high-sensitivity" (hs) troponin assays. A second criterion for high sensitivity has been proposed[3] viz. that levels should be measurable in at

least 50% of subjects below the 99th percentile. However, since this parameter is not likely to impact the diagnostic accuracy in ACS and would rule out most contemporary TnI assays as not high sensitivity, for the purposes of this guideline, we define high sensitivity on the basis of the first criterion alone. Since 2009 hs troponin measurements have been proven to improve the sensitivity for diagnosis of myocardial infarction.[4,5]

Former troponin assays were either "positive" or "negative" for cardiomyocyte injury. However, it is now clear almost everyone has detectable levels of Tn in their circulation, and particularly so in the presence of cardiovascular disease such as heart failure, hypertension, LV hypertrophy, stable coronary artery disease, diabetes or renal dysfunction. This increased sensitivity with a concomitant loss of specificity has resulted in significant numbers of "false positive" tests for ACS, resulting in unnecessary hospitalisation, angiography and in some instances revascularisation, thus culminating in unwarranted inconvenience and risk to patients as well as the misuse of resources.

The lower specificity of hsTn has made clinicians wary of their use, despite increasing evidence supporting their value in diagnosis. This situation prompted the SA Heart Association to convene a meeting of cardiologists, pathologists, ER physicians and industry representatives under the proctorship of an international expert, Prof H.D. White, to discuss the current status of hsTn assays and formulate a statement for guidance on their clinical implementation. Apart from the authors, other participants in this conference were: Prof J.D. Marx, Prof P. Mntla, Dr A. Snyders (cardiologists), Dr C. Gous, Dr W. Lubinga (emergency medicine specialists), Dr V. Keti, Dr S. Naidu, Dr T. Padayachi, Dr J. Tjiattas, Dr P. Tsaagane (chemical pathologists), Ms H. de Beer, Ms M. Engelbrecht, (Beckman-Coulter), Ms D. Moodley, Dr T. Moodley, Mr S. Roopnarain, Ms G. Caunter (Roche), Ms T. Buchmelter, and Mr D. van Graan (Siemens). The meeting took place at O.R. Tambo International Airport on 26 May 2012. What follows is a summary of recommendations from that meeting.

PRE-ANALYTICAL AND ANALYTICAL ISSUES

There is one hsTnT assay and several hsTnI assays on the market. The collection, preservation, storage and transport of specimens vary with each assay, which means that the manufacturer's instructions need to be followed. Although serum or plasma (preferably heparinised) are appropriate samples, serial measurements in a given patient must be done from the same sample type to minimise variation. Haemolysed, lipaemic and icteric samples may introduce error with some methods and should be reported by the laboratory if relevant.

Laboratories currently report hsTn values in a variety of units i.e. µg/L or ng/ml e.g. 0.015-0.053, and ng/L or pg/ml e.g. 15-53. It has generally been found that the decimal point placement causes confusion[6] and it was agreed that, in future, whole numbers and specifically ng/L will be used as the unit of measurement by all laboratories. This means that large MI's will result in levels of several thousands.

The upper limit of normal for hsTn is the 99th percentile of a normal reference population. For high sensitivity assays, the coefficient of variation (CV) should ideally be less than 10% at or below this level, although a CV of 10 - 20% is clinically usable. Assays with a CV of >20% should not be used.

The one hsTnT assay available in South Africa (Roche diagnostics) is not harmonised with the TnT assay used previously. For values below 100ng/L, the hsTnT value reads 23ng/L higher than the former TnT assay, which means that 53ng/L in hsTnT is equivalent to the cutoff of 30ng/L used with the former assay.

The several hsTnI assays on the market are not standardised with each other, and there is little prospect of standardisation in the foreseeable future. The lowest limit of detection and the 99th percentile are also variable and assay-specific. Therefore it is mandatory that each institution/ laboratory use a single TnI assay and familiarise users with its values and ranges. Table 1 lists these values for assays that are currently in use in South Africa.

TABLE 1: List of contemporary sensitive troponin assays available in South Africa, with the values relevant to the algorithm in Figure 1 (ng/L).

Assay		99th percentile (upper limit of normal)	WHO MI rule-in*
Roche hsTnT	TnT	14	100
Abbott ARCHITECT	TnI	28	300
Beckman AccuTnI	TnI	40	500
Siemens Centaur Ultra	TnI	40	600
Siemens Dimension RxL	TnI	70	600
Siemens Stratus CS	TnI	70	600

**Information from manufacturers*

Falsely high and falsely low test results are rare but possible because of heterophile antibodies and human auto-antibodies interfering with the assay.

Results should be reported from the laboratory within 60 minutes.

HIGH SENSITIVITY TROPONINS IN ACUTE CORONARY SYNDROMES

High sensitivity troponins have a number of significant advantages over the former assays. They allow for earlier identification of MI, making former Tn assays, myoglobin and CK-MB redundant. They speed up chest pain triage to 4 hours (vs. 7 hours with former assays). They have a superior negative predictive value, i.e. are a better "rule-out" test than former assays. They are able to predict the risk for subsequent myocardial infarction and/or death in a group of patients previously undetected by former Tn assays.[7,8]

The improved sensitivity comes at a cost of decreased specificity. Thus hsTn levels may be mildly raised in a number of other clinical settings (Table 2), notably in stable coronary artery disease, heart failure, left ventricular hypertrophy, cor pulmonale, renal failure and even in the normal general population. This lack of specificity can lead to over-diagnosis of MI, resulting in unnecessary cardiac consultations, hospitalisations and inappropriate treatment.

It is recommended that high sensitivity troponins become the standard of care for chest pain triage and the diagnosis of cardiomyocyte injury, replacing forthwith all previously used biomarkers such as myoglobin, CK-MB, and troponin assays with a CV more than 20% at the 99th percentile (which includes some point-of-care testing). A method is proposed hereunder for the triage of acute chest pain, using hsTn. It must be emphasised that careful clinical evaluation particularly of chest pain characteristics and a risk assessment e.g. with TIMI or GRACE risk scoring, together with accurate ECG interpretation, are fundamental to the diagnosis of chest pain and that hsTn levels must not be seen in isolation.

TABLE 2: Causes of cardiac troponin elevation (other than acute coronary syndromes).

Acute	**Acute**
Ischaemic mechanism	**Other mechanisms**
Acute heart failure	Cardiac contusion
Pulmonary embolism	Procedural trauma:
Tachy-arrhythmias	Cardiac surgery
Brady-arrhythmias	Uncomplicated PCI
Accelerated hypertension	ASD closure
Hypotension / shock	Endomyocardial biopsy
Sepsis	Pacing
ARDS	ICD shocks
Aortic dissection	RF/cryo ablation
Carbon monoxide poisoning	External cardiac massage
	External cardioversion / defibrillation
Chronic	Myo-pericarditis
Stable atherosclerotic coronary artery disease	Endocarditis
Other coronary disease e.g. SLE, scleroderma, Kawasaki's disease, transplant vasculopathy	Stroke
	Tako-tsubo cardiomyopathy
	Rhabdomyolysis
Atrial fibrillation	COPD exacerbation
Chronic heart failure	Acute renal failure
Chronic renal failure	Burns >30%
Hypertension/ LV hypertrophy	Snake venoms
Pulmonary arterial hypertension	Chemotherapy: Adriamycin, 5-fluoro-uracil, herceptin
Aortic valve disease	Sympathomimetic drugs
Hypertrophic cardiomyopathy	Strenuous exertion
Infiltration: amyloidosis, haemochromatosis, sarcoidosis	After non-cardiac surgery
Peri-partum cardiomyopathy	
Hypothyroidism	
Diabetes	

The consensus of the meeting was that:

- The diagnosis of ST-elevation myocardial infarction is made by typical ECG findings in patients with a suggestive clinical presentation, and not by elevation of troponins (or any other cardiac biomarker). Treatment must be initiated immediately and not delayed until assays are completed.
- Although in unstable angina hsTn remains normal, admission for further management may be warranted nevertheless.
- The use of hsTn abolishes the need for other biomarkers, specifically myoglobin and CK-MB.[9]
- An initial normal hsTn level in a patient with a reliable history of chest pain onset more than 6 hours prior to sampling, **rules out MI**.
- A hsTn value above the WHO cut-off value (Table 1) **rules in MI**.
- Serial samples demonstrating rising or falling levels of hsTn differentiate acute from chronic cardiomyocyte necrosis.
- The timing of the 2nd of serial samples should be no sooner than 3 hours after the first.
- The percentage change (rise or fall) in hsTn levels in 2 samples 3 hours apart, is used to establish a diagnosis of MI when the Tn level is below the WHO cut-off. For TnI a 50% change in an initial value is diagnostic of MI. In the case of TnT, a 50% change in an initial value of <53, or a 20% change in an initial value between 53-100ng/L, is diagnostic of MI.
- The algorithms in Figure 1 embody the above principles. These algorithms are TnT or TnI specific, and in the case of TnI, appropriate numerical values need to be inserted from Table 1, because of lack of standardisation of the assays.[3]
- The definition of MI according to hsTn may in the future have to take into account biological variations, viz. age, gender, race, active vs sedentary lifestyle and body mass[10] but, for the present, the same values apply to all comers.
- The biomarker of choice for the diagnosis of MI associated with percutaneous coronary interventions remains controversial.[11] This is firstly because uncomplicated successful interventions are often followed by a small Tn rise, and secondly because Tn kinetics (ie an abrupt rise followed by prolonged elevation) make post-procedural levels difficult to interpret. This has prompted some interventionalists to regress to the use of CK-MB, which results in significant underestimation of peri-procedural cardiomyocyte necrosis.

Aspects of hsTn use in MI diagnosis which require clarification through further research include:

- Whether a single undetectable level of hsTn at the time of presentation, even earlier than 6 hours from pain onset, rules out MI, as has been suggested in one study.[12]
- Whether the time between successive samples can be abbreviated to 2 hours, as has been proposed in 3 studies.[9,13,14]
- Whether changes in absolute values are more reliable than relative (%) changes, as one study reported.[15]
- Whether specific treatments or treatment strategies in the newly identified group of ACS patients positive for hsTn who would have tested "negative" with the former assays, are valuable. Preliminary evidence is that this is indeed so.[16]

HIGH SENSITIVITY CARDIAC TROPONINS IN CHRONIC SETTINGS

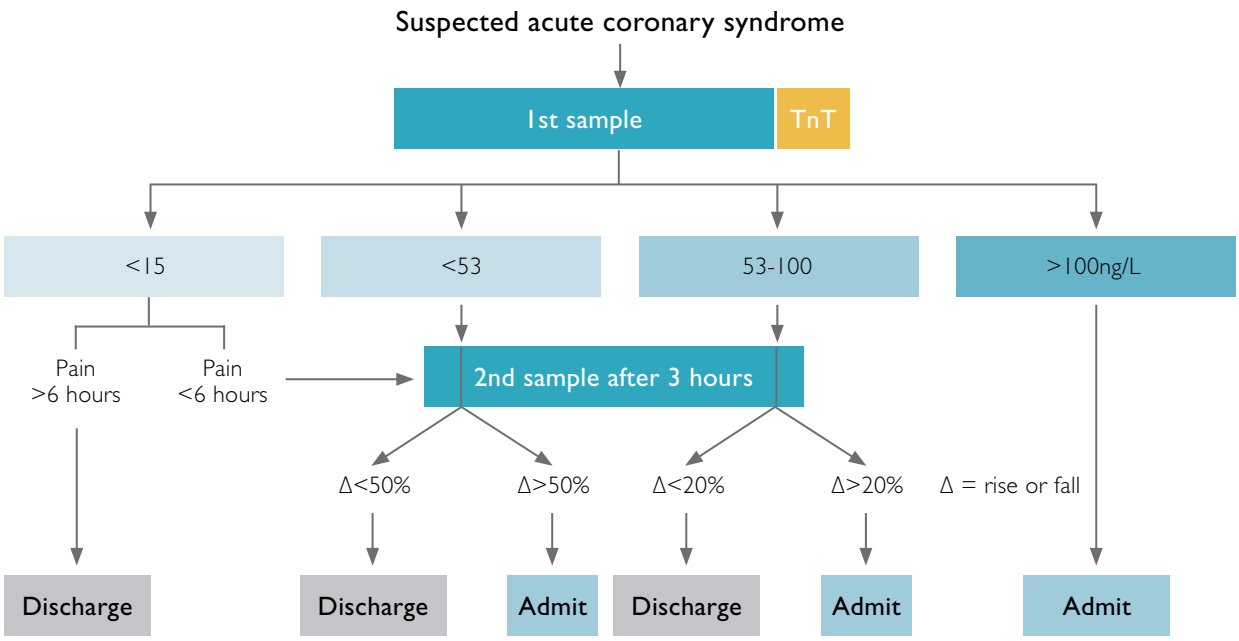
In the general population (Dallas Heart Study), hsTnT was detectable in 25% of subjects, compared to conventional Tn assays where it was 0.7%.[10] In another study it was detectable in 80.9%.[17]

In patients with stable coronary artery disease in the PEACE trial, hsTnT was detectable in 97.7% of subjects, and elevated (>13ng/L) in 11.1% of subjects.[18]

In chronic heart failure (in Val-HeFT), hsTnT was detectable in 92% of subjects (median value 12ng/L) vs 10.4% of subjects with a standard TnT assay.[19]

High sensitivity Tn retains prognostic value in all these chronic settings, independent of other risk factors. In the general population, it predicted all-cause mortality[10] and cardiovascular disease risk.[17] In stable coronary artery disease it predicted cardiovascular death and heart failure, but not MI.[18] In chronic heart failure, it predicted death and hospitalisation for heart failure.[19]

The consensus of the meeting was that the use of hsTn for risk stratification is not recommended in the general population.



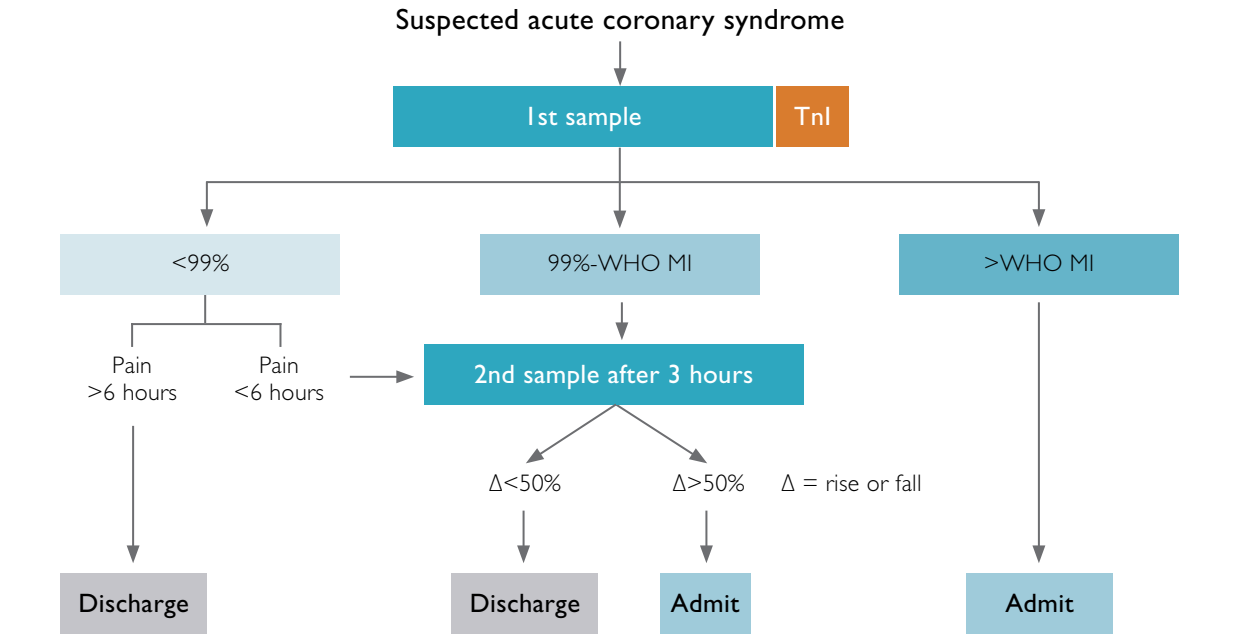


FIGURE 1: Algorithms for interpretation of high-sensitivity cardiac troponin levels in suspected acute coronary syndrome. Note that there are different algorithms for TnT and TnI. For TnI, the numerical values indicated in Table 1 must be inserted.

Notes:

1. Admit = Admit and treat for ACS.

2. Discharge = Discharge – symptomatic treatment / stress test / investigations for other causes of chest pain.

3. In the TnT algorithm, <53ng/L includes 2 sub-groups: <15 who are "normal", and 15-52 who are those patients who have abnormal hsTnT but would have tested normal with formerly used Tn assays. If the initial value is <15, the second value must exceed 14 for the diagnosis of MI, eg a rise from 8 to 13 is not diagnostic.

4. On occasions, a 3rd sample at 6 hours may be necessary for clarity of diagnosis. Follow-up measurements after admission for MI may of course be necessary, e.g. for estimation of infarct size.

There may be some use for establishing prognosis in certain patient populations, viz. heart failure, pulmonary embolism and renal failure, but it must be emphasised that the primary value of this test is for the diagnosis of MI.

CONCLUSION

Dissemination of this consensus statement will include publication in the SA Heart Journal and the South African Medical Journal. It is recommended that pathology laboratories distribute this statement to their various branches, and the Emergency Medicine Society of SA to emergency rooms and emergency doctor firms. Furthermore it is recommended that pathology laboratories standardise the reporting of high sensitivity troponin results, specifically to report values in ng/L, and to report percentage change in cases of serial measurement. Clinicians are urged to adopt high sensitivity troponins in preference to any other biomarkers for cardiomyocyte damage in ACS diagnosis and management. System changes are required to make hsTn testing available throughout South Africa, in rural as well as urban areas, so as to supplant unsuitable point-of-care tests or older assays that may currently be in use. The insurance industry should be made aware of these recommendations, which will impact on risk and claim frequency.

In the future new knowledge is likely to refine this information, specifically in regard to absolute vs relative change in hsTn levels, and the selection of specific therapies or strategies in ACS management according to hsTn levels. An update to this guideline will then be necessary.

ACKNOWLEDGEMENTS

Drs M. Ntsekhe and S. Ponnusamy contributed to the planning and development of the meeting but were unable to attend. Mrs S. du Plessis of Londocor PR was responsible for the logisitics and organisation of the conference. Mrs C. Jardine provided secretarial assistance.

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