Analyte Monographs alongside the National Laboratory Medicine Catalogue

Author: Rebecca Jones
Reviewed by: David Gaze
Edited by: Gina Frederick
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1 Name and description of analyte

1.1 Name of analyte
Cardiac troponin (cTn)

1.2 Alternative names
Cardiac troponin I (cTnI), cardiac troponin T (cTnT), high-sensitivity troponin I (hs-TnI), high-sensitivity troponin T (hs-TnT)

1.3 NLMC code: To follow

1.4. Function(s) of analyte
The troponin complex is formed from three subunits (troponins T, I and C), which together have a key role in regulating skeletal and cardiac muscle contraction. The troponin isoforms exclusively expressed within the contractile apparatus of cardiac myocytes are cardiac troponin T (cTnT) and cardiac troponin I (cTnI). Troponin C is structurally the same in cardiac and skeletal muscle. cTnI (209 amino acids long; 24 kDa) inhibits ATPase activity and cTnT (287 amino acids long; 35.9 kDa) interacts with tropomyosin and anchors the troponin complex to the actin filament. The half-life of both cardiac troponins is relatively short (~120 minutes). Increased concentrations can be detected for two weeks or more following a myocardial infarction (MI) due to their sustained release from myocytes during necrosis[1].

2 Sample requirements and precautions

2.1 Medium in which measured.
Serum, plasma (lithium heparin, EDTA). Caution with some cTnI assays in EDTA. Check manufacturer's instructions for preferred sample type.

2.2 Precautions re sampling, handling etc.
Blood samples should be drawn on first assessment and repeated 3–6 h later.[1] Use of a single sample type is recommended when collecting serial samples from the same patient.[1]

3 Summary of clinical uses and limitations of measurements

3.1 Uses
Diagnosis of cardiac ischemia

In patients with absent or equivocal electrocardiogram changes and in the context of symptoms of cardiac ischaemia, the detection of a rise and/or fall of [cTn] with at least one value above the 99th percentile is central to the diagnosis of non-ST elevation MI.
Chronic disease monitoring
Higher [cTn] are associated with worse prognosis in patients with CHD. This is also true for CKD patients undergoing haemodialysis.[2]

3.2 Limitations
Increased [cTn] is associated with both cardiac and non-cardiac conditions (see section 7.1.1. for full list) therefore diagnosis of MI cannot be based solely on troponin measurement.[1] Serial sampling is required to distinguish acute myocardial necrosis from chronic myocardial injury. Incorrect timing may result in misinterpretation.

4 Analytical considerations

4.1 Analytical methods
Sandwich immunoassay is the principal method used to measure cTn, including both contemporary (detection of cTn in < 50% of healthy individuals) and high-sensitivity (detection of cTn in 50–100% of healthy individuals; <10% total imprecision coefficient of variation at the 99th percentile) assays. Roche manufacture the single high-sensitivity cardiac troponin T assay (hs-TnT) and there are numerous cTnI assays (both conventional and high-sensitivity). The National Institute for Health and Care Excellence diagnostic guidance (DG15) recommends use of the Elecsys® hs-TnT (Roche Diagnostics) and the ARCHITECT® STAT hs-TnI (Abbott Laboratories) to rule out MI.[3] In 2018, the U.S. Food and Drugs Administration and Health Canada approved two additional high sensitivity assays, Beckman Coulter Access hs-TnI and Siemens ADVIA Centaur TNIH.[4]

4.2 Reference method
No current reference method

4.3 Reference materials
Standard Reference Material 2921, Human Cardiac Troponin Complex

4.4 Interfering substances
Heterophilic antibodies, biotin supplementation, human anti-mouse antibodies (HAMA), rheumatoid factor. Raised gamma globulin levels may decrease [cTn] due to the presence of troponin-specific autoantibodies. Haemolysis can cause positive or negative bias depending on assay platform. The level of haemolysis at which this bias occurs also varies between assays. Haemolysis has a minimal effect on [cTnI][5] but can cause falsely low [cTnT].[6] Macrotroponinaemia has been described.[7]

4.5 Sources of error
Positive flyers have been reported for both hs-TnT and hs-TnI assays. Sample type (plasma vs. serum) has been implicated as a potential cause.

5 Reference intervals and variance

5.1.1 Reference interval (adults)
The 99th percentile of a healthy reference population will be assay and population specific. The analytical characteristics of contemporary, point of care and high-sensitivity cTn assays can be found here: Biomarkers Reference Tables - IFCC

5.1.2 Reference intervals (others): None

5.1.3 Extent of variation

	Healthy individuals[8]		CKD^ patients[9]	
	Troponin I*	Troponin T$	Troponin I*	Troponin T$
Interindividual CV %	16	8	15	7
Intraindividual CV %	26	27	106	78
Index of individuality %	0.8	0.5	0.2	0.1
Critical difference (increase %)	77	42	60	24
Critical difference (decrease %)	-44	-30	-38	-20

^eGFR CKD category G3 (GFR 30 to 59mL/min/1.73 m^2)
* Abbott Architect
$Roche Elecsys

5.1.4 Sources of variation
[cTn] exhibits a diurnal rhythm, peaking at approximately 08:30 followed by a decline during daytime and a gradual rise during the night. [cTnI] remains relatively stable over 24 hours.[10]

6 Clinical uses of measurement and interpretation of results

6.1 Indications and interpretation
The basis of interpretation depends on [cTn], onset of chest pain and time of sample.

6.2 Confounding factors
See section 7.1.1 for conditions other than MI which are associated with elevated [cTn].

7 Causes of abnormal results

7.1 High values[1]
7.1.1 Causes
Primary myocardial ischaemia:
Plaque rupture, intraluminal coronary artery thrombus formation

Injury related to supply/demand imbalance:
Tachy-/brady-arrythmias, aortic dissection or severe aortic valve disease, hypertrophic cardiomyopathy, cardiogenic, hypovolaemic or septic shock, severe respiratory failure, severe anaemia, hypertension with or without LVH, coronary spasm, coronary embolism or vasculitis, coronary endothelial dysfunction without significant CAD

Injury not related to myocardial ischaemia:
Cardiac contusion, surgery, ablation, pacing or defibrillator shocks, rhabdomyolysis with cardiac involvement, myocarditis, cardiotoxic agents (e.g. anthracyclines, Herceptin)

Multifactorial or indeterminate myocardial injury:
Heart failure, stress, severe pulmonary embolism or pulmonary hypertension, sepsis and critically ill patients, CKD, stroke, subarachnoid haemorrhage, infiltrative disease (e.g. amyloidosis, sarcoidosis), strenuous exercise.

7.1.2 Investigation
Early rule-out protocols typically include a blood sample for cardiac

troponin I or T taken at initial assessment in an emergency department and a second blood sample taken after 3 hours.[3]

The APACE study supports the use of the 0/1-h protocol for rule out of MI using the Beckmann Access, with comparable diagnostic accuracy to hs-TnT (Roche) and hs-TnI (Abbott).

When baseline [cTn] is <99th percentile, a critical difference of >50% is considered to be diagnostic for MI. A critical difference of 20% is considered diagnostic in patients with baseline [cTn] >99th percentile.[1] See Section 5.1.3 'Extent of variation' for reference change values for troponin I and T in healthy individuals and patients with CKD. Data suggests that independent critical differences for cTnI and cTnT should be used for the interpretation of serial measures of cTn in patients with stage 3-5 CKD. Application of separate positive and negative critical differences should be considered, particularly for cTnI.[9]

Baseline [cTnT] in patients with stage 3-5 CKD more commonly exceed the 99th percentile of a healthy reference population compared to [cTnI] for reasons that cannot be currently explained.[8,9]

8 Performance

8.1 Sensitivity, specificity etc.[11]

		Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Troponin I*	Male (34 ng/L)	72.6	92.2	95.2	61.4
	Female (16 ng/L)	87.4	86.0	97.6	51.5
Troponin T$	Male (16 ng/L)	90.1	83.8	97.9	50.2
	Female (9 ng/L)	97.5	63.3	99.3	32.6

* Abbott Architect
$ Roche Elecsys

9 Systematic reviews and guidelines

9.1 Systematic reviews

1. Thygesen K. et al, 2019. Fourth universal definition of myocardial infarction (2018), *European Heart Journal*, Volume 40, Issue 3, Pages 237–269, https://doi.org/10.1093/eurheartj/ehy462
   Follow up to the Third Definition of Myocardial Infarction (2012) includes new concepts in differentiating myocardial infarction from myocardial injury and the use of imaging as a diagnostic tool.
2. Park, K.C. et al, 2017. Cardiac troponins: from myocardial infarction to chronic disease. Cardiovascular research, 113(14), pp.1708-1718.
   Discusses causes for myocardial injury and elevated cTn, which could be attributable to a myriad of underlying causes, emphasizing the notion that cTn is an organ-specific, not disease-specific biomarker.
3. National Institute for Health and Care Excellence Diagnostics guidance [DG15] . Myocardial infarction (acute): Early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays) Published date: October 2014
   Evidence-based recommendations for use of the Elecsys Troponin T high-sensitive assay, ARCHITECT STAT High Sensitive Troponin-I assay and AccuTnI+3 assay for measuring cardiac troponin in patients with chest pain and suspected acute coronary syndrome.

4. Kavsak PA. et al, 2018. Evaluation of the Siemens ADVIA Centaur high-sensitivity cardiac troponin I assay in serum. *Clinica Chimica Acta*, *487*, pp.216-221.
In serum, the Siemens ADVIA Centaur hs-cTnI assay had excellent clinical performance for MI in an early chest pain onset population.
5. Ryan JB. et al, 2015. Evaluation of Abbott Architect high-sensitivity troponin I assay for haemolysis interference. Pathology-Journal of the RCPA, 47(7), pp.716-718.
The new Abbott high-sensitivity cTnI assay shows minimal interference due to haemolysis and this is not a confounding factor for clinical interpretation in most situations.
6. Bais R, 2010. The effect of sample hemolysis on cardiac troponin I and T assays. *Clinical Chemistry*, 56(8), pp.1357-1359.
Studies indicate that the contemporary cTnI and high-sensitivity cTnT assays tested are sufficiently affected at relatively low degrees of hemolysis indicating that interference must be monitored for every specimen.
7. Warner JV and Marshall GA, 2016. High incidence of macrotroponin I with a high-sensitivity troponin I assay. *Clinical Chemistry and Laboratory Medicine (CCLM)*, *54*(11), pp.1821-1829.
Circulating macrotroponin I causes elevated hsTnI results with the Architect High Sensitive Troponin-I assay with the potential to be clinically misleading.
8. Aakre K. et al, 2014. Weekly and 90-minute biological variations in cardiac troponin T and cardiac troponin I in hemodialysis patients and healthy controls. *Clinical Chemistry*. 60(6):838-47.
When using a cardiac troponin change of 20%-50% to diagnose an MI, the false-positive rate is likely to be lower for the hs-cTnT assay than for the hs-cTnI assay.
9. Jones, RA. et al, 2020. Biological variation of cardiac troponins in chronic kidney disease. Annals of Clinical Biochemistry, 57(2), pp.162-169
The incorporation of separate RCVs for cardiac troponin I and cardiac troponin T, and separate RCVs for rising and falling concentrations of cardiac troponin, should be considered when developing guidance for interpretation of sequential cardiac troponin measurements.
10. Klinkenberg L. et al, 2016. Diurnal rhythm of cardiac troponin: consequences for the diagnosis of acute myocardial infarction. *Clinical Chemistry*;62(12):1602-11.
11. Boeddinghaus J. et al, 2019. High-sensitivity cardiac troponin I assay for early diagnosis of acute myocardial infarction. *Clinical Chemistry*;65(7):893-904.
Diagnostic accuracy and clinical utility of the Beckman hs-cTnI Access assay are very high and at least comparable to Roche hs-cTnT and Abbott hs-cTnI assays.
12. Goodman SG. et al, 2006. The diagnostic and prognostic impact of the redefinition of acute myocardial infarction: lessons from the Global Registry of Acute Coronary Events (GRACE). *American Heart Journal*, *151*(3), pp.654-660.
The prognostic value of cardiac troponin, beyond that supplied by CK status or important baseline characteristics, assists in the identification of patients with ACS who are at increased risk for death.

10 Links

10.1 Related analytes

Myoglobin is no longer recommended as a marker of MI. Creatine kinase MB isoform (CK-MB) is a less sensitive and less specific marker for MI.[12]

10.2 Related tests

None