

Expert Answers

From the IFCC Committee on Clinical Applications of Cardiac Bio-Markers

CARDIAC Q&A SERIES IV: CARDIAC TROPONIN ASSAY DIFFERENCES AND HOW THEY AFFECT CLINICAL USE

Do cardiac troponin I and T increase at the same rate in a patient following an acute myocardial infarction (MI)?

It is well established in the peer-reviewed literature that cardiac troponin I (cTnI) and cardiac troponin T (cTnT) do not have similar release or clearance characteristics.

1. Differences may be due to differences in the proteins but also to the analytical sensitivity of the assay and the assay calibration. In addition, circulating interferents (such as macrotroponin, heterophile antibodies, and auto antibodies) may also affect each assay differently.
2. Type 1 MI appears to have higher peak concentrations for both cTnT and cTnI compared to type 2 MI. This indicates type 1 MI typically has a larger infarct size.
3. cTnI has a shorter circulating half-life (clearance) than cTnT. Thus, the time to peak for cTnT (24 to 48 hours) appears to be longer than cTnI (12 to 36 hours) after acute injury. Further, cTnT often has a secondary peak that some speculate is due to less-than-ideal reperfusion of the infarct anatomic location and possibly circulating fragments.
4. The absolute concentrations expressed as a ratio of cTnI to cTnT appear to be substantially higher in acute myocardial injury compared to apparently normal / healthy individuals and in patients with chronic diseases. Typically, cTnI concentrations are several times higher compared to cTnT because of different release mechanisms from necrotic tissue and related to the lack of assay standardization.

Key reference: Wu AHB, Christenson RH, Greene DN, Jaffe AS, Kavsak PA, Ordonez-Llanos J, Apple FS. Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. *Clin Chem* 2018 Apr;64:4:645-55

Additional reading: Arnadottir A, Pedersen S, Bo Hasselbalch R, Goetze JP, Friis-Hansen LJ, Bloch-Munster AM, et al. Temporal Release of High-Sensitivity Cardiac Troponin T and I and Copeptin After Brief Induced Coronary Artery Balloon Occlusion in Humans. *Circulation* 2021 Mar 16;143:11:1095-104

Kristensen JH, Hasselbalch RB, Strandkjaer N, Jorgensen N, Ostergaard M, Moller-Sorensen PH, et al. Half-Life and Clearance of Cardiac Troponin I and Troponin T in Humans. *Circulation* 2024 Oct 8;150:15:1187-98

Hammarsten O, Wernbom M, Mills NL, Mueller C. How is cardiac troponin released from cardiomyocytes? *Eur Heart J Acute Cardiovasc Care* 2022 Sep 29;11:9:718-20

Sandoval Y, Chapman AR, Mills NL, Than M, Pickering JW, Worster A, et al. Sex-Specific Kinetics of High-Sensitivity Cardiac Troponin I and T following Symptom Onset and Early Presentation in Non-ST-Segment Elevation Myocardial Infarction. *Clin Chem* 2021 Jan 8;67:1:321-4

What are the major clinical differences observed between monitoring hs-TnI and hs-TnT?

1. In general, cTnI and cTnT assays appear to provide equivalent diagnostic information regarding clinical sensitivities and clinical specificities for diagnosis of acute myocardial infarction (AMI). Clinically, the biggest differences are observed in the frequency of chronic non-ischemic myocardial injury with cTnT being more prevalent compared to cTnI.
2. Risk assessment and outcomes studies have shown both short term (30 days) and long term (> 180 days) outcome prediction, with cTnT providing greater risk assessment for all cause death compared to cTnI. On the other hand, cTnI provides a greater risk assessment for major adverse cardiac events (MACE) compared to cTnT.
3. cTnT is more commonly increased than cTnI in patients with severe renal dysfunction. The increased concentrations provides long-term prognostic information and may reflect the ability of the cTnT assays to detect different sized fragments of degraded cTnT that persist in the circulation.

Key reference: Wu AHB, Christenson RH, Greene DN, Jaffe AS, Kavsak PA, Ordonez-Llanos J, Apple FS. *Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine.* Clin Chem 2018 Apr;64:4:645-55

Additional reading: Steiro OT, Langorgen J, Tjora HL, Bjorneklett RO, Skadberg O, Bonarjee VVS, et al. *Prognostic significance of chronic myocardial injury diagnosed by three different cardiac troponin assays in patients admitted with suspected acute coronary syndrome.* Clin Chem Lab Med 2024 Mar 25;62:4:729-39

Saeed N, Steiro OT, Langorgen J, Tjora HL, Bjorneklett RO, Skadberg O, et al. *Diagnosing Myocardial Injury in an Acute Chest Pain Cohort; Long-Term Prognostic Implications of Cardiac Troponin T and I.* Clin Chem 2024 Oct 3;70:10:1241-55

Why isn't it possible to compare two cardiac troponin methods by normal means of method comparison?

Primarily the difference in assay configurations is the number of antibodies used in individual cTnI and cTnT assays, as well as the epitope regions recognized by capture and detection antibodies used in the assays. This does not allow for the uniform recognition of the various cardiac troponin fragments. In addition, assay calibration differs between assays, i.e. lack of standardization.

What is the implication of not being able to compare two assay results?

The use of several different cTnI and cTnT assays is not recommended in a given medical center due to the lack of assay standardization to avoid confusion given the different metrics/cutoffs used for each assay. One potential way to use different cTn assays in the same institution lies with the use of a dedicated hs-cTnI or hs-cTnT assay within the core / central laboratory whilst a POC assay is used in another part of the health care system. POC hs-cTn assays are most often used in the emergency department for early risk assessment for MI with a dedicated training and information program, including details about specific cutoffs and clinical interpretation. If two non-standardized assays are used within the healthcare system/hospital as noted, the POC assay samples should be made available to the central laboratory to provide a new baseline if patients are admitted.

Key reference: Collinson P, Aakre KM, Saenger A, Body R, Hammarsten O, Jaffe AS, et al. *Cardiac troponin measurement at the point of care: educational recommendations on analytical and clinical aspects by the IFCC Committee on Clinical Applications of Cardiac Bio-Markers (IFCC C-CB).* Clin Chem Lab Med 2023 May 25;61:6:989-98

What is the future for standardization of cardiac troponin?

Standardization of cTnI or cTnT assays will not occur except in the unlikely event that every assay uses the same capture and detection antibody materials. Currently, the IFCC working group for “Standardization of Troponin I (WG-TNI)” is aiming to prepare a secondary reference material for cTnI, which may have a potential for harmonization between methods by transferring values between different assays using a common calibrator. However, it is unlikely this will harmonize different assays to be used interchangeably in the same medical institution.

Key reference: Wu AHB, Christenson RH, Greene DN, Jaffe AS, Kavsak PA, Ordonez-Llanos J, Apple FS. *Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine.* Clin Chem 2018 Apr;64:4:645-55

Why are the 99th percentiles so different across cTn assays?

The numerous cTnI assays have substantial differences in their design with different manufacturers using different capture and detection antibodies. In addition, a standardized reference standard is not available. Whilst the 6th generation cTnT assay from Roche has been standardized using a plasma panel spiked with recombinant human cTnT (tracable to NIST reference materials (SRM 350 and SRM 84) it is likely that assay-dependent differences will be present also for the cTnT assays as different non-Roche hs-cTnT assays (i.e. ET Healthcare, Mindray) become available in the commercial marketplace.

Do all assays meet the criteria for 99th percentile 10% CV_A for females?

The criteria of high-sensitivity assays includes that the assay should show measurable concentrations in at least 50% of men and 50% of women (when measured in a cohort of > 400 men and > 400 women) and have a $\leq 10\%$ CV_A at the 99th percentile. Assays that do not meet these requirements should be labeled contemporary, and not high-sensitivity, assays.

Key reference: Aakre KM, Saenger AK, Body R, Collinson P, Hammarsten O, Jaffe AS, et al. *Analytical Considerations in Deriving 99th Percentile Upper Reference Limits for High-Sensitivity Cardiac Troponin Assays: Educational Recommendations from the IFCC Committee on Clinical Application of Cardiac Bio-Markers.* Clin Chem 2022 Jul 27;68:8:1022-30

Why is the 99th percentile different for females compared to males?

Studies describing the 99th percentiles for cTn consistently show higher concentrations in men compared to women. Differences in heart size and sex hormones may play a major role.

Key reference: Apple FS, Wu AHB, Sandoval Y, Sexter A, Love SA, Myers G, et al. *Sex-Specific 99th Percentile Upper Reference Limits for High Sensitivity Cardiac Troponin Assays Derived Using a Universal Sample Bank.* Clin Chem 2020 Mar 1;66:3:434-44

🔍 Explain the variances between different cardiac troponin assays and the factors to consider when transitioning between them and comparing them.

Many of the responses to other questions have addressed the variances between cTn assays. It is important to acknowledge there will never be a one-to-one concordance. There will need to be educational efforts within the clinical and laboratory staff to understand variations that will occur within individual patients by assay. Although different assays will yield different results, it is not generally true that one is more “accurate”; the clinical context is critical to interpreting the assay and its implications. It needs to be recognized that cTn is never a stand-alone test. It is one part of overall patient assessment.

Key reference: Wu AHB, Christenson RH, Greene DN, Jaffe AS, Kavsak PA, Ordonez-Llanos J, Apple FS. *Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine.* Clin Chem 2018 Apr;64:4:645-55.

🔍 Explain the feasibility of establishing global cutoffs for cardiac troponin assays.

Answer: The most important efforts to establish global cutoffs for cardiac troponin I and cardiac T assays have been championed by the IFCC Committee on the Clinical Application of Cardiac Bio-markers (C-CB, initiated in 2011). The C-CB was an outgrowth of the IFCC Committee on Standardization of Markers of Cardiac Damage initiated in 1998 which was transformed to a Task Force (TF-CB). A tabulation of all assays can be found on the IFCC website.

- High Sensitivity Cardiac Troponin I and T Assay Analytical Characteristics Designated by Manufacturer
- Contemporary Cardiac Troponin I and T Assay Analytical Characteristics Designated By Manufacturer
- IFCC Cardiac Troponin Interference Table

The power of these tables allows global accessibility to all clinical and laboratory medicine fields to understand the rapidly growing characteristics of cardiac troponin assays. The tables are cited and endorsed by the Universal Definition of Myocardial Infarction (UDMI), soon to be released as the 5th version in 2026, as well as numerous Cardiology, Emergency Medicine, and Laboratory Medicine professional organizations.

Key reference: IFCC Cardiac Biomarkers Reference Tables. <https://ifcc.org/ifcc-education-division/emd-committees/committee-on-clinical-applications-of-cardiac-bio-markers-c-cb/biomarkers-reference-tables/>

The information provided above is a brief summary of common questions and answers developed by consensus of the IFCC C-CB committee, however it is important to recognise that greater knowledge and understanding is recommended and can be sourced from the referenced resources and <https://ifcc.org/ifcc-education-division/emd-committees/committee-on-clinical-applications-of-cardiac-bio-markers-c-cb/> including links to detailed papers, podcasts and presentations.