

Access AccuTnI+3 in the cardiac continuum



INTRODUCTION

The clinical utility of cardiac troponin continues to evolve as assays constantly improve. Since the introduction of the first diagnostic cardiac troponin test in 1996, assay improvements have been quickly followed by changes in utility due to the unique sensitivity and specificity of cardiac troponin for cardiac injury. These changes in utility have directly impacted the evolution of myocardial infarction (MI) definitions, driving toward earlier diagnosis of MI and improved patient outcomes.



AccuTnl has contributed to this rich history through several hallmark publications; with AccuTnl+3, advances have continued. With the initial introduction of cardiac troponin, the excitement was for a more specific marker to replace CKMB. However, adoption was slow due to the poor reproducibility of the assays. Assay designs changed to recognize the stable region of the troponin molecule, and AccuTnl was the first of these contemporary troponin assays that was commercialized.

As analytical performance of cardiac troponin continues to improve, better precision around the clinical decision point is enabling earlier rule-in and rule-out for non-ST-elevation AMI. We're also able to reliably measure troponin in healthy individuals. The current thinking is that one day, troponin will play a role in preventive medicine as a more definitive indicator of subclinical cardiovascular disease.

Beckman Coulter is dedicated to advancing these new clinical utilities and developing a high-sensitivity troponin assay to be commercially available in the future.

The publications cited herein illustrate highlights of the cardiac troponin assay advantage. Beckman Coulter is your committed partner for moving troponin assays and cardiac research forward so, together, we can improve patient care for every person.

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1 Diagnostic performance of cardiac troponin I for early rule-in and rule-out of acute myocardial infarction: results of a prospective multicenter trial

Publication/Authors

Clinical Biochemistry 2015; 48(4-5):254-259 Storrow AB, et al.

Study overview

> Prospectively measured Tnl (using AccuTnl+3) at serial time intervals in subjects with chest pain or equivalent symptoms of ACS

> n = 1,929 patients

Study objective

The objective of this study was to compare ED TnI sampling intervals, determine optimal diagnosis thresholds and report representative diagnostic performance characteristics for early rule-in and rule-out of MI.

Key study points

- > This study demonstrated high diagnostic accuracy of AccuTnI+3 at early observation times and reinforced consensus recommendations for sampling on admission and three hours later, repeated at six hours when clinical suspicion remains high
- > Tnl is ≥ 0.03 ng/mL provided 96.0% sensitivity and 89.4% specificity one to three hours after admission, and 94.9% sensitivity and 86.7% specificity at three to six hours. NPV (rule-out, non-MI) was 99.5% at one to three hours, and 99.0% at three to six hours. when Tnl is < 0.03 ng/mL. NPV was 99.1% when Tnl is < 0.03 ng/mL and time of symptom onset is ≥ 8 h

Conclusion

This study on AccuTnI+3 was the first in the U.S. that:

- > Evaluated a contemporary troponin assay using a prospective clinical study of the intended use population (patients presenting to the ED with chest pain)
- > Determined clinical sensitivity and specificity with the contemporary use of troponin assays in mind (using low cutoffs such as the URL, which is recommended in the third universal definition of MI)
- > Found that all other FDA-cleared assays still had labeling referencing the WHO MI guidelines with much higher cutoffs, consistent with the standard of care in 1979/1980

2. Evaluation of analytical performance and comparison of clinical results of the new generation method AccuTnI+3 for the measurement of cardiac troponin I using both patients and quality control plasma samples¹

Publication/Authors

Clinica Chimica Acta 2015; 451(Pt B):129-134 Storti S, et al.

Study overview

> Evaluated Beckman Coulter AccuTnI+3 assay compared to Abbott Diagnostics hs-TnI, ADVIA Centaur® TnI-Ultra® and TOSOH cTnI third-generation assay

> n = 122

Study objective

This study evaluated the analytical performance and clinical results of AccuTnI+3 for the determination of cTnI with DxI 800 and Access 2 platforms and compared the clinical results obtained with those of three cTnI immunoassays recently introduced in the European market.

Key study points

- > The LoB, LoD and LoQ at 20% CV and 10% CV were 4.5 ng/L and 10.9 ng/L, and 17.1 and 30.4 ng/L, respectively. This data indicated that estimated values found in the study were similar to those reported by the manufacturer
- > There were no significant differences between the mean values respectively measured with the DxI and Access 2 platforms

Conclusion

- > This study compared the clinical results obtained using the AccuTnI+3 assay with those of three other immunoassay methods and found very close correlations (R values ranging from 0.901 to 0.994)
- > The results of the study indicated that AccuTnI+3 exhibited good reproducibility, and based on its analytical performance, should be defined as a clinically acceptable contemporary assay

3. Analytical performance and clinical decision limit of a new release for cardiac troponin I assay¹

Publication/Authors

Ann Clini Biochem 2015 Jan; 52(Pt 1):169-72 Moretti M, et al.

Study overview

> Analytical performance evaluation of AccuTnl+3
 > n = 330

Study objective

The aim of the study was to establish if AccuTnI+3 could achieve 10% CV at the 99th percentile URL of a healthy population. The LoB, LoD and LoQ were determined according to CLSI EP17-A and EP5-A2 protocols, and the 99th percentile URL was determined by analyzing serum samples from healthy blood donors.

Key points

- > The 10% CV was at 18 ng/L; the 99th percentile URL was 22 ng/L
- > AccuTnI+3 improved low-end analytical performance and reached the goal of having a total imprecision ≤ 10% at 99th percentile of a healthy reference population

Conclusion

- > AccuTnI+3 improved low-end analytical performance and reaches the goal of having a total imprecision ≤ 10% at 99th percentile of a healthy reference population (guideline acceptable)
- > With AccuTnI+3 assay, was possible to utilize the 99th percentile as a decision level for myocardial injury detection

4. Assessing the requirement for the six-hour interval between specimens in the American Heart Association classification of myocardial infarction in epidemiology and clinical research studies²

Publication/Authors

Clin Chem 2006; 52(5):812-818 MacRae AR, et al.

Study overview

- > Retrospective study
- > The AHA case definition was used to retrospectively assign a diagnosis in patients presenting to the ED with symptoms of cardiac ischemia
- **>** n = 258

Study objective

The study aimed to determine AMI prevalence, using protocols with shorter intervals between measurements, with and without incorporating the time from onset of symptoms.

Key study points

- > The AHA six-hour requirement between serial troponin measurements can be shortened using AccuTnI
- > AccuTnI can enable two specimens in a three-hour period, cutting triage time in half
- > Reduction in triage time observed was directly related to the clinical sensitivity of AccuTnI

Conclusion

This was the first study suggesting that the previous AHA six-hour requirement between serial troponin measurements could be shortened using the Access AccuTnI assay for cTnI measurement. In other words, Access AccuTnI provided information that was instrumental in establishing today's contemporary guidelines.

5. The impact of the ESC/American College of Cardiology (ACC) redefinition of myocardial infarction and new sensitive troponin assays on the frequency of acute myocardial infarction

Publication/Authors

Am Heart J 2006; 152(1):118-125 Kavsak PA, et al.

Study overview

- > Contemporary troponin I measurements were performed with AccuTnI on plasma specimens originally assayed in 1996 for CKMB
- > n = 486 (ED patients presenting within 24 hours of onset of symptoms suggestive of cardiac ischemia)

Study objective

The objective of this study was to compare the diagnosis of AMI using a contemporary cTnI biomarker and the 2003 AHA case definition with diagnoses made using the 1994 WHO MONICA definition.

Key points

- > This study shows the importance of using the contemporary cutoff (99th percentile URL) for AMI diagnosis, which provides an opportunity for earlier patient intervention
- > High sensitivity and great precision at the low end of the assay range are key elements for achieving success with these new guidelines
- > AccuTnl is shown in this study to fulfill the sensitivity and robustness criteria required to use the 99th percentile URL cutoff

Conclusion

A large percentage of patients who were admitted with chest pain in the past will now be classified as having AMI. The ability to identify these patients will result in better care and likely better outcomes as well.

IMPROVED PATIENT CARE

6. Early and late outcome prediction of death in the emergency room setting by point-of-care and laboratory assays of cardiac troponin I assays

Publication/Authors

Am Heart J 2010; 160(5):835-841 Venge P, et al.

Study overview

> cTnI measured by POC and laboratory assays and results were compared using death in early and late follow-up

- POC tests: i-STAT (Abbott) and Stratus CS (Siemens)
- Laboratory tests: AccuTnI and ARCHITECT cTnI (Abbott)

> n = 1,069

Study objective

POC assays of cardiac troponins are common in the ED setting. The objective of this study was to determine the clinical impact of results of POC assays of cardiac troponins as compared to that of sensitive laboratory assay results.

Key study points

- > The central laboratory assays identified more patients with elevated troponin results compared to the POC assays
- > At their respective 99th percentile URLs, AccuTnl identified 88% and ARCHITECT cTnl identified 81% of all patients who died of CVD, compared to 50% and 54% for i-STAT and Stratus CS, respectively

Conclusion

- > The Access AccuTnI assay shows high clinical sensitivity and NPV and outperforms the POC assays with respect to identifying patients at risk of death from CVD
- > The clinical judgment of the patient with suspected myocardial ischemia should not solely rely on results from POC assays

7 Clinical performances of two highly sensitive cardiac troponin I assays

Publication/Authors

Clin Chem 2009; 55(1):109-116 Venge P, et al.

Study overview

> This study compared the clinical performance of two sensitive cTnl assays (AccuTnl and Centaur Tnl-Ultra)

> n = 1,251

Study objective

The aim of this study was to compare the clinical performance of two sensitive cTnl assays with 10% CV imprecision below the 99th percentile URL.

Key study points

- > Significant differences were seen in the Centaur TnI-Ultra vs. the Access AccuTnI assay capacity to identify patients at risk of premature death or death/MI
- > AccuTnI demonstrated overall superior clinical sensitivity

Conclusion

The study concluded that when using comparable cutoffs, the AccuTnI assay identified more patients with poor outcomes and at risk of premature death from CVD than the Centaur TnI-Ultra assay did.

8. Persistent cardiac troponin I elevation in stabilized patients after an episode of acute coronary syndrome predicts long-term mortality³

Publication/Authors

Circulation 2007; 116(17):1907-1914 Eggers KM, et al.

Study overview

> cTnI was measured (using AccuTnI) in patients at six weeks, three months and six months post-enrollment

> n = 1,092

Study objective

This study assessed the prevalence and the prognostic importance of minor troponin elevation in a larger cohort of patients who were stabilized after an episode of ACS and followed for up for five years.

Key study points

- > With the use of AccuTnI, persistent minor cTnI elevation can be detected frequently in patients stabilized after an episode of ACS
- > Elevated cTnl levels > 0.01 µg/L predict mortality during long-term follow-up
- > cTnI elevation was associated with increased age and other high-risk cardiovascular features

Conclusion

In this study, a high prevalence of cTnl elevation over at least six months from the index event was found. Importantly, elevated cTnl levels were strong predictors of increased mortality during five-year follow-up.

9. Long-term health outcomes associated with detectable troponin I concentrations³

Publication/Authors

Clin Chem 2007; 53(2):220-227 Kavsak PA, et al.

Study overview

- > Retrospective study
- > n = 448 (originally presented in 1996 with ACS)
- > AccuTnI utilized to analyze cTnI concentrations in frozen plasma samples
- > Peak cTnI concentration used for risk assessment

Study objective

It was previously demonstrated that low but detectable concentrations of cTnl ($\geq 0.021 \,\mu g/L$) were associated with long-term risks for coronary heart disease and death in an older, healthy, male population. In this study, it was investigated whether similar findings were evident in men and women presenting to an ED with chest pain.

Key study points

- > AccuTnI was prognostic for adverse outcomes when there was a detectable cTnI value > 99th percentile
- > A direct relationship was found between increasing concentrations of cTnl and long-term higher probability of MI and/or CHF
- > Increased cTnI concentrations identified both males and females with long-term risk

Article conclusion

- > The findings from this study support the notion of a cTnI concentration-dependent relationship for an increased long-term risk for subsequent death/AMI/CHF events after two years
- > This data is consistent with prior publications identifying 0.02 μ g/L as the optimal cutoff value for risk stratification with the AccuTnI assay
- > This data supports the observation that there is significant future cardiac risk for patients who have detectable cTnI concentrations near the 99th percentile

10. Evaluation of the AccuTnI cardiac troponin I assay for risk assessment in acute coronary syndromes³

Publication/Authors

Clin Chem 2003; 49(8):1396-1398 Morrow DA, et al.

Study overview

> This study evaluated the prognostic performance (risk stratification) of the Access AccuTnI assay

> n = 1,736

Study objective

The objective of this study was to evaluate AccuTnI for the assessment of the short-term risk of death and recurrent ischemic events among patients with suspected ACS.

Key points

This study demonstrates a strong prognostic performance of the AccuTnI assay with respect to short- and long-term risk of death, as well as the composite endpoint of death or recurrent ischemic events at both the 99th percentile URL and the functional sensitivity as a cutoff.

Conclusions

> These results provided a basis for evidence-based application of the AccuTnI assay for risk stratification among patients presenting with ACS

EFFICIENCY IN THE HEALTHCARE SYSTEM

11. Two-hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial²

Publication/Authors

JACC 2012; 59(23): 2091-2098 Than M, et al.

Study overview

> Prospective observational study

> n = 1,975

- > AccuTnI was used at one site; Abbott ARCHITECT TnI STAT was used at the other
- > TIMI risk score of zero, no new ischemic changes

in electro cardiogram (ECG) and negative Tnl values at zero and two hours were criteria for low-risk patient discharge

Study objective

The objective of this study was to determine whether a new a ADP for possible cardiac chest pain could identify low-risk patients suitable for early discharge and shorter hospital stays.

Key study points

- > 392 patients (20%) were identified as low risk and were successfully ruled out within two hours. Of the low-risk patients, only one had a MACE
- > The ADP delivered a sensitivity of 99.7% and a specificity of 23.4%
- > Clinical sensitivity is the most important factor for assessing early rule-out and discharge of low-risk patients

Conclusion

Using an ADP can reduce the length of stay in a hospital, having significant benefits for health services. This approach could decrease the observation period required for some patients with chest pain.

FUTURE UTILITY

12. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes

Publication/Authors

New Engl J Med 2008; 358(20):2107-2116 Zethelius B, et al.

Study overview

- > Plasma troponin was measured using AccuTnl
- **>** n = 1,135

Study objective

Data from a community-based cohort of elderly men was used to investigate whether a combination of biomarkers improved the risk stratification of a person beyond assessment that was based on the established risk factors for CVD.

Key study points

- > The study data suggests that in elderly men, with or without prevalent CVD, the simultaneous addition of several biomarkers substantially improved the risk stratification for death from cardiovascular causes beyond that of a model based only on established risk factors
- > This was the first publication to report such findings

Conclusion

- > The extraordinary clinical sensitivity of AccuTnI contributed to its prognostic information in this study population and the model used for risk calculation
- > In this community-based sample of elderly men, the incorporation of a combination of biomarkers with established risk factors improved the risk stratification for death from cardiovascular causes

TROPONIN I VS. TROPONIN T

13. Comparison of contemporary troponin assays with the novel biomarkers, heart fatty acid binding protein and copeptin, for the early confirmation or exclusion of myocardial infarction in patients presenting to the emergency department with chest pain

Publication/Authors

Heart 2014; 100(2):140-145 Collinson P, et al.

Study overview

- > Randomized prospective study
- > n = 850 (low-risk patients presenting with chest pain in six EDs)
- This study compared several contemporary and high-sensitivity troponin assays by ROC analysis and comparison of AUC

Study objective

The objective of this study was to examine the diagnostic accuracy of novel biomarkers of myocardial injury and troponin assays for the diagnosis of MI.

Key points

- > AUCs for Beckman AccuTnI, Stratus CS cTnI, ADVIA Centaur® TnI-Ultra® and Roche high-sensitivity TnT were similar
- > Overall, cTn measurement (cTnT or cTnI) was diagnostically superior to HFABP and copeptin as assessed by a comparison of the area under the ROC
- > Copeptin was not a useful test measured alone or in combination with cTn

Conclusion

Hs-cTn is the best single marker. The addition of HFABP to high-sensitivity troponin increased diagnostic sensitivity and should be considered for future studies.

14. Comparison of high-sensitivity troponin T and I assays in the diagnosis of non-ST elevation acute myocardial infarction in emergency patients with chest pain²

Publication/Authors

Clinical Biochemistry 2014; 47(6):321–326 Cullen L, et al.

Study overview

- > Retrospective study
- > n = 800; Roche Diagnostics Elecsys Troponin T high sensitivity assay (New Zealand)
- > n = 771; Beckman Coulter DxI Access Accu TnI assay (Australia)

Study objective

The goal of this study was to compare the performance of hs-cTnT and hs-cTnI assays and report sensitivity, specificity and predictive values for AMI in ED patients presenting with symptoms of possible ACS.

Key points

- > Both the hs-cTnT and hs-cTnI assays demonstrated equal sensitivity for the diagnosis of AMI two hours after presentation for ED patients presenting with possible cardiac chest discomfort
- > A significant difference was found in the specificity for AMI between hs-cTnI and hs-cTnT assays two hours after presentation (see table below)

	hs-cTnT	hs-cTnl	
ROC analysis	0.95	0.98	
Sensitivity	94.1%	95.6%	
Specificity	79.0%	92.5%	

Conclusion

- > Both assays had modest specificity for AMI, with the hs-cTnl assay proving more specifity for AMI than the hs-cTnT assay
- > The use of the hs-cTnl assay for evaluation may potentially lead to less misclassification and fewer consequent further investigations for ED patients with chest pain

Troponin I vs. troponin T: what we know

- > Troponin T assays cannot be used with samples that show visible signs of hemolysis (due to significant interference)
- > There is no evidence to support that Troponin T is superior to troponin I

AccuTnI+3 vs. Troponin T STAT

	AccuTnI+3	Troponin T STAT
	(one to three hours at AMI cutoff)	(three hours at AMI cutoff)
Sensitivity	DxI: 94% Access: 96%	96%
Specificity	DxI: 91% Access: 89%	86.6%

Reference Beckman Coulter AccuTnI+3 Instructions for Use Reference

Roche Diagnostics Troponin T STAT Instructions for Use

AccuTnI+3: MAKE TANGIBLE ADVANCES IN PATIENT CARE WITH BECKMAN COULTER DIAGNOSTICS

Laboratories around the world rely on Beckman Coulter's promise of quality, integrity and innovation. Our total laboratory solutions deliver accurate information for medical research breakthroughs, clinical trials and laboratory diagnostics. Your partnership with Beckman Coulter extends far beyond our products. With proven expertise in analyzing laboratory test processes, we collaborate with you to understand your requirements and create flexible solutions that meet your evolving needs.

AccuTnI+3 advantage

AccuTnI+3 is the gold standard for troponin assays.

- > AccuTnl+3 is the only assay on the market that follows the 2010 FDA guidance document for troponin assays
- > AccuTnI+3 completed a prospective clinical trial on the intended-use population using contemporary cutoffs

Abbreviations

AF	Atrial fibrillation
ACC	American College of Cardiology
ACS	Acute coronary syndrome
ADP	Accelerated diagnostic protocol
AHA	American Heart Association
AUC	Area Under the Curve
CHF	Congestive heart failure
CLSI	Clinical Laboratory Standard Institute
cTnl	Cardiac troponin I
cTnT	Cardiac troponin T
CV	Coefficient of variation
CVD	Cardiovascular disease
ECG	Electrocardiogram
ED	Emergency department
ESC	European Society of Cardiology
HFABP	Heart-type fatty acid binding protein
hs	High sensitivity

LoB	Limit of blank
LoD	Limit of detection
LoQ	Limit of quantitation
MACE	Major coronary event
MI	Myocardial infarction
NPV	Negative predictive value
POC	Point-of-care
PPV	Positive predictive value
R Value	Correlation coefficient
ROC	Receiver operating curve
STEMI	ST-elevation myocardial infarction
TIA	Transient ischemic attack
TIMI	Thrombolysis in myocardial infarction
Tnl	Troponin I
TnT	Troponin T
URL	Upper reference limit

1. This independent study presents data and conclusions different from the performance reported in Beckman Coulter's instructions for use (IFU). Per the IFU, AccuTnI+3 on Access 2 achieves 10% CV and 20% CV at 0.04 ng/mL and 0.02 ng/mL, respectively. AccuTnI+3 on DxI achieves 10% CV and 20% CV at 0.03 ng/mL and 0.04 ng/mL, respectively. The reported 99th percentile URL is 0.02 ng/mL.

2. This study was performed on the previous generation Access AccuTnI assay. The IFU for Access AccuTnI report sensitivity of 46% and specificity of 96% for samples taken between zero and six hours after admission (using a cutoff of 0.5ng/mL). Assay performance at specific timepoints within the zero- to six-hour range has not been evaluated by Beckman Coulter.

3. This study was performed on the previous generation Access AccuTnI assay, which included a risk stratification claim. Beckman Coulter's Access AccuTnI+3 assay has not been evaluated for use in risk stratification.

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