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Diagnostic Effectiveness of High-sensitivity Troponins

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## **Abstract:**

**Background:** Acute myocardial infarctions (AMI) are a leading cause of death in the United States. The key to increasing survivability is early recognition to expedite the proper treatment modalities. In conjunction with the clinical presentation and electrocardiograms, the use of cardiac biomarkers is exponentially important in not only recognizing a cardiac event but also determining the extent of injury. Advancement in laboratory technology has led to the development of high-sensitive troponin (hs-troponin) assays which can detect smaller cardiac troponin serum levels compared to conventional troponin assays. This implies that the use of hs-troponin assays is more effective in the early detection and extent of tissue ischemia, increasing the chances of AMI survival.

**Objective:** The purpose of this review is to determine whether the use of hs-troponin assays have a superior diagnostic value compared to conventional troponin assays in earlier identification or ruling-out AMI in patients who present with chest pain or other AMI symptoms.

**Methods:** A PubMed search was conducted using the following search terms and filters: high-sensitive troponin, cardiac biomarkers, hs-troponin vs. conventional troponin, articles in the last 10 years, English language, randomized control trials, meta-analysis reviews. Articles were excluded if direct comparison between hs-troponin and conventional was not observed, no full text of the article was available, and low participant numbers.

**Conclusion:** While their use is not fully adopted in the United States, hs-troponin assays can detect lower concentrations of serum troponin levels at the time of presentation compared to conventional assays, which increases their sensitivity but comes with a reduction in specificity. This is promising in early recognition of tissue ischemia and can lead to earlier detection of an AMI and expedite proper treatment pathways but raises the concern of an increase in AMI over diagnosis that may be factitious. When collected as serial markers, the hs-sensitivity troponins were equal with conventional assays in their sensitivity/specificity, which leads to the determination that they are no more effective in cardiac monitoring compared to conventional testing.

**Introduction:**

Acute myocardial infarctions (AMI) fall under the umbrella term of acute coronary syndromes (ACS), which is the result of occlusion to the coronary arteries preventing oxygenated blood from reaching specific areas of the myocardium. The Center for Disease Control and Prevention (CDC) in the United States reports that a person suffers an AMI every 43 seconds which equates to 735,000 people per year.<sup>1</sup> The key to increasing the chances of survival in an acute myocardial infarction (AMI) event is early recognition and rapid treatment. The cornerstone for early recognition of an AMI includes the use of electrocardiograms (EKG) and cardiac biomarkers aligned with the clinical presentation. While EKG recordings are easily obtained, they alone are often insufficient in determining an actual AMI event or detailing the severity of tissue ischemia. Cardiac troponins are proteins that can be measured and directly correlate to cardiac muscle tissue. The troponin biomarkers allow healthcare providers to determine damage to the myocardium, which releases stored troponin into the bloodstream upon injury. The problem with conventional troponin assays is that they have a low sensitivity in acute situations. Often with these markers, serial levels are collected to determine the level of elevation and can take up to 8-12 hours before elevations are seen. This delay can lead to a decrease in rapid treatment which reduces morbidity and mortality. It also reduces ruling-out an AMI, which can lead to overcrowding in emergency departments, unnecessary hospital admission, and raises false anxiety to the individual patient and their families.

Advances in laboratory technology have allowed the development of high-sensitive (hs) troponin assays, which increase the biomarkers sensitivity in early symptom onset, increasing the recognition of an AMI. These high-sensitive assays have a lower serum level detection below the 99<sup>th</sup> percentile in the normal population.<sup>2</sup> This means that smaller elevations in serum troponin levels can be picked up earlier when compared to conventional assays. The purpose of this review is to determine, whether these hs-troponin assays are more effective in identifying AMI events, when directly compared to conventional troponin assays and the implications this has on the general well-being of individual patients. Detailed are two prospective control trials and one meta-analysis, which look at the diagnostic value and performance of utilizing hs-troponin assays in early onset myocardial infarctions and if it provides a better clinical outcome when compared to conventional biomarker assays.

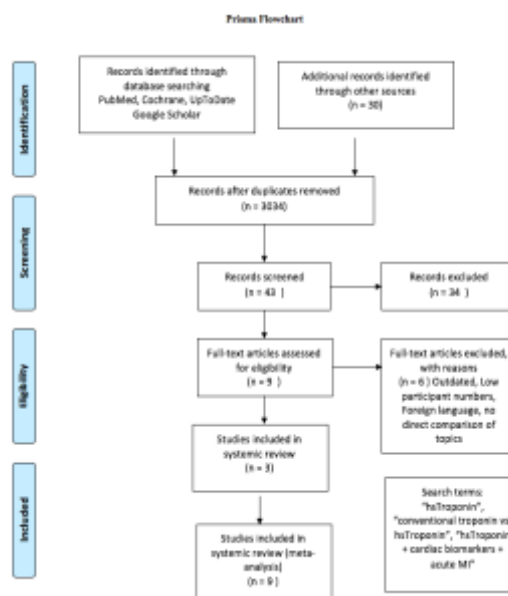
Clinical Question: *Does the use of new high-sensitivity troponin serum biomarkers increase the effectiveness in identifying a myocardial infarction compared to the use of conventional troponin biomarkers in patients who present with acute chest pain?*

## Methods:

In September of 2016, a literature review search was conducted using PubMed, UpToDate, Google Scholar, and the Cochrane Database to identify studies that compared high-sensitive troponin to conventional troponin assays. The following search terms were used: “high sensitive troponin,” “hs troponin,” “conventional troponin vs. hs troponin,” and “hs troponin + cardiac biomarkers + acute MI.” These key words identified 3034 articles. Next, restrictions to this search were applied to exclude non-English articles, older than five year

publications, and editorials. Given these parameters, the number of articles was narrowed down to 43 that were screened. An additional 34 articles were excluded, because they did not directly compare high sensitivity troponin against conventional troponin assays. This left nine full text articles for assessment, and only three were chosen based on the measured outcomes used to distinguish the diagnostic performance and clinical outcomes between high-sensitivity and conventional troponin assays.

From the chosen articles, two of the studies investigating different high sensitivity troponin against conventional troponin assays looked at the diagnostic performance of each by comparing the sensitivity, specificity, positive predictive values, and negative predictive values. This direct comparison of each assay was further illustrated with the use of receiver operating characteristic (ROC) curves that showed the discriminatory ability of the different troponins to diagnose acute myocardial infarction. The same use



of statistical comparison tools between the Reichlin et al. and Al-Saleh studies made the interpretation of the findings easier to understand.<sup>2,3</sup>

Recognizing the diagnostic superiority of high sensitivity troponin compared to conventional troponin assays, the goal of the Chew et al. article was to instead investigate the impact these assays have on the measures of care and clinical outcomes of patients presenting with suspected ASC symptoms.<sup>4</sup> They used hazard ratios to look at relative risk of events that included specific clinical outcomes such as new or recurrent myocardial infarction and death. Also, Kaplan-Meier survival plots were used to illustrate clinical outcomes of specific events in this case being the diagnosis of recurrent ACS and the endpoint of death found among participants that were follow up to 12 months.

## **Results:**

**Study #1:** *Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays. Reichlin et al.*<sup>2</sup>

### Study Objective:

To determine whether the use of newer high-sensitive troponin assays can lead to an earlier diagnosis of acute myocardial infarction in patients presenting to one of the selected emergency departments.

### Study Design

The study was a randomized, prospective, multicenter study, coordinated by the University of Basel in Switzerland. The study was conducted between April 2006 through April 2008 and totaled 786 patients who presented to participating emergency departments with a clinical suspicion of myocardial infarction. Table 1 depicts the baseline characteristics for the participants included in the study.

Certain parameters were established for inclusion/exclusion into the study and can be seen in detail in Table 2. In general, patients who reported to the emergency department were included if their symptoms were suggestive of an acute myocardial infarction (i.e. chest pain or angina) and had started within 12 hours of presentation. Each of the participants underwent a thorough clinical assessment which included a clinical history, physical examination, 12-lead EKG, continuous cardiac monitoring, standard blood markers, and chest x-ray. The standard blood markers included conventional cardiac biomarkers used in the diagnosis of acute myocardial infarctions. These tests were a cardiac troponin I or cardiac troponin T, CK-MB, and myoglobin and were measured at the patient's presentation to the emergency department, and 6 to 9 hours after presentation. Each participant was placed in a final diagnosis category, which was determined by two independent cardiologists. When a diagnosis couldn't be determined between the cardiologists, a third cardiologist was used to make a final diagnosis. The diagnosis categories included acute myocardial infarction, unstable angina, cardiac but no coronary causes, noncardiac causes, and symptoms of unknown origin. To categorize each participant, review of the history, clinical presentation, blood marker levels, and EKG interpretation were utilized. As seen in Table 1, 17% of the patients received the final diagnosis of acute myocardial infarction, 16% received the final diagnosis of unstable angina, 13% received the final diagnosis of cardiac symptoms other than coronary causes, 46% received the diagnosis of noncardiac issues, and the remaining 8% were diagnosed as symptoms of unknown origin.

Characteristic	All Patients (N=718)	Patients Who Had an Acute Myocardial Infarction (N=121)	Patients Who Did Not Have an Acute Myocardial Infarction (N=597)	P Value
Age — yr				<.001
Median	64	72	62	
Interquartile range	51–75	59–86	49–74	
Male sex — no. (%)	471 (66)	88 (72)	383 (64)	0.13
Risk factors — no. (%)				
Hypertension	438 (61)	87 (71)	351 (59)	0.02
Hypercholesterolemia	311 (43)	68 (56)	243 (40)	0.05
Diabetes	128 (18)	25 (20)	103 (17)	0.17
Current smoking	173 (24)	35 (29)	138 (23)	0.11
History of smoking	242 (34)	37 (30)	205 (34)	0.15
History — no. (%)				
Coronary artery disease	251 (35)	43 (35)	208 (35)	1.00
Previous myocardial infarction	182 (25)	32 (26)	150 (25)	0.85
Previous revascularization	202 (28)	29 (24)	173 (29)	0.32
Peripheral artery disease	47 (7)	13 (11)	34 (6)	0.05
Previous stroke	45 (6)	14 (11)	31 (5)	0.01
Clinical findings				
Heart rate — beats/min				0.18
Median	75	80	75	
Interquartile range	66–88	66–89	66–88	
Blood pressure — mm Hg				
Systolic				0.04
Median	141	135	142	
Interquartile range	127–160	129–158	127–160	
Diastolic				0.35
Median	86	84	86	
Interquartile range	77–95	76–97	77–95	
Body-mass index*				0.94
Median	26.3	26.6	26.3	
Interquartile range	23.8–29.4	23.6–28.0	23.9–29.4	
Electrocardiographic findings — no. (%)				
Left bundle-branch block	23 (3)	11 (9)	12 (2)	<.001
ST-segment elevation	51 (7)	35 (28)	16 (3)	<.001
ST-segment depression	68 (9)	25 (20)	43 (7)	<.001
T-wave inversion	50 (7)	18 (15)	32 (5)	<.001
No clinically significant abnormalities	524 (73)	34 (28)	490 (82)	<.001
Glomerular filtration rate — mL/min/1.73 m <sup>2</sup>				<.001
Median	93	83	94	
Interquartile range	74–109	61–104	76–111	

\* The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 1. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med.* 2009;361(9):858-867.

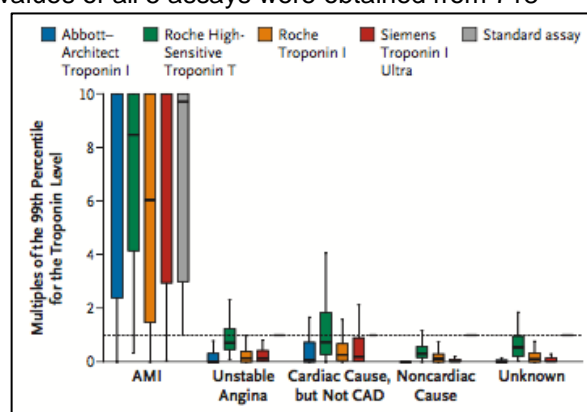
Inclusion Criteria	Exclusion Criteria
Chest pain and angina symptoms	Patients with terminal kidney failure requiring dialysis
Onset or peak of symptoms within 12 hours	
All 5 investigational cardiac troponin assays collected at presentation	

All the participants were further tested using 5 investigational cardiac troponin assays which included 4 high sensitive markers and 1 conventional marker. Testing was conducted at the initial presentation and repeated at 1, 2, 3, and 6 hours after presentation. Each of the assays were donated by the manufacturer and were tested in conjunction with the manufacturer specifications. Each of the different assays have different lower limit detections and can be observed in Table 3. Continuous variables were compared using the Mann-Whitney U test and categorical variables were used with the Pearson chi-square test. Receiver-operating-characteristic (ROC) curves were used to compare the sensitivity and specificity amongst the different assays with a p-value <0.05.

Troponin Assay	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value
<b>High-sensitive assays</b>				
<i>Abbot-Architect Troponin I</i>				
Limit of detection – 0.010µg/liter	.94 (.88-.97)	.87 (.84-.89)	.98 (.97-.99)	.59 (.52-.66)
<i>Roche High-Sensitive Troponin T</i>				
Limit of detection – 0.002µg/liter	.100 (.97-100)	.14 (.12-.18)	.100 (.96-100)	.19 (.16-.23)
<i>Roche Troponin I</i>				
Limit of detection – 0.100µg/liter	.92 (.86-.96)	.88 (.86-.91)	.98 (.97-.99)	.62 (.55-.69)
<i>Siemens Troponin I Ultra</i>				
Limit of detection – 0.006µg/liter	.97 (.91-.99)	.68 (.64-.72)	.99 (.97-.100)	.38 (.32-.44)
<b>Standard assay</b>				
<i>Roche Troponin T 4<sup>th</sup> Generation</i>				
Limit of detection – 0.010µg/liter	.83 (.75-.90)	.93 (.91-.95)	.97 (.95-.98)	.72 (.64-.79)

## Study Results

Of the 786 patients included in the study, baseline values of all 5 assays were obtained from 718 of them with the remaining 68 having had fewer than the 5 assays. In the patients who received the AMI diagnosis, all the obtained cardiac troponin assays were significantly higher when compared with patients who received other diagnoses. This can be visualized in Figure 1, which details the elevation in troponin levels amongst the different diagnosis categories. When comparing the high-sensitive troponin assays to the conventional assays inside the AMI category, the high-sensitive assays were significantly higher with detection of serum elevations compared to the conventional assay, detailed in Table 3, which lists the determined



**Figure 1.** Levels of Cardiac Troponins at Presentation, assessed by the 5 Troponin Assays Used.

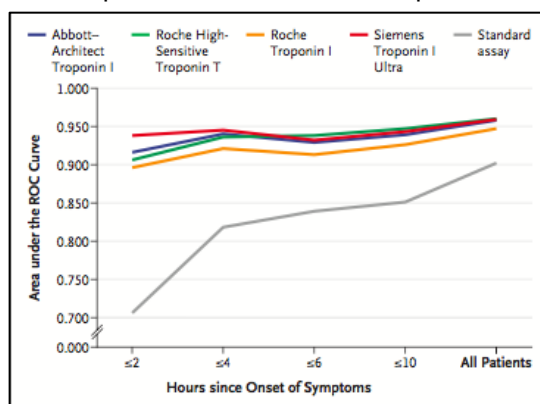
Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl*



sensitivity and specificity for each of the assays. There is a trade-off with the high-sensitivity assays, whereas when using a high-sensitive assay rather a conventional assay, you gain a higher sensitivity in detecting lower serum troponin levels for a lower specificity. This means that in the initial presentation an AMI can be more effectively ruled-out but not necessarily ruled in. With the conventional assay, the sensitivity is significantly lower than the high-sensitivity but maintains a much higher specificity, which entails the opposite in the initial presentation period. The problem that arises with a significantly lower specificity is the over diagnosis of AMI in patients presenting with similar symptoms. Due to a lower specificity, healthcare clinicians cannot definitively say an AMI is/has occurred with a positive test leading to an increase in false positives. This is a typical occurrence with tests that have a high sensitivity but low specificity, which “often leads to many patients who are disease free being told of the possibility that they have the disease and are then subject to further investigation”.<sup>5</sup> This can lead to excessive testing, worry amongst patients and family members, and unnecessary hospitalization and use of resources.

The most significant benefit of utilizing the high-sensitive troponins was observed with patients presenting with early onset of chest pain. The area under the curve (AUC) for patients presenting with symptoms starting within 3 hours was markedly higher with high-sensitive troponins vice conventional assays. This can be depicted in Figure 2, which compares the serum troponin levels with the time of presentation. The AUC at the initial presentation for the hs-troponins was above .90, which indicates the test is excellent at separating patients being tested who are having or had an AMI and who are not having an AMI. The AUC for the conventional assays had

a very low AUC, near .70, which indicates a fair separation of patients being tested with or without an AMI. As serial markers were obtained, the differences between the high-sensitive assays and conventional assays leveled off, where detection of serum elevations was consistent amongst all 5 of the assays. This leads to the assumption that no matter the sensitivity of the troponin assay used, as time progresses any method of serum troponin detection is suitable.



**Figure 2.** Accuracy of Troponin Assays at Presentation According to Time since Onset of Chest Pain,

Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl*

In regards to the other diagnosis categories, no significance in utilizing high-sensitive troponin assays was observed. The levels of troponin are not markedly elevated in conditions causing chest pain outside of coronary involvement. This brings into light the low specificity of high-sensitive assays and the concerns with their use over conventional assays, which are currently more accessible and accepted.

### Study Critique

This study was very effective in directly comparing the use of high-sensitive cardiac troponin assays to conventional assays. It showed that high-sensitive assays have a role in early detection of AMI syndromes, but a few concerning questions remain unanswered with the study's findings. First, this study only utilized 4 high-sensitive assays and 1 conventional assay. The assays used were donated by the manufacturers to the research facilities and had no influence on the study design, analysis of the data or publication of the results. One of the authors receives grants and funding from the manufacturers listed in the study. This raises questions of a conflict of interest in the specific assays selected for the study and not including other manufacturers and assay tests currently available. There are a variety of testing procedures and manufacturers available for troponin level testing and without incorporating these tests leaves a true comparison of high-sensitive versus conventional unaccomplished. The sensitivity and specificity of unused assays is not presented and raises the questions of how they compare to what is presented in the study.

Second, since this study was a prospective, cohort, observational study the authors are not able to quantify the clinical effect these assays have on diagnostic accuracy. The patients used were diagnosed based off an array of clinical findings and not solely on elevations of their troponin levels. The authors recognize this flaw and recommend further interventional studies be conducted. Third, patients who presented with terminal kidney function were excluded from the study. This eliminates a subgroup of patients, who due to their poor state of health, may be at an increased risk of myocardial infarction. Without their representation in the study, a consensus of whether high-sensitive assays provide earlier detection in people at a high risk of cardiac ischemia due to comorbidities cannot be determined. Finally, the diagnosis of the patients was not made based off the investigated troponin levels. This means that some of the patients placed in categories outside of AMI may have sustained an AMI that was not

detected by the conventional troponin used in the diagnostic process. This alters the number of participants in each identified category and could have contributed to a fluctuation of the sensitivity and specificity reported with the high-sensitive assays. In addition, the study's findings are unique to the selected population in the research groups and represents a small sample of Switzerland's diversity. Although Switzerland and the United States are both well developed nations, there are always intrinsic variabilities such as cardiovascular function influenced by genetic and lifestyle factors as well as extrinsic differences including medical practice. Therefore, the findings of any study need to be carefully analyzed before trying to apply the results to another population that is different than the one included in a research group.

**Study #2:** *Randomized Comparison of High-Sensitivity Troponin Reporting in Undifferentiated Chest Pain Assessment. Chew et al.*<sup>4</sup>

Study Objective:

To compare the impact of high sensitivity troponin against conventional troponin assays on the clinical care and outcomes among patients presenting to emergency departments with a suspected acute coronary syndrome.

Study Design:

This study was a prospective, single blinded, randomized control trial that included 1937 patients presenting with acute chest pain to one of five public emergency departments in Adelaide, South

Australia. Refer to Table 4 for inclusion and exclusion criteria. Patients were randomized to the high-sensitivity or standard troponin test assay by using premade sequentially numbered sealed envelopes indicating which test to run. All the participants had troponin testing

Inclusion Criteria	Exclusion Criteria
Patients presenting to one of five emergency departments with all the following: <ul style="list-style-type: none"> <li>• Between the hours of 9 AM to 5 pm</li> <li>• At least 18 years of age and above</li> <li>• Willing to give written informed consent</li> <li>• Clinical features suggestive of an acute coronary syndrome (ACS)               <ul style="list-style-type: none"> <li>○ Chest pain</li> <li>○ Shortness of breath                   <ul style="list-style-type: none"> <li>▪ &gt;10 minutes at rest</li> <li>▪ &lt;24 hours from the time of presentation</li> </ul> </li> </ul> </li> </ul>	Patients presenting to one of five emergency departments with <b>any</b> of the following: <ul style="list-style-type: none"> <li>• Before 9 AM and after 5 pm</li> <li>• Under 18 years of age</li> <li>• Showing ST-segment elevation on initial ECG</li> <li>• Requiring permanent dialysis</li> <li>• Suspected of having ACS secondary to other causes</li> <li>• Presenting with a comorbidity</li> <li>• Inability to complete clinical history questionnaires due to language barriers</li> </ul> Unable/unwilling to give written informed consent

done in the hospital as soon as they were identified of having symptoms of acute coronary syndrome and at 3 then 6 hours after the initial test. Physicians were provided with either the standard or high-sensitivity troponin test results for their patients and all medical care decisions were determined by them. To keep the two different study groups separated, all troponin tests were performed using the Elecsys Troponin T high-sensitivity-cobas assay developed by Roche Diagnostics.

Researchers used specific indicators to assess measures of care and clinical outcomes to compare the impact of using high sensitivity troponin or conventional troponin assays on participants. Refer to Table 5 for measures of care and clinical outcomes. These measures of care and clinical outcomes

Measures of Care	Clinical Outcomes
<ul style="list-style-type: none"> <li>• Functional testing</li> <li>• Echocardiography</li> <li>• Invasive angiography</li> <li>• Use of guideline-recommended therapies               <ul style="list-style-type: none"> <li>○ Aspirin</li> <li>○ P2Y12 inhibitors</li> <li>○ Statins</li> <li>○ Beta Blockers</li> <li>○ ACE inhibitors or ARB</li> <li>○ Revascularization</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Death</li> <li>• Myocardial infarction</li> <li>• Recurrent myocardial infarction</li> <li>• Unstable angina</li> <li>• Bleeding</li> <li>• Stroke</li> </ul>

were noted in-hospital in addition to follow up intervals (30 days, 6-months, 12-months).

### Study Results:

There was no difference in the number of patients discharged home from the emergency department (ED) with high sensitivity troponin compared to conventional troponin assays. This means that despite the superior discrimination of novel cardiac troponin assays, this does not necessarily translate into better clinical outcomes such as earlier hospital release. Among patients classified as either low or no risk by the Heart Foundation Criteria, there was a higher rate of discharge from the ED among the hs-troponin compared to the standard troponin. Furthermore, there was no difference in subsequent inpatient cardiac investigating and clinical care among the two study groups evident in the same frequency of antiplatelet and statin therapy prescribed in both groups after 30 days. The other main finding in regards to clinical outcome, showed that the use of hs-troponin had a modest reduction in recurrent ACS and mortality; however, the authors say this should be interpreted with caution. Despite this finding being statistically significant, as evidenced by a p value of equal to or less than 0.05, the finding is not clinically significant.

This difference in clinical outcome found among the two troponin assay groups corresponds to both the 30 day and 12-month time frame from the onset of acute coronary artery syndrome symptoms. Table 6 details the event rates and hazard ratios for the different time frames and expected clinical outcomes. There were several clinical outcomes measures but for this paper, focus was given to the events categorized as MI, death, or any cardiovascular outcomes that occurred

**Table 6. Event Rates and Hazard Ratios at 30 Days & 12 Months by Troponin Type among All Randomized Patients in Chew et al.**

Troponin Assay	High-Sensitivity (hs-Troponin) hazard for given outcome n=973	Conventional (c-Troponin) hazard for given outcome n=964	Hazard Ratios (95% CI)	P Values
<b>Clinical outcomes at 30 days</b>				
MI	0.62	0.93	0.86 (0.61-1.27)	.500
Death	0.62	0.83	0.74 (0.26-2.11)	0.580
Any CV Event	9.66	7.16	1.37 (1.00-1.89)	0.047
<b>Clinical outcomes at 12-months</b>				
MI	3.06	2.18	0.94 (0.84-1.40)	0.766
Death	3.08	4.15	0.74 (0.50-1.10)	0.135
Any CV Event	24.67	24.07	1.04 (0.87-1.25)	0.639

among the high sensitivity versus conventional troponin assay tested groups. The calculation of the hazard ratios for these clinical outcomes were verified by calculating the ratio of the event to outcome rate of each. The event rate however was not verifiable due to the researchers use of a statistical software program called Stata 13.1. The more statistically significant hazard ratios can be found by looking at the confidence intervals that do not include the number one, because if they do it means that the event rates are the same in both group; thus, indicating no difference. All the confidence intervals for the three selected events of interest for this analysis included a p value equal to or less than 0.05, which indicates a statistically significant result that rejects the null hypothesis. In this case, the only statistically significant outcome was seen at 30 days with the category of any cardio vascular event, which does not directly answer the clinical question that is concerned specifically with the clinical outcome of MI. Overall, researchers led by Chew et al. found that there is a modest reduction in MI and mortality among the high sensitivity compared to the conventional troponin assay group, which means the finding is statistically significant; however, the results are not clinically significant when interpreted by the researchers. Furthermore, the researchers believe that subtle differences among patients with other non-coronary cardiac conditions may account for difference in outcomes observed.

#### Study Critique:

There were many strengths in the study including the 12 month follow up of patients, universal definition of troponin levels above 30 ng/mL as the end-point of new or recurrent acute myocardial infarction, and blinded evaluation of the primary end-point. This study excluded patients below 18 years of age, which made the research applicable to more patients. However, it also excluded complicated subgroups with comorbidities or patients requiring renal dialysis. This exclusion of these patients limits the extrapolation of these findings among others who do not share the same characteristics of this study population.

**Study #3:** *Performance of the high-sensitivity troponin assay in diagnosing acute myocardial infarction: systematic review and meta-analysis. Al-Saleh et al.*<sup>3</sup>

#### Study Objective:

Conduct a systemic review and develop a meta-analysis comparing the sensitivity, specificity, and receiver operating curve characteristics of high-sensitivity troponins assays to conventional troponin assays being used as a clinical diagnostic tool in acute myocardial infarctions.

#### Study Design

The study was a systemic review of literature searching MEDLINE, EMBASE and the Cochrane Central Register and looked at the direct comparison between high sensitivity troponin assays and conventional troponin T and I assays in patients presenting to emergency departments with symptoms suggestive of an acute MI. Articles for review were excluded if they were not in English, included heart failure patients, designed to assess the prognostic impact of troponin assays, or if a direct comparison between the two assay types was not made. Each of the selected articles were reviewed by 2 of the meta-analysis authors, and the kappa statistic which is a more robust qualitative measurement of agreement than percentages, with a p-value of <0.001 was used indicating an agreement amongst the studies.

Assessment of bias was determined using the Cochrane tool, which details criteria that allows reviewers to perform an assessment of the accuracy of diagnostic studies. Heterogeneity was determined using the  $I^2$  test, and all sensitivity and specificities of each assay were calculated by extracting information from reported measures in each study. The original search yielded 1,123 articles and after screening resulted in 50 articles being isolated. 17 of these articles were further excluded due to the lack of comparison between the two assays and 13 of the articles included patients with comorbidities discussed in the original exclusion criteria. This left 11 studies being included in the meta-analysis, which were published between 2009 and 2012, which met all the inclusion criteria. The characteristics of each of the studies chosen can be seen in Figure 3.

The patients observed in the studies all underwent an initial clinical assessment, which included a thorough history, physical exam, and 12-lead EKG. Troponin levels were measured at the time of presentation and repeated in a timeframe of 2-24 hours later. In 9 of the studies high sensitivity troponin T assays were collected and in the remaining 3 studies high sensitivity troponin I assays were utilized. The final diagnosis of each of the participants was determined by event adjudicators and AMI was defined in accordance with the 2007 ESC/ACCF/AHA guidelines in 9 of the selected studies. All the studies used an accepted standard troponin test for comparison between the troponin assays, and blinding of the standard assays was clear in only 6 of the studies and blinding of the index test was clear in 10 of the studies.

## Study Results

Study	Participants, no. (% male)	Funding	Design	Centre(s)	Timing of troponin measurement	Outcome, no. (%)	Follow-up period
<b>Troponin T</b>							
Reichlin et al. 2009 <sup>a</sup>	718 (98)	Swiss Heart Foundation, University Hospital, Basel, Abbott, Roche, Siemens	Prospective	Multicentre: Switzerland, Italy and Spain	At presentation and 6-9 h later	MI 123 (17)	90 d
Christ et al. 2002 <sup>b</sup>	2340 (94)	Roche Diagnostics	Retrospective	Single centre: Germany	At presentation and about 6 h later	MI 20 (15)	2 wk
Aldous et al. 2011 <sup>c</sup>	332 (90)	National Heart Foundation of New Zealand, Christchurch Hospital, Roche Diagnostics	Prospective	Single centre: New Zealand	At presentation and 6-24 h later	MI 110 (33)	Not reported
Body et al. 2011 <sup>d</sup>	703 (61)	Manchester NHS Foundation Trust, Roche Diagnostics	Prospective	Single centre: United Kingdom	At presentation and (at least) 12 h after onset of symptoms	MI 130 (18)	6 mo
Freund et al. 2011 <sup>e</sup>	317 (85)	Université Pierre et Marie Curie-Paris 6, Roche Diagnostics	Prospective	3 centres: France	At presentation and 3-9 h later (if clinically indicated)	MI 45 (14)	30 d
Melki et al. 2011 <sup>f</sup>	233 (67)	Stockholm County Council and Karolinska Institute, Swedish Heart and Lung Foundation, National Board of Health and Welfare, Roche Diagnostics	Prospective	Single centre: Sweden	At presentation and 6-12 h later	MI 114 (48)	Discharge from hospital
Raker et al. 2011 <sup>g</sup>	1098 (67)	Swiss Heart Foundation, University Hospital, Basel, Abbott, Roche, Siemens	Prospective	Multicentre: Switzerland, Italy and Spain	At presentation and 6-9 h later	MI 159 (14)	90 d
Weber et al. 2011 <sup>h</sup>	2506 (90)	Kerckhoff-Stiftung Foundation, Sanofi-Aventis, Roche Diagnostics	Retrospective analysis of data from 2 acute coronary syndrome registries	Multicentre: Germany and Argentina	At presentation	MI 1062 (43)	6 mo
Aldous et al. 2012 <sup>i</sup>	939 (59)	National Heart Foundation of New Zealand, Health Research Council of New Zealand, Roche Diagnostics	Prospective	Multicentre: 9 countries in the Asia-Pacific region	At presentation, 2 h and 6-12 h later	MI 255 (21)	1 yr
<b>Troponin I</b>							
Reichlin et al. 2009 <sup>a</sup>	718 (98)	Swiss Heart Foundation, University Hospital, Basel, Abbott, Roche, Siemens	Prospective	Multicentre: Switzerland, Italy and Spain	At presentation and 6-9 h later	MI 123 (17)	90 d
Keller et al. 2009 <sup>h</sup>	1816 (98)	Not available	Prospective	Multicentre: Germany	At presentation and 3-6 h later	MI 413 (23)	30 d
Shardewaj et al. 2011 <sup>g</sup>	316 (54)	Inverness Medical Innovations	Prospective	Multicentre: United States	At presentation and repeated if clinically indicated	ACS 62 (20)	90 d

Figure 3 Study characteristics used in the meta-analysis

The high-sensitivity troponin T assay used at the initial presentation period was utilized in 9 of the analyzed studies. The averaged sensitivity amongst the studies was found to be 93% with confidence

intervals between 89 and 95%. The averaged specificity was found to be 74% with confidence intervals between 66 and 81%. Heterogeneity amongst the sensitivities was 32.53%, and the specificities were 32.35% using the  $I^2$ , which is in the low to moderate range. The  $I^2$  statistic describes the percentage of variation between the studies being analyzed, which didn't occur due to chance. 8 of these studies directly compared high-sensitivity assay to conventional assay, which allowed a direct

**Table 7. Summary performance of high-sensitivity troponin vs. conventional assay at presentation. Al-Saleh et al.**

Study	High-sensitive assays		Conventional assay	
	Sensitivity	Specificity	Sensitivity	Specificity
<i>Reichlin et al. 2009</i>	0.95	0.80	0.72	0.97
<b>High-sensitivity troponin T</b>				
<i>Christ et al. 2010</i>	0.95	0.62	0.65	0.91
<i>Aldous et al. 2011</i>	0.84	0.84	0.43	0.97
<i>Body et al. 2011</i>	0.85	0.82	0.75	0.95
<i>Freund et al. 2011</i>	0.93	0.82	0.71	0.97
<i>Melki et al. 2011</i>	0.97	0.74	0.79	0.94
<i>Reiter et al. 2011</i>	0.98	0.49	0.76	0.96
<i>Weber et al. 2011</i>	0.96	0.61	0.82	0.90
<i>Aldous et al. 2012</i>	0.88	0.82	N/A	N/A
<b>High-sensitivity troponin I</b>				
<i>Reichlin et al 2009</i>	0.89	0.92	0.72	0.97
<i>Bhardwaj et al. 2011</i>	0.57	0.86	0.22	0.97
<i>Keller et al. 2009</i>	0.91	0.90	0.64	0.97

head to head comparison amongst the sensitivity and specificity of the two assays. For the high-sensitivity troponin T assay, the averaged sensitivity was found to be 94%, and specificity was 73%. For the conventional troponin T and I assay, the average sensitivity was 72%, and specificity was 95%. It is apparent that the use of high-sensitivity troponin assays is much more useful at the initial presentation timeframe for patients with myocardial infarction symptoms. With a higher sensitivity, you lose value in the specificity of these newer assays, where the specificity was much greater in conventional assays.

Only 2 of the analyzed articles evaluated the usefulness of high-sensitivity troponin T assays for serial measurement. The findings were presented as area under the curve values, which were 98% at 3 hours and 98% at 6 hours. For the conventional assays, the area under the curve was 97% at 3 hours and 98% at 6 hours. This suggests the usefulness of either assay is equal as time progresses and the levels of troponin can be measured effectively using either high-sensitivity or conventional assays.

Troponin I was evaluated in 3 of the studies, and the results were much different than what was found in the troponin T cases. The sensitivities reported using the high-sensitivity troponin I assay included 89%, 57%, and 91%, while the specificities were 92%, 86%, and 90%. These assays were



compared to conventional troponin T assays, which yielded sensitivities of 72%, 22%, and 64% and specificities of 97%, 97%, and 97%. These findings suggest there is obvious variability in troponin protein accumulation and depending on the timeframe troponin T may be a better indicator of myocardial infarction.

### Study Critique

The authors recognize that the use of different analyzers with different cutoff points amongst the articles make it difficult to truly summarize a general sensitivity and specificity. This was apparent in the evaluation of the troponin I assays, which had extreme variability amongst the reported values. Some consistency was seen analyzing the values of high-sensitivity troponin T assays where the values were quite similar amongst the studies. The fact that most of the articles chosen for analysis included a direct comparison between high-sensitivity assays and conventional assays allows practitioners to see the value of using these newer assays and how they could benefit the early recognition of myocardial infarction. The problem is only 3 of the studies evaluated the high-sensitivity being used as serial markers, which is where conventional assays are known to be the most useful.

Other critiques found in the study include the use of conventional assays being used to define whether the included patients had a myocardial infarction. Due to their lower sensitivity, this could lead to exclusions of participants that had an infarction, but were not included because the used assay didn't pick it up. In turn, this could underestimate the true sensitivity and specificity of high-sensitive assays.

### **Discussion:**

The focus of this research is on heart attacks also known as acute myocardial infarctions (MIs), which are just one kind of pathology grouped under coronary artery syndromes.

Learning about the pathophysiology of acute MIs and understanding that the severity depends on three factors—level of coronary artery occlusion, duration of occlusion, and presence or absence of collateral circulation—helps clinical providers think through the

Treatment Options for Heart Attacks
Analgesics
Angiotensin-Converting Enzyme Inhibitors
Angiotensin-Receptor Blockers
Anti-platelet
Anti-thrombotic agents
Beta-adrenergic blockers
Glycoprotein IIb/IIIa Inhibitors
Oxygen
Thrombolytics
Vasodilators

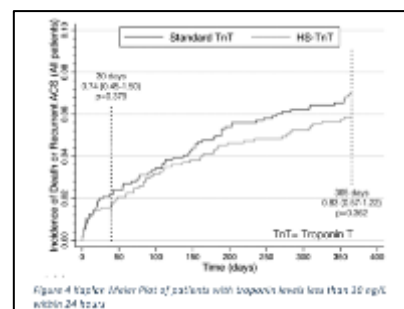
treatment plan options (Table 8).<sup>7</sup> There are specific clinical signs and symptoms that healthcare

providers look out for to identify acute MIs; however, some individuals may be asymptomatic or present with sudden cardiac arrest (Table 9).<sup>7</sup> Given the different combination of possible acute MIs clinical indicators, the importance of documenting a careful history and physical exam is crucial to differentiate this diagnosis from others and there are several diagnostic tools to help detect MIs. This analysis chose to investigate the performance of one diagnostic tool: serum troponin assays.

Common Heart Attack Warning Signs
Pain or discomfort in chest
Pain or discomfort in one or both arms, back, neck, jaw, or stomach
Nausea
Vomiting
Lightheadedness
Shortness of breath
Diaphoresis
Others

The purpose of this review is to address the following two-part clinical question concerning the use of high sensitivity compared to conventional troponin (c-troponin) assays: 1) can acute MIs be detected earlier based on diagnostic performance referring to the sensitivity versus specificity over time from the onset of symptoms; and 2) can one over the other provide better clinical care as well as better outcomes? Finding out if there is a troponin assay that will help identify acute MI earlier is crucial since half of deaths due to a heart attack occur in the first 3 or 4 hours from the onset of symptoms.<sup>6</sup> Both the Reichlin et al. and Al-Saleh MD et al. studies investigated this part of the clinical question. The Chew et al. study addressed the impact of troponin assay type on the clinical care and outcomes of patients presenting with acute coronary artery syndrome symptoms.

An overview of the three studies analyzed in this paper is provided to help summarize the sample size, demographics, methods, and key findings (Table 10). The Reichlin et al. and Al-Saleh MD et al. studies are more like each other, because they both directly compared the diagnostic performance of high sensitivity against conventional troponin assays. The Chew, et al. study calculated hazard ratios to show the clinical outcomes of death and recurrent MI's from all randomized patients who participated in the study (Table 6) . Then those hazard ratios were plotting into a Kaplan Meier Curve to illustrate the difference found among subjects in the standard versus high sensitivity troponin groups who had a statistically significant but clinically insignificant difference in time to incidence of death or recurrent acute coronary syndrome among patients who presented with a serum troponin level of less than 30 ng/L within the first 24 hours from symptom onset (Figure 4).



The study by Reichlin et al. is referenced by many other researchers investigating the diagnostic discrimination of troponin assays to detect coronary artery syndromes. They demonstrated that several hs-troponin assays can detect troponin serum levels earlier from the onset of symptoms at lower levels over the c-troponin assay. However, they also showed that both hs- and c-troponin assays performed similarly in detecting troponin serum levels when used as serial markers past 6 hours from the onset of CAS symptoms. This finding is important because it shows that the use of c-troponin assays still having clinical application valuable further out in time from the initial onset of heart attack symptoms.

Similar findings were verified by the Al-Saleh MD et al. article that concluded high sensitivity assay for cardiac troponin has higher sensitivity but lower specificity than the conventional assay. Of the 12 studies that were reviewed by these researchers, only 9 studies were considered in this analysis since they specifically covered troponin type T that is the one unifying diagnostic test of all the three studies used to answer the clinical question of this paper. In addition, three of the studies reviewed by them evaluated serial markings of hs-troponin assays and found that 6 hours past the onset of MI symptoms the hs-troponin did not perform any better than the c-troponin assay.

Unlike the studies by Reichlin et al. and Al-Saleh MD et al., the researcher led by Chew et al. was different in three key ways. First, it was a randomized control trial that has more statistical validity compared to the Reichlin et al. prospective study that does not randomize sample groups, thus it cannot ensure that any difference in outcomes can be linked to the intervention.<sup>2</sup> However, the meta-analysis by Al-Saleh MD et al. is regarded as having more reliable evidence than a single randomized control trial since a meta-analysis is a compilation of multiple studies that can include randomized control trials to combine data sets to improve statistical power by increasing the sample size of those individual studies.<sup>3</sup> Second, the researchers did not look at serial markings of the two troponin assays at several time intervals but instead grouped the results within 24 hours. This decision was not explained in the study, and it was different from the other two studies that recorded data for troponin within smaller intervals of time from the initial clinical presentation of MI symptoms. Third, the primary goal was not to investigate the diagnostic sensitivity and specificity of hs-troponin compared to c-troponin assays. Instead, the purpose was to explore the impact of hs-troponin against c-troponin assays on the clinical care and

outcomes among patients presenting with suspected acute coronary syndromes, which differs from our main focus of AMI's.

Despite these key differences, the study by Chew et al. was included in our analysis due to the relevance of our clinical question designed to understand why certain high troponin assays are favored over others and find out if there is a clinical significant advantage to using high sensitivity over

conventional troponin assays among patients who present with heart attack symptoms.<sup>4</sup>

This study used Troponin Type T as did the other two studies in this analysis, which made comparison among the articles possible. The main finding that high sensitivity troponin assay alone is

	Reichlin et al. Prospective study	Chew et al. Randomized Control Trial	Al-Saleh MD et al. Meta-Analysis
Patients (n)	718	1937	9186
Population	Median age: 64 (51-75)	Median age: 61 (48-74)	Median age: n/a
Gender	Men: 66% Women: 34%	Men: 53.7% Women: 46.3%	Men: 100% Women: 0%
Conventional (reference) assay	Standard Assay (Roche Troponin T)	Standard Assay (4 <sup>th</sup> gen. Roche Troponin T)	3 conventional assays used (Troponin T and I)
Hs-Troponin assay	4 sensitive assays	1 sensitive assay (5 <sup>th</sup> gen. Troponin T high-sensitivity by Roche)	2 hs-troponin T assays and 3 hs- troponin I assays
Blinding	Yes	Yes	N/A
Final diagnosis interpretation	2 cardiologists	Clinical event committee chaired by 1 cardiologist	2 authors
Conclusion (averaged for hs-troponin and MI)	Sensitivity: 95% Specificity: 65%	HR at 30 days: 0.82 HR at 12-months: 3.06	Sensitivity: 93% Specificity: 74%
Conclusion (averaged for conventional troponin and MI)	Sensitivity: 0.83 Specificity: 0.93	HR at 30 days: 0.93 HR at 12-months: 2.18	Sensitivity: 72% Specificity: 95%

associated with only a modest reduction in recurrent acute coronary syndromes and mortality was the one difference in clinical outcomes. Yet, there was no difference found in the clinical care provided to patients belonging to either high sensitivity or conventional troponin assay groups. This finding is reassuring that despite the superior diagnostic performance of high sensitivity troponin, this does not necessarily translate into better or worse care to the patient. Furthermore, the researchers advise that an adoption of high sensitivity troponin assay is likely to require management protocols that will guide the interpretation and care for the benefits of more efficient diagnostic discrimination to be exploited.

## Conclusion:

*Does the use of new high-sensitivity Troponin serum biomarkers increase the effectiveness in identifying a myocardial infarction compared to the use of conventional Troponin biomarkers in patients who present with acute chest pain?*

Due to the high prevalence of myocardial infarction in the United States, an effective diagnostic plan to quickly identify heart tissue damage is vital in the prevention of increased mortality and morbidity in susceptible patients. Traditional work-ups for patients presenting to emergency departments with symptoms of an MI include an assortment of diagnostic modalities, including the use of conventional troponin serum markers. Advancements in assay technology has led to the development of high sensitivity troponin assays that can detect smaller protein levels earlier in the disease process. A systemic review of literature comparing the use of high sensitive assays to conventional assays confirmed the increased sensitivity in these newer assays. There is a significant tradeoff with a high sensitivity where specificity is lost with the newer assays. This raises concerns of an increase in misdiagnosis of MI, which ultimately leads to unnecessary testing and hospitalization. It was also discovered that high sensitive assays were equivalent to conventional assays when used as serial markers. This implies their use may only be beneficial in the early hours of MI symptoms. Finally, all of the studies reviewed measured high sensitive troponins after the diagnosis of MI was already made or ruled-out. To truly determine if these high sensitive assays are more effective in diagnosing an MI, they need to be used in trials where they are the main modality used in the diagnosis process. High sensitive troponins have a place in the early work-up of MI and show promise in ensuring an accurate diagnosis is made. While it is early in their development to decide their actual effectiveness, the future is bright at better reducing the number of patients who succumb to the high occurrence of myocardial infarctions.

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