Clinical impact of a high-sensitivity troponin assay introduction on patients presenting to the Emergency Department

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Contribution:
All authors were involved in the design of the study and manuscript preparation. Daniel Peck collected the data and Jonathan Knott and Daniel Peck undertook the analysis.

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Abstract

Objective

Biomarkers are a critical component in the investigation of patients with potential ischaemic heart disease. The proposed benefits of a high-sensitivity troponin (hs-Tn) assay include earlier diagnosis of myocardial infarction. However the decreased specificity may adversely affect clinical practice.

This study aims to investigate the impact that the introduction of a hs-Tn assay had on patients presenting to the ED.

Methods

A pre- and post- interventional analysis was performed on all patients presenting to the Royal Melbourne Hospital ED, and had a troponin, in the 12 months before and after the introduction of the hs-Tn assay. The main outcome measures were; ED length of stay, admission rates, proportion of patients undergoing interventional cardiac procedures, and proportion diagnosed with myocardial infarction.

Results

There were 6557 patients who had a conventional assay and 7335 patients who had a hs-Tn assay. The introduction of a hs-Tn was associated with an increased abnormal troponin rate (23.4% vs. 28.1%, $p<0.001$). The median length of ED stay decreased by 9.1% ($p<0.001$). The proportion admitted to hospital increased (60.9% vs. 65.9%, $p<0.001$), however there was no difference in the proportion undergoing revascularisation or the proportion diagnosed with myocardial infarction.

Conclusion

Although the introduction of a hs-Tn led to an increase in hospital admissions, the unchanged rate of cardiac procedures or final diagnoses of acute myocardial infarction and ischaemic heart disease suggests that the hs-Tn did not improve the detection of these conditions. It remains unclear whether there was a benefit admitting the additional cohort of patients.

Key Words

Emergency Department, myocardial ischaemia, myocardial infarction, troponin

Introduction

According to the universal definition consensus document, myocardial infarction (MI) is defined as having evidence of myocardial necrosis, in a clinical context consistent with myocardial ischaemia. A key component of this evidence includes the rise and/or fall of cardiac biomarker values, with at least one value above the 99th percentile of a normal reference population. According to this consensus, the preferred cardiac biomarkers are the Troponin I or Troponin T, due to high myocardial tissue specificity and high clinical sensitivity (1).

High-sensitivity troponin (hs-Tn) assays have been increasingly introduced into clinical practice. They detect the same proteins as conventional assays, but at lower concentrations. A troponin assay is classified as high-sensitivity if the coefficient of variance (total imprecision) is ≤10% at the 99th percentile, and if measurable concentrations below the 99th percentile are attainable in at least 50% (ideally >95%) of a healthy population (2). With this improved analytical accuracy comes the proposed clinical benefit of earlier diagnosis of MI (3, 4). Waiting up to eight hours in an Emergency Department (ED) or Chest Pain Evaluation Unit (CPEU) before performing a serial troponin to assess for a rise or fall may no longer be required (5). It has also been proposed that the new assays could potentially allow the diagnosis of MI's that were previously undetectable using conventional assays (6).

Whilst these benefits are promising, especially for EDs, there is criticism in the literature regarding the utility of the hs-Tn assay in clinical practice. This relates to the decreased specificity for the diagnosis of MI, resulting from troponin elevations due to causes other than ischaemia (1, 7, 8). It has been found that circulating troponin can be detected in as many as 80% of healthy individuals using a hs-Tn assay (9). In addition, higher troponin levels have also been noted with increasing age, male gender and certain comorbid diseases (10). This may lead to misdiagnosis, unnecessary admission or invasive cardiac investigations. The literature is also unclear on the impact that introducing a hs-Tn assay will have on clinical practice with respect to rates of cardiac procedures and ED length of stay (6, 11-13). The aim of this study was to determine the clinical impact that the introduction of a hs-Tn assay has had on patients presenting to the ED.

Methods

Study Design

The design of this study is a retrospective, pre- and post- interventional analysis.

Setting

The RMH is a tertiary referral hospital that has over 65 000 presentations per annum, with a 40% admission rate. There are 3600 patients admitted with a high risk of acute coronary syndrome (ACS) under cardiology (occasionally in conjunction with another parent unit) to the Coronary Care Unit. The CPEU is used for patients with low to moderate risk of ACS, and consists of approximately 900 admissions per annum. The CPEU has four monitored beds and is managed within the Short-Stay unit of the ED. The CPEU strategy is a 12 hour observation with serial cardiac markers and ECG and discharge planning.

Study period and inclusion criteria

The study ran for 26 months from 15 January 2013 to 15 March 2015. The conventional assay group included all patients who presented to the ED and had a troponin ordered in the 12 months prior to the introduction of the new assay.

For two months, RMH ran conventional and hs-Tn assays on all troponins as part of a transition period with the new assay. This transition period was excluded.

The high-sensitivity troponin group was the same population in the 12 months after the transition period.

Intervention

On 15 January 2014, RMH introduced the *Abbott Architect* hs-Tn I assay. The limit of detection of this assay is 1.9ng/L, and the coefficient of variance is 5.3% at 11ng/L. The 99th percentile and diagnostic threshold was 16ng/L for females, and 26ng/L for males. This was determined by the *Abbott User's Group* using >600 healthy controls after exclusion of cardiac disease with clinical assessment, transthoracic echocardiogram, ECG and BNP. This is in comparison to the 34ng/L for males specified

by the *Abbott Architect* packet insert. This replaced the conventional assay in use, the *Siemen's Centaur* troponin I assay, which had a limit of detection of 20ng/L, a 99th percentile of 40ng/L, and a coefficient of variance of 10% at 30ng/L.

During our study period, RMH defined an abnormal troponin result as one that was greater than the 99th percentile, or a result that demonstrated a >50% rise between subsequent troponin orders. Clinical staff in the ED determined whether patients had a troponin order, and determined the initial investigation and management plans. There was no change in clinical practice or hospital protocol regarding the diagnosis and management of ACS in the ED throughout our study period. The only noted difference was the introduction of the hs-Tn assay.

Outcome Measures

The primary outcome measures were the proportion of patients admitted to hospital and the proportion of patients who had an interventional cardiac procedure (coronary angiography, coronary angioplasty and coronary artery bypass graft surgery) during the same admission.

Secondary outcome measures included:

- the abnormal troponin result rate
- ED length of stay
- CPEU admission rate
- hospital length of stay
- a final hospital diagnosis of acute MI.

Data Collection

Data was extracted from the ED information system (Symphony®, Ascribe, www.emishealth.com) for all included patients. Variables included demographic data, ED flow and disposition. The results from all troponins ordered whilst the patient was in the ED, and subsequent test results whilst a RMH patient during the same presentation, were also collected. Finally, hospital inpatient data was obtained for all patients admitted to RMH, from the ED, who had had least one troponin ordered during their ED stay. This data was merged into a single dataset.

Statistical Analysis and Ethics

The study was run over two near consecutive 12 month periods to reduce seasonal variation. Based on an expected admission rate of 3600 patients for the 65 000 presentations, alpha set at 0.05 and power at 0.9, 37690 patients would be required in each arm to detect a clinically important change of 10%.

Non-parametric variables are presented as medians with the 25-75 interquartile range (IQR). Proportions are expressed as percentages with 95% confidence intervals (95%CI). Proportions were compared using the chi-square test, and continuous variables were compared using the Wilcoxon signed rank sum test. The statistical analysis was performed using *STATA*® (*Stata* intercooled version 10, *StataCorp* LP, stata@stata.com), and a p-value <0.05 was considered statistically significant. Melbourne Health Human Research and Ethics Committee approved the study.

Results

Patient Characteristics

127 454 patients presented to the ED during our 24-month study period, 61 920 (49.6%) during the conventional assay period, and 65 534 (51.4%) during the hs-Tn assay period.

During the conventional assay period, 6 557 (10.6%, 95%CI: 10.4-10.8) patients had a troponin ordered and were included in this study, 7 335 (11.2%, 95%CI: 11.0-11.4) had a troponin ordered during the hs-Tn assay period (p=0.04).

Table 1 shows the characteristics of the two populations are very similar, although there is an apparent fall in acuity in patients presenting to the ED during the hs-Tn period.

Emergency Department

The proportion of patients returning an abnormal troponin result on the 1st test ordered increased after the hs-Tn assay was introduced. The proportion of patients with abnormal troponins based on at least

a 50% rise between subsequent tests also increased. This was no difference in the proportion of patients who had more than one troponin order pre- and post-changeover (Table 2).

The median length of stay in the ED decreased by 9.1%. For patients who had more than one troponin order, the median time to the second troponin decreased by 7.6% (Table 3).

Admissions

There was an increase in the admission rate to hospital for patients who had a troponin ordered (60.9% vs. 65.9%, $p<0.001$). Figure 1 shows that there was also a change in disposition from the ED after the introduction of the new assay. Admission to the Coronary Care Unit, the Intensive Care Unit or transferred to another healthcare institution did not change but admission to general wards and the CPEU rose, whilst admission to Short-Stay or discharge to home fell. The length of admission did not change (Table 3).

Investigations

During the same stay that the initial troponin was ordered, the proportion of patients that went on to have coronary angiography, coronary angioplasty or coronary artery bypass graft surgery did not change significantly. The proportion of patients undergoing revascularisation (either coronary angioplasty or coronary artery bypass graft surgery) also did not change (Figure 2).

Final Inpatient Discharge Diagnosis

There was no difference in the proportion of patients that went on to be diagnosed with IHD or with an acute MI. There was an increase in the proportion diagnosed with angina pectoris and unstable angina and the proportion diagnosed with chronic kidney disease (Figure 3).

Discussion

This study showed that the introduction of a hs-Tn assay was associated with an increased rate of abnormal results. However, there was no increase in the proportion of patients finally diagnosed with IHD or acute MI. There was a higher hospital admission rate but no change in invasive cardiac procedures performed.

The increase in abnormal troponin results with use of a higher sensitive assay is consistent with other studies. This study found a relative increase of 20%, which is less than described in other studies reporting a relative increase of close to 60% (6, 14). However, there is concern regarding the reasons underlying the abnormal rate rise. Although the hs-Tn assay is more sensitive for detecting cardiac troponin, the ability to detect elevations from causes other than ischaemia has led to uncertainty about interpretation of abnormal results (1, 8). Whilst some studies have found that a hs-Tn assay can detect small MI's that were previously undetectable using a conventional assay (6), patients with underlying co-morbid diseases (e.g. renal impairment) may have an elevated baseline level of troponin (15). As a result, there may be decreased clinical specificity for the diagnosis of MI when utilising a hs-Tn assay in clinical practice, especially at the first test result. This is supported by the increased rate of patients with a final diagnosis of chronic kidney disease.

Despite an increased abnormal troponin rate, ED length of stay fell by nearly 10%, which has been found previously, an Australian study describing an 11.5% decrease (11). This decrease may be due to an improved turnaround time from pathology or to a willingness by ED clinicians to use the hs-Tn at an earlier time post onset of pain to make a disposition decision. It is not possible to rule out the effects of the on-going efforts to meet time-based targets implemented by the Australian government (National Emergency Access Target) (16). There may be scope to decrease the length of stay further with rapid rule-in and rule-out protocols. Studies have suggested that two or three hours may be a sufficient length of time to wait before performing a second troponin order to assess for a rise or fall in levels (17-19). The current Australian guidelines advise that patients with an initially negative troponin should wait three hours before a subsequent troponin is performed. It also advises that patients with an initially abnormal troponin result should wait six hours before a subsequent troponin is performed

(20). Those who had a subsequent troponin ordered in our study waited a median time of 5.5 hours to this second troponin (7.6% less than during the conventional assay period). It is evident that there is a need for further studies to develop and validate appropriate interpretation algorithms in order to improve the utility of the hs-Tn in clinical practice.

In contrast to other studies (11) that demonstrated no change in admission rates post-introduction of a hs-Tn assay, this study found an increased hospital admission rate, but to general wards designed for lower acuity patients. This, and the unchanged rate of interventional cardiac procedures, suggests that the additional admissions might be lower acuity. This is in keeping with findings presented by Cullen *et al.,* in their study using the SNAPSHOT registry, which also found no differences in the rates of angiography or revascularisation in patients tested with a hs-Tn assay (12). This study and SNAPSHOT contrast with findings by other groups of angiography rates increasing 8% to 22% and revascularisation rates increasing 14% (11, 13). Despite an apparently lower acuity population being admitted to hospital, the median inpatient length of stay did not change. As such, given the rates of invasive cardiac procedures did not change and the proportion of patients with a final diagnosis on the acute coronary syndrome spectrum did not change, it is unclear what the benefit to the additional cohort of patients admitted to hospital was.

This study had several limitations. Being retrospective meant reliance on the accuracy of inpatient databases, particularly coding of patient diagnoses but this was not expected to have changed over the study period. Similarly, clinician behaviour can impact the outcomes measured but there was no change in hospital protocol regarding diagnosis coding, or ACS investigation and management protocols between the two periods other than the introduction of the new assay. The study looked at only the immediate changes following the introduction of the hsTn and a limitation is the lack of long-term follow up of the cohort. Finally, data for our study was collected from a single centre and may not be generalisable.

Conclusions

After the introduction of a hs-Tn assay, this study demonstrated that there was no change in the proportion of patients undergoing interventional cardiac procedures, or those diagnosed with acute MI or IHD. This suggests that the hs-Tn assay did not improve our identification of patients with such conditions. Despite this, there was an increase in the proportion of patients admitted to hospital. It is likely that these patients are a lower acuity population, and there was no obvious short-term benefit to these extra-admitted patients. Whilst the inpatient length of stay did not change, there was a significant decrease in the time spent in ED by patients who had a troponin order. Our findings demonstrate that whilst the hs-Tn assay has had a beneficial impact on several areas of clinical practice, further study needs to be done in order to develop protocols that minimise the effect of the assays decreased specificity for MI diagnosis.

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Illustrations and Figures

Figure 1: Departure destination from Emergency Department
Coronary Care Unit (CCU), Chest Pain Evaluation Unit (CPEU), Assessment and Planning Unit (APU), Intensive Care Unit (ICU)

Figure 2: Proportion of patients undergoing interventional cardiac procedures during the concurrent admission
Coronary artery bypass graft surgery (CAGS); Note: Revascularisation = CAGS or Angioplasty

Figure 3: Diagnosis of admitted patients
Acute Myocardial Infarction (AMI), Ischemic Heart Disease (IHD), Chronic Kidney Disease (CKD)

Tables

Table 1. Patient characteristics

	Conventional Assay (n = 6557)		**hs-Tn Assay** (n = 7335)		***p*-value**
Male: n (%, 95%CI)	3664	(55.9, 54.7-57.1)	4151	(56.6, 55.5-57.7)	0.398
Age (years): Median (IQR)	65	(51-78)	66	(51-79)	0.112
Triage Category: n (%, 95%CI)					<0.001
1	170	(2.6, 2.2-3.0)	185	(2.5, 2.2-2.9)	
2	3170	(48.4, 47.1-49.6)	2986	(40.7, 39.6-41.8)	
3	2701	(41.2, 40.0-42.4)	3409	(46.5, 45.3-47.6)	
4	508	(7.8, 7.1-8.4)	743	(10.1, 9.5-10.9)	
5	8	(0.1, 0.1-0.3)	12	(0.2, 0.1-0.3)	

Table 2: Troponin results

	Conventional Assay (n = 6557)		**hs-Tn Assay** (n = 7335**)**		**p-value**
Troponin Result: n (%, 95%CI)					
Initially abnormal troponin	1442	(22.0, 21.0-23.0)	1764	(24.1, 23.1-25.1)	0.004
Troponin rise*	214	(3.3, 2.9-3.7)	463	(6.3, 5.8-6.9)	<0.001
Combined	1532	(23.4, 22.4-24.4)	2062	(28.1, 27.1-29.2)	<0.001

*A minimum 50% rise in troponin level over consecutive samples

Table 3: Patient flow

	Conventional Assay Median (IQR)		**hs-Tn Assay** Median (IQR)		**p-value**
Time to be seen by Doctor (min)	35	(12-77)	33	(11-76)	0.117
Time to second troponin (min)	357	(293-390)	330	(237-380)	<0.001
Length of ED stay (min)	297	(206-468)	270	(199-431)	<0.001
Length of hospital stay (day)	2	(1-5)	2	(1-4)	0.088

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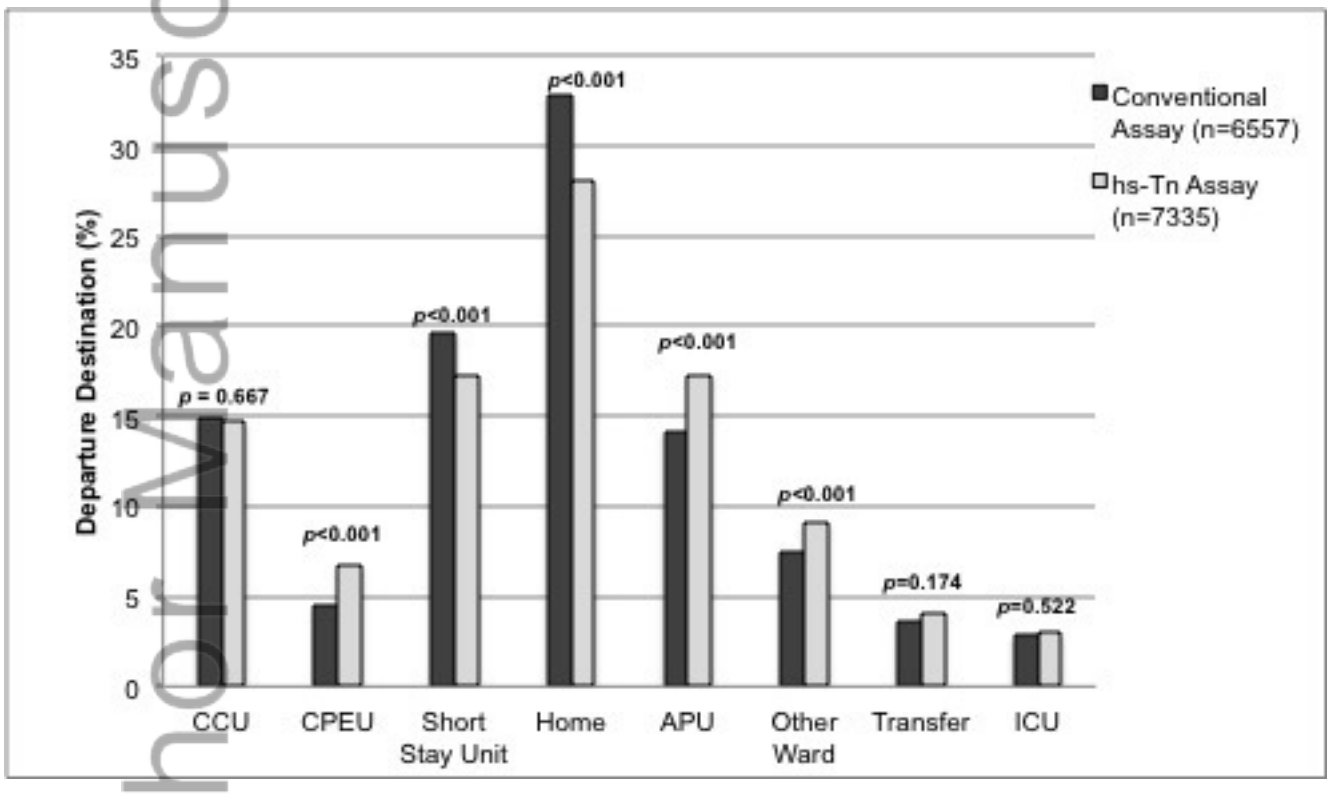

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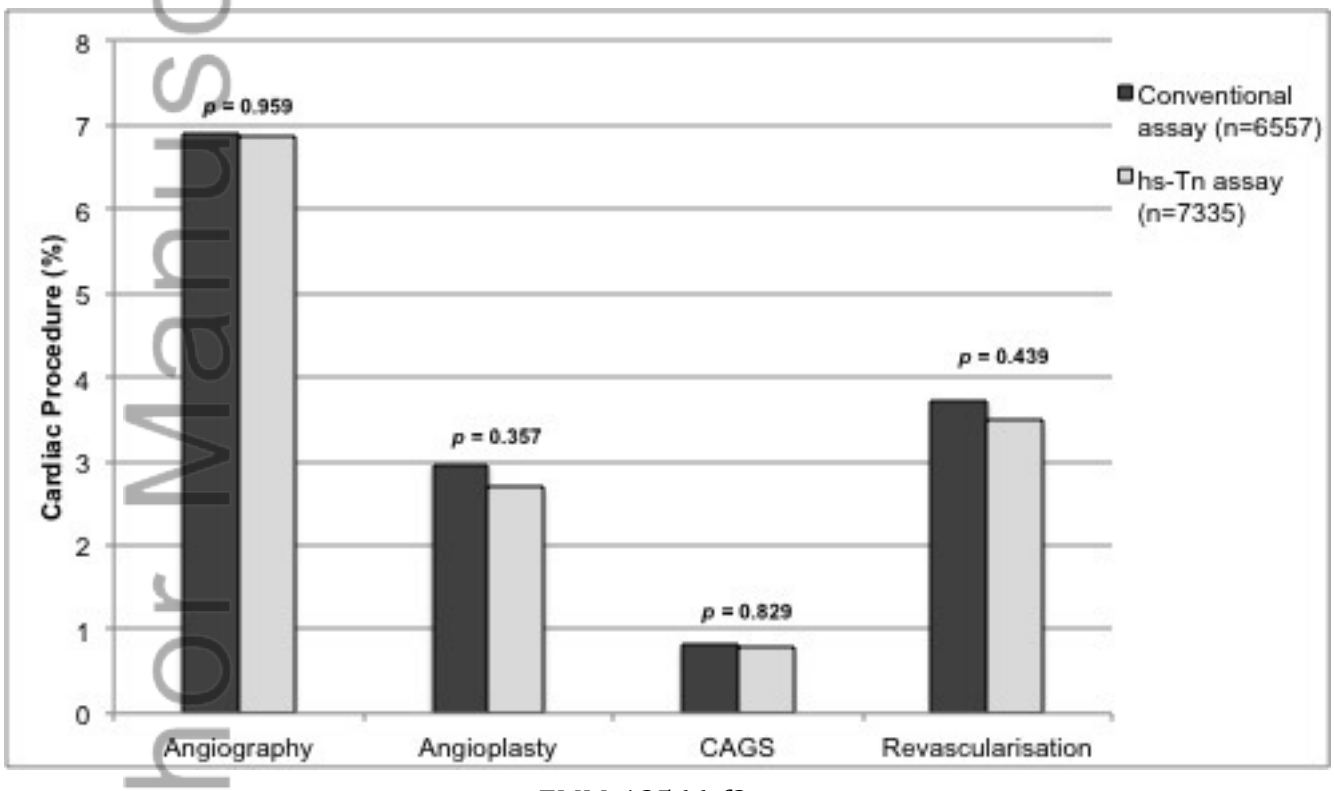

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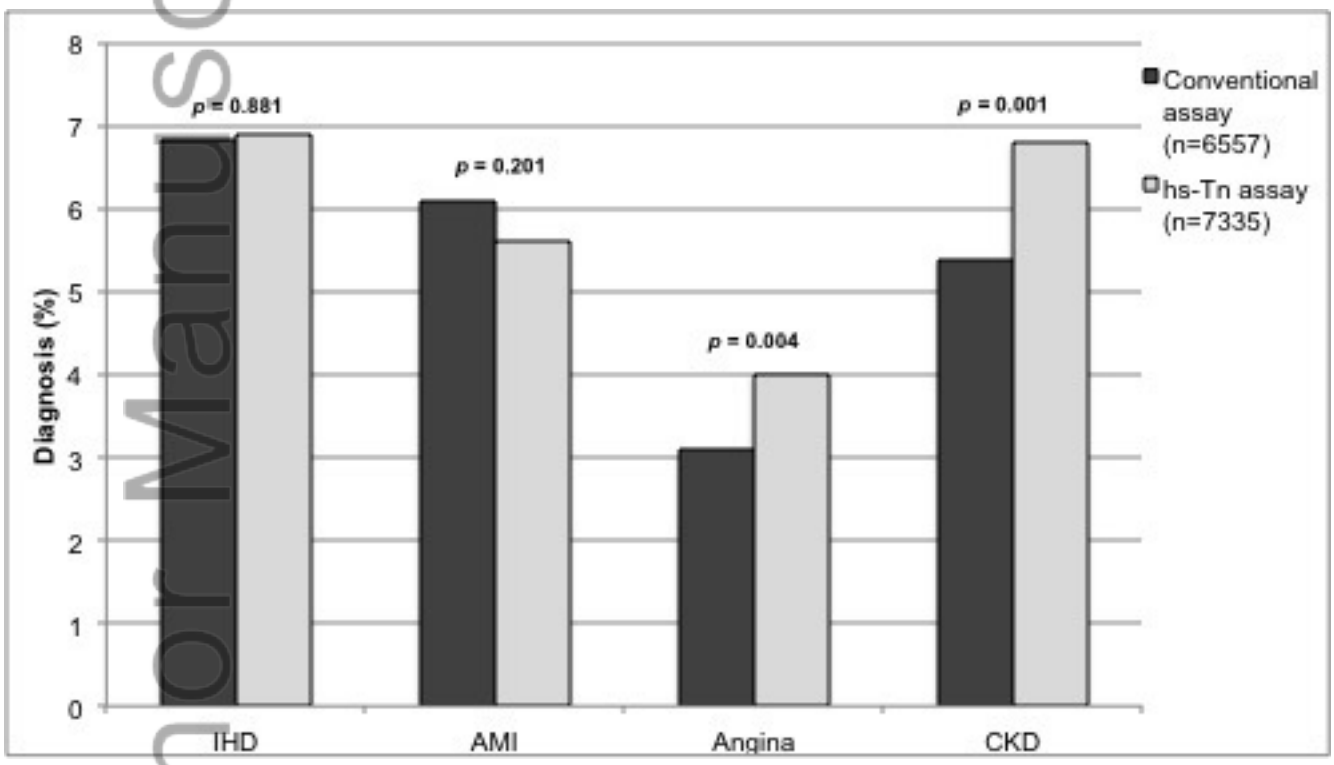

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