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## **Single Troponin Measurement to Rule-out Myocardial Infarction**

### **Running head: Single Troponin to Rule-out MI**

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#### **Conflicts of interest:**

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Dr. Body has received consulting fees from Roche, Aptamer Group, Abbott, Psyros, Siemens Healthineers, Beckman Coulter, and Radiometer and participated in advisory boards for FORCE Trial (NIHR funded), REWIRE trial (Queen Mary University, London), PRONTO trial (NIHR funded), LumiraDx (advisory board)

Dr Mills reports receiving research grants from Abbott Diagnostics and Siemens Healthineers and personal fees for participation in advisory boards or speaking from Abbott Diagnostics, Roche Diagnostics, Siemens Healthineers, LumiraDx and Psyros.

Dr. Aakre is an associate editor of Clinical Biochemistry and chair of the IFCC Committee on Clinical Applications of Cardiac Bio-Markers (C-CB), she has served on advisory board for Roche Diagnostics and SpinChip, received consultant honoraria from CardiNor, lecturing

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Dr. Saenger has received consulting fees from Radiometer

Dr. Hammarsten has stock options with <https://www.alignedbio.com/>

Dr. Wereski - none

Dr. Omland has received consultant fees from Roche, Bayer and CardiNor. He has received honoraria from Roche, has a patent pending with Roche, has participated in advisory board for Bayer and Roche, has a fiduciary role in CardiNor, has stocks in CardiNor, received equipment/material from Novartis and Abbott.

Dr. Sandoval has been on advisory boards and a speaker for Abbott Diagnostics and Roche Diagnostics and holds patent #20210401347 along with others.

Dr. Ordonez-Lanos reports receiving consultant fees from AWE Medical and Hemcheck.

Dr. Apple reports consulting fees from HyTest Ltd. and AWE Medical, advisory fees from Werfen, Siemens Healthineers, and Qorvo Biotechnology, non-salaried grant support through the Hennepin Healthcare Research Institute from Abbott Diagnostics, Abbott POC, Roche Diagnostics, Siemens Healthineers, Quidel/Ortho, Becton Dickinson, and Beckman Coulter; fees for serving as Associate Editor for Clinical Chemistry.

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Twitter handle: Educational recommendations from the IFCC Committee on Clinical Applications of Cardiac Bio-Markers @IFCC\_CCB: the single sample MI rule-out strategy using high-sensitivity troponin has excellent performance, however, clinical judgement remains essential & areas of caution exist. Learn more in the latest #JACC issue.

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## **Abstract**

The term single sample rule out refers to the ability of very low concentrations of high sensitivity cardiac troponin (hs-cTn) measurements on presentation to exclude acute myocardial infarction with high clinical sensitivity and negative predictive value.

Observational and randomized studies have confirmed this ability. Some guidelines endorse use of a hs-cTn concentration at the assay's limit of detection while other studies have validated the use of higher concentrations, allowing this approach to identify a greater proportion of patients at low risk. In most studies, at least 30% of patients can be triaged with this approach. The concentration of hs-cTn vary according to the assay used and sometimes how regulations permit reporting. It is clear that patients need to be at least 2 hours from the onset of symptoms being evaluated. Caution is warranted particularly with older patients, women and patients with underlying cardiac comorbidities.

## **Condensed abstract**

The ability to rely on very low cardiac troponin concentrations using high sensitivity assays to exclude acute myocardial infarction has been confirmed in observational and randomized trials. The approach must manifest a negative predictive value of >99.5%. Some have advocated for sensitivity of at least 97% which is appropriate when there are large study populations. Patients need to be at least 2 hours after the onset of symptoms. Caution is advised in older individuals, women and patients with high GRACE scores. The literature suggests the approach is applicable in at least 30% of most emergency department populations.

## **Abbreviations**

cTn – cardiac troponin , can be T or I

hs – high sensitivity

MI – myocardial infarction

ED – emergency department

NPV – negative predictive value

kDa – kilodaltons

LoB – limit of blank

LoD – limit of detection

LoQ – limit of quantation

## Introduction

A major advance associated with high sensitivity cardiac troponin (hs-cTn) assays is the ability to exclude acute myocardial infarction (MI) safely and rapidly.<sup>(1,2)</sup> This ability has the potential to rapidly identify those where the likelihood of an MI is low and short-term outcomes should be good. If the approach has adequate sensitivity, it will allow patients to be safely discharged from emergency departments (ED) earlier.<sup>(1,2)</sup> This ability will benefit ED overcrowding. The data are persuasive that when there are too many ED patients and wait times are long, that all patients regardless of their diagnosis are at increased risk for adverse events including mortality.<sup>(3,4)</sup> ED overcrowding also has a negative impact on patient satisfaction.<sup>(5)</sup>

hs-cTn assays detect low concentrations of cTn with improved analytic precision.<sup>(6)</sup> This allows for thresholds below the 99<sup>th</sup> percentile upper reference limit (URL) to be probed. By setting the cutoff below the limit of detection (LoD) of the assay, i.e. the lowest concentration measured which is different from zero, it is possible to exclude myocardial injury and thus MI with a single blood test on arrival to the ED.<sup>(2)</sup> This approach is used in patients who are clinically at low risk. This is a key component to its success.

The initial studies in this area were observational. Many did not include consecutive patients and in some studies the time from symptoms to sample acquisition was delayed for informed consent.<sup>(7)</sup> The metrics for ruling out MI differ when one has complete ascertainment rather than a selected cohort because the frequency of MI and thus the pre-test probability of disease is less in the unselected cohort (8). In addition, the low values obtained may or may not result in patient discharge. Thus, observational studies cannot evaluate the real-world impact of implementing these early rule-out strategies. This can be done by randomized implementation trials which we strongly endorse.<sup>(9)</sup>



The present review is part of an educational series from the International Federation of Clinical Chemistry (IFCC) Committee on the Clinical Application of Cardiac Bio-markers (C-CB) concerning the use of cardiac biomarkers. The report focuses on the single-sample rule-out and its potential benefits and limitations. While we review available data, the report is not a guideline nor a meta-analysis. It will provide readers with an understanding of the approach and recommendations to facilitate optimal utilization.

### **Safety metrics required for the single-sample rule-out**

There are several important concepts. Emergency medicine physicians advocate that the risk of missing major adverse cardiac events in patients who have MI ‘ruled out’ should be <1% at 30 days.<sup>(10)</sup> This is a high bar, but guideline supported.<sup>(11,12)</sup> There is controversy over how one implements this approach. Many studies define the optimal cut-off as the highest cTn concentration that enables the greatest proportion of patients to be ruled out (effectiveness) with a negative predictive value (NPV) of >99.5% (safety) for MI or cardiac death at 30 days.<sup>(13)</sup> This equates to a false negative every 1 in 200 patients. However, unlike sensitivity, NPV is influenced by the frequency of the event.<sup>(14,15)</sup> When the frequency of MI is low, any cut-off will provide a high NPV. It is therefore essential that the cut-off also provide high sensitivity. It has been proposed by the National Institute for Health and Care Excellence (NICE) of the UK that the optimal cut-off should provide sensitivity of at least 97% and ideally >99% when incorporated into a clinical pathway which includes the electrocardiogram and the clinical presentation.<sup>(16)</sup> This works well when sample sizes are large, there is complete clinical ascertainment of events and the frequency of MI is not exceptionally low. In small studies NPV can be misleading and reporting sensitivity is essential. Confirmation of the metrics for these assays ideally should depend on randomized implementation trials and be compared to usual care.<sup>(8)</sup>

We recommend that studies defining the optimal cut-off using the NPV also report the sensitivity, along with 95% confidence intervals, and the frequency of MI and cardiac death at 30 days. Typically, this approach is implemented in patients without evidence of myocardial ischemia on the electrocardiogram (ECG) who are tested at least 2 hours from symptom onset.<sup>(2)</sup> Clinicians can select an approach that has been evaluated in a population with a similar frequency of MI to their local population and is best suited to their healthcare system to maximize efficiency (largest proportion suitable for outpatient management) or to be more conservative (hospital admissions to minimize false negatives). A graphic illustration of this approach is shown in Figure 1. Recent data suggest an approach using values below the LoD of the assay might help in those who present <2 hours from symptom onset (17). This approach may also be of help in patients with nonspecific ECG changes.<sup>(18)</sup>

Another important area is the endpoint measured to support safety. Some studies focus on type 1 MI and/or cardiovascular death and others include all MI subtypes. The original High-STEACS study had a primary outcome of a composite of index type 1 MI and cardiac death at 30-days.<sup>(13)</sup> Other guidelines have included emergent coronary revascularization as part of MACE.<sup>(19)</sup> We advocate that studies report the MI subtypes evaluated to support safety.

Finally, it should be appreciated that single measurements are subject to uncertainty based on the rounding of concentrations which is guideline mandated.<sup>(1,6)</sup> The imprecision associated with this factor can be calculated (Table 1).

### **The Single Sample Rule Out**

The single sample rule out relies on hs-cTn assays to measure low hs-cTn concentrations around the assay's LoD. With low concentrations on arrival in the ED, the likelihood of acute MI is small using the criteria from the 4<sup>th</sup> Universal Definition of MI.<sup>(19)</sup>

The first study comprehensively evaluating this approach used the limit of blank (LoB) as a cut off.<sup>(20)</sup> The LoB is the lowest concentration that can be distinguished from noise analytically.<sup>(6)</sup> Other studies have used the LoD, but most have used higher optimized concentrations that identify a larger proportion of the population as suitable for safe discharge. The assumptions undergirding the approach are as follows.

First, there is a relationship between the molecular weight of proteins and the rapidity with which it reaches the circulation.<sup>(21)</sup> The rapid release of cTn, which is a small molecular weight molecule (cTnT = 33.5 kDa; cTnI = 23.5 kDa), is supported by one study showing increased systemic concentrations of after occluding a coronary artery for 90 seconds<sup>(22)</sup> with one hs-cTnI assay increasing within 15 minutes. Second, release of biomarkers following cardiac injury, depends on blood flow. If coronary blood flow is absent, it will take longer for cTn to be released. This is a problem with ST elevation MI (STEMI) where the incidence of total occlusion is high.<sup>(23)</sup> With NSTEMIs the frequency of total occlusion is about 30% and such patients come to the hospital later than patients with STEMI.<sup>(24)</sup> For the subset of patients who present early with total occlusions, this approach is not advocated.<sup>(7,25,26)</sup> The European Society of Cardiology Guidelines suggests the single sample rule out only in patients without ST-segment elevation who are at least 3 hours after symptom onset.<sup>(27)</sup> This may have evolved because many studies required informed consent, delaying patient evaluations until after 3 hours.<sup>(28)</sup> A real world evaluation of this timing occurred with the High-STEACS (High-Sensitivity Troponin in the Evaluation of patients with suspected Acute Coronary Syndrome) study, which reported the NPV of the single sample rule out approach was lower in those within 2 hours of symptom onset compared to those presenting >2 hours (97·6%, 95% CI 95·8–99·2 *versus* 99·8%, 95% CI 99·6–100·0).<sup>(13)</sup>

Third, cardiovascular risk factors associated with atherosclerosis and cardiovascular comorbidities cause a graded increase in the hscTn concentrations within the reference

range.<sup>(29)</sup> Thus, low concentrations suggest that few risk factors for underlying atherosclerotic disease or cardiovascular comorbidities exist. This factor augments the sensitivity of the approach by identifying a group with a low pre-test probability of disease. Accordingly, patients who might potentially be poorly triaged with this approach are those with non-atherothrombotic reasons for MI and few traditional risk factors, for example, those with microvascular dysfunction, vasospasm, spontaneous coronary artery spasm, and/or coronary embolic disease.<sup>(19)</sup>

## **Clinical Studies**

The metrics for the use of this approach varies tremendously.<sup>(30)</sup> While the initial paper utilized LoB (6,18), this threshold has not been adopted for because of the high degree of assay imprecision at LoB concentrations. Therefore, the LoD where imprecision is <20-25% is preferred.<sup>(6)</sup> The LoD does not guarantee high precision and it is for that reason that the US Federal Drug Administration (FDA) has restricted the reporting of hs-cTn concentrations to the limit of quantitation (LoQ), which is the lowest concentration with a CV of 20%.<sup>(31)</sup>

Result reporting is further complicated because for some hs-cTn assays there is variability in precision depending upon the analytical platform one and the sample matrix.<sup>(32)</sup> For many hs-cTn assays it is not necessary to use concentrations that as low as the LoD or even at the LoQ. Studies have documented that for many hs-cTn assays concentrations >LoD can establish an NPV of >99.5%. These higher concentrations allow the rule-out of a larger number of patients and increase effectiveness (Figure 1). The IFCC C-CB and the AACC Academy advocate that reporting below the 20% CV concentration is likely of value and should not negatively impact on the safety.<sup>(33)</sup> This issue impacts most directly on the hscTnT assay from Roche Diagnostics, where the LoD is 3 ng/L or 5 ng/L depending on the

analyzer. Yet, the FDA only allows reporting to a concentration of the LoQ of 6 ng/L. Only recently has data been published to suggest that this concentration can be relied for the single sample rule out.<sup>(34)</sup>

There are many observational studies that have validated the single sample rule out as well as systematic reviews and individual patient level meta-analyses.<sup>(2,14,35)</sup> Recently 3 randomized trials have provided more robust validation. The first, a stepped-wedge randomized controlled trial called HiSTORIC (High-Sensitivity Cardiac Troponin On Presentation to Rule Out Myocardial Infarction), used the Abbott hs-cTnI assay.<sup>(36)</sup> This non-inferiority trial compared standard care with serial sampling to the single sample rule-out using a validated optimized cutoff of <5 ng/L,<sup>(13)</sup> well above the 1.9 ng/L LoD in over 31,000 patients. The incidence of MI or cardiac death was very low in both groups. ED length of stay was significantly lower in the single sample group. Furthermore, the proportion of patients discharged increased from 50% in standard care to 71% with the single sample rule-out. This strategy was only deployed in those who presented  $\geq 3$  hours after symptom onset. The incidence of MI or cardiac death at 30 days was low (0.3% in with the early rule out strategy and 0.4% with standard care). This small difference did not meet the pre-specified criteria to conclude that it was non-inferior to standard care. Nonetheless, the frequency events was so low that it meets the metrics desired for adequate identification of these patients. Follow up at 1 year also demonstrated no increase in cardiac events suggesting that discharge did not compromise care.<sup>(9)</sup>

The second randomized trial was called RAPID-TnT (Rapid Assessment of Possible Acute Coronary Syndrome in the Emergency Department with High-Sensitivity Troponin T).<sup>(37)</sup> It was designed with a so-called masked and unmasked group. The masked group clinicians were not informed of the hs-cTnT concentrations that were very low, and therefore treated patients as if they had a less sensitive cTn assay. In the unmasked group, the

concentrations were shared and single sample rule out was permitted. The analysis was more complicated because the early rule out strategy involved both a 0/1-hour protocol as well as the single sample rule out. It should be noted that 13% of patients came back to the ED because of chest pain, and readmission was more common in the unmasked (4.0%) versus the masked arm (2.7%). During long-term follow-up,<sup>(34)</sup> there was an increased signal for mortality in patients who had an elevation of hs-cTnT in the unmasked group. One explanation for that might be that when clinicians did not have the hs-cTn concentrations, they were more conservative.

These conflicting data caused ambivalence about the strategy in the United States where the ability of some hs-cTn assays to report the concentrations associated with success of the single sample strategy were precluded by the FDA. This has led to controversy over whether this approach should be used with hs-cTnT. There were 4 studies probing the use of hs-cTnT concentrations of <6 ng/L. Two small trials used hs-cTnT with 0 and 3 hour sampling. Both suggested that the approach was successful.<sup>(39,40)</sup> Both studies utilized a higher 99<sup>th</sup> percentile (19 ng/L as recommended in the U.S. package insert) for diagnosing MI compared to those used in Europe (common cut off of 14 ng/L, 9 ng/L in women and 17 ng/L in men) and in the Universal Sample bank.<sup>(41)</sup> A third trial from Canada used lower 99<sup>th</sup> percentile concentrations (<8 ng/L in men or <7 ng/L in woman and had a sensitivity of 98.5% for 7 day outcomes.<sup>(42)</sup> Fourth, a recent large report with a very small number of MIs (2.1%) also reported that single sample rule-out was worthwhile.<sup>(43)</sup> However, the low incidence of MI raises the question as to whether such an effect would be seen if the incidence of MI were higher.

Third, the 'Limit of Detection in the ED' (LoDED) randomized trial included 632 low risk patients with suspected MI and a normal ECG at eight hospitals in the UK.<sup>(44)</sup> In this trial, patients were individually randomized to MI rule-out based on an initial hs-cTnI or hs-

cTnT concentration <LoD of the assay in use or standard care. No patients who met criteria for single sample rule-out had major adverse cardiac events within 30 days. However, there was not a statistically significant increase in early discharges from the ED (46% within 4 hours in the intervention group vs 37% in standard care, adjusted odds ratio 1.58, 95% CI 0.84 – 2.98). Although the difference in the proportion discharged between arms was almost identical to that observed in RAPID-TnT the confidence intervals were wide, and the study may have been under powered. LoDED suggests that the approach using the LoD cutoff is safe, but the effectiveness of the strategy cannot be taken for granted. Hospitals must work to ensure protocol adherence and alter their clinical workflow to maximize the benefits.

A more definitive observational validation for hs-cTnT has recently been published.<sup>(34)</sup> In approximately 86,000 patients studied at multiple sites, the frequency with which those who had a concentration for hs-cTnT <6 ng/L who developed myocardial injury (d a subsequent concentration above the sex specific 99<sup>th</sup> percentile URL) was roughly 1%. It was lower in men and the only signal for possible concern was in women who were older (>65 years) and had comorbidities for cardiac disease who had lower NPVs (97%). When this approach was applied to an extensively adjudicated cohort of nearly 2,000 patients with a non-ischemic ECG, it was more robust. Thus, it is clear the single sample approach works with hs-cTnT as well as most of the hs-cTnI assays.<sup>(34,45,46)</sup> The number of patients in which this strategy is applicable varies by study but ranges from 29-74% depending on the study cited and the approach used.<sup>(34-37,45,46)</sup>

It is notable however, that the concern in regard to older patients is similar to that reported from Israel.<sup>(47)</sup> These patients had lower NPVs when they were older and had higher GRACE scores.<sup>(47)</sup> No study has specifically addressed whether sex specific thresholds would improve this strategy in women. The concept that those with a high pre-test probability of cardiovascular disease are those in whom this approach may fail is supported by the recent

evaluation comparing patients with and without known coronary artery disease where the ESC 0/1 hr algorithm had an NPV of only 96.6% and a sensitivity of 93.2% using hscTnT , It is unclear whether the problems were with the single sample rule out using a value  $<6$  ng/L or the change in values over one hour or both. The data call attention to the need for clinical oversight when implementing this strategy.<sup>(48)</sup>

Point of care (POC) assays have been touted as useful for the single sample rule out, but most have relied on stored plasma samples and not fresh whole blood.<sup>(49-54)</sup> Recently, a novel hs-cTnI POC assay (Atellica VTLi,  $<8$  min) has been validated on whole blood. It derived (fresh whole blood) and validated (stored plasma) a cutoff concentration ( $< 4$  ng/L) to identify patients at low risk of index MI and low risk at 30-days ( $< 1\%$ ). Up to 40% of patients presenting with symptoms suggestive of ischemia might be discharged.<sup>(53)</sup> We are likely to see more reports from POC hs-cTn assays as they are evaluated and validated for single sample MI rule-out strategies. Given the rapid turnaround time of these assays, this could provide further efficiencies for crowded EDs.

**The data above as summarized in the central illustration lead to these recommendations**

1. The evidence-based studies demonstrate that the single sample rule out strategy based on low concentrations of hs-cTn and a non-ischemic ECG is a safe way to exclude MI. Recent data suggest perhaps a low HEAR score may help as well.<sup>(55)</sup>
2. At present, this strategy should only be used in patients presenting  $> 2$  hours after symptom onset.
3. Clinical judgement and not hs-cTn concentrations alone must be employed to safely implement the single sample rule out strategy. Particular care in older patients, women and those with cardiac comorbidities is advised.



4. For each hs-cTn assay and the analytical platform that is used, individualized cut off concentrations should be derived and validated that optimize the performance of the assay by maintaining at minimum NPV of >99.5%. NPV can be misleading in smaller data sets or when the prevalence of MI is low. Accordingly, all studies should report both NPV and sensitivity and their respective confidence intervals. When incorporated into a clinical pathway for 30-day risk of MI or death, this will maximize the proportion of patients eligible for early discharge (29 to 74%) (Table2).
5. POC hs-cTn assays must be validated using fresh whole blood for single sample MI rule-out strategies. They should meet the same clinical safety and efficacy standards as central laboratory hs-cTn assays. POC testing may solve cTn measurement TAT issues when present.

## Highlights

- Rapid, safe and accurate exclusion of acute myocardial infarction can facilitate triage of patients in the Emergency Department
- Observational and randomized studies have found that a single low assay-dependent, hs-cTn measurement taken >2 hours after symptom onset in a patient with a non-ischemic electrocardiogram can effectively exclude acute MI.
- Additional studies are needed to assess the utility of this approach in patients undergoing evaluation earlier after the onset of symptoms and to establish optimum blood level thresholds for women and patients with specific comorbidities.

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## Figure Legends

**Figure 1. Cardiac troponin concentration at presentation and risk of MI.** a) Negative predictive value (NPV) of a range of hs-cTnI concentrations (Abbott Architect<sub>STAT</sub>) on presentation for the composite outcome of index myocardial infarction, and myocardial infarction or cardiac death at 30 days; b) Proportion of patients with suspected acute coronary syndrome with troponin concentrations below each threshold. (from reference 20 with permission).

**Central Illustration. Single sample rule-out for myocardial infarction with cardiac troponin.** The central illustration depicts the metrics and application of the single sample rule out approach. It emphasizes the need for safety first while attempting to maximize efficiency. Thus the application of clinical judgement and the presence of a non ischemic ECG. Areas where additional information would be helpful is listed in boxes on the left. NPV = negative predictive value; CVa = coefficient of analytical variation. \* NPV can be misleading in smaller data sets or when the prevalence of MI is low. Accordingly, all studies should report both NPV and sensitivity and their respective confidence intervals.

**Table 1.** Imprecision and rounding associated with various cardiac troponin cut off concentrations. At a concentration of 3 ng/L patients will be admitted with a cTn concentration of 3.5 ng/L or greater (upper threshold 0.5 ng/L) then  $CV_a = (0.5/3)*100$  (16.7%) whilst discharge will be at 2.4 ng/L (minimum lower threshold 0.6 ng/L) then  $CV_a = (0.6/3)*100$  (20.0%).

Threshold (ng/L)	Retain (ng/L)	%CV	Discharge (ng/L)	% CV
1	1.5	50.0	0.4	60.0
2	2.5	25.0	1.4	30.0
3	3.5	16.7	2.4	20.0
4	4.5	12.5	3.4	15.0
5	5.5	10.0	4.4	12.0
6	6.5	8.3	5.4	10.0
7	7.5	7.1	6.4	8.6
8	8.5	6.3	7.4	7.5
9	9.5	5.6	8.4	6.7
10	10.5	5.0	9.4	6.0

**Table 2.** Single sample rule out threshold values for commercially available high-sensitivity cardiac troponin assays.

Assay	Threshold (ng/L)	N	Proportion ruled-out (%)	Outcome prevalence (%)	Rule-out performance						Outcome	Reference
					NPV (95%CI)	Sensitivity (95%CI)	TN	FN	TP	FP		
<b>Abbott ARCHITECT-STAT hs-cTnI</b>	< 5	3,799	61 <sup>†</sup>	3.8 <sup>†</sup>	99.6 (99.3 to 99.8)	†	2,302	9	136	1,352	Type 1 myocardial infarction or cardiovascular death at 30 days	<i>Shah et al. <sup>1</sup></i>
	< 5	32,837	71 <sup>†</sup>	1.6 <sup>†</sup>	99.8 (99.7 to 99.8)	†	23,205	55	462	9,115	Type 1 myocardial infarction or cardiovascular death at 30 days	<i>Bularga et al. <sup>2</sup></i>
	< 5	1,326	50	19.9	98.9 (98.2 to 99.6)	94.7 (91.4 to 98.1)	803	9	162	352	Type 1 myocardial infarction or cardiovascular death at 30 days	<i>Sandoval et al. <sup>3</sup></i>
	< 5	18,601	49	12.5	99.5 (99.3 to 99.7)	98.0 (96.4 to 98.9)	9081	49	2268	7203	Type 1 myocardial infarction or cardiovascular death at 30 days	<i>Chapman et al. <sup>4</sup></i>
	< 2	1,631	27	10.5	99.6 (98.9 to 100)	98.8 (97.2 to 100)	442	2	169	1,018	Type 1 myocardial infarction or cardiovascular death at 30 days	<i>Sandoval et al. <sup>3</sup></i>
	< 2	971	23	13.1	99.3 (97.4 to 99.8)	98.4 (94.4 to 99.8)	219	3	124	625	NSTEMI during index hospitalization	<i>Tjora et al. <sup>5</sup></i>
	< 5	2,212	46	12.5	99.6 (99.2 to 100)	98.6 (97.2 to 100)	1,040	4	273	895	Acute myocardial infarction or cardiovascular death at 30 days	<i>Sandoval et al. <sup>6</sup></i>
	< 2	2,212	21	12.5	99.8 (99.3 to 100)	99.6 (98.9 to 100)	455	1	276	1,480	Acute myocardial infarction or cardiovascular death at 30 days	<i>Sandoval et al. <sup>6</sup></i>

<b>Siemens Atellica IM hs-cTnI</b>	< 5	2,212	47	12.5	99.6 (99.2 to 100)	98.6 (97.2 to 100)	1,015	4	273	920	Acute myocardial infarction or cardiovascular death at 30 days	<i>Sandoval et al.</i> <sup>6</sup>
	< 2	2,212	23	12.5	99.6 (99.1 to 100)	99.3 (98.3 to 100)	505	2	275	1,430	Acute myocardial infarction or cardiovascular death at 30 days	<i>Sandoval et al.</i> <sup>6</sup>
<b>Beckman-Coulter Access hs-cTnI</b>	< 2	1,871	34	5.2	99.8 (99.1 to 100)	99.0 (94.4 to 100)	637	1	97	1,136	Type 1 myocardial infarction or cardiac mortality during index hospitalization	<i>Greenslade et al.</i> <sup>7</sup>
	< 4	686	30	15	100 (98.2 to 100)	100 (96.5 to 100)	206	0	106	374	NSTEMI during index hospitalization	<i>Boeddinghaus et al.</i> <sup>8</sup>
<b>Roche Elecsys Gen 5 hs-cTnT</b>	< 5	971	31	12.1	99.3 (97.4 to 99.8)	98.4 (94.4 to 99.8)	296	2	125	625	NSTEMI during index hospitalization	<i>Tjora et al.</i> <sup>5</sup>
	< 5	9,241	31	15.4	99.3 (97.3 to 99.8)	98.7 (96.6 to 99.5)	2,811	14	1,409	5,007	Index myocardial infarction	<i>Pickering et al.</i> <sup>9</sup>
	< 3	7,651	20	17.0	99.0 (93.7 to 99.8)	99.1 (97.4 to 99.7)	1,495	7	1,293	4,856	Index myocardial infarction	<i>Pickering et al.</i> <sup>9</sup>
<b>Roche Elecsys Gen 5 hs-cTnT (U.S.A. only)</b>	< 6	1,979	32 (624)	7 (141)	99.8% (99.1 to 100)	99.3% (96.1 to 100)	623	1	140	1,215	Adjudicated index myocardial infarction	<i>Sandoval et al.</i> <sup>10</sup>

† analysis population restricted to patients with a presentation concentration of high-sensitivity cardiac troponin below sex-specific 99<sup>th</sup>-centile threshold