Evaluation of the diagnostic performance of current and next-generation assays for cardiac troponin I in the BWH-TIMI ED Chest Pain Study

Marc P Bonaca, Christian T Ruff, Joshua Kosowsky,
Michael J Conrad, Sabina A Murphy, Marc S Sabatine,
Petr Jarolim and David A Morrow

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Abstract

Background: Rapid diagnosis of acute coronary syndrome is a clinical and operational priority in busy emergency departments (ED). We examined the performance of an investigational troponin I (TnI) assay with 10–100-times greater sensitivity than current commercial assays.

Methods: Among patients with non-traumatic chest pain enrolled in the BWH-TIMI ED Chest Pain Study, we measured TnI ($n=381$) at baseline, 4–6 h, and 12–24 h with an investigational assay (S-TnI; Singulex, detection-limit 0.0002 $\mu\text{g/l}$, 99th percentile 0.009 $\mu\text{g/l}$) and a contemporary sensitive assay (TnI-Ultra; Siemens, detection-limit 0.006 $\mu\text{g/l}$, 99th percentile 0.04 $\mu\text{g/l}$). Final diagnosis was adjudicated using all diagnostic data and local hospital-based cardiac TnI (Siemens), blinded to investigational cardiac TnI.

Results: The adjudicated diagnosis was myocardial infarction (MI) in 96 patients, unstable angina in 41, and acute non-coronary cardiovascular conditions in 50 patients. Baseline S-TnI was highly sensitive for MI (97%, 95% CI 91–99%) with specificity 81% (95% CI 76–86%) and positive predictive value 63% (95% CI 55–71%). The negative predictive value with S-TnI was 99% (95% CI 96–100%). S-TnI had better diagnostic accuracy than the local assay (area under the curve 0.976 vs. 0.916, $p=0.003$). Among 20 patients with negative baseline TnI and diagnosis of MI, 19 had elevated baseline S-TnI. Compared to TnI-Ultra, S-TnI trended toward higher sensitivity (97 vs. 94%, $p=\text{NS}$) but did not differ significantly in negative predictive value (99 vs. 98%) or area under the curve ($p=0.29$).

Conclusion: Current and investigational Tn assays substantially increased clinical sensitivity and improved diagnostic accuracy for MI, despite a decline in specificity. A contemporary sensitive assay delivered similar overall accuracy to the investigational test, suggesting that we have reached a point of maximum diagnostic return with increasing analytical sensitivity.

Keywords

Biomarkers, chest pain, myocardial infarction, unstable angina

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Introduction

Acute non-traumatic chest pain is the second most common reason for presentation to the emergency department (ED), accounting for approximately 9 million ED visits per year in the USA alone.¹ While the number of patients presenting with chest pain has been constant over the past decade, the percentage who are ultimately diagnosed with an acute

Harvard Medical School, Boston, MA, USA

Corresponding author:

Marc Bonaca, TIMI Study Group, Cardiovascular Division, 350

Longwood Avenue, Office Level 1, Boston, MA 02115, USA.

Email: mbonaca@partners.org

coronary syndrome (ACS) has decreased.² As a consequence, the resources consumed in the evaluation of non-ischaemic chest pain have been increasing steadily. The ability to diagnose rapidly and accurately diagnose the 15–25% of patients who present with chest pain that is a manifestation of ACS is of critical importance because the short-term mortality for patients with myocardial infarction (MI) who are mistakenly discharged from the hospital is double the rate of those who are admitted.^{3–5} In addition, diagnostic uncertainty may delay initiation of definitive treatment in those ultimately diagnosed with ACS.

The diagnosis of ACS, and differentiation between unstable angina (UA) and MI, depends upon presenting clinical symptoms, electrocardiographic criteria, and assessment of biomarkers of myocardial injury. Although changes in the first two criteria over the past few decades have been modest, progressive and important advances in the sensitivity and specificity of biomarkers for MI have occurred.⁶ Conventional assays for cardiac troponin (cTn) have been limited in their capacity to reliably detect very low concentrations reflective of myocardial damage within the initial hours after onset of ischaemia. Emerging, more sensitive assays that deliver improved analytic performance are able to detect circulating cTn at a concentration 10–100-fold lower than previous assays.⁷ However, application of more sensitive assays has come with a trade off between clinical sensitivity and specificity, rendering it critical to evaluate prospectively the overall diagnostic performance of new candidate assays and their proposed cut-off points.⁷

We previously demonstrated the ability of a highly sensitive, investigational assay for cTnI (Erenna hS-TnI, Singulex), to detect changes in cTnI during transient ischaemia.⁸ The diagnostic performance of this assay has yet to be fully characterized in a population of patients with non-traumatic chest pain. Therefore, we tested this next-generation, highly sensitive cTnI assay in a single-centre prospective study of subjects presenting to the ED with chest pain.

Methods

Study design and patient population

We designed a prospective, single-centre study coordinated by the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Brigham and Women's Hospital (BWH), Boston, MA. From July 2005 through May 2007, we enrolled 443 patients ≥ 18 years of age who presented within 24 hours of onset of non-traumatic chest pain suspicious for ACS. Qualifying symptoms were to have occurred at rest and lasted at least 10 minutes or to have had a clear crescendo pattern culminating in symptoms occurring with minimal exertion. Exclusion criteria included recent hospitalization for ACS (with the previous 28 days), severe renal insufficiency (creatinine clearance < 30 ml/min), and known chronic

or acute systemic inflammatory disease or infection. All patients provided written informed consent and the study was approved by the hospital institutional review board.

Troponin testing

Blood samples for determination of cTnI in serum were collected at enrollment, and serially (if not already discharged) at 4–6 hours, 12–24 hours, and 36–48 hours and were stored at -70°C until thawed for analysis. cTnI was measured using two sensitive assays: (i) an investigational highly sensitive TnI (S-TnI; Erenna hS-TnI; Singulex, Berkeley, CA, USA) which has a lower limit of detection of 0.2 pg/ml (0.0002 $\mu\text{g/l}$), and a 99th percentile reference limit of 9 pg/ml (0.009 $\mu\text{g/l}$), with a total imprecision of 10% at that concentration;⁹ and (ii) a commercially available sensitive assay (TnI-Ultra; Siemens Healthcare Diagnostics, Deerfield, IL, USA) which has a lower limit of detection of 6 pg/ml (0.006 $\mu\text{g/l}$), a 99th percentile reference limit of 40 pg/ml (0.04 $\mu\text{g/l}$), and a total imprecision of 10% at a concentration of 30 pg/ml (0.03 $\mu\text{g/l}$).¹⁰ In addition, the prior-generation TnI assay (local TnI; Centaur cTnI, Siemens) was used locally as part of clinical care and for adjudication of the final diagnosis. This assay has a lower limit of detection of 30 pg/ml (0.03 $\mu\text{g/l}$) and an established cut point of 100 pg/ml (0.1 $\mu\text{g/l}$) with a total imprecision of 20% at that concentration.¹¹

Adjudication of final diagnosis

Each patient's final presenting diagnosis was adjudicated by a clinical end-points committee comprised of two separate reviewers using established criteria for MI¹² and all available diagnostic data during the hospitalization, including the local cTnI results. Reviewers were blinded to the two sensitive cTnI assays. If there was disagreement about the final diagnosis, a third reviewer refereed. In addition, we performed an exploratory analysis after reclassification of the diagnosis based upon use of the more sensitive assays investigated in this study.

The presenting diagnosis was adjudicated and categorized into the following: acute coronary ischaemic events (MI, UA, ACS); non-coronary acute cardiopulmonary process (NCACP; e.g. myocarditis, non-ischaemic heart failure, or pulmonary embolism); and non-cardiac chest pain. MI was further categorized into STEMI, NSTEMI or unknown, and by the Universal MI Classification system: type 1 (spontaneous), type 2 (secondary/demand), type 3 (sudden cardiac death), type 4a (PCI related), type 4b (stent thrombosis), type 5 (CABG related).^{12,13}

Statistical analysis

Continuous variables are presented as medians (interquartile range) and categorical variables as numbers and percentages.

Baseline characteristics were compared using the chi-squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Sensitivity, specificity, and positive and negative predictive values were calculated for baseline and peak measurements for the three cTnI assays using the 99th percentile cut point for each assay. The diagnostic accuracy of the assays at baseline were compared using the area under the curve (AUC) derived from receiver operating characteristic (ROC) curves.¹⁴ An additional analysis of diagnostic performance was performed for both S-TnI and TnI-Ultra using the change in cTn concentration between baseline and a subsequent sample. Based on the approach reported by Reichlin and colleagues,¹⁵ an absolute change in concentration equal to 20 pg/ml for TnI-Ultra and 4.5 pg/ml for S-TnI (analogous 50% of the 99th percentile) was evaluated as an additional diagnostic criterion along with a value >99th percentile. McNemar's test was used to compare sensitivity and specificity of the cTn assays. Two-tailed *p*-values <0.05 were considered significant. All analyses were performed using STATA version 9.2 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics

A total of 443 patients were enrolled. Patients were mostly male (61%), non-smokers (82%), and approximately a third had a prior history of MI (29%) or PCI (34%). The final adjudicated diagnoses for the 381 subjects with results available for each of the cTn assays who were therefore included in this analysis are listed in Table 1. A total of 96 (25%) patients had a MI with the majority being type 1 (spontaneous, 90%) events. Only 13 (14% of MIs) were STEMI. There were 178 (47%) patients with non-cardiac diagnoses with the largest components being gastrointestinal (*n*=41, 62%) and musculoskeletal (*n*=18, 27%). There were 50 (13%) patients with NCACP and 41 (11%) patients with unstable angina. Overall, there were 137 (36%) patients with ACS.

Patients with MI were more likely to be male, smokers, have a history of percutaneous intervention (PCI), and present with ST-changes (Supplementary Table S1, available online). Patients without results for each of the cTn assays (local, TnI-Ultra, and S-TnI) were similar to patients with samples with the exception of higher median body weight (Supplementary Table 1). The median time from symptom onset to presentation was 3 h (IQR 1.6–6.5 h). Time to presentation was similar for patients with ACS (3.4 h, IQR 1.6–7 h) compared to those without ACS (3 h, IQR 1.5–6.3 h, *p*=0.27). Within the ACS group, patients with STEMI presented with a numerically shorter delay than those with NSTEMI (2.5 h, IQR 2–17 h vs. 3.6 h, IQR 2–6.5 h; *p*=0.65). Patients with NCACP presented at a median 4.8 h (IQR 2–8 h).

Table 1. Adjudicated final diagnoses of patients with non-traumatic chest pain enrolled in the BWH-TIMI ED Chest Pain Study.

Diagnosis	Study population (<i>n</i> =381)
Myocardial infarction	96 (25)
NSTEMI	83 (86)
STEMI	13 (14)
Type 1	86 (90)
Type 2	10 (10)
Unstable angina	41 (11)
Stable angina	16 (4)
NCACP	50 (13)
Non-cardiac	178 (47)
Gastrointestinal	41 (62)
Musculoskeletal	18 (27)
Neurogenic	3 (5)
Pulmonary	2 (3)
Cocaine use	1 (2)
Other	1 (2)

Values are *n* (%).

NCACP, non-coronary acute cardiopulmonary process.

Diagnostic performance at presentation

The diagnostic performance characteristics of each of the assays tested for MI are shown in Table 2. Troponin measured using the locally available assay had a sensitivity for the diagnosis of MI at presentation of 78% (95% CI 69–86%) and a specificity of 97% (95% CI 95–99%). S-TnI was substantially more sensitive for the diagnosis of MI at baseline (97%, 95% CI 91–99%, *p*<0.001) but less specific for MI when considered as the only reason for elevated cTn (81%, 95% CI 76–86%, *p*<0.001). In comparison, TnI-Ultra was more sensitive (94%, 95% CI 87–98%) than the local assay (*p*=0.004) but numerically less sensitive than S-TnI (*p*=0.32) and had a specificity of 92% (95% CI 88–95%). The greater sensitivity of TnI-Ultra and S-TnI translated into a higher negative predictive value (NPV) for MI (93% for local TnI, 98% for TnI-Ultra, 99% for S-TnI) but their reduced specificity was reflected in their decreased positive predictive value (90% for local TnI, 80% for TnI-Ultra, 63% for S-TnI).

Of patients with a positive cTn, a greater proportion had a diagnosis other than ACS using the more sensitive assays (9% local vs. 18% TnI-Ultra vs. 30% S-TnI; Figure 1). The most common diagnosis after MI in those with an elevated cTn across the assays was NCACP. The proportion of patients with a final diagnosis of UA who had an elevated cTn concentration at baseline increased with the more sensitive assays (0% local vs. 3% TnI-Ultra vs. 7% S-TnI), as did the proportion with elevated cTn for patients a final diagnosis of non-cardiac chest pain (1% local vs. 4% TnI-Ultra vs. 12% S-TnI).

Table 2. Diagnostic performance for MI of baseline and peak cTnI by assay.

Diagnosis	Myocardial infarction (n=381)			
	Sensitivity	Specificity	PPV	NPV
Baseline cTnI				
Local	78 (69–86)	97 (95–99)	90 (82–96)	93 (89–96)
TnI-Ultra	94 (87–98)	92 (88–95)	80 (71–87)	98 (95–99)
S-TnI	97 (91–99)	81 (76–85)	63 (55–71)	99 (96–100)
Peak cTnI				
Local	97 (91–99)	91 (87–94)	78 (69–85)	99 (97–100)
TnI-Ultra	95 (88–98)	84 (80–89)	67 (59–75)	98 (95–99)
S-TnI	98 (93–100)	74 (69–79)	56 (48–64)	99 (97–100)

Values are % (95% CI).

cTnI, cardiac troponin I; NPV, negative predictive value; PPV, positive predictive value; S-TnI, Erenna hS-TnI, Singulex; TnI-Ultra, Siemens Healthcare Diagnostics.

Figure 1. Distribution of diagnosis in patients with a positive cardiac troponin at baseline by assay.

MI, myocardial infarction; NCACP, non-coronary acute cardiopulmonary process (e.g. pulmonary embolism); non-cardiac, non-cardiopulmonary diagnoses (e.g. gastro-oesophageal reflux disease); SA, stable angina; UA, unstable angina.

S-TnI at presentation was elevated in 20 (21%) patients with a diagnosis of MI whose baseline concentration was undetectable using the local assay (Figure 2a). Of these patients, 19 were detected with TnI-Ultra. In the broader population of patients with ACS (MI or UA), baseline TnI-Ultra was elevated in 22 patients (16%) that were negative using the local assay and an additional eight patients had elevated S-TnI (Figure 2b).

Diagnostic accuracy in ACS

The overall diagnostic accuracy of each assay for MI was evaluated using the AUC (Table 3 and Figure 3). When measured using either the TnI-Ultra or S-TnI, the more sensitive assays delivered significantly greater accuracy compared to the local cTnI assay (S-TnI $p=0.003$; TnI-Ultra $p=0.017$). This difference was more marked when

examining patients who presented within 6 hours of symptom onset in whom the diagnostic accuracy of the prior-generation local assay was decreased (AUC 0.840) compared with S-TnI (AUC 0.998, $p=0.009$; Figure 3b) and TnI-Ultra (AUC 0.999, $p=0.009$). There was no significant improvement in diagnostic accuracy with S-TnI compared with TnI-Ultra overall ($p=0.29$, Figure 3c) or in those who presented within 6 hours of symptom onset ($p=0.48$, Figure 3d).

Serial measurement

With serial testing using the peak value and a threshold at the 99th percentile, the sensitivity of S-TnI and TnI-Ultra increased to 98% and 95% with specificity declining to 74% and 84%, respectively (Table 2). In addition, the proportion of patients with a final diagnosis of UA who had an elevated cTn was increased (TnI-Ultra 7% at baseline vs. 27% peak; S-TnI 24% at baseline vs. 39% peak).

Application of a criterion for an absolute change (delta) in concentration in patients with serial samples resulted in a non-significant increase in the sensitivity for MI (S-TnI 99 vs. 97%, TnI-Ultra 96 vs. 94%) with an associated decrease in specificity (S-TnI 68 vs. 81%, TnI-Ultra 79 vs. 92%). Use of the delta criterion for S-TnI identified 15 additional cases of non-ACS chest pain as MI. Overall 44% of patients with a NCACP had dynamic changes in S-TnI that met the delta criteria. The sensitivity for capturing patients with a final diagnosis of ACS (MI or UA) increased significantly using the delta cTnI compared with peak values only: S-TnI (85 vs. 75%) and TnI-Ultra (79 vs. 68%) with modest changes in specificity (S-TnI 72 vs. 82%, TnI-Ultra 82 vs. 92%).

Exploratory analyses

In an exploratory analysis in which patients with an adjudicated diagnosis of UA or stable angina and an

Figure 2. Additional cases of MI (a) and ACS defined as a final diagnosis of either MI or UA (b) diagnosed using TnI-Ultra and Singulex TnI compared to the local troponin assay.

ACS, acute coronary syndrome; MI, myocardial infarction; UA, unstable angina.

Table 3. Overall diagnostic accuracy for myocardial infarction (area under the ROC curve) of baseline cTnI.

	Local cTnI	S-TnI	p-value ^a	TnI-Ultra	p-value ^a
Full cohort	0.916 (0.88–0.95)	0.976 (0.96–0.99)	0.003	0.965 (0.94–0.99)	0.29
Early presenters (<6 h of symptoms)	0.840 (0.72–0.96)	0.998 (0.99–1.00)	0.009	0.999 (0.99–1.00)	0.48

^ap-value for comparison of local TnI vs. S-TnI.

^bp-value for comparison of S-TnI vs. TnI-Ultra.

cTnI, cardiac troponin I; S-TnI, Erenna hS-TnI, Singulex; TnI-Ultra, Siemens Healthcare Diagnostics.

elevated experimental cTnI (S-TnI) were reclassified as MI, baseline S-TnI had a sensitivity for MI of 90% and specificity of 85%. Serial S-TnI provided a specificity of 81%. Specificity remained higher for TnI-Ultra (93%) and the local assay (97%). The AUC for diagnosis of MI using baseline cTnI measured with S-TnI (0.940) did not differ significantly from that with TnI-Ultra (0.922) ($p=0.15$) but was significantly higher than that using the local assay (0.829) ($p<0.001$). Importantly, diagnostic accuracy using baseline S-TnI alone was better than the local assay using serial samples (0.940 vs. 0.902, $p=0.03$).

Discussion

In this prospective evaluation of an investigational cTnI assay based on single-molecule counting (Singulex hS-TnI), along with a current-generation commercial sensitive assay (TnI-Ultra), compared with the prior-generation assay, we found that the two more-sensitive assays delivered significantly improved overall diagnostic accuracy and a NPV $\geq 98\%$. Notably, while the investigational assay improved sensitivity and NPV at baseline, we did not find a significant improvement in overall diagnostic accuracy

compared with a current-generation commercial sensitive assay. These findings suggest that we may have reached a point of maximum clinical return for the diagnosis of ACS with the increasing analytical sensitivity offered by newer and emerging assays for cTnI. It appears likely that any incremental clinical advantages from further enhancements to analytical sensitivity will come in other areas of application such as in patients with stable ischaemic heart disease or screening of individuals at risk for structural heart disease.

Because this cohort included a broad population of patients presenting to a ED with non-traumatic chest symptoms, a significant proportion (13%) had a NCACP. Some of the diagnoses represented in this cohort included patients with rapid arrhythmia, hypertensive urgency, pulmonary embolism, symptomatic severe aortic stenosis, stress-induced cardiomyopathy, and cocaine-induced chest pain. Importantly, 36% of these patients had an elevated S-TnI that met MI criteria on their baseline sample with an increase to 44% when incorporating the delta over serial samples. These findings highlight that patterns of detectable myocardial injury may be dynamic in acute non-coronary processes and reveal a limitation that should be taken into account when using a delta to help discriminate

Figure 3. Receiver operating curves for the diagnosis of myocardial infarction: S-TnI and local TnI for all subjects (a) and presenters within 6 hours of symptom onset (b) and S-TnI and TnI-Ultra for all subjects (c) and presenters within 6 hours of symptoms (d).

between patients with ACS and those with other acute processes.

Diagnostic use of sensitive assays for troponin

Our findings expand upon previous studies, with evaluation of a next-generation investigational assay. We found that using S-TnI, we were able to detect more MIs than the prior-generation assay (97 vs. 78%) or the current-generation sensitive commercial assay (97 vs. 94%) at baseline. Of the 41 patients with UA, we were able to reclassify 10 (24%) as NSTEMI using S-TnI at baseline. Importantly, a negative baseline S-TnI provided an extremely high NPV of 99% allowing early identification of a group of patients at very low likelihood of MI and potentially suitable for early discharge from the ED.

This increased sensitivity, however, came at the expense of clinical specificity with a greater proportion of cTn positive patients having alternative diagnoses using the more

sensitive assays (S-TnI 14%, TnI-Ultra 6%). Notably, myocardial injury could be attributed to a non-coronary cardiopulmonary cause in the majority (61%) of these cases. In our cohort, 30 patients (20 with MI) presenting with a diagnosis of ACS were not detected using the local assay at baseline but were using the investigational high-sensitivity assay. The ability to identify such patients quickly could facilitate more rapid triage and treatment. Moreover, those patients with NCACP with an elevated cTn (44% S-TnI, 32% TnI Ultra, and 19% local) are important to recognize and triage for inpatient evaluation and care. Although the detection of both NCACP as well as ACS with elevated cTn translates into reduced specificity for MI, it also defines the Tn negative patients as a group at very low risk of a cardiopulmonary process. The ability to rapidly identify patients with very low likelihood of either a coronary or non-coronary acute cardiopulmonary event should be of value to ED physicians.

In contrast to recent studies, we found that use of absolute change in cTn concentration as a diagnostic criterion

did not meaningfully increase diagnostic specificity, in part because patients with NCACP also had changes over time in our study. While the utilization of changes in serial troponin to increase diagnostic specificity is conceptually appealing, our study illustrates several potential limitations that should be taken into account as clinical adoption of using delta troponin progresses.¹⁶ The determination of optimal delta criteria in clinical studies is very dependent on the specific distribution of presenting syndromes and the timing of both symptom onset to clinical evaluation and blood sample acquisition. As these variables differ from study to study, and certainly from routine clinical practice, it will require extensive validation and careful thought to choose reasonable criteria that is broadly applicable. Moreover, the delta criteria for one troponin assay, whether absolute or relative, is not likely translatable to other assays. This results in the possibility that each assay would require its own unique delta threshold.¹⁶

In our study of real-world patients presenting to the ED several hours after the onset of chest symptoms, we found that the excellent NPV of cTn assessed in the initial sample with a highly sensitive assay was useful in identifying a group of patients potentially suitable for discharge. Our findings thus add to the accumulating evidence that supports the viable application of rapid rule out protocols,^{17,18} particularly using sensitive assays for cTn. This diagnostic approach, however, needs to be validated in larger populations that include adequately powered evaluation of outcomes after discharge.

Limitations

There are several important limitations of this analysis. First, while our cohort size was sufficient to observe a difference between the newer assays and the local assay overall, it is possible that a larger sample size would support detection of a difference between S-TnI and TnI-Ultra. Nevertheless, our findings indicate that even if statistically significant in a larger population, the magnitude of difference in the AUC is not likely to be large. Second, we had relatively few patients within 3 hours of symptom onset, a group in whom the more sensitive assays may have a greater incremental advantage. Another important limitation is that the study cohort was obtained from a single institution and clinical outcomes other than diagnosis were not collected. Multicentre evaluations with clinical outcomes will be important to defining any clinical role of newer investigational assays for cTn.

Conclusions

Measurement of cTn using newer more sensitive assays in patients presenting with non-traumatic chest pain enables more rapid and accurate diagnosis of MI compared to prior-generation assays and results in a very high NPV with a

single baseline sample. We did not find a significant incremental improvement in overall accuracy with an investigational newest-generation assay compared with a contemporary sensitive assay. It is possible that we have reached a ceiling of diagnostic benefit with the increasing analytical sensitivity offered by newer assays for cTn.

Conflict of interests

MPB is an investigator and receives salary support from the TIMI Study Group and has received remuneration for consulting from Roche. CTR is an investigator and receives salary support from the TIMI Study Group and has received remuneration for consulting from Alere, Beckman Coulter, Daiichi Sankyo, and Boehringer-Ingelheim. MSS is an investigator and receives salary support from the TIMI Study Group and research grant support through Brigham and Women's Hospital from Abbott Laboratories, Nanosphere, and Roche Diagnostics. PJ has received research support from Daiichi Sankyo, Roche Diagnostics, AstraZeneca, Siemens, Abbott, and Merck and has received remuneration for consulting from T2 Biosystems and Quantarix. DAM is an investigator and receives salary from the TIMI Study Group and has received remuneration for consulting from Beckman-Coulter, Boehringer Ingelheim, Critical Diagnostics, Genentech, Gilead, Instrumentation Laboratory, Johnson & Johnson, Merck, Roche Diagnostics, and Servier. JK, MJC, and SAM declare no conflicts of interest.

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