

# Finding acute coronary syndrome with serial troponin testing for rapid assessment of cardiac ischemic symptoms (FAST-TRAC): a study protocol

W. Frank Peacock<sup>1</sup>, Alan S. Maisel<sup>2</sup>, Christian Mueller<sup>3</sup>, Stefan D. Anker<sup>4</sup>, Fred S. Apple<sup>5</sup>, Robert H. Christenson<sup>6</sup>, Paul Collinson<sup>7</sup>, Lori B. Daniels<sup>2</sup>, Deborah B. Diercks<sup>8</sup>, Salvatore Di Somma<sup>9</sup>, Gerasimos Filippatos<sup>10</sup>, Gary Headden<sup>11</sup>, Brian Hiestand<sup>12</sup>, Judd E. Hollander<sup>13</sup>, Juan C. Kaski<sup>7</sup>, Joshua M. Kosowsky<sup>14</sup>, John T. Nagurney<sup>15</sup>, Richard M. Nowak<sup>16</sup>, Donald Schreiber<sup>17</sup>, Gary M. Vilke<sup>2</sup>, Marvin A. Wayne<sup>18</sup>, Martin Than<sup>19</sup>

<sup>1</sup>Department of Emergency Medicine, Baylor College of Medicine, Houston, TX, USA

<sup>2</sup>Department of Cardiology, University of California, La Jolla, CA, USA

<sup>3</sup>Department of Cardiovascular Research Institute Basel (CRIB), University Hospital Basel and University of Basel, Basel, Switzerland

<sup>4</sup>Department of Cardiology, Charité Campus Virchow-Klinikum, Berlin, Germany

<sup>5</sup>Department of Lab Medicine, Hennepin Healthcare/Hennepin County Medical Center & University of Minnesota School of Medicine, Minneapolis, MN, USA

<sup>6</sup>Department of Lab Medicine, University of Maryland Medical Center, Baltimore, MD, USA

<sup>7</sup>Department of Lab Medicine, St. George's University of London, London, UK

<sup>8</sup>Department of Emergency Medicine, University of Texas Southwestern, Dallas, TX, USA

<sup>9</sup>Department of Emergency Medicine, Sapienza University, Rome, Italy

<sup>10</sup>Department of Critical Care, University Hospital Attikon, Athens, Greece

<sup>11</sup>Department of Emergency Medicine, Medical University of South Carolina, Charleston, SC, USA

<sup>12</sup>Department of Emergency Medicine, Wake Forest University, Winston-Salem, NC, USA

<sup>13</sup>Department of Emergency Medicine, Thomas Jefferson University, Philadelphia, PA, USA

<sup>14</sup>Department of Emergency Medicine, Brigham & Women's Hospital, Boston, MA, USA

<sup>15</sup>Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA, USA

<sup>16</sup>Department of Emergency Medicine, Henry Ford Health System, Detroit, MI, USA

<sup>17</sup>Department of Emergency Medicine, Stanford University School of Medicine Palo Alto, CA, USA

<sup>18</sup>Department of Emergency Medicine, PeaceHealth St. Joseph Medical Center, Bellingham, WA, USA

<sup>19</sup>Department of Emergency Medicine, Christchurch Hospital, Christchurch, New Zealand

**Objective** To determine the utility of a highly sensitive troponin assay when utilized in the emergency department.

**Methods** The FAST-TRAC study prospectively enrolled > 1,500 emergency department patients with suspected acute coronary syndrome within 6 hours of symptom onset and 2 hours of emergency department presentation. It has several unique features that are not found in the majority of studies evaluating troponin. These include a very early presenting population in whom prospective data collection of risk score parameters and the physician's clinical impression of the probability of acute coronary syndrome before any troponin data were available. Furthermore, two gold standard diagnostic definitions were determined by a pair of cardiologists reviewing two separate data sets; one that included all local troponin testing results and a second that excluded troponin testing so that diagnosis was based solely on clinical grounds. By this method, a statistically valid head-to-head comparison of contemporary and high sensitivity troponin testing is obtainable. Finally, because of a significant delay in sample processing, a unique ability to define the molecular stability of various troponin assays is possible.

**Trial registration** ClinicalTrials.gov Identifier NCT00880802

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Correspondence to: W. Frank Peacock  
Baylor College of Medicine, Ben Taub  
General Hospital, 1504 Taub Loop,  
Houston, TX 77030, USA  
E-mail: Frankpeacock@gmail.com



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## Capsule Summary

### What is already known

*High sensitivity troponin is an excellent predictor of adverse events in emergency department patients.*

### What is new in the current study

*This is one of the very few investigations to not use local troponin results to define the gold standard diagnosis (by having a nontroponin independent comparator), it required enrollment in <6 hours of symptom onset (providing a large population of early presenters), it collected prospective risk score data (to evaluate risk scores after high sensitivity troponin testing), it required physician documentation of acute coronary syndrome probability before any lab results were available, and it is the only study able to report on troponin stability in serum libraries.*

## INTRODUCTION

Over 10 million patients present to US emergency departments (EDs) annually with a chief complaint consistent with a suspected acute coronary syndrome (ACS).<sup>1,2</sup> The majority of these patients are ultimately found to be experiencing noncardiac chest pain.<sup>3-7</sup> Myocardial infarction (MI) is diagnosed in a minority and includes non-ST-segment elevation MI and ST-segment elevation MI. Patients who have symptoms consistent with an MI diagnosis, but without objective evidence of myocellular death, represent the disposition challenge. Those ultimately found to have a myocardial ischemic etiology for their symptoms may be termed unstable angina (UA), a condition that is often a precursor to MI. Together, the spectrum of MI and UA represents ACS.

The universal definition of MI<sup>8</sup> stratifies evidence of myocellular death into diagnostic categories by the dynamic changes of an elevated troponin concentration and if there is evidence of myocardial ischemia. A type I MI results from coronary artery plaque rupture. Its definition requires a rise or fall of cardiac troponin (cTn), with at least one value above the 99th percentile upper reference level (URL) obtained from a healthy population, and evidence of myocardial ischemia. Pathologically, UA may also be associated with plaque rupture, but is limited to only partial coronary artery occlusion and, by definition, has no measurable necrosis. When UA occurs, no troponin rise is detectable with contemporary assays. Since contemporary assays cannot clearly distinguish UA from noncardiac chest pain, patients with UA have historically been at risk of ED discharge, despite suffering from a high-risk ischemic event.

Advancements in assay technology have enabled lower levels of troponin detection and improved precision at low concentrations. The improved analytical performance of these assays is reflected in their definition, requiring the total imprecision (coefficient of variation) at the 99th percentile value to be  $\leq 10\%$  and

measurable concentrations below the 99th percentile, but above the level of detection, attainable in at least 50% of healthy individuals.<sup>9</sup> None of the troponin assays described previously as 'contemporary' can achieve these benchmarks.

The importance of the improved analytic performance is supported by large studies that have demonstrated that a detectable troponin level, but below the 99th percentile of a healthy population, may be associated with unacceptable rates of short and long-term adverse cardiac events.<sup>10,11</sup> Regardless of the underlying etiology, and even if not associated with MI, higher troponin concentrations are a poor prognostic finding. Because high sensitivity cTn (hs-cTn) assays can detect at lower concentrations than contemporary assays, their value in prediction and exclusion of adverse events is superior. The current definition of MI that requires troponin levels to exceed the 99th percentile, can diagnose acute MI (AMI) with a contemporary troponin assay accurately but does not allow precise risk stratification of the entire population at risk for ACS.<sup>8</sup> Furthermore, because of the poor precision at low levels, contemporary assays cannot stratify the risk to patients until the troponin has risen significantly. This is in contradistinction to high sensitivity assays, which can give precise low concentration results, and can identify pathologic changes in troponin as early as 1 to 2 hours after symptom onset, which contemporary assays cannot.

The hs-cTn assays may add value both by revealing abnormal cTn at ED presentation that may progress to MI or by detecting an acute myocardial injury that may not progress to MI (for instance, UA). High sensitivity assays may thus enhance the clinical utility of testing for suspected ACS in the ED, and other cardiac care settings, with earlier detection that can lead to directed therapies via improved risk stratification. There is also significant potential for high sensitivity assays to enable early exclusion of MI and UA if troponin concentrations are undetectable or very low, and unlikely to rise to significant levels. This provides early

reassurance to the patient and can rationalize the use of fewer resources and facilitate an early discharge from the ED. Therefore, high sensitivity assays have the potential to enable improved patient outcomes by indicating the need for early directed investigations and therapies and reduce the health system burden of low-risk patients otherwise requiring extensive "work-up" to exclude ACS. These benefits may be present both on initial assessment in the ED and medium-term follow-up.

## METHODS

### Purpose

The finding acute coronary syndrome with serial troponin testing for rapid assessment of cardiac ischemic symptoms (FAST-TRAC) study was designed to determine the incremental value of a hs-cTn assay compared to a contemporary troponin assay to rule out ACS in ED patients experiencing signs and symptoms consistent with acute cardiac ischemia.

This study had two *a priori* defined primary aims: (1) to determine if hs-cTnI (cardiac troponin I) could provide improved diagnostic accuracy for ACS (including MI and/or UA) within the first 2 hours after ED presentation compared with a contemporary troponin assay. (2) To determine if hs-cTnI could provide improved prognostic information for 180-day major adverse cardiac event outcomes, compared with contemporary troponin assays.

### Study population

All participating institutions obtained local ethics committee approval to participate, and all enrolled patients provided written informed consent. Inclusion criteria specified that patients were at least 18 years of age and presenting to an ED within 6 hours of symptoms consistent with ACS, defined as chest discomfort/pain, squeezing/fullness in the chest, pain radiating to left or both arms, jaw pain, pain in back/neck/stomach, shortness of breath, cold sweat, nausea/vomiting, or lightheadedness. Patients were excluded if they were in acute distress requiring immediate life-saving intervention, if they had cardiopulmonary resuscitation (defibrillation or cardioversion within 24 hours of presentation to the ED), could not provide informed consent, had a terminal illness and were not expected to survive 6 months, or had trauma likely to be the cause of their ACS symptoms (e.g., penetrating wounds).

Case report forms included baseline patient demographics, history, physical exam, ECG results, diagnostic and laboratory test results, with data handling guidelines that provide definitions and specifications on how to complete the case report form. All information recorded on the case report form was required to have

verifiable source documentation.

The definition of MI used was based on cTn, with any value above the 99th percentile of the assay's reference range population defined as abnormal. The hs-TnI used for this analysis was the Access hs-TnI (Beckman Coulter, Brea, CA, USA). It has a level of detection of 2.0 pg/mL and a 99th percentile URL of 17.5 pg/mL, and sex-specific 99th percentile URLs of 19.8 and 11.6 pg/mL for males and females, respectively. For FAST-TRAC, if the hs-TnI URL was lower than the URL of the local institution's assay, all values above the hs-TnI URL but below the local assay's URL were considered "UA" on the local assay and were defined as MI when measured on the hs-TnI assay. This standard may result in the "UA" category being removed as an ACS categorization in the hs-TnI cohort.

Physicians evaluated and documented the presence of MI, UA, cardiac ischemia, and noncardiac ACS-like symptoms. At the time of the index visit, two visual analog scales were used. These defined the clinical impression of the probability of ACS and the probability of AMI and were performed by the physician who examined the patient. Another unique feature of FAST-TRAC is that the "visual analog scales at presentation" were completed within 15 minutes of the physician seeing and assessing the patient. Few studies have included such an early assessment of the clinical judgment. Additionally, the "visual analog scales after the 1st troponin" were completed after the initial local troponin result had been seen. The assessment of early clinical impression and judgment is unique and rarely reported elsewhere, it is of significant value in the evaluation of clinical assessment and the application of risk scores for disposition decisions.

After informed consent was obtained, blood draws were obtained at presentation, and 1, 2, 3 to 4, and 6 to 12 hours later. All blood draw times were  $\pm 30$  minutes from the target and could occur while in the ED or after hospitalization. All draws were required for each subject, except patients who were clinically ruled out for ACS. Those discharged before 6 hours only had serial draws obtained up to the time of discharge.

The recorded outcomes included mortality, cardiac rehospitalization, cardiac events, and revascularization at 30, 90, 180, and 365 days by telephone interviews. Follow-up periods were calculated from the day of the initial event that brought the patient to the ED. Primary outcomes assessed at follow-up were defined as major adverse cardiac event and included cardiac death, revascularization (coronary artery bypass grafting, angioplasty, or stent placement), and rehospitalization due to cardiac symptoms. Secondary outcomes included all-cause death and comorbidities that have been described as potentially increasing cTnI to low abnormal levels (e.g., pulmonary embolism, heart failure, cardiomyopa-

thy, myocarditis, cardiotoxic drugs, cardiac surgery, renal failure, sepsis, and vigorous exercise) and will be analyzed for any impact on the clinical performance of the test.

### Specimen handling

The FAST-TRAC study enrolled patients and collected blood samples during 2008. After collection at each site, samples were sent to the Core Laboratory (University of Maryland, Baltimore, MD, USA) for analysis using a hs-cTn assay that was not available commercially at the time of the study. Samples remained stored at  $-80^{\circ}\text{C}$  until analysis. Samples were never thawed, and all troponin testing was performed in the latter half of 2020 with validated assays and run on equipment by experienced laboratory personnel at the Core Laboratory. For biomarkers investigated in FAST-TRAC, the description of the technology, sample volume, and test procedures will be described in the respective analyses. Blood was collected in a 7.5-mL heparin tube, with no separation gel. The tube was filled to at least three-quarters, centrifuged, and plasma was transferred to cryovials, then frozen and stored to at least  $-70^{\circ}\text{C}$  within 1 hour of collection. Freezer temperature was monitored daily during the extended storage period and was without deviation.

### "Gold standard" diagnosis guidelines

When comparing test results between two assays, a different test result must serve as the arbitrator (a test may not serve as its own gold standard). Most hs-cTn studies use the locally obtained troponin as the gold standard (and thus the contemporary troponin serves as its own gold standard). FAST-TRAC is unique in that it obtained two gold standard diagnoses (GSDs); one with and one without (and thus a solely clinical GSD) the local troponin information. These two GSDs were adjudicated independently.

Once the 30-day follow-up was complete, case report forms were reviewed by at least two board-certified cardiologists, blinded to each other's report, to provide two separate GSD, made without access to the treating physician's discharge diagnoses. In the typical case where the same two cardiologists performed both evaluations, the GSD evaluation provided two GSDs; one without the local troponin result and a second with the local troponin result. All cases were presented to the reviewing cardiologists in a separate order and  $> 14$  days apart to minimize bias. All evaluations were reviewed for consistency by a designated Endpoints Committee. When the GSDs were not in agreement between the two reviewing cardiologists, a third cardiologist served as the tie-breaker.

### GSD evaluation no. 1

This evaluation was made without discharge diagnoses from the ED or hospital and without any diagnostic information in the medical record that referred to ST-segment elevation MI, non-ST-segment elevation MI, or UA. In addition, any local troponin, creatine kinase MB fraction, or myoglobin values were blinded, as was the high sensitivity cTn result, and redacted from the case report form received by the adjudicators. This evaluation determined if the primary diagnosis for the subject was ACS. If it was not ACS, a single alternative primary diagnosis was indicated.

### GSD evaluation no. 2

This evaluation used the local troponin and all information that would normally be used to assess the diagnosis (including discharge diagnoses and references to AMI and UA). Creatine kinase MB fraction and myoglobin values remained blinded.

### Definitions

AMI was defined by current guidelines.<sup>8</sup> If the diagnosis was AMI, the type of AMI (type 1 or type 2) was then determined by definitions derived from current guidelines.

#### Type 1

Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection.

#### Type 2

MI secondary to ischemia due to either increased oxygen demand or decreased supply (e.g., coronary artery spasm or embolism, anemia, arrhythmias, etc.), with evidence of ischemia.

#### UA

As detailed in the reporting guidelines<sup>12</sup> described by the Multidisciplinary Standardized Reporting Criteria Task Force.

### Other predefined primary and secondary diagnosis category

Other predefined primary and secondary diagnosis categories included "cardiovascular disease but non-ACSs" (e.g., pericarditis, myocarditis, tachyarrhythmias), "noncardiac symptoms," and "symptoms of unclassified cause." If AMI was excluded in the ED but no further diagnostic procedures were performed for a conclusive diagnosis, symptoms were defined as of unclassified origin.

## Statistics

The statistical analyses will use SPSS ver. 13.0 (SPSS Inc., Chicago, IL, USA) and Analyse-it ver. 2.12 (Analyse-it Software Ltd., Leeds, UK), with significance defined as  $< 0.05$ . All data will be analyzed on an intention-to-treat basis. Comparisons will be made using a t-test (analysis of variance), Fisher exact test, survival analysis (Kaplan-Meier method), and chi-square test, as appropriate. All hypothesis testing will be two-tailed. For primary endpoints 1 and 2, a comparison of receiver operating characteristic (ROC) curves for paired data will be conducted.

The sample size was calculated based on the first primary endpoint (see Purpose section above). Therefore, for ACS patients at  $\leq 2$  hours, if area under the ROC curve 1 = 0.85 for the hs-cTnI assay and area under the ROC curve 2 = 0.80 for a current cTnI assay, the correlation between measures is 0.80, the prevalence of ACS is 10% (extremely conservative assumption), and the power is 90%, the sample size should be at least 1,250 enrollees.

A rate of rise analysis will be used to differentiate acute from chronic heart disease and the severity of the disease. In addition, a Likert scale analysis was used to correlate *a priori* clinical diagnosis to test results.

To ensure the prognostic primary endpoint (risk stratification endpoint) was covered adequately with this sample size, detectable hazards were computed by the Schoenfeld formula.<sup>13</sup> Power was set to 80% with level  $\alpha = 0.05$  (two-tailed), assuming 1,250 subjects without censorship due to loss to follow-up. The predictor was assumed split at the median, giving 625 in each group. Time-to-event analysis was to be performed, the event rate was assumed at a single sentinel time point to define the primary test. However, since the actual time of the event will be known for every subject, the Kaplan-Meier curves will be shown (with a reference line at the sentinel time point). The model assumes no censoring (since death is an event). If subjects are lost to follow-up, then this rate would be incorporated into the model (increasing the hazard ratio detectable or decreasing power).

## DISCUSSION

FAST-TRAC is one of the few studies where both the clinical judgment of the care team was assessed and a GSD is adjudicated without a troponin result being known. This unique strategy allows the accurate determination of diagnostic and prognostic differences between contemporary and hs-cTn assays. Furthermore, by prospectively requiring the treating physician to provide an estimate of the probability of ACS, the additive value of the physician impression can be evaluated. Additionally, because the risk score data were obtained prospectively, its utility in determining

disposition decisions can be evaluated in the post-hs-cTn era. Finally, because the entry criteria required less than 6 hours of symptoms, a metric that is uncommonly evaluated in the contemporary literature, an objective measure of the utility of troponin testing in very early presentation will be determined. These unique study features will contribute significantly to the clinical applicability of hs-cTn.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

## ORCID

W. Frank Peacock	<a href="https://orcid.org/0000-0002-2730-6742">https://orcid.org/0000-0002-2730-6742</a>
Alan S. Maisel	<a href="https://orcid.org/0000-0001-7467-0195">https://orcid.org/0000-0001-7467-0195</a>
Christian Mueller	<a href="https://orcid.org/0000-0002-1120-6405">https://orcid.org/0000-0002-1120-6405</a>
Stefan D. Anker	<a href="https://orcid.org/0000-0002-0805-8683">https://orcid.org/0000-0002-0805-8683</a>
Fred S. Apple	<a href="https://orcid.org/0000-0002-5920-6498">https://orcid.org/0000-0002-5920-6498</a>
Robert H. Christenson	<a href="https://orcid.org/0000-0003-2612-9083">https://orcid.org/0000-0003-2612-9083</a>
Paul Collinson	<a href="https://orcid.org/0000-0002-7000-5996">https://orcid.org/0000-0002-7000-5996</a>
Lori B. Daniels	<a href="https://orcid.org/0000-0002-4841-9922">https://orcid.org/0000-0002-4841-9922</a>
Deborah B. Diercks	<a href="https://orcid.org/0000-0003-2043-7405">https://orcid.org/0000-0003-2043-7405</a>
Salvatore Di Somma	<a href="https://orcid.org/0000-0002-1717-6585">https://orcid.org/0000-0002-1717-6585</a>
Gerasimos Filippatos	<a href="https://orcid.org/0000-0002-5640-0332">https://orcid.org/0000-0002-5640-0332</a>
Gary Headden	<a href="https://orcid.org/0000-0002-5680-7191">https://orcid.org/0000-0002-5680-7191</a>
Brian Hiestand	<a href="https://orcid.org/0000-0002-0568-1269">https://orcid.org/0000-0002-0568-1269</a>
Judd E. Hollander	<a href="https://orcid.org/0000-0002-1318-2785">https://orcid.org/0000-0002-1318-2785</a>
Juan C. Kaski	<a href="https://orcid.org/0000-0001-8068-0189">https://orcid.org/0000-0001-8068-0189</a>
Joshua M. Kosowsky	<a href="https://orcid.org/0000-0003-4891-6598">https://orcid.org/0000-0003-4891-6598</a>
John T. Nagurny	<a href="https://orcid.org/0000-0001-7193-4896">https://orcid.org/0000-0001-7193-4896</a>
Richard M. Nowak	<a href="https://orcid.org/0000-0002-7453-9426">https://orcid.org/0000-0002-7453-9426</a>
Donald Schreiber	<a href="https://orcid.org/0000-0003-1111-310X">https://orcid.org/0000-0003-1111-310X</a>
Gary M. Vilke	<a href="https://orcid.org/0000-0002-1156-7200">https://orcid.org/0000-0002-1156-7200</a>
Marvin A. Wayne	<a href="https://orcid.org/0000-0002-6190-958X">https://orcid.org/0000-0002-6190-958X</a>
Martin Than	<a href="https://orcid.org/0000-0001-9399-5227">https://orcid.org/0000-0001-9399-5227</a>

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